

Case Report**Prognostic factors for refractory
chronic rhinosinusitis concomitant with asthma****Kartika Dwiyani*, Eka Dian Safitri**, Yupitri Pitoyo*****Department of Otolaryngology Head and Neck Surgery Persahabatan Hospital- Faculty of
Medicine Universitas Indonesia**Clinical Epidemiology and Evidence Based Medicine Unit CiptoMangunkusumo Hospital
– Faculty of Medicine Universitas Indonesia
Jakarta**ABSTRACT**

Background: In chronic rhinosinusitis (CRS) patients concomitant with asthma, more severe sinus disease has been reported and recurrence rate remains significant after optimal management. In this review, patients with CRS concomitant with asthma which had optimal management will be analyzed. Did several factors e.g. mucosal eosinophilia, high eosinophil count, high Lund MacKay score, severity of asthma, peripheral blood count and type of surgery, affect the recurrence of rhinosinusitis? **Purpose:** To investigate prognostic factors for the recurrence or refractory in CRS patients concomitant with asthma. **Case Report:** Female, 31 years old, suffered CRS with nasal polyp concomitant with asthma. She had a recurrence of her sinus disease although she had already received optimal management. **Methods:** Using Medline, Cochrane database, and Hand searching to search for the evidence. The evidence selected was appraised by at least two members of our group using Oxford Centre for Evidence-based Medicine (CEBM) worksheet. **Result:** Two valid prognostic articles were appraised for the validity, importance and applicability in our clinical scenario. **Conclusion:** In this evidence-based case report, the type of surgery could affect the olfactory function and endoscopic postoperative score in CRS patients concomitant with asthma. It was found that Extensive Endoscopic Sinus Surgery (EESS) contributed as a prognostic factor to improve olfactory Visual Analog Scale (VAS) score and endoscopic postoperative score.

Keywords: chronic rhinosinusitis, asthma, eosinophilic polyp, EESS**ABSTRAK**

Latar belakang: Pada pasien rinosinusitis kronis (RSK) yang disertai dengan asma telah banyak dilaporkan gejala sinus yang lebih berat dan angka kekambuhan yang signifikan walaupun pasien telah mendapatkan tatalaksana optimal. Dalam laporan ini, akan dianalisis pasien RSK yang disertai asma, yang telah mendapat terapi optimal. Apakah faktor-faktor eosinofilia pada mukosa, tingginya hitung jumlah eosinofil, tingginya skor Lund-MacKay, derajat keparahan asma, hitung jenis darah perifer dan jenis operasi, berperan terhadap kekambuhan rinosinusitis? **Tujuan:** Mengetahui faktor prognostik yang memengaruhi kekambuhan pada pasien RSK yang disertai asma. **Laporan kasus:** Pasien wanita 31 tahun, dengan diagnosis RSK dengan polip yang disertai asma. Pasien mengalami kekambuhan rinosinusitis walaupun telah mendapatkan terapi optimal. **Metode:** Pencarian bukti dilakukan melalui Medline, Cochrane, Hand searching. Artikel yang didapat ditelaah oleh setidaknya dua anggota kelompok dengan menggunakan lembar kerja yang diperoleh dari Oxford Centre for Evidence-based Medicine (CEBM). **Hasil:** Dua artikel prognosis yang didapat, ditelaah kritis untuk dinilai validitas, pentingnya, dan kemampuan untuk dapat diaplikasikan dalam skenario klinis. **Kesimpulan:** Pada laporan kasus berbasis bukti ini, jenis operasi dapat merupakan faktor prognostik dalam memperbaiki skor Visual Analog Scale (VAS) olfaktori dan skor endoskopi pasca operasi. Extensive endoscopic sinus surgery (EESS) memiliki kontribusi sebagai faktor prognostik dalam memperbaiki skor VAS olfaktori dan skor endoskopi pasca operasi.

Kata kunci: *rhinosinusitis kronis, asma, polip eosinofilik, EESS*

Corresponding author: Kartika Dwiyani, MD, ORL. Otorhinolaryngology Department Persahabatan Hospital-Faculty of Medicine Universitas Indonesia. E-mail: tikadwiyani@gmail.com

INTRODUCTION

Rhinosinusitis (RS) is an inflammatory condition of the nose and paranasal sinuses. It is a broad umbrella term covering multiple disease entities, including acute rhinosinusitis (ARS), chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) and CRS without nasal polyps.¹ The prevalence of physician diagnosed CRS ranged 1%-9% of the general population. In 2011, a large scale adult population study in Europe performed by Hastan et al showed the prevalence of CRS to be 10,9%.²

Bronchial asthma is frequently associated with CRS with and without polyps, and may have influence on sinus surgery outcomes.³

Connection between asthma and CRS may be related to neural pathways, which can trigger the release of inflammatory mediators, less likely is the role of micro aspiration from the upper to the lower airways. Another possibility is a systemic immunologic crosstalk between the upper and lower airways. There is evidence that markers such as Interleukin 5 and Staphylococcus enterotoxin (SE)-IgE within the nasal polyp tissue are associated with co-morbid asthma.¹

Chronic rhinosinusitis (CRS) is defined as an inflammation of the nose and the paranasal sinuses, characterized by two or more symptoms, one of which should be either nasal blockage or nasal discharge (anterior/ posterior nasal drip) accompanied with facial pain and/or reduction or loss of smell for ≥ 12 weeks, confirmed by either endoscopic signs of nasal polyp and/or mucopurulent

discharge primarily from middle meatus and/or oedema primarily in middle meatus and/or mucosal changes within ostiomeatal complex (OMC) and/or sinuses in CT scan examination.²

Asthma is a chronic inflammation of the lower airways involving episodic breathlessness and wheezing, with airway hyper-responsiveness to environmental stimuli, with a prevalence of 5%–10% in the general population.¹

More severe sinus disease in CRS patients concomitant with asthma has been reported.³ Bilodeau et al cited by Langdon⁴ showed that, among asthmatic subjects, those with CRSwNP presented more poorly controlled asthma than those without CRSwNP. Patients suffering from asthma and CRS reporting a poorer quality of life.³⁻⁵ Batra et al⁶ in their study found that statistical increase was noted for endoscopy and CT scores in the asthmatic versus nonasthmatic patients. Seybt cited by Fokkens³ reported that patients with asthma require significantly more revision of sinus surgeries.

CRS is commonly managed with medical treatments, but some patients fail to benefit from a purely medical approach. Endoscopic sinus surgery (ESS) is often undertaken in this group, and generally has a very high initial success rate for symptomatic improvement in the quality of life. Unfortunately, some cases still showing recurrences or even need revision following surgery and make the long-term management of this condition challenging for patients and clinicians.⁷ Despite advances in the diagnosis and treatment of CRS, the recurrence rate remains

significant. There is an undeniable need for more effective prognostic parameters enabling rhinologists to detect patients at higher risk of CRS recurrence after sinonasal surgery. These parameters could make it easier to: (a) provide an appropriate information to patients; (b) adopt rational follow-up protocols; and (c) provide a dedicated postoperative medical treatments for patients at high risk of recurrence.

There is still a lack of understanding of the pathomechanisms and predictors for disease recurrence.¹ At present, the literature does not supply the clinician with long-term data regarding risk factors that might increase those conditions.⁷

In this review, we will analyze the prognostic factors for recurrence/refractory CRS in CRS patients concomitant with asthma. We formulated our clinical question: **(P)** Patient with CRS concomitant with asthma; **(I)** Risk factors mucosal eosinophilia, high eosinophil count, high Lund MacKay score, severity of asthma, peripheral blood count and type of surgery: Extensive Endoscopic Sinus Surgery (EESS) or Functional Endoscopic Sinus Surgery (FESS); **(C)** No risk factors; **(O)** Recurrence/ refractory CRS concomitant with asthma.

The proposed question in this study are the list of prognostic factors such as mucosal eosinophilia, high eosinophil count, high Lund-MacKay score, severity of asthma, peripheral blood count and type of surgery (EESS or FESS); did these factors affect the recurrence/refractory CRS in CRS patients concomitant with asthma?

CASE REPORT

A female, 31 years old, complained there was a facial pain at the maxillary region, nasal obstruction for more than

10 years, hyposmia, nasal secretion and post nasal drip. She had grade 2 polyp and mucoid secretion from bilateral middle meatus and post nasal drip. Patient already diagnosed as persistent severe asthma and had frequent recurrences of severe acute asthma attack. We managed the patient as a chronic rhinosinusitis with nasal polyp concomitant with asthma. The skin prick test result was negative. After optimal medication, functional endoscopic sinus surgery (FESS) was performed. The pathologic examination result was eosinophilic sinonasal polyp in chronic rhinosinusitis. The asthma controlled test score showed good improvement after surgery. Since five months after surgery, the patient complained for recurrent nasal symptoms. She had no complaint of the lower airway.

We wondered what factors affect the recurrence or refractory of chronic rhinosinusitis in this patient.

METHODS

We defined the keywords based on PICO and search the evidence through bibliographic database (Medline, Cochrane, and hand searching) and filtered with eligibility criteria. The eligibility criteria were: 1) Type of study, we projected the study with systematic review of prognostic, or cohort study with prospective or retrospective design. 2) Type of population, chronic rhinosinusitis (CRS) which was defined by European Position Paper on Rhino- sinusitis and Nasal Polyps (EPOS) 2012. Asthma was defined as a chronic inflammation of the lower airways involving episodic breathlessness and wheezing, with airway hyper-responsiveness to environmental stimuli. 3) Type of intervention, risk factors in refractory chronic rhinosinusitis concomitant with asthma comprised of the severity of asthma, high Lund

Mackay CT score, mucosal eosinophilia, peripheral blood count and type of surgery: extensive endoscopic sinus surgery (EESS) or functional endoscopic sinus surgery (FESS). 4) Type of the outcome of recurrence/refractory after optimal management, was defined by EPOS as patients who do not reach an acceptable level of control despite adequate surgery, intranasal corticosteroid treatment and up to short courses of antibiotics or systemic corticosteroid in the last year. Symptoms characteristic are nasal blockage, rhinorrhea/post nasal drip, facial pain/headache, smell disturbance, sleep disturbance or fatigue, objective findings in nasal endoscopy and systemic medication needed to control the disease.

The evidence selected was appraised by at least two members of our group using Oxford Centre for Evidence-based Medicine (CEBM) worksheet for prognostic study.

RESULTS

After conducting literature searching on two large database of Medline, Cochrane, and also hand-searching, we found 109 articles related to our term. In the end, the authors obtained two cohort studies to be appraised, fit to our clinical setting i.e. Brescia et al⁹ and Chen et al.¹⁰

Both studies were cohort studies and evaluating risk factors in the recurrence of rhinosinusitis in CRS patients concomitant with asthma after adequate management. Brescia et al⁹ in their study evaluated the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) and eosinophil-to-lymphocyte ratio (ELR), and also of the basophil-to-lymphocyte ratio (BLR) for CRS recurrence in a large series of CRSwNP, while Chen¹⁰ evaluated the clinical outcomes and safety of extensive

endoscopic sinus surgery (EESS) for CRSwNP patients with concomitant asthma.

EESS procedure started with a delicate polypectomy. A partial middle turbinate (MT) resection was the second step. The inferior two-thirds of MT was resected by an endoscopic turbinate scissor, just spared the superior, sagittal-oriented portion as a landmark for the skull base and a small stump posteriorly in the region of the sphenopalatine foramen.

The inferior two-thirds of the superior turbinate (ST) was then resected as the third step. For the fourth step, a total ethmoidectomy was performed. Antrostomies of maxillary, frontal and sphenoid sinuses were then performed.

From the assessment of validity, based on criteria from CEBM prognostic critical appraisal sheet, the validity of those studies were good, with sufficiently long and complete follow up. In the study by Brescia et al,⁹ they had 24 months observations, 48 patients had recurrence, but the author did not differentiate the co-morbid in those CRS patients. In CRS concomitant with asthma group, recurrent and non recurrent group had a significant difference in BLR mean value. However Brescia⁹'s study did not explain about blinding in their outcome measurement, so there was a possible risk for bias.

In this evidence-based case report, we found two prognostic factors for recurrence/refractory CRS in CRS concomitant with asthma patients after optimal management. The first predictor we found in Chen's¹⁰ study that EESS give an improvement for olfactory VAS score and endoscopic postoperative score higher than FESS for CRSwNP concomitant asthma patients in 1 year observation. Mean difference for endoscopic postoperative

(E) score was 0.35 (CI 95% 0.21-0.49) and olfaction VAS score was -2.7 (CI 95% -4.92 - -0.48).

However, there was a wide range of confidence interval in both outcomes.

The second prognostic factor we found in Brescia's⁹ study in CRS patients who suffered from asthma, there was no difference for the mean of basophil-to-lymphocyte ratio (BLR) between the recurrence and nonrecurrence group with mean difference basophil-to-lymphocyte ratio (BLR) was -0.009 (CI 95% -0.02 – 0.00). In this evidence based case report, we did not find a study that showed mucosal eosinophilia, asthma severity and high Lund-Mackay score as prognostic factors of recurrence/ refractory in CRS with asthma patients.

There was no difference in the characteristic of the patients in those studies with patients in Indonesia, therefore the prognostic factors could be applied as prognostic factors for refractory chronic rhinosinusitis in CRS patients concomitant with asthma.

DISCUSSION

The upper and lower respiratory tracts formed a continuum structure, allowing the passage of air came into and out of the lung. They shared common structure, including the ciliary epithelium, basement membrane, lamina propria, glands and goblet cells, forming the so-called united airway.¹¹

Evidence in recent literature, demonstrates a systemic and not only anatomical connection between upper and lower airways. Inflammatory diseases of the upper airways, such as allergic rhinitis and chronic rhinosinusitis, determine a systemic immune response, with elevated levels of IL-5 in blood and increased

bone marrow eosinopoiesis.¹² Ponikau, Sherries et al¹³ in their study found a striking epithelial damage and basement membrane thickening in all 22 patients with CRS. Moreover, CRS and asthma shared similar histopathologic features, namely, an intense eosinophilic inflammation, basement membrane thickening and erosion of the epithelium. An eosinophil infiltration was demonstrated in the nasal mucosa of CRS individuals which was similar between allergic and nonallergic patients. These findings along with the high clinical overlap, suggested that CRS and asthma were part of the same disease process: an eosinophilic inflammation of airway mucosa stretching from the nostril down to the alveoli.¹³

IL-5 activates and mobilises eosinophils, and stimulates differentiation and growth of B lymphocytes. Findings presented by Fan et al, cited by Peric¹⁵ suggested that T-cell-secreted IL-5 and autosecretion of IL-5 from activated eosinophils may be the reasons for persistent and growing eosinophil inflammation in the nasal polyp tissue. The cytotoxic proteins and transforming growth factors released by activated eosinophil had caused epithelial injury, basement membrane thickening, glandular hyperplasia, stromal fibrosis, and angiogenesis. Elevated levels of IL-5 and eotaxin in association with chemokines are responsible for the recruitment and activation of eosinophils. Both eosinophils and cytokines determined epithelial damage which can be repaired via increased cell proliferation. Due to this circle, the inflammatory reaction is up-regulated existing a “self-perpetuating” inflammatory reaction.^{14,15}

In this evidence-based case report, two cohort studies were found fit with our search strategy that we believe to be suitable to answer our clinical question.

Two studies that we chose to review were published by Brescia⁹ and Chen.¹⁰

The first study reviewed was Chen¹⁰ which evaluate the clinical outcomes and safety of extensive endoscopic sinus surgery (EESS) for patients with CRSwNP and asthma at reducing the inflammatory load. However, in this study, there was no clear explanation about the indication to determine which type of surgery (EESS vs FESS) should be chosen. The study result supported by Saitoh et al cited by Peric,¹⁴ found a significant correlation in eosinophilic infiltration between the epithelium and lamina propria. Therefore, it is likely that eosinophils migrating into the epithelium, continue to secrete cytotoxic mediators and eventually directly add to the epithelial damage. Furthermore, the correlation between eosinophilic infiltration in the epithelium and epithelial damage was higher than that between eosinophilic infiltration of lamina propria and epithelial damage, which suggests that epithelial eosinophils may contribute much more to an aggressive model of nasal polyposis. So, the goal of the treatment should be to minimize the accumulation of the eosinophils in the sinus mucosa in order to eradicate the “local eosinophil pool” and to reduce the recurrences.

It is important to note that there seems to be a specific distribution of eosinophils in the nasal cavity. Rinia et al¹⁶ have cited several studies, there were significantly more activated eosinophils in polyp samples compared with middle and inferior turbinates from healthy controls. However, other authors have specifically investigated the distribution of eosinophils throughout the nose in nasal polyp patients. They reported that polyp samples contained a significantly higher amount of eosinophils than the middle and inferior turbinate samples

in the same nasal polyp patients, with a significantly higher number of eosinophils in the middle turbinate than in the inferior turbinate. These reasons could be a rationale for extensive sinus surgery in diffuse polyposis.^{14,16}

Marchioni et al¹⁷ compared the result of two type sinus surgery in nasal polyposis, FESS with preservation of middle turbinate compared to a more radical surgery which was FESS with resection of the middle turbinate. They performed resection of the middle turbinate with a criteria: the presence of middle turbinate instability due to compression or destabilization that may occur during surgery, extended involvement of the turbinate from polyposis, reduced volume of middle meatus with difficult access at the frontoethmoid recess, and resection of a middle turbinate of one side as a condition for a contralateral middle turbinate resection to obtain a symmetrical postoperative surgical cavity. The results showed a better control of nasal pathology relaps in patients subjected to radical surgery, compared to conservative surgery on middle turbinate.¹⁷

Brescia et al¹⁸ investigated the outcomes of partial middle turbinectomy during FESS in patients with nasal polyposis. They found no difference in nasal airway resistance and in postoperative complication rate (1-year follow up period) between patients who had undergone partial resection of the middle turbinate and patients who had FESS with middle turbinate preservation.

Choby et al¹⁹ performed a systematic review of clinical effects of middle turbinate resection after endoscopic sinus surgery. They found no significant difference in the rates of postoperative frontal sinusitis or stenosis between middle turbinate resection and preservation groups and also no difference in patients’

quality of life outcomes. In olfactory function examination showed better outcomes in the middle turbinate resection group compared to middle turbinate preservation group. The technique used in the studies involved resection of the anterior-inferior portion of the middle turbinate, which would theoretically leave the superior olfactory fibers unaffected, airflow to the olfactory cleft may actually be improved and thus, giving result in the improvement on olfaction scores of those studies. However, this systematic review is limited by a lack of high-level evidence, with only a single Randomized Controlled Trial (RCT) available for review. The addition of more level I evidence would help to further clarify the issues.

The second study reviewed was Brescia⁹ which evaluated the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) and eosinophil-to-lymphocyte ratio (ELR), and also of the basophil-to-lymphocyte ratio (BLR) in a large series of CRSwNP. In the group of patients who suffered from asthma, there was no difference for the mean of basophil-to-lymphocyte ratio (BLR) between the recurrence and nonrecurrence group.

Mahdavinia et al²⁰ found a significantly higher number of basophils in the nasal polyp tissue CRSwNP patients than in the uncinata tissue of controls. In an environment rich with potential activators, and considering their ability to produce multiple inflammatory mediators, basophils may thus make an important contribution to the pathogenesis and symptomatology of CRS.

Siracusa et al²¹ found that basophil have a role in the chronic inflammation in an experiment that creating an inflammation in a mice ear by injecting an antigen. When basophils, which were representing only 1-2 % of the cellular

infiltrate in the ear were depleted, there was a dramatic reduction in the number of infiltrating eosinophils and neutrophils and a marked reduction in ear thickness. These data suggest that lesion-resident basophils may either directly produce chemokines that recruit inflammatory granulocytes, or produce mediators that indirectly induce the production of chemokines from tissue resident cells. Furthermore, these studies demonstrated the potency of small numbers of basophils and illustrated their ability to significantly influence inflammatory responses. Brescia et al⁸ found significant associations between CRSwNP recurrence and serum basophil count, and between CRSwNP recurrence and serum basophil percentage.

More research are needed to find out how basophils exert their functions, and their beneficial roles under physiologic and pathologic conditions in the immune system. But it is now clear that basophils play crucial and non-redundant roles in allergy, protection against parasitic infections, and other types of inflammation and immunological disorders.²²

Nevertheless, there is still a weakness in this evidence-based case report, i.e. the database that is being used was very limited. More extensive searching is required in order to obtain more comprehensive result.

In conclusion, according to our result, the type of surgery could affect the olfactory function and endoscopic postoperative score in CRS patients concomitant with asthma. We found that EESS contributed as a prognostic factor to improve olfactory VAS score and endoscopic postoperative score. As the answer to our clinical question, we had performed FESS instead of EESS to our patient, thus, the extent of surgery could be the prognostic factor that may

cause the recurrence of our patient's nasal symptoms. However, we recommend a randomized controlled trial (RCT) research to prove whether EESS is indeed effective to control recurrence in CRS patients concomitant with asthma.

REFERENCES

- Bachert C, Pawankar R, Zhang L, Bunnag C, Fokkens WJ, Hamilos DL, et al. ICON: Chronic rhinosinusitis. World Allergy Organization Journal. 2014; 7:25.
- Akdis CA, Bachert C, Cingi C, Dykewicz MS, Hellings PW, Naclerio RM, et al. Endotypes and phenotypes of chronic rhinosinusitis: A PRACTALL document of the European academy of allergy and clinical immunology and the American academy of allergy, asthma and immunology. J Allergy Clin Immunol 2013;131:1479–90)
- Fokkens WJ, Lund VJ, Mullol J, Bachert C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinology official journal of the European and International Societies. 2012. Volume 50. Supplement 23.
- Langdon C, Mullol Joaquim. Nasal polyps in patients with asthma: prevalence, impact, and management challenges. Journal of Asthma and Allergy. 2016; 9: 45–53.
- Hakansson K, Bachert C, Konge L, Thomsen SF, Pedersen AE, Poulsen SS, et al. Airway Inflammation in Chronic Rhinosinusitis with Nasal Polyps and Asthma: The United Airway Concept Further Supported. PLOS ONE DOI: 10.1371/journal.pone.0127228.2015.
- Batra PS, Tong L, Citardi MJ. Analysis of comorbidities and objective parameters in refractory chronic rhinosinusitis. Laryngoscope. 2013;123: E1–11.
- Mendelsohn D, Jeremic G, Wright ED, Rotenberg BW. Revision rates after endoscopic sinus surgery: a recurrence analysis. Annals of Otolaryngology & Laryngology. 2011; 10(3) : 162–6.
- Brescia G, Marioni G, Franchella S, Ramacciotti G, Velardita C, et al. Can a panel of clinical, laboratory, and pathological variables pinpoint patients with sinonasal polyposis at higher risk of recurrence after surgery?. American Journal of Otolaryngology-Head and Neck Medicine and Surgery. 2015; 36: 554–8
- Brescia G, Pedruzzi B, Barion U, Cinneto F, Giacomelli L, Martini A, et al. Are neutrophil-, eosinophil-, and basophil-to lymphocyte ratios useful markers for pinpointing patients at higher risk of recurrent sinonasal polyps?. American Journal of Otolaryngology-Head and Neck Medicine and Surgery. 2016; 37: 339–45.
- Chen FH, Deng J, Hong HY, Xu R, Guo JB, Hou WJ, et al. Extensive versus functional endoscopic sinus surgery for chronic rhinosinusitis with nasal polyps and asthma: A 1-year study. Am J RhinolAllergy. 2016; 30: 143–8.
- Giavina-Bianchi P, Aun MV, Takejima P, Kalil J, Agondi RC. United airway disease: current perspectives. Journal of asthma and allergy. 2016 : 9: 93–100.
- Licari A, Caimmi S, Bosa L, Marseglia A, Marseglia GL, Caimmi D. Rhinosinusitis and Asthma: A very long engagement. Int J Immunopathol Pharmacol. 2014. Vol 27 (4): 499–508.
- Ponikau JU, Sherris DA, Kephart GM, Kern EB, Gaffey TA, Tarara JE, et al. Features of airway remodeling and eosinophilic inflammation in chronic rhinosinusitis: Is the histopathology similar to asthma?. J Allergy Clin Immunol. 2003; 112: 877–82.
- Peric A, Vojvodic D, Vukomanovic-Durdevic B, Baletic N. Eosinophilic inflammation in allergic rhinitis and nasal polyposis. Arh Hig Rada Tokiskol 2011; 62: 341–8.
- Sarafoleanu C, Enache R. Do we need aggressive surgery in recurrent chronic rhinosinusitis with nasal polyposis? A point of view. Romanian Journal Of Rhinology. 2013(3) 9.
- Rinia AB, Kostamo, Ebbens FA, Van Drunen CM, FokkensWJ. Nasal polyposis : a cellular-based approach to answering questions. Allergy, 2007 (62): 348–58.
- Marchioni D, Alicandri-Ciufelli M, Mattioli F, Marchetti A, Jovic G, Massone F, Presutti L. Middle turbinate preservation versus middle turbinate resection in endoscopic surgical treatment of nasal polyposis. Acta Oto--Laryngologica, 2008 (128) : 1019–26.

18. Brescia G, Pavin A, Giacomelli, Boninsegna M, Florio A, & Marioni G. Partial middle turbinectomy during endoscopic sinus surgery for extended sinonasal polyposis: short- and mid-term outcomes. *Acta Oto-Laryngologica*, 2008 (128): 73–7.
19. Choby GW, Hobson CE, Lee S, Wang EW. Clinical effects of middle turbinate resection after endoscopic sinus surgery: a systematic review. *Am J Rhinol Allergy*, 2014 (28): 502–7.
20. Mahdavinia M, Carter RG, Ocampo CJ, Stevens W, Kato A, Tan BK, et al. Basophils are elevated in nasal polyps of patients with chronic rhinosinusitis without aspirin sensitivity. *J Allergy Clin Immunol*. 2014.
21. Siracusa MC, Artis D. Basophil functions during type 2 inflammation: initiators, regulators and effectors. *The open Allergy journal*. 2010; 3: 46–51.
22. Yamanishi Y, Karasuyama H. Basophils and mast cells in immunity and inflammation. *Semin Immunopathol*. 2016; 38: 535–7.