Microbiological Factors and Inflammatory Cytokines in Acute and Chronic Rhinosinusitis

Sema Başak[1], Murat Telli[2], Yeşim Başal[1], Çiğdem Yenisey[3]

[1]Department of Otolaryngology, Aydın Adnan Menderes University School of Medicine, Aydın, Turkey
[2]Department of Microbiology, Aydın Adnan Menderes University School of Medicine, Aydın, Turkey
[3]Department of Biochemistry, Aydın Adnan Menderes University School of Medicine, Aydın, Turkey

Abstract

Objective: We aimed to use middle meatus aspiration technique (MMAT) in both microbiological diagnosis and detection of cytokines and to compare the groups having ARS and non-polyp CRS after determining the microbiological agents and the levels of IL-4, IL-5, IL-13, IL-32, TGF-beta, and thymic stromal lymphopoietin (TSLP).

Material and Methods: The patients were classified as ARS and non-polyp CRS. The microbiological samples were grown on 5% defibrinated sheep blood agar, chocolate agar, Eosin-Methylene Blue agar (EMB), and Sabouraud- dextrose agar (SDA) media. IL-4, IL-5, IL-13 IL-32, TLR2, TSLP, and TGF-beta levels of biochemical samples were studied by ELISA method using commercial kits.

Results: Samples of nasal discharge were collected in a total of 44 patients. The difference between ARS Group and Non-polyp CRS Group regarding the culture growth of pathogens was statistically significant. The levels of TSLP, TGF-beta, IL-4, IL-5, IL-13 and IL-32 were not in conformity with a normal distribution. The differences between ARS Group and Non-polyp CRS Group were not significant regarding these variable.

Conclusion: We have the opinion that, MMAT is a non-invasive method that can be performed at the circumstances of an outpatient clinic and can be used for microbiological diagnosis as well as routine identification of inflammatory processes

Keywords: Acute rhinosinusitis, chronic rhinosinusitis, inflammation, microbiology, pathophysiology

Presented in: This study was presented at the 41st Turkish National Otolaryngology Head and Neck Surgery Congress, Nov/13-17/2019, Antalya, Turkey.

Cite this article as: Başak S, Telli M, Başal Y, Yenisey Ç. Microbiological Factors and Inflammatory Cytokines in Acute and Chronic Rhinosinusitis. Eur J Rhinol Allergy 2021; 4(1): 16-20.

Address for Correspondence: Yeşim Başal

E-mail: yesimdurgun@gmail.com

Received: 11.02.2021

Accepted: 16.03.2021

DOI: 10.5152/ejra.2021.20036

INTRODUCTION

The etiology and pathophysiology of rhinosinusitis, which can manifest various clinical characteristics, are still under discussion. Various proinflammatory cytokines are manifested in the mucosa of the upper respiratory tract during viral and bacterial rhinosinusitis infections (1, 2). The innate immune system can activate pathogen-related molecular patterns against viral and bacterial pathogens. After such activation, pathogen-related receptors known as toll-like receptors (TLRs), located on the immune cells and other types of cells, can be activated (3). A total of 10 different types of TLR were found to be present in humans. The activation of these receptors can initiate the intracellular signal cascade leading to hemostasis, inflammation, apoptosis, and the activation of the adaptive immune system. The activation of the adaptive immune system is stimulated by the regulation of cytokines, chemokines, and other costimulatory mediators. Even though these mechanisms have been investigated extensively in patients with chronic rhinosinusitis (CRS), they have rarely been assessed in patients with acute rhinosinusitis (ARS) (3).

Determining the presence of inflammatory and other biomarkers in nasal secretions and nasal cells is essential for both diagnosing and treating RS (2, 4). However, there is currently no standard method available to determine the type of an inflammatory cell and/or the presence of inflammatory mediators, which is probably why the detection of inflammatory cells and/or mediators has not been a part of routine diagnostic and therapeutic decisions (2). Various methods have been used to determine the types of inflammatory cells and/or the presence of inflammatory mediators; these methods include obtaining samples from nasal discharge, nasal lavage, nasal tampons, nasal brush swabs, and tissue biopsy. Furthermore, although the middle meatus aspiration technique (MMAT) has been used for the microbiological diagnosis of both ARS and CRS for many years, the recommendation for its use as a diagnostic tool in the detection of inflammatory and other biological markers is relatively new (4). One of the significant advantages of obtaining a sample using the MMAT is that it allows the same sample to be used for microbiological diagnosis. In

this study, we used MMAT for both microbiological diagnosis and to detect cytokines and compared groups of patients with ARS with those with nonpolyp CRS after determining the presence of microbiological agents and the levels of interleukin (IL)-4, IL-5, IL-13, IL-32, transforming growth factor (TGF)-β1, and thymic stromal lymphopoietin (TSLP) in the patients.

MATERIAL AND METHODS

The study was approved by the ethics committee for non interventional clinical studies at the Adnan Menderes University Medical Faculty with protocol number 2017/1254 dated December 7, 2017. The study groups comprised patients with adult ARS and patients with nonpolyp CRS who presented to the outpatient clinic of the Ear, Nose, and Throat Department of Adnan Menderes University and met the criteria for inclusion in the study. The inclusion criteria were having at least 1 of the following symptoms: nasal obstruction, purulent nasal discharge, postnasal discharge, facial fullness, or anosmia together with an absence of a polyp in a endoscopic nasal examination; the presence of a quantity of purulent drainage within the nasal passage and/or middle meatus that allowed sampling; and no use of an antibiotic, nasal steroid, or systemic anti-inflammatory drug within the last 10 days. The patients were classified as having ARS if their symptoms had lasted <3 months and as having nonpolyp CRS if their symptoms had lasted >3 months.

The Microbiological Method

The samples used in the study were collected via nasal endoscopy using a special collector (a Juhn-Tymp tap Xomed Treace Products, Jacksonville, FL, USA). The purulent discharge sample was sent to the Medical Microbiology Laboratory as soon as it was collected from the nasal cavity and/or middle meatus. Samples were grown on 5% defibrinated sheep blood agar, chocolate agar, Eosin-Methylene Blue (EMB) agar, and Sabouraud-dextrose agar (SDA) media. The chocolate agar was incubated at 35 °C for 24–48 h in a waxed jar containing 5-10% carbon dioxide. The EMB and SDA agar were incubated at 35 °C for 24-48 h, creating an aerobic environment. The growth in the culture media was assessed according to colony morphology and gram-staining characteristics. Further identification procedures were performed after the growth of the bacterial or fungal agents.

Biochemical Methods

Sample Preparation. Each sample obtained via the MMAT was placed in 1.0 ml of 50 mM phosphate buffer (pH 7.4) containing a protease inhibitor (0.2 μM phenyl methane sulphonyl fluoride) and 1 mM ethylene diamine tetraacetic acid before being homogenized at 4 °C using an ultrasonic sonicator. The homogenates were centrifuged at 10,000 rpm for 10 min. The supernatant was distributed equally in Eppendorf tubes and frozen at -80 °C to allow investigation of the other parameters.

Enzyme-Linked Immunosorbent Assay Study of the Samples. IL-4, IL-5, IL-13, IL-32, TLR2, TSLP, and TGF-β levels were studied using commercial enzyme-linked immunosorbent assay (ELISA) kits. Samples were placed in the wells of the antigen-coated plates and incubated at 37 °C before the antibodies were added. The substrate solution was added after washing. After a blue color appeared, the reaction-terminating reagent was added. The resultant yellow color was read at 450 nm in a microplate reader (ELx800, BioTek,Instruments Winooski, Vermont, USA). The concentrations in the samples were calculated automatically from the graph generated by the instrument using the standards contained within the kit. The results were read automatically at 450 nm on the microplate reader with the aid of a standard curve. The graph was plotted automatically in the ELISA reader and concentrations were calculated automatically.

Calculating the IL-4 Level in the Samples. The IL-4 level in the samples was investigated using the commercial Elabscience human ELISA kit (catalog number: E-EL-H0101, Elabscience, Wuhan, China). The sensitivity of the test was 18.75 pg/mL and the detection range was 31.25–2000 pg/mL. The coefficient of variation (CV) was <10%.

Calculating the IL-5 Level in the Samples. The IL-5 level in the samples was investigated using the commercial Elabscience human ELISA kit (catalog number: E-EL-H0191, Elabscience, Wuhan, China). The sensitivity of the test was 9.38 ng/mL, the detection range was 1.56–1000 pg/mL, and the CV was <10%.

Calculating the IL-13 Level in the Samples. The IL-13 level in the samples was investigated using the commercial Elabscience human ELISA kit (catalog number: E-EL-H0104, Elabscience, Wuhan, China). The sensitivity of the test was 9.38 pg/mL, the detection range was 15.63-1000 pg/mL, and the CV was <10%.

Calculating the IL-32 Level in the Samples. The IL-32 level in the samples was investigated using the commercial Elabscience human ELISA kit (catalog number: E-EL-H0216, Elabscience, Wuhan, China). The sensitivity of the test was 9.38 pg/mL, the detection range was 15.63-1000 pg/mL, and the CV was <10%.

Calculating the TGF-β1 Level in the Samples. The TGF-β1 level in the samples was investigated using a commercial Elabscience human ELISA kit (catalog number: E-EL-H0110, Elabscience, Wuhan, China). The sensitivity of the test was 18.75 pg/mL, the detection range was 31.25–2000 pg/mL, and the CV was <10%.

Calculating the TLR2 Level in the Samples. The TLR2 level in the samples was investigated using the commercial Elabscience human ELISA kit (catalog number: E-EL-H0951, Elabscience, Wuhan, China). The sensitivity of the test was 0.19 ng/mL, the detection range was 0.31-20 ng/mL, and the CV was <10%.

Calculating the TSLP Level in the Samples. The TSLP level in the samples was investigated using the commercial Elabscience human ELISA kit (catalog number: E-EL-H1598, Elabscience). The sensitivity of the test was 18.75 pg/mL, the detection range was 31.25-2000 pg/mL, and the CV was <10%.

Statistical Analysis

Statistical analysis was performed using the software Statistical Package for the Social Sciences 22.0 (SPSS Statistics v 22.0, IBM Corp®, Armonk, NY, USA). In addition to generating descriptive statistics, the Mann–Whitney U and chi-square tests were used for intergroup comparisons of the numerical and categorical variables, respectively. The conformity of the variables with a normal distribution was tested using the Kolmogorov–Smirnov test. A value of $p<.05$ was considered statistically significant.

RESULTS

Samples of nasal discharge were collected in 44 patients who met the inclusion criteria (21 females and 23 males). The mean patient age was 36.20±17.763 years and the range was 18–85 years. Of these patients, 25 were in the ARS group and 19 were in the nonpolyp CRS group (Tables 1 and 2, respectively). No culture growth was detected in samples from 13 patients in the ARS group and 2 patients in the nonpolyp CRS group. In

Table 1. Results from cultured samples from 25 patients with acute rhinosinusitis

No	Patient name	Result
1	EA	No growth
2	NS	*Staphylococcus aureus, Streptococcus pneumoniae*
3	SD	No growth
4	UK	No growth
5	NA	*Hemophilus influenzae*
6	MAT	*S. aureus*
7	FA	*Klebsiella pneumoniae*
8	AY	*Moraxella catarrhalis*
9	RÖ	*S. pneumoniae, H. influenzae*
10	ÖM	No growth
11	YA	No growth
12	AE	*K. pneumoniae*
13	VÜ	No growth
14	GNE	*M. catarrhalis*
15	MBK	*H. influenzae*
16	MA	*S. pneumoniae*
17	EA	No growth
18	ST	No growth
19	ÇK	No growth
20	EA	No growth
21	RY	No growth
22	CB	*H. influenzae*
23	HS	No growth
24	HA	No growth
25	EE	M. catarrhalis

No: number.

Table 2. Results from cultured samples from 19 patients with chronic rhinosinusitis

No	Patient name	Culture result
1	NR	*Citrobacter freundii*
2	EY	*Staphylococcus aureus, Streptococcus pneumoniae, Hemophilus influenzae*
3	AA	*S. pneumoniae, H. influenzae*
4	BE	*H. influenzae*
5	YC	*H. influenzae*
6	AB	*H. influenzae*
7	ÖE	*Bacteria from mixed flora*
8	KT	*Bacteria from mixed flora*
9	NA	*S. aureus*
10	EGD	*S. pneumoniae, H. influenzae*
11	NM	*Pseudomonas aeruginosa*
12	EB	*Mold fungi*
13	HB	*S. aureus*
14	SŞ	*Neisseria meningitidis*
15	NG	No growth
16	HY	No growth
17	AY	*Moraxella catarrhalis*
18	SÖ	*S. pneumoniae, H. influenzae*
19	SK	*S. pneumoniae, M. catarrhalis*

No: number.

the ARS group, a single microbiological agent was obtained in 10 samples and >1 agent was found in 2 samples. In the samples from these patients, the bacteria *Streptococcus pneumoniae, Hemophilus influenzae,* and *Moraxella catarrhalis* were the most common. In the nonpolyp CRS group, a single microbiological agent was obtained in 10 samples and >1 agent was found in 9 samples. In the samples from this group, *S. pneumoniae, H. influenzae,* and *M. catarrhalis* were the most common microbiological agents; however, *Pseudomonas aeruginosa* and mold fungus were also detected. The microorganisms grown in the sample from the whole group are presented in order of frequency in Table 3. There was a statistically significant ($\chi^2 = 6.521$, P=.011) difference between the ARS group and nonpolyp CRS group in terms of the culture growth of pathogens.

Samples of a sufficient amount for biochemical investigation were present in 15 patients in the ARS group and 16 patients in the nonPolyp CRS group. The mean TSLP, TGF-β1, IL-4, IL-5, IL-13, and IL-32 values for both groups and for the entire group are shown as pg/mg protein in Table 4 and ml/mg protein in Table 5. The TSLP, TGF-β1, IL-4, IL-5, IL-13, and IL-32 levels did not conform to a normal distribution. The differences between

Table 3. Microorganisms grown in all patient groups

Single agent	Frequency
Hemophilus influenzae	6
Moraxella catarrhalis	4
Staphylococcus aureus	3
Bacteria of mixt flora	2
Klebsiella pneumoniae	2
Pseudomonas aeruginosa	1
Streptococcus pneumoniae	1
Citrobacter freundii	1
Mold fungi	1
Neisseria meningitidis	1
>1 agent	
S. pneumoniae+S. aureus	1
S. pneumoniae+H. influenzae	4
S. pneumoniae+M. catarrhalis	1
S. pneumoniae+S. aureus+H. influenzae	1

the ARS group and the nonpolyp CRS group were not significant (p>.05) in terms of these variables. When the entire group was considered, there was no significant difference (p>.05) in the levels of the cytokines investi-

Table 4. Distribution of TSLP, TGF-β1, IL-4, IL-5, IL-13, and IL-32 values (pg/mg Protein) for both acute and chronic patient groups

Variable (pg/mg protein)	Acute (n=15)		Chronic (n=16)		Total (n=31)		Statistics
	Mean	Median	Mean	Median	Mean	Median	
TGFβ1	578.47±437.29	493 (382-620)	444.53±250.36	461 (196-652)	509.34±353.85	478 (382-620)	*P*=.740
TSLP	530.22±304.01	484(382-620)	509.49±292.93	497 (294-628)	519.52±293.51	484 (293-634)	*P*=.984
IL13	238.91±170.88	189 (170-251)	215.65±97.15	192 (158-255)	226.90±135.96	190 (166-251)	*P*=.922
IL4	545.50±492.78	347(96-1088)	461.66±370.68	349 (161-828)	502.23±428.77	347 (161-861)	*P*=.711
IL32	312.22±165.98	241 (208-462)	237.72±145.05	216 (198-270)	273.77±157.51	220 (202-300)	*P*=.247
IL5	177.40±106.57	142 (127-215)	143.76±76.78	141 (96-177)	160.04±92.41	142 (118-195)	*P*=.520

TSLP: thymic stromal lymphopoietin; TGF-β1: transforming growth factor β1; IL: interleukin.

Table 5. TSLP, TGF-β1, IL-4, IL-5, IL-13, and IL-32 values (mL/mg protein) for the entire patient group

Variable (mL/mg)	Acute (n=15)		Chronic (n=16)		Total (n=31)		*P*-value
	Mean	Median	Mean	Median	Mean	Median	
TGFβ1	453.34±327.77	502 (450-704)	453.34±396.68	429 (147-559)	512.28±359.51	485 (351-636)	.131
TSLP	523.61±276.89	462 (364-626)	514.76±332.10	507 (243-737)	519.48±298.52	478 (292-645)	.790
IL13	234.77±99.78	191 (173-274)	222.64±175.34	192 (151-233)	229.11±137.73	191 (169-254)	.498
IL4	566.67±471.76	538 (113-886)	452.95±388.29	306 (145-601)	513.60±431.32	390 (145-869)	.580
IL32	315.10±181.42	212 (158-284)	232.01±121.82	212 (158-284)	276.33±159.54	223 (203-305)	.085
IL5	166.73±88.66	152 (130-177)	155.31±102.12	135 (69-213)	161.40±93.67	142 (117-198)	.608

TSLP: thymic stromal lymphopoietin; TGF-β1: transforming growth factor β1; IL: interleukin.

gated in terms of the presence of culture growth. Moreover, the growth of either a single agent or >1 agent was not effective on the cytokine level in the ARS group (*p*>.05).

DISCUSSION

Rimmer et al. (4) recently presented an updated status report on the diagnostic tools that can be used in rhinologic disorders. According to this report, an MMAT performed by a special collector is one of the methods recommended for both investigations of inflammatory markers and the identification of microbiological agents. In our study, we investigated inflammatory markers and microbiological agents in samples of nasal secretions from patients with ARS and nonpolyp CRS that we collected using the MMAT.

ARS is the most common primary care disorder and one of the leading disorders among those necessitating the prescription of antibiotics. The inflammatory mechanisms and clinical presentations of viral, postviral, and bacterial ARS were reported to manifest significant similarities.[1] The question of whether antibiotics are necessary in cases of ARS, which is considered to be manifested mostly secondary to viral infections, is controversial (5). In our study, no culture growth was detected in half the ARS group in only 2 samples in the nonpolyp CRS group. A significant difference was found between these 2 groups in terms of microbiological growth in culture. Therefore, this situation might be considered as pointing out the presence of viral etiology in the ARS group. This consideration can be clarified by including viral cultures in the study. In previous studies, the microorganisms most frequently identified in patients with bacterial ARS were *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* (1, 5). This was also true in our ARS group.

There are microbiological differences between ARS and CRS. *Staphylococcus aureus, S. epidermidis,* and anaerobic gram-negative bacteria are commonly identified in CRS (6); however, a transition from ARS to CRS was reported to be possible (7). In patients for whom this was the case, it is possible to identify pathogens such as *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* acting as ARS agents (6). *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* were identified in samples from many patients in our nonpolyp CRS group. In our nonpolyp CRS group, the identification of *P. aeruginosa* growths in samples from 1 patient and mold fungi in the sample from another showed the diversity of microbiology in the chronic form of the disease. One of the limitations of this study was a lack of anaerobic cultures performed.

Investigations on the etiology of rhinosinusitis initially focused mainly on microbiological agents. In later years, other studies reported that processes leading to bacterial colonization were associated with disruption of the barrier function of the epithelium (8, 9). Subsequent research on inflammatory processes revealed the significance of the T-cell-related inflammatory response in ARS and CRS (10, 11). We investigated the presence of TSLP, TGF-β1, IL-4, IL-5, IL-13, and IL-32 cytokines in nasal secretions that we obtained using the MMAT.

TSLP, a protein in the cytokine family, plays a significant role in the maturation of the T cells. TSLP induces T helper type 2 (Th2) cytokine-dependent inflammation and plays a crucial role in the immune response of the respiratory tract mucosa (12). Therefore, TSLP expression has been suggested to play a role in disorders such as asthma, CRS, and numerous allergic disorders (13-16). There are currently no studies investigating TSLP levels in ARS in the medical literature; our study was the first study of this kind in the literature. Doğan et al. reported a difference in TSLP between

tissue samples of patients with CRS with polyps and those of a control group; however, our study did not show any difference between the ARS group and the nonpolyp CRS group in terms of TSLP.

Milonski et al. (17) reported that revealing the clinical biomarkers is essential for individualized treatments and investigated the expressions of POSTN and its immune mediators, such as IL-4 and IL-13, in patients with CRS. They reported that the gene expressions of POSTN, IL4, and IL-13 were higher in patients with CRS who had polyps and those that did not than in their control group. IL-4 increased Th2 activation whereas IL-13 had no such effect (18). As with IL-4, IL-5 is one of the most investigated major Th2 cytokines in nasal polyp studies (19). TGF-β1 plays a crucial role in tissue remodeling processes in patients with CRS (20). Watelet et al. (21) reported that they found higher levels of TGF-β1 in samples from patients with the nonpolyp form of CRS (21). Eloy et al. (22) emphasized that TGF-β1 played a critical role in the etiology of nonpolyp CRS (22). Our results did not reveal any difference between ARS and nonpolyp CRS groups in terms of the levels of these cytokines.

CONCLUSION

This study investigated various cytokines and microbiological agents obtained using the MMAT. One of the significant limitations of this study was the difficulty encountered in constituting a control group. Contrary to the studies conducted with nasal irrigation fluids or tissue samples, a sufficient quantity of sample fluid cannot be obtained from a healthy individual via the MMAT. Therefore, there is no healthy control group in this study. Comparisons were made between patients with ARS and those with nonpolyp CRS. A second limitation was the exclusion of patients with CRS who had polyps. We plan to include these patients in further studies. A final limitation of our study was the lack of viral cultures and/or anaerobic cultures performed. The most important reason for this limitation was the insufficiency of the sample quantities gathered for various microbiological and biochemical tests. The most significant advantage of the study was the inclusion of patients with ARS.

We consider the MMAT a noninvasive method that can be performed in an outpatient clinic setting for microbiological diagnosis and the routine identification of inflammatory processes.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Trials Ethics Committee of Aydin Adnan Menderes University Medical Faculty (Number: 2017/1254, date: December 7, 2017).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.B., M.T., Y.B.; Design - S.B., M.T., Y.B.; Supervision - S.B., M.T., C.Y.; Resource - M.T., Y.B., C.Y.; Materials - S.B., Y.B., C.Y.; Data Collection and/or Processing - S.B., M.T., C.Y.; Analysis and/or Interpretation - S.B., M.T., Y.B.; Literature Search - S.B., Y.B.; Writing - S.B., Y.B., C.Y.; Critical Reviews - S.B., M.T., C.Y.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: This study was supported by BAP Project of Aydın Menderes University.

REFERENCES

1. Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. Rhinol Suppl 2012; 23: 3: 1-298.
2. Ren HL, Li JD, Yue FS, Sun JL, Rebeiz EE, Theoharides TC. Nasal cytology with empha-sis on mast cells can improve the diagnosis and treatment of chronic rhinosinusitis. Chin Med J 2019; 132: 2237-41. [Crossref]
3. Scheckenbach K, Wagenmann M. Cytokine patterns and endotypes in acute and chronic rhinosinusitis. Curr Allergy Asthma Rep 2016; 16: 3. [Crossref]
4. Rimmer J, Hellings P, Lund VJ, et al. European position paper on diagnostic tools in rhinol-ogy. Rhinology 2019; 5: 1-41. [Crossref]
5. Smith SS, Ference EH, Evans CT, Tan BK, Kern RC, Chandra RK. The prevalence of bac-terial infection in acute rhinosinusitis: A Systematic review and me-ta-analysis. Laryngoscope 2015; 125: 57-69. [Crossref]
6. Brook I. Microbiology of chronic rhinosinusitis. Eur J Clin Microbiol Infect Dis 2016; 35: 1059-68. [Crossref]
7. Brook I, Frazier EH, Foote PA. Microbiology of the transition from acute to chronic maxil-lary sinusitis. J Med Microbiol 1996; 45: 372-5. [Crossref]
8. Jiao J, Wang C, Zhang L. Epithelial physical barrier defects in chronic rhinosinusitis. Expert Rev Clin Immunol 2019; 15: 679-88. [Crossref]
9. Georas SN, Rezaee F. Epithelial barrier function: At the front line of asthma immunology and allergic airway inflammation. J Allergy Clin Immunol 2014; 134: 509-20. [Crossref]
10. Pistochini A, Rossi F, Gallo S, et al. Multiple gene expression profiling suggests epithelial dysfunction in polypoid chronic rhinosinusitis. Acta Otorhinolaryngol Ital 2019; 39: 169-77. [Crossref]
11. Kaya Z, Yayla M, Cinar I, et al. Effect of Montelukast, a Cysteinyl Leukotriene Receptor-1 Antagonist, on a Rat Model of Acute Bacterial Sinonasal Inflammation. Am J Rhinol Allergy 2019; 33: 559-66. [Crossref]
12. Kato T, Kouzaki H, Matsumoto K, Hosoi J, Shimizu T. The effect of calprotectin on TSLP and IL-25 production from airway epithelial cells. Allergol Int 2017; 66: 281-9. [Crossref]
13. Ying S, O'Connor B, Ratoff J, et al. Thymic stromal lymphopoietin expression is increased in asthmatic airways and correlates with expression of Th2-attracting chemokines and dis-ease severity. J Immunol 2005; 174: 8183-90. [Crossref]
14. Nagata Y, Maruoka S, Gon Y, et al. Expression of IL-25, IL-33, and thymic stromal lym-phopoietin in nasal polyp gland duct epithelium in patients with chronic rhinosinusitis. Am J Rhinol Allergy 2019; 33: 378-87. [Crossref]
15. Dogan M, Sahin M, Yenisey C. Increased TSLP, IL-33, IL-25, IL-19, IL 21 and amphiregu-lin (AREG) levels in chronic rhinosinusitis with nasal polyp. Eur Arch Otorhinolaryngol 2019; 276: 1685-91. [Crossref]
16. Kim DK, Kang SI, Kong IG, et al. Two-track medical treatment strategy according to the clinical scoring system for chronic rhinosinusitis. Allergy Asthma Immunol Res 2018; 10: 490-502. [Crossref]
17. Milonski J, Zielinska-Blizniewska H, Majsterek I, et al. Expression of POSTN, IL-4, and IL-13 in chronic rhinosinusitis with nasal polyps. DNA Cell Biol 2015; 34: 342-9. [Crossref]
18. Baykal Y, Karaayvaz M, Kutlu M. Interleukins. T Clin J Med Sci 1998; 18: 77-83. [Crossref]
19. Otto BA, Wenzel SE. The role of cytokines in chronic rhinosinusitis with nasal polyps. Curr Opin Otolaryngol Head Neck Surg 2008; 16: 270-4. [Crossref]
20. Kou W, Hu GH, Yao HB, et al. Regulation of transforming growth factor-beta1 activation and expression in the tissue remodeling involved in chronic rhinosinusitis. ORL J Otorhino-laryngol Relat Spec 2012; 74: 172-8. [Crossref]
21. Watelet JB, Claeys C, Perez-Novo C, Gevaert P, Van Cauwenberge P, Bachert C. Transforming growth factor beta1 in nasal remodeling: Differences between chronic rhinosi-nusitis and nasal polyposis. Am J Rhinol 2004; 18: 267-72. [Crossref]
22. Eloy P, Poirrier AL, De Dorlodot C, Van Zele T, Watelet JB, Bertrand B. Actual concepts in rhinosinusitis: A review of clinical presentations, inflammatory pathways, cytokine profiles, remodeling, and management. Curr Allergy Asthma Rep 2011; 11: 146-62. [Crossref]