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This graduate thesis was made at Sisters of Charity University Hospital in Zagreb (KBC Sestre milosrdnice), department of ORL HNS mentored by Prof. dr. sc Tomislav Baudoin and was submitted for evaluation in the academic year 2017/2018,

Abbreviations

CF = cystic fibrosis

CRS = chronic rhinosinusitis

CRSsNP = chronic rhinosinusitis without nasal polyps

CRSwNP = chronic rhinosinusitis with nasal polyps

CSF = cerebrospinal fluid

CT = computed tomography

ENT = ear nose throat

ESS = endoscopic sinus surgery

FESS = functional endoscopic sinus surgery

NP = nasal polyps

NSAID = nonsteroidal anti-inflammatory drug

HNS = head and neck surgery

OR = odds ratio

ORL= otorhinolaryngology

VAS = visual analogue scale

Abstract

Characteristics of patients with chronic rhinosinusitis who underwent endoscopic sinus surgery

Author: Jeffry Mattar

This study assessed the characteristics of patients with CRS, with or without nasal polyps, who underwent ESS as part of their treatment for sinonasal disease at the Department of ORL HNS, Sisters of Charity University Hospital in Zagreb and compared the results to other studies done on CRS patients.

Patients who were operated during a year period of 2016 were audited. The data collected included demographic features of patients, risk factors exposure, diagnosis, and type of endoscopic surgical procedures which were performed to treat the sinonasal disease. The purpose of the study was to understand the characteristics of patients who need ESS as part of their treatment course. In total, 189 patients were included in the study. Of which, 67% of the participants (85 males and 46 females) are diagnosed with CRSwNP and 31% (30 males and 28 females) are diagnosed with CRSsNP, 2% are diagnosed with CRS with tumor. In this study 13 patients were in the age group of <18 years (6.8%), followed by 28 in the age group of 19-30 (14.8%), 54 patients were in the age group of 31-45 (28.5%), 57 patients were in the age group of 46-60 (30%), and 37 patients were above 60 years (19.5%). The mean age for patients with CRSwNP was 49.2 and for the patients with CRSsNP was 38.7. The results showed that male gender was more associated with nasal polyps and that the frequencies of allergy, asthma, and aspirin sensitivity were significantly higher than for patients diagnosed with CRSsNP. Patients with CRSwNP tend to undergo more than one endoscopic procedure compared to patient without polyps. Septal deviation was more prevalent in the CRSsNP group (55%) when compared to CRSwNP (25.2%). The majority of the patients who underwent surgery had multiple sinuses involved (40%). Single-sinus operations were more common among ethmoid (17%) and maxillary (13%) sinuses.

Key words: Chronic rhinosinusitis, Chronic rhinosinusitis with nasal polyps, Nasal polyps, Endoscopic sinus surgery

Sažetak

Značajke bolesnika s kroničnim rinosinusitisom liječenih endoskopskom sinusnom kirurgijom

Autor: Jeffry Mattar

U ovom istraživanju proučavaju se značajke pacijenata s dijagnozom kroničnog rinosinusitisa, od kojih neki imaju pridruženu nosnu polipozu, a liječeni su endoskopskom sinusnom kirurgijom na Klinici za otorinolaringologiju i kirurgiju glave i vrata u KBC Sestre milosrdnice u Zagrebu tijekom 2016. godine.

Prikupljeni podaci uključuju demografske karakterisitke pacijenata, faktore rizika, dijagozu i vrstu endoskopske operacije koja je izvedena. Svrha ovog istraživanja je istražiti značajke pacijenata kojima je potrebna endoskopska operacija sinusa kao dio liječenja. U istraživanje je uključeno ukupno 189 pacijenata, od kojih je 67% (85 muškaraca i 46 žena) imalo dijagnozu kroničnog rinosinusitisa s nosnim polipima, a 31 % (30 muškaraca i 28 žena) imalo dijagnozu kroničnog rinusinusitisa bez nosnih polipa. Samo 2% pacijenata imalo je pridruženi tumor uz dijagnozu kroničnog rinosinusitisa. U ovom istraživanju 13 pacijenata nalazi su u dobnoj skupini mlađoj od 18 (6.8%), 28 pacijenata je u grupi od 19-30 (14.8%), 54 pacijenata u grupi od 31-45 (28.5%) godina, 57 njih nalazi se u grupi od 46-60 (30%) godina i 37 pacijenata je starije od 60 godina (19,5%). Prosječna dob pacijenata s nosnim polipima je 49.2, a onih bez polipa je 38.7. Rezultati su pokazali da je prisutnost polipa veća u muškog spola te da je učestalost polipa veća u pacijenata koji imaju astmu, alergije ili su preosjetljvi na aspirin. Pacijenti s polipima su češće operirani više puta u odnosu na pacijenete s kroničnim rinosinusitisom bez polipa. Prevalencija septalne devijacije je veća u pacijenata bez polipa (55%) u odnosu na pacijente s polipima (25.2%). Većina pacijenata koji su endoskopski operirani imali su bolest prisutnu u više sinusa, s time da je najčešće upala bila prisutna u etmoidnim (17%) i maksilarnim (13%) sinusima.

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Ključne riječi: kronični rinosinusitis, kronični rinosinusitis s nosnim polipima, nosni polipi, endoskopska kirurgija sinusa

Contents

1. Introduction

Rhinosinusitis, in its various forms, constitutes, one of the commonest conditions encountered in medicine and may present to a wide range of clinicians, including primary care, pulmonologists, allergists, otorhinolaryngologists, neurosurgeons and more, especially when complications occur. The introduction part of this paper will present the basics of rhinosinusitis disease, as well as explain its various types and subtypes, while concentrating on chronic cases, diagnosis and clinical severities. In addition to these, treatment modalities, in particular endoscopic sinus surgery will also be addressed.

1.1. Rhinosinusitis

Rhinosinusitis is inflammation of the mucosa of the nose and paranasal sinuses characterized by two or more symptoms; one of each should be either nasal discharge (anterior or posterior nasal drip), obstruction, blockage, congestion:

- +/- facial pain or pressure,
- +/- smell disturbances

and either endoscopic signs of:

- nasal polyps, and/or
- mucopurulent discharge primarily from the middle meatus, and/or
- edema/mucosal obstruction primarily in the middle meatus

And/or CT changes that demonstrate mucosal changes within the osteomeatal complex or sinuses.

The disease is divided into acute (i.e. <12 weeks with complete resolution of symptoms) and chronic (i.e. >12 weeks without complete resolution of symptom).

1.1.1. Viral and bacterial rhinosinusitis

Viral rhinosinusitis should be diagnosed when symptoms or signs of acute rhinosinusitis are present for <10 days and the symptoms are not worsening.

Bacterial rhinosinusitis is presumed when symptoms or signs of acute rhinosinusitis fail to improve within 10 days beyond the onset of upper respiratory symptoms, or the symptoms worsen within 10 days after an initial improvement (double worsening)

1.2. Chronic rhinosinusitis

1.2.1. Classification of chronic rhinosinusitis

For research purposes, chronic rhinosinusitis is defined as per the clinical definition mentioned above. For the purpose of this study, CRS is further divided endoscopically into chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP):

- Chronic rhinosinusitis with nasal polyps: bilateral, endoscopically visualized in the middle meatus
- Chronic rhinosinusitis without nasal polyps: no visible polyps in the middle meatus

In order to avoid overlap, this definition accepts the idea that there is a spectrum of disease in CRS, which includes polypoid changes in the sinus and/or middle meatus but, excludes those with polypoid disease presenting in the nasal cavity. In case of past sinus surgery, in which the anatomy of the lateral wall has been altered, the presence of polyps is defined as bilateral pedunculated lesions >6 months after surgery on endoscopic examination.

1.2.2. Epidemiology of chronic rhinosinusitis

CRSsNP- due to the heterogeneity of the disorder and the diagnostic imprecision often made by clinicians, accurate prevalence of CRS remains speculative. In surveys of chronic conditions, CRS was found to affect 15.5% of the total adult population in one survey [16] and 16% in the second, defined as having 'sinus trouble' for more than 3 months in the years before the interview [17]. However, the prevalence of doctor-diagnosed CRS is much lower, a prevalence of 2% [18]. The majority of primary care physician do not have the equipment necessary to properly diagnose CRS, which leads

to overdiagnosis. The prevalence rate is higher in female with a female/male ratio of 6/4 [16]. In a postal questionnaire sent to a random sample of adults aged 15-75 years in 19 centers in Europe, The Global Allergy and Asthma Network of Excellence (GA2LEN) concluded that the overall prevalence of CRS by EP3OS criteria was 10.9% (range 6.9-27.1) [19].

CRSwNP- studies rely on nasal endoscopy and/or questionnaires to report on the prevalence of nasal polyps. Large nasal polyps can be visualized by anterior rhinoscopy, whereas nasal endoscopy is need for smaller nasal polyps. Recently, a panel of French experts specializing in ENT elaborated a questionnaire/algorithm with 90% sensitivity and specificity [21]. For the epidemiologic research, a distinction between asymptomatic nasal polyps and symptomatic nasal polyps needs to be made. Asymptomatic polyps may transiently be present and hence remain undiagnosed. Symptomatic polyps may remain undiagnosed, either because they are missed during anterior rhinoscopy or because patients do not seek medical attention for this problem. In comparison, patients who are actively seeking medical care for CRSwNP had more extensive nasal polyps with greater reduction in peak inspiratory flow and more impairment of the sense of smell. In a population-based study done in Sweden, 2.7% of nasal polyps were diagnosed endoscopically and were more frequent in males with a ratio of 2.2/1, the elderly (5% at 60 years or over) and asthmatic [20]. Nasal polyps occur in all races and become more common with age (uncommon under the age of 20). There was a close linear association between the mean age at onset of rhinitis, asthma, NSAID intolerance and nasal polyps.

1.2.3. Factors associated with CRSsNP and CRSwNP

1. Ciliary impairment- the ciliary in the body is responsible for the clearance of the sinuses and prevention of prolonged inflammation. CRS with long history of respiratory infections is common, as expected, in patients with primary disorders involving the ciliary function, including Kartagener's syndrome and primary ciliary dyskinesia. In Cystic fibrosis (CF), the viscous mucous that is produced causes malfunction of the cilia and consequently CRS. Nasal polyps (primarily neutrophilic) are present in about 40% of patients with CF [22]. Secondary ciliary

dyskinesia is found in patients with CRS, and is probably reversible, but restoration of function takes some time.

2. Nasal septal deformation- nasal septal deviation is a common disorder that presents in up to 62% of the population, and its role in the pathogenesis of chronic sinusitis remains uncertain. Nasal septal deviation may either cause osteomeatal obstruction or may interfere with proper airflow and results in sinusitis.
3. Allergy- articles on CRS have suggested that atopy with allergic inflammation in the nose has a role in its development [23,24]. The swelling of the nasal mucosa in atopic patients may compromise ventilation and even obstruct the sinus ostia, leading to mucus retention and infection. A number of studies report the atopic markers are more prevalent in CRS patients; 54% of outpatients with CRS had a positive skin test [25]. Among CRS patients undergoing sinus surgery, the prevalence of positive skin testing ranges from 50% to 84%, of which the majority (60%) have multiple sensitivities [29,26,27]. It was clear that failure to address allergy as a contributing factor to CRS diminishes the probability of success of a sinus surgery [28]. Taking all into account, epidemiologic data show an increased prevalence of allergic rhinitis in patients with CRS, but the role of allergy in CRS remains unclear.
4. Asthma- CRSwNP and asthma are frequently associated in the same patients, though the inter-relationship is poorly understood [30]. The association of CRS with asthma was stronger in those reporting both CRS and allergic rhinitis. Wheezing and respiratory symptoms are present in 31% and 42% of patients with CRSwNP, and asthma is reported by 26% of patients with CRSwNP, compared to 6% of control group [31,32]. In addition, 7% of patients with asthma has NP [34]. NP take between 9 to 13 years to develop, but only two years in aspirin-induced asthma [34]. 10% develop both polyps and asthma simultaneously and the remainder develop first polyps and asthma later [35].
5. Aspirin sensitivity- in patients with aspirin sensitivity 36-96% have CRSwNP [36-42] and up to 96% have radiographic changes affecting their paranasal sinuses [43].
6. Immunocompromised state- development of dysfunctional immunity may occur later in life and present with CRS. Congenital immunodeficiencies manifest

themselves with symptoms early in life. An unexpectedly high incidence of immune dysfunction was found in a retrospective review of patients with refractory sinusitis [44]. Low Immunoglobulin levels, IgA and IgM titers were found in 18%, 17%, and 5%, respectively. Common variable immunodeficiency was diagnosed in 10% and selective IgA deficiency in 6% of patients. Thus, immunological testing should be an integral part of the diagnostic pathway of patients with CRS.

7. Genetic factors- genetic factors have been shown to have a role such as patients with cystic fibrosis and primary ciliary dyskinesia [45] and there is some evidence for CRSwNP. Although CRSsNP have been observed in family members, no genetic abnormalities have been linked to CRSsNP.
8. Pregnancy and endocrine state- nasal congestion occurs in approximately one-fifth of pregnant women [46]. The pathogenesis is unclear but several theories have been proposed: direct hormonal effect of estrogen, progesterone, and placental growth hormone on the nasal mucosa, and indirect effects such as vascular changes, may be involved. In addition, thyroid dysfunction has been implicated in CRS, but the data is limited.
9. Local host factors- several anatomic variations have been suggested to contribute to the development of CRS such as nasal septal deviation, concha bullosa, and uncinate process displacement [47]. However, studies have failed to reveal any significant correlation between anatomical variation and increased prevalence of CRSs or wNP than in a control group [48-50]. In spite of the observation that sinonasal complaints often resolve after nasal surgery, this does not imply that anatomical variation is etiologically involved. Taken all together, so far, there is no supportive evidence for a casual association between nasal anatomic variations and incidence of CRS.
10. Biofilms- the surface of nasal polyps is colonized by many biofilm-forming pathogenic bacteria that may not be the primary etiologic agent in NP, but a contributor significantly adding more inflammation.
11. Environmental factors- several studies have demonstrated the association of smoking with CRS, including exposure to secondhand smoke [51]. Other life-style related factors are also involved in the chronic inflammatory process. Studies have

investigated the relationship between CRS and occupational exposure and have concluded that there was an increased prevalence ratio in plant and machinery operators and assemblers, elementary occupations, craft workers and the unemployed.

1.2.4. Pathogenesis of CRS

Few hypotheses have been proposed in order to explain the pathophysiology of CRS; the first attempt to address it was the "fungal hypothesis", which attributed all CRS to an excessive host response to Alternaria fungi [52,53]. This was rejected by many investigators as originally proposed; however, fungi are still believed to play a role in at least some forms of CRS.

Defects in eicosanoid pathway have also been proposed as a potential cause of CRSwNP [54,55]; specifically, increased synthesis of pro-inflammatory leukotrienes and decreased synthesis of anti-inflammatory prostaglandins (PGE2). This theory is controversial due to lack of clinical efficacy with leukotriene pathway inhibitors.

The microbiology of CRS differs from that of acute rhinosinusitis. In addition to standard pathogens; Streptococcus pneumonia, Haemophilus influenza, and Moraxella catarrhalis, there is an increased prevalence of S. aureus, Pseudomonas aeruginosa and anaerobic bacteria in CRS. The "staphylococcal superantigen hypothesis" suggested that exotoxins have a key role in nasal polyposis via effects on multiple cell types [56,57]. The net effect is Th2 skewing, Treg inhibition, increased eosinophils and mast cell activity, and increased tissue damage and remodeling.

The "immune barrier hypothesis" suggests that dysfunction in the mechanical barrier and/or innate immune response of the sinonasal epithelium manifests as CRS. This, theoretically, leads to colonization of the mucosa with increased multiple microbial agents, heightened barrier damage, and a compensatory adaptive immune response [58,59].

Lastly, biofilm formation is said to be facilitated by a defect in the innate immune barrier, the mechanism in CRS is unclear, but biofilms on the sinus mucosa have been linked to those mediating periodontal disease [60,61].

Thus, host susceptibility to complex diseases such as CRS involves multiple genetic factors but also environmentally-determined epigenetic changes. Ongoing environmental stresses confront the susceptible host, which may lead to the development of the chronically inflamed state of CRS.

1.2.5. Diagnosis and Symptomatology of CRS

Assessment of rhinosinusitis is based on symptoms:

- Nasal blockage, congestion, or stuffiness;
- Nasal discharge or postnasal drip, often mucopurulent;
- Facial pain or pressure, headache, and
- Reduction or loss of smell.

In addition, distant and general symptoms occur; distant symptoms are pharyngeal, laryngeal and tracheal irritation causing sore throat, dysphonia and cough, whereas general symptoms include malaise, drowsiness and fever. The symptoms are principally the same in acute and chronic rhinosinusitis with and without polyps, but the symptom pattern and intensity may vary. Acute forms of infections have usually more distinct and severe symptoms.

1.2.5.1. Diagnosis of CRS

Chronic rhinosinusitis, with or without nasal polyps in adults is defined as:

- Inflammation of the nose and paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip)
- +/- facial pain or pressure
- +/- reduction or loss of smell

For >12 weeks

This should be supported by demonstrable disease. Either endoscopic signs of:

- Nasal polyps, and/or
- Mucopurulent discharge primarily from middle meatus, and/or
- Edema/mucosal obstruction primarily in middle meatus

And/or CT changes:

- Mucosal changes within osteomeatal complex and/or sinuses.

It is appropriate that the definition is symptoms based, as it is this that drives patients to seek medical care for their CRS. However, the presence of supporting findings is important to exclude differential diagnoses. For the majority of patients, diagnosis is made in primary care based on symptoms alone.

1.2.5.2. Symptoms reported in CRS

In addition to the symptoms listed above, there are several minor symptoms including ear pain or pressure, dizziness, halitosis, dental pain, distant and general symptoms including nasal, pharyngeal, laryngeal and tracheal irritation, dysphonia and chough, drowsiness, malaise and sleep disturbances, presenting in numerous combinations [62,63].

Nasal obstruction is one of the most common symptoms reported with CRS. Its components include: congestion due to dilation of venous sinusoids as a result of inflammation and edema, nasal fibrosis and nasal polyposis. Nasal discharge, either anterior or posterior, may vary greatly in composition. Patients may report profuse watery discharge or thick purulent discharge.

Facial pain is one of the most variable symptoms, with reported prevalence in patients with CRS ranging from 18%-77.9% [64,65]. In addition, diagnosis of CRS is associated with a 9-fold increased risk of reporting chronic headache compared with the general population, and symptoms were significantly improved with surgery and nasal corticosteroids treatment [1].

Olfactory disturbance is common too, due to edema in the area and physical prevention odorants reaching the olfactory cleft. In a study of 367 patients with a diagnosis of CRS, the presence of polyps was associated with increased risk of hyposmia (OR 2.4 95% CI

1.3-4.2, P=0.003) and anosmia (OR 13.2, 95% CI 5.7-30.7, P<0.001) compared with non-polyp CRS [67].

Sleep impairment is another common disturbance associated with CRSwNP and CRSsNP patients. The key cause is thought to be sleep-disordered breathing that is associated with nasal congestion. This can lead to fatigue, daytime somnolence, impaired daytime functioning as reflected in lower level of productivity at work or school, and a reduced quality of life [68-70]. There is a growing amount of evidence that reduction in congestion with nasal corticosteroids is associated with improved sleep, reduced daytime sleepiness, and enhanced quality of life [71].

1.2.5.3. Assessment of symptom severity

Different grading tools can be used to estimate the severity of the overall symptoms of CRS;

- Recorded as severity: no symptom, mild, moderate or severe
- Recorded as numbers: from 0 to 5 degrees or more
- Recorded as VAS score on a line giving measurable continuum (1-10).

Strength, degree and duration should be assessed in each patient. The duration of symptoms is evaluated as symptomatic or symptom-free periods (expressed as hours per day or as days per week). According to VAS score, a validation study has shown 'mild disease' to be defined as a VAS score of 0-3, moderate >3-7, and severe as >7. In general, quality of life is affected with scores of 5 or more.

1.2.6. Complications of Chronic rhinosinusitis

Complication of chronic rhinosinusitis, with or without polyps, are rare and largely due to its effects on the surrounding bone. They generally result from an imbalance in the normal process of bone resorption, regeneration and remodeling, and are far less common than those associated with acute infection and inflammation. In some cases, they may be considered as a manifestation of the natural history of the disease. The complications may include:

1. Mucocele formation
2. Osteitis
3. Bone erosion and expansion
4. Metaplastic bone formation
5. Optic neuropathy

There is no evidence the CRS is associated with neoplastic changes, either benign or malignant.

2. Treatment modalities in CRS

The goal of the treatment in CRS is to reduce mucosal inflammation, to control infections, and to restore mucociliary clearance within the sinuses. Eosinophilic inflammation is one of the hallmarks of CRS [73], and reducing mucosal eosinophilia is one of the therapeutic goals. In the management of CRS no one regimen exists, and treatment should be individualized. For those patients with whom allergy, pollution, or mold exposures appear to be a risk factor, environmental control is an important modality. Sinus surgery is generally reserved for patients who remain symptomatic despite maximal medical therapy. In this section, different treatment modalities will be presented, with further focus on endoscopic sinus surgery.

2.1 Corticosteroids

Topical corticosteroids constitute the first-line therapy in the management of CRS. Long term treatment with intranasal steroids has been shown to reduce sinus inflammation and nasal polyp size and improve associated symptoms [74-76]. Oral steroids are used in the treatment of CRS with nasal polyps and in the cases of severe CRS when rapid symptomatic improvement is needed [75,77]. Topical and systemic steroids reduce eosinophil chemotaxis and increase their apoptosis, they also decrease white blood cell migration, production of inflammatory mediators, antibody production, histamine release, and swelling [78].

- Topical nasal steroids- several studies have demonstrated that topical steroids are beneficial in the treatment of CRS, especially when small to medium-sized polyps are involved and for rhinitis symptoms [78,79]. In addition, corticosteroids have been shown to delay recurrence of polyps after surgery [80]. Common side effects with intranasal steroid use include nasal irritation, mucosal bleeding, and crusting [76,77].
- Systemic steroids- oral steroids have been effective in treating allergic rhinitis, providing rapid relief of facial pain or pressure, nasal blockage by reducing mucosal edema, especially in patients with CRSwNP [81,82]. In a study of 25 patients with CRSwNP with massive polyps, treatment with high-dose oral prednisolone was associated with both subjective and objective improvement and involution of nasal polyps [83].

The daily usage of topical nasal steroids appears to be associated with minimal risks, however, long-term systemic steroids is associated with significant side effects [76,77]. Therefore, a tapered regimen of oral steroid is given during severe flare-ups of CRS or in the postoperative period after sinus surgery.

2.2 Nasal irrigation

Saline nasal irrigation has been advocated as an adjunct therapy for CRS. The procedure promotes mucociliary clearance by flushing out mucus, crusts, and irritants. In addition, cavity irrigation brings enhancement of ciliary activity, removal of antigen, biofilm, or inflammatory mediators, and a protective role on the sinonasal mucosa [84]. Nasal irrigation is also useful after endoscopic sinus surgery to clear crusts and mucus that appear postoperatively. Hypertonic saline is often used and have been described to have a beneficial role in decongesting the nose through an osmotic mechanism [85]. Budesonide have been added too as an adjuvant method of treating sinus inflammation. Its use after sinus surgery decreases mucosal inflammation, shortening the stage of epithelization and accelerates the recovery of the mucosa [86]. Topical antibiotics and topical steroids have been added too [87].

2.3. Antibiotics

Most experts agree the antimicrobials for the treatment of CRS should provide broad-spectrum coverage. Commonly used antibiotics include amoxicillin-clavulanate, ciprofloxacin or levofloxacin, clindamycin, and trimethoprim/sulfamethoxazole. The bacterial flora cultured from purulence in cases of CRS tend to demonstrate increased antibiotic resistance. Antibiotics are typically used for 3-4 weeks in order to maximize the anti-inflammatory effect, to lower bacterial loads, and to treat acute exacerbations of CRS. The potential association between fungi and inflammation in CRS has generated interest in the use of antifungal agents too.

2.4. Other medical treatments

No randomized clinical trials for the treatment of CRS were found regarding antihistamines, mucolytics and expectorants, homeopathic remedies, proton pump inhibitors, and surfactants including baby shampoo or nasal decongestants. These treatment modalities are not recommended, but may provide temporary symptomatic relief.

2.5. Surgical Modalities

If medical treatments have not been successful in improving sinus symptoms, endoscopic sinus surgery may be helpful. The main goal of sinus surgery is to improve the drainage pathway of the sinuses. By widening the natural drainage pathway of the unhealthy sinuses, sinus infections should be reduced. Patients with obstruction or blockage of their sinuses due to their sinus anatomy do very well with sinus surgery. Many patients also have a problem with inflammation of the sinus lining (mucous membrane). Patients with mucous membrane disease also usually improve with sinus surgery because creating the larger sinus opening will allow better sinus drainage and more rinses/medication to get into the sinuses and help treat the diseased lining. One of the most important benefits of surgery is the ability to deliver medications (sprays, rinses, nebulized drugs) to the lining of the sinuses after they have been opened. Therefore, sinus surgery is done in addition to, and is not a replacement for, proper medical treatment of the sinuses. It is important to note that the patients who have diseased mucous membranes or a form of nasal

polyps, no amount of surgery can change this fact. For many patients, surgery may not be a cure for sinusitis, but it is one of the many critical steps in managing sinus disease.

Surgical interventions used for CRS primarily involve open surgery, which is aimed at mucosal stripping within the maxillary or frontal sinuses, or ethmoidectomy performed with limited visualization. Such surgery has almost completely been replaced by endoscopic sinus surgery (ESS). ESS is associated with significantly lower morbidity and higher success rates than previous surgical approaches [88].

ESS may be done under local or general anesthesia. Local anesthesia involves numbing the nasal/sinus cavity, but the patient remains awake (or lightly sedated). General anesthesia means that the patient goes to sleep with anesthesia for the surgery. ESS involves the use of a small telescope (nasal endoscope) that is inserted through the nostril to view the nose and sinuses. The goal of the surgery is to identify the narrow channels that connect the sinuses to the nose, enlarge these narrow openings/channels, and improve the drainage from the sinuses into the nose. Most people have four sinuses on each side of their face, for a total of eight sinuses. These are the maxillary, ethmoid, sphenoid, and frontal sinuses. The maxillary sinuses are in the cheek, the ethmoid sinuses are between the eyes, the sphenoid sinuses are almost exactly in the center of the head, and the frontal sinuses are in the forehead. It is possible that one may not have all of these sinuses due to differences from person to person, or one's sinus may have already been opened by previous surgery. Sinusitis may affect some or all of the sinuses.

2.5.1. Surgery for CRSwNP

Twenty percent of CRS patients have nasal polyps. From a clinical, radiological, and histological point of view the mucosal inflammatory response is more florid in CRS patients with nasal polyps than in those without, and the relapse rate after surgery for nasal polyps is much higher [72]. Surgical intervention in the treatment of nasal polyps is preserved for patients who fail to improve after a trial of maximal medical therapy. Functional Endoscopic Sinus Surgery (FESS) involves the clearance of polyps and polypoid mucosa and opening of the sinus ostia. Removal of the inflammatory tissue and

the reduction in load of antigens mediating this inflammation, as well as the improvement of the sinus ventilation and mucociliary clearance, are the probable mechanisms whereby FESS improves symptoms in CRSwNP.

The outcome of sinus polypoid surgery is influenced by whether the polyps are idiopathic or related to an underlying mucosal condition such as aspirin-induced respiratory disease, cystic fibrosis, or primary ciliary dyskinesia. However, in both idiopathic and secondary cases, the long-term efficacy of ESS is dependent on the regimen of medical treatment prescribed postoperatively and the subsequent compliance to this regimen.

2.5.2. Efficacy of surgery for nasal polyps

Endoscopic sinus surgery for nasal polyposis has been generally reported to be a safe and effective procedure. A number of series have demonstrated that sinus surgery in patients with nasal polyps can result in a prolonged reduction of nasal symptoms and an improvement in quality of life. Dalziel et al. evaluated 33 articles published between 1978 and 2001 [89]. The review included three studies comparing FESS with Caldwell-Luc or other endonasal procedures (n=240), three nonrandomized studies comparing different surgical approaches (n=2,699) and 27 case series (n=8,208). Seven studies included only patients with polyps and 26 had CRS with and without polyps. Patients judged their symptoms to be 'improved' or 'greatly improved' in 75 to 95% of cases. The percentage of overall complications was low (1.4% for FESS compared to 0.8% for traditional procedures). The implications of this review are that FESS is safe and effective treatment for the great majority of patients.

2.5.3. Efficacy of surgery for nasal polyps compared to CRSsNP

The efficacy of FESS in patients with nasal polyps is at least as great as in patients with CRSsNP. There is some evidence that a significantly higher rate of recurrent surgery is required in patients with nasal polyposis than those without polyps [90]. Despite the increased rates of revision, patients with polyps may have more improvement following sinus surgery than CRSsNP patients [92]. In one large series, FESS was performed in 251

patients with medically refractory CRS, 86 with polyps and 165 without, and the patients were followed for at least 12-months. Symptoms scores improved significantly ($p<0.001$). There were no major differences between the groups except in oropharyngeal symptoms, which were improved more in the non-polyp patients [91].

2.5.4. Efficacy of surgery for nasal polyps compared to medical therapy

As surgery for nasal polyposis is usually not considered until medical therapy has failed to provide adequate relief, a clinically relevant comparison of relative efficacies between surgical and medical treatments is difficult to make since the patient populations in whom these treatment modalities are indicated are different.

However, if untreated patients are randomized into either a medical treatment or a surgical one comparisons of the relative efficacies of these approaches can be made.
In a randomized controlled trial comparing the effect of medical and surgical treatment of CRS on quality of life, 90 patients were evaluated before and after 6 and 12 months of follow up after either medical or surgical therapy [93]. Both medical and surgical treatment of CRS improved most of the domains of SNOT-20 (sinonasal outcome test) and SF-36 (short form health survey) ($p<0.05$), with no significant difference being found between the two groups ($p>0.05$). Nasal symptoms and polyp size improved after both medical and surgical treatment at 6 and 12 months. These results suggest that both medical and surgical treatment can lead to similar effects in improving quality of life.

Although this study provides an interesting insight into the relative efficacies of both modalities in unselected patients, it doesn't reflect currently accepted practice guidelines in which surgery is preformed in medically refractory patients. In other words, the efficacy of FESS is equivalent to the efficacy of medical therapy, which includes systemic corticosteroids treatment, in CRSwNP patients randomized to receive one or other treatment.

2.5.5 Complications of sinus surgery

The list of the complications in this paragraph is not intended to be all-inclusive, but rather to highlight some of the more common complications the are worth mentioning [94];

- Bleeding**:** It is normal to have some degree of bleeding after surgery on the nasal septum or turbinates. Rarely does this require additional intervention and extremely rarely does it require blood transfusion. Non-steroidal anti-inflammatory and certain over-the-counter supplements such as vitamin E and gingko can increase the risk of bleeding, so patients should consult with their physicians regarding the use of any medications before or after surgery. Postoperative bleeding most commonly occurs within the first 24 hours of the procedure, but can be delayed days or even weeks. In case of septal hematoma removal of the hematoma is necessary, and the development of scar tissue or even nasal collapse could occur.
- Infection: The most common reason to undergo sinus surgery is a chronic sinus infection that does not resolve with medications. The patient with sinusitis is therefore at risk of developing certain other infections in this area (abscesses, meningitis, etc.) from sinus surgery, although it important to recognize that this is also a complication of not undergoing surgery for a refractory chronic sinus infection.
- Impaired sense of taste or smell: The sense of smell usually improves after the procedure because airflow is restored, although in sporadic cases it could worsen depending on the extent of swelling, infection, or allergy. This impairment is often temporary, but can be prolonged.
- Voice changes: One of the functions of the sinuses is to affect resonance, so vocal professionals should be aware of potential changes in their voice after sinus surgery.
- Nasal obstruction: Surgery typically improves airflow, but in some patients, it may not improve or rarely may worsen. Small scar bands may occur in the nose and require removal by the surgeon at postoperative visits.

- Numbness: Numbness of the front upper teeth, lip or nose may occur after surgery, but it is usually self-limiting and does not require further treatment.
- Pain and dryness: turbinates are “swell bodies” that are present along the sidewall of the nasal cavity. They often become too enlarged and their size is physically reduced during nasal surgeries, and this often improves symptoms such as nasal congestion of obstruction. However, in some patients this may leave them with the sensation of being overly dry or even cause chronic pain; a very rare, but severe form of this is referred to as “empty nose syndrome.”
- Intraorbital complications: The eye is situated directly next to several of the paranasal sinuses and is separated from them by a thin layer of bone. Because of the close proximity, in rare cases, bleeding may occur into the orbit, requiring treatment at the time of the initial surgery. Visual loss and blindness have been reported, but are extremely rare. Another uncommon problem is damage to the muscles that move the eye, leading to double vision, which can be temporary or permanent. In certain circumstances, there may be a change in the function of the tear ducts causing excessive tearing. Since the eye is in close proximity to the sinuses, a major orbital complication or blindness could possibly occur even without surgery for patients with severe or refractory CRS.
- Intracranial complications: The floor of the brain is where the septum attaches to the roof of the nose. If this thin bony layer is fractured, CSF can leak into the nose. While rare, this is likely to be identified and repaired in the operating room at the time of the primary surgery. In rare cases, this could lead to infection of the meninges, bleeding into the brain, or the need for further intracranial surgeries.

2.5.6. Recovery

Some nasal packing may be used during surgery, although in general, this is less common than it was in the past. The operating surgeon will determine whether nasal packing will be used. The recovery period will vary depending on the surgery performed and the individual patient. Many people do not have much pain after sinus surgery, but every patient is different. Depending on the extent of the surgery, one may be prescribed stronger pain medicine. Generally, postoperative discomfort, congestion, and drainage

should improve after the first few days, with mild symptoms sometimes lingering several weeks after the surgery. Because sinus surgery is just one step in treating sinus disease, the surgeon may also place you on medications that can include saline rinses, nasal steroid sprays, and possibly antibiotics.

3. Aim

The aim of this study is to investigate the incidence of different sinonasal diagnoses and their distribution according to demographics, risk factor, and type of endoscopic surgical procedures which were performed to treat sinonasal diseases, in the Department of ORL HNS Sisters of Charity University Hospital, during the period of January 1 to December 31 of the year 2016.

4. Material and Methods

This study is a randomized retrospective study of a surgical database, from the ENT department at Sisters of Charity hospital in Zagreb, of the characteristics of 189 patients who were diagnosed with CRS and who underwent ESS in 2016. The data collected included disease phenotype, age, sex, sinuses involved, previous operations, and risk factor exposure; septal deformation, allergy, asthma, cystic fibrosis, and smoking.

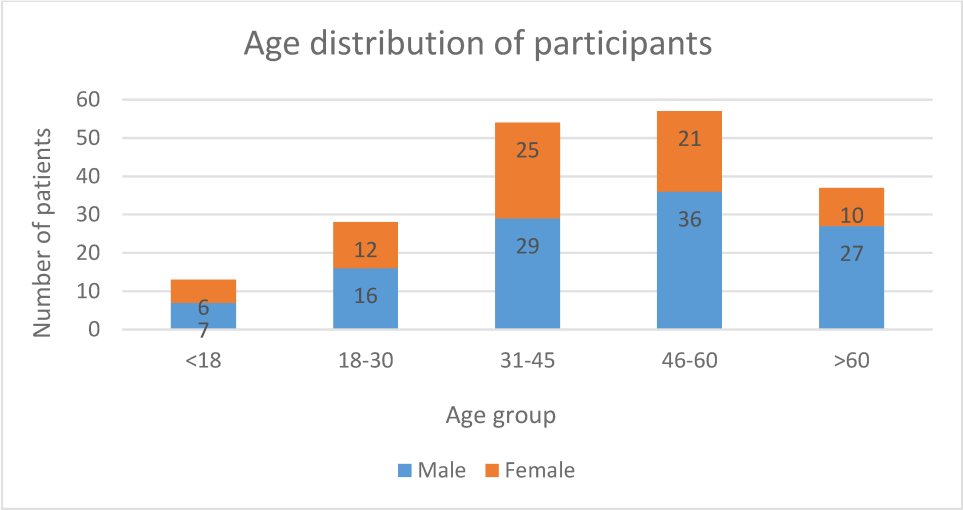
The patient files were collected from the archive room. Out of 246 patients with CRS who were admitted to the ENT department in 2016, a total of 189 patients underwent endoscopic sinus surgery in a period of a year. This study was done to review the demographic characteristics of those patients who had ESS and analyze them. For views and statistical calculations, Microsoft Excel Office was used.

5. Results

A total of 189 patients were reviewed, 115 males (60.8%) and 74 females (39.2%), male to female ratio is 1.55:1.

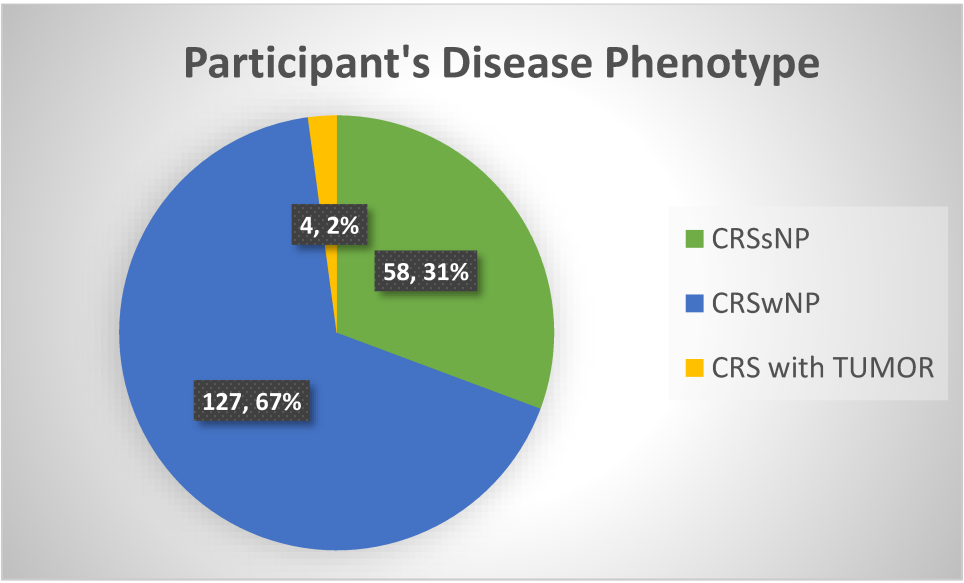
In this study 13 patients are in the age group of <20 years (6.8%), followed by 28 in the age group of 19-30 (14.8%), 54 patients are in the age group of 31-45 (28.5%), 57 patients

are in the age group of 46-60 (30%), and 37 patients are above 60 years (19.5%) (Graph 1).



Graph 1- Age distribution of participants in relation to sex

The youngest participant is 8 years old, and the oldest is 78 years old. The patients were divided into 2 main groups according to the disease phenotype;



Graph 2- disease phenotype of the participants.

67% of the participants are diagnosed with CRSwNP while 31% are diagnosed with CRSsNP. 4 patients were diagnosed with CRS with tumor (2%). An interesting fact is that 74 patients with CRSwNP are affected bilaterally and 66 unilaterally, and 10 patients with CRSsNP are affected bilaterally while most of CRSsNP patients, 44, are affected unilaterally.

Different variables were taken from the participants and they include demographic view and risk factor exposure as well as previous endoscopic sinus surgeries performed.

Out of the 131 patients with CRSwNP 85 are males and 46 are females, in the CRSsNP group 58 participants, 30 patients are males and 28 are females. The mean age for CRSwNP group and for CRSsNP group is 49.2 and 38.7 respectively. 4 Patients with CRS with tumor are counted in the table as CRSwNP (see table 1).

25.2% (33) of patients diagnosed with CRSwNP had septal deformation, 21 (16%) of them had it operated on the same day with the ESS. In the CRSsNP group, 55% (32) had septal deformation and 23 (40%) of them had it operated on the same day with the ESS. 1 patient with CRSwNP and 1 patient with CRSsNP had septal reconstruction operation done on different occasions (table 1).

A view on the risk factors given shows that 45 patients (34.3%) with CRSwNP and 18 patients (31%) with CRSsNP have allergy, 27(20.6%) of CRSwNP patients have asthma while 2 (3.4%) of CRSsNP patients have asthma. Aspirin sensitivity is found in 8 patients with CRSwNP (6.1%) and 2 patients (1.5%) with CRSwNP have Cystic Fibrosis, both aged 9. 30 patients with CRSwNP (22.9%) and 19 patients with CRSsNP (32.7%) are smokers (table 1).

Variables	CRSwNP	*CRSsNP*
Sex M/F	85/46	30/28
Mean Age	49.2	38.7
Septal deformation	33 (25.2%)	32 (55%)
Allergy	45 (34.3%)	18 (31%)
Asthma	27 (20.6%)	2 (3.4%)

Aspirin sensitivity	8 (6.1%)	0
Smoking	30 (22.9%)	19 (32.7%)
Cystic fibrosis	2 (1.5%)	0
Previous ESS	46 (35.1%)	10 (17%)
ESS+Septal reconstruction	21 (16%)	23 (40%)

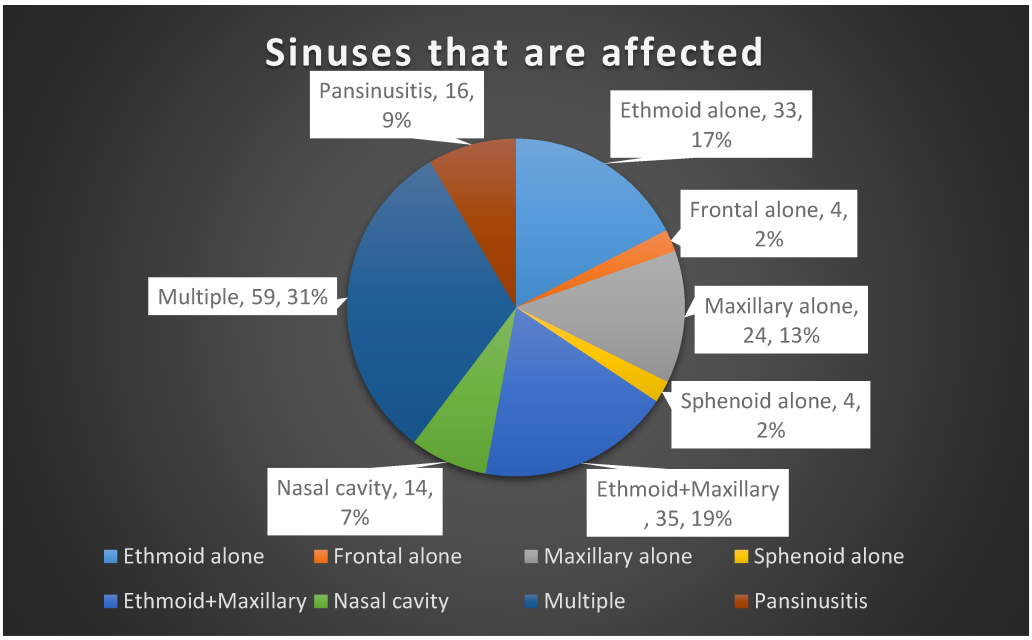
Table 1- Characteristics of participants in relation to main disease phenotype.

CRS is a chronic condition that, in many cases and especially for patients with nasal polyps, requires more than one operation during the course of the disease. 46 patients (35%) with CRSwNP and 10 patients (17%) with CRSsNP have had an ESS procedure before. 35 patients had undergone one ESS procedure before; 28 patients (80%) with CRSwNP and 7 (20%) patients. 8 patients with CRSwNP and 1 patient with CRSsNP had two procedures. 8 patients with CRSwNP had 3-5 previous operations and 4 patients had more than 5 operations, the highest amount of procedures per participant was 21 (table 2).

Number of previous ESS	Number of patients
One	35
Two	9
Three- five	8
More than five	4

Table 2- Amount of previous endoscopic sinus surgery per participant

Sinuses are formed in childhood by the nasal cavity eroding into surrounding bone. As they are outgrowths of the nasal cavity, they all drain back into it. Openings to the paranasal sinuses are found on the roof and lateral walls of the nasal cavity. The inner surface is lined by a respiratory mucosa. CRS with or without polyps is a disease that is very variable among patients with different sinuses involved and, in many cases, more than one sinus or even all of the sinuses can be involved (graph 3).



Graph 3 – Sinuses that were affected in participants who underwent ESS

Involvement of ethmoid sinus alone was found in 17% of cases, maxillary sinus alone was associated with 13%, while involvement of both, ethmoid and maxillary sinuses was found in 19% of cases. Frontal sinus and sphenoid sinus by themselves were diseased in 2% of participants each. Involvement of multiple sinuses or different combinations was found in 31%, whereas 16 patients (8%) had all sinuses affected (pansinusitis).

6. Discussion

Sinusitis is one of the most common diseases of the nose and paranasal sinuses. Recent data have demonstrated that CRS affects approximately 5–15% of the general population [4,136-139]. The prevalence of doctor-diagnosed CRS was found to be 2-4% [4]. The term 'rhinosinusitis' refers to a group of disorders characterized by inflammation of mucosa of nose and paranasal sinuses. CRS occurs when the duration of symptoms is longer than 12 weeks duration. CRS is usually further categorized based on the absence or presence of nasal polyps, CRSsNP or CRSwNP. Nasal polyposis is considered as a subgroup of CRS with an incidence of 4% in general population [140] and 25–30% in patients suffering from CRS [141]. Although both are characterized by mucopurulent drainage and nasal obstruction, CRSsNP is frequently associated with facial pain/pressure/fullness whereas

CRSwNP is frequently characterized by hyposmia. Nasal polyps (CRSwNP) are defined as pedunculated lesions as opposed to cobblestoned mucosa, endoscopically visualized in middle meatus [96]. CRSwNP reportedly occurs in 0.5% to 4.3% of the population [97]. The prevalence tends to increase with age and the disease occurs more often in men. In our study, in the CRSsNP group, out of the participants who underwent ESS there were 30 males and 28 females while in the CRSwNP there were 85 males and 46 females, a ratio of 2:1, higher than in the CRSsNP group of participants. Most of the patients were in age groups 30-60 (111 patients, 58%), the mean age for CRSwNP and CRSsNP was 49.2 and 38.7 respectively. For comparison, a study that was done in patients with CRS who underwent ESS [142] consisted of 38 patients with CRSsNP with a mean age of 31.2 years and male female ratio of 9:10. 52 patients with CRSwNP with a mean age of 37.5 years and male female ratio of 9:17. Another study included 116 patients with CRSwNP, 75 (64.7%) were male and 41 (35.3%) were female patients, male to female ratio of 1.8:1. Mean age of presentation in males was 39.1 years and that of females was 36.7 years. As in our study the mean age for CRSwNP is older than for CRSsNP, the male to female ratio is variable. The rates of CRSwNP to CRSsNP in our study (67% CRSwNP and 31% CRSsNP) match the results in the largest study of its kind [92], the UK National Sinonasal audit was a multi-center prospective cohort study from 87 hospitals and 298 UK Consultant Otorhinolaryngologists about patients who underwent ESS, in which 70 % of the 3128 patients had nasal polyps, and 30 % didn't have nasal polyps.

ESS has been found to have a beneficial impact on the sinonasal outcome in patients of chronic rhinosinusitis with 85–93% of patients reporting relief from symptoms and improved QOL [98,99] In spite of the success in CRS and the use of ESS commonly for CRSwNP, it was found CRSwNP patients to have refractory disease with a tendency to recur even after prolonged medication and surgical intervention; Darsum et al. have observed a lower success rate in NP group (54.3%) as compared to CRS group (93.7%) after ESS [99]. In the UK national sinonasal audit mentioned above [92], 52 % had previous sinonasal surgery, compared with 34 % in those without nasal polyps. In our study, 56 patients in total had at least one previous ESS, 46 of them are patients with CRSwNP in comparison to 10 patients with CRSsNP. In addition, 21 participants had more than one previous ESS, 20 CRSwNP patients and 1 CRSsNP patient.

Any anatomical, physiological or pathological features which in a way or other obstructs free drainage from the sinuses, permits the stasis of secretion and thus predisposes to infection. Many factors have been described as playing a role in the development of chronic sinusitis. These include allergy, asthma, dental disease, nasal polyps, immunodeficiency, mucociliary disorders, trauma, medications, surgery, noxious chemicals and micro-organisms (viral, bacterial and fungal), anatomic abnormalities such as a septal deviation, concha bullosa, septal spur or paradoxical turbinate [95]

A proposed mechanism by which allergy leads to the development of sinusitis is allergy-induced mucosal inflammation leading to ostial obstruction. Ostial obstruction in turn may promote an environment for bacterial overgrowth and/or perpetuation of inflammation. Certainly, in the nasal passages, IgE-mediated degranulation of mast cells leads to mucosal edema. Whether this same process occurs in the paranasal sinuses is less clear. Impaired ciliary function and mucociliary clearance are often observed in CRSsNP. Cilia from patients with CRSsNP have demonstrated a blunted response to substances that typically stimulate cilia in healthy controls [100,101].

Allergy is possibly more prevalent in CRSwNP compared with CRSsNP. As far as an association between allergy and CRSwNP, several studies have demonstrated an increased prevalence for perennial allergies in patients with CRSwNP compared with controls, with reports varying between 45% to 77.4% [102-106]. Additionally, 2 studies showed a strong association between perennial allergies and CRSwNP with odds ratios of 2.69 and 6.0 described. [102,106]. In our study, 34.3% (45) patients with CRSwNP and 31% (18) patients with CRSsNP have allergy. Taking all into account, it is difficult to come to any conclusions on the role of allergy in CRSsNP and in CRSwNP patients, the prevalence of allergy in patients with CRSwNP is higher than that of the general population and may be higher than in CRSsNP.

There is a high prevalence of CRS among patients with asthma, and the presence of CRS is associated with poor asthma outcomes, especially with CRSwNP [107-110]. Moreover, comorbid asthma is an important risk factor for resistance to therapeutic interventions for CRS, such as endoscopic sinus surgery [111,112]. Compared to patients who do not have asthma, patients with asthma and CRS have poorer outcomes, less quality of life

improvement, and a higher rate of revision surgery after ESS [115,116]. In our study, 20.6% (27) of patients with CRSwNP have asthma, while in the CRSsNP group of patients, 3.4% (2) are diagnosed with asthma. In sense of pathogenesis, in CRSwNP, there is an increase in the Th2 cytokines like IL-4, IL-5 and IL-13 [113,114] and the intensity of eosinophils in the tissues of these patients is markedly increased in the presence of co-existing asthma or positive allergy skin tests. Based on family studies, it has been estimated that CRS exhibits a heritability of 13% to 53% [117-119] with highest heritability seen in the asthma and aspirin intolerance [118]. Asthma, a disease with an even higher heritability, has been reported to occur in 20% to 31.9% of CRS subjects [120,121]. In our study, 8 patients with CRSwNP (6.1%) had aspirin intolerance in comparison to 0 patients from the CRSsNP group.

Mucociliary clearance is grossly impaired in CF because of alterations in the transepithelial passage of anions (chloride and bicarbonate) caused by genetic mutations in the CFTR [122]. Disturbances in anion transport result in viscous secretions that obstruct sinus ostia and create hypoxic conditions with increased edema, secondary ciliary dyskinesia, and subsequent bacterial overgrowth [123,124]. Patients with classic CF have a high incidence of CRS approaching 100%. CF patients have a high incidence of nasal polyposis associated with CRS (7–48%) [125]. in our study 2 CF patients aged 9 diagnosed with CRSwNP had undergone ESS.

Tobacco smoke exposure is considered an important negative prognostic factor for CRS, and smoking has been demonstrated to increase the risk for CRS [128]. There is clear evidence in the literature that tobacco smoke, either through active smoking or passive exposure to secondhand smoke, contributes to CRS [129]. The prevalence of CRS has been reported to be higher in smokers [130,131]. 22.9% of CRSwNP patients are smokers and 32.7% of CRSsNP patients. In our study we did not follow the outcome of our patients but the impact of tobacco smoke exposure on ESS outcomes has been investigated and smokers have a less favorable response to ESS [132,133]. It has been reported that both secondhand smoke-sensitive and –nonsensitive individuals had increased symptoms of rhinorrhea, nasal congestion, and headache following sidestream smoke exposure [134]. However, there is little evidence of the role of tobacco smoke as a causal agent of CRS.

A total of 65 patients (34%) with CRS had septal deformation (33 -CRSwNP, 32-CRSsNP). There are three theories explaining the relation between the nasal septal deviation and chronic rhinosinusitis. The first of these is the mechanical theory, which states that secretions accumulates in the sinus as a result of narrowing of the ostiomeatal complex and thus infections ensue in the retained secretions and causes chronic rhinosinusitis. The second theory is the aerodynamic theory. According to this theory, the mucociliary activity decreases following the nasal flow rate increase and mucosal dryness in relation with the nasal septal deviation and consequently, chronic rhinosinusitis develops. The third theory is the Bachert's pressure theory. According to this theory, deviation of the posterior nasal septum causes chronic rhinosinusitis by creating pressure and air flow changes within the maxillary sinuses [95,126].

In our study we presented the sinuses that were operated in each patient, ethmoid sinus alone and maxillary sinus alone were most commonly involved with 17% and 13% of operations respectively. Operation on both sinuses together was found in 19% of cases.

We have observed that involvement of sphenoid and frontal sinuses alone was quite rare, 2% each. However, operation on multiple sinuses/all sinuses (pansinusitis) was found in 40% of patients.

Lastly, most patients with CRS have involvement of more than one sinus. In a study done in Karnataka, India [127], they calculated the frequency of involvement of paranasal sinuses in CRS patients, Maxillary sinus (99%) was the most commonly involved sinus, followed by Anterior Ethmoids (89%), Frontal (64%), Posterior Ethmoids (61%) and Sphenoid sinus (31%).

7. Conclusion

-We concluded that most patients who needed surgery had the CRSwNP phenotype, and the tendency for refractory disease and revision of surgery was almost exclusively associated with CRSwNP patients.

-Risk factors; mean age, male gender, allergy, asthma, aspirin sensitivity, CF, and previous ESS rates were higher for patients diagnosed with CRSwNP.

-Male patients with CRSwNP were significantly more often operated.

-Most predominant age groups were 31-45 and 46-60. Children were rarely operated.

-Sinuses most commonly involved in CRS are maxillary and ethmoid as a single-sinus involvement, but most of the patients who needed surgery had involvement of multiple sinuses. Frontal and sphenoid were the least involved.

-Moreover, we concluded septal deviation to be a major associating factor for CRS with 34% of our patients having septal deviation and 16% were operated on the same occasion together with the endoscopic sinus procedure.

Chronic rhinosinusitis is most common rhinological problem encountered worldwide which has greater propensity to cause morbidity. This study brings light on the various characteristics implicated in causation or association with CRS patients who were in need of a surgical treatment. Although it recently has been established that chronic rhinosinusitis is a frequent disease in Europe and the US, data from other continents are scarce, but are needed to recognize race differences and factors associated with CRS prevalence. Factors predisposing to CRS, such as smoking need to be confirmed and others identified. The tools to screen for CRS in epidemiological studies need to be further developed, specifically in terms of differentiation between CRS types. This goes in parallel with the need to “pheno- and endotype” CRS, most likely involving tissue biomarkers and their surrogates in serum and secretion. Again, these studies need to be performed in various areas of the world, as inflammation in CRS may considerably vary from region to region, and also may show alterations over time.

8. Acknowledgements

I would like to thank my Mentor, Prof. dr. sc. Tomislav Baudoin for his guidance, expertise, help and kindness throughout the process of this thesis. I want to thank my parents, my brothers, and my sister, for the humongous support system they have built for me during

the last 6 years, without whom my dream of becoming a Medical Doctor would have stayed a dream. Their endorsement throughout the years of Medical School never faded and their financial support made my student life much easier than it could have ever been. My girlfriend, a future colleague, also played a major role in my support system and the graduate work and I want to thank her for always pushing me forward and being so patient with me throughout the last 2 years. Last, but not least, I want to thank my grandmother, whose emotional guidance and love was and is infinite. Being surrounded with such amazing people is something to be thankful for.

9. References

1. Collins JG, Blackwell DL, Tonthat L, Shashy RG, Moore EJ, Weaver A, et al. Prevalence of selected chronic conditions: United States, 1990-1992 Summary health statistics for the U.S. population: National Health Interview Survey, 1997 Prevalence of the chronic sinusitis diagnosis in Olmsted County, Minnesota the role of nasal endoscopy in outpatient management. Vital Health Stat 10. 1997;130(194):1-89.
2. Blackwell DL, Collins JG, Coles R. Summary health statistics for U.S. adults: National Health Interview Survey, 1997. Vital Health Stat 10. 2002 May(205):1-109.
3. Shashy RG, Moore EJ, Weaver A Prevalence of the chronic sinusitis diagnosis in Olmsted County, Minnesota. Archives of otolaryngology--head & neck surgery. 2004 Mar;130(3):320-3.
4. Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, et al. Chronic rhinosinusitis in Europe—an underestimated disease. A GA(2)LEN study. Allergy. 2011 Sep;66(9):1216-23.
5. el Hasnaoui A, Jankowski R, Serrano E, Pribil C, Neukirch F, Klossek JM. Evaluation of a diagnostic questionnaire for nasal polyposis: an observational, cross-sectional study. Rhinology. 2004 Mar;42(1):1-7.
6. Johansson L, Akerlund A, Holmberg K, Melen I, Bende M. Prevalence of nasal polyps in adults: the Skovde populationbased study. The Annals of otology, rhinology, and lar yngology. 2003 Jul;112(7):625-9.
7. Hadfield PJ, Rowe-Jones JM, Mackay IS. The prevalence of nasal polyps in adults with cystic fibrosis. Clinical otolaryngology and allied sciences. 2000 Feb;25(1):19-22.
8. Kaliner M. Treatment of sinusitis in the next millennium. Allergy and asthma proceeding: the official journal of regional and state allergy societies. 1998 Jul-Aug;19(4):181-4.
9. Krause HF. Allergy and chronic rhinosinusitis. Otolaryngology- Head & Neck Surgery. 2003;128(1):14-6.
10. Benninger MS. Rhinitis, sinusitis and their relationships to allergies. American journal of rhinology. 1992;6:37-43.
11. Savolainen S. Allergy in patients with acute maxillary sinusitis. Allergy. 1989 Feb;44(2):116-22.

12. Emanuel IA, Shah SB. Chronic rhinosinusitis: allergy and sinus computed tomography relationships. Otolaryngology- head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery. 200 Dec;123(6):687-91.

13. Grove R. chronic hyperplastic sinusitis in allergic patients: a bacteriologic study of 200 operative cases. The journal of allergy and clinical immunology. 1990(11):271-6.

14. Lane AP, Pine HS, Pillsbury HC, 3rd. Allergy testing and immunotherapy in an academic otolaryngology practice: a 20-year review. Otolaryngology- Head and Neck surgery: official journal of American Academy of Otolaryngology Head and Neck Surgery. 2001 Jan;124(1):9-15.

15. Bousquet J, Van Cauwenberge P, Khaltaev N, et al. Allergic rhinitis and its Impact on Asthma. The Journal of allergy and clinical immunology. 2001;108(5 Suppl):S147-334.

16. Collins JG, Blackwell DL, Tonthat L, Shashy RG, Moore EJ, Weaver A, et al. Prevalence of selected chronic conditions: United States, 1990-1992 Summary health statistics for the U.S. population: National Health Interview Survey, 1997 Prevalence of the chronic sinusitis diagnosis in Olmsted County, Minnesota.

17. The role of nasal endoscopy in outpatient management. Vital Health Stat 10.1997;130(194):1-89. Blackwell DL, Collins JG, Coles R. Summary health statistics for U.S. adults: National Health Interview Survey, 1997. Vital Health Stat 10. 2002 May(205):1-109.

18. Shashy RG, Moore EJ, Weaver A. Prevalence of the chronic sinusitis diagnosis in Olmsted County, Minnesota. Archives of otolaryngology--head & neck surgery. 2004 Mar;130(3):320-3.

19. Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, et al. Chronic rhinosinusitis in Europe—an underestimated disease. A GA(2)LEN study. Allergy. 2011 Sep;66(9):1216-23.

20. Johansson L, Akerlund A, Holmberg K, Melen I, Bende M. Prevalence of nasal polyps in adults: the Skovde population-based study. The Annals of otology, rhinology, and lar yngology. 2003 Jul;112(7):625-9.

21. El Hasnaoui A, Jankowski R, Serrano E, Pribil C, Neukirch F, Klossek JM. Evaluation of a diagnostic questionnaire for nasal polyposis: an observational, cross-sectional study. Rhinology. 2004 Mar;42(1):1-7.

22. Hadfield PJ, Rowe-Jones JM, Mackay IS. The prevalence of nasal polyps in adults with cystic fibrosis. Clinical otolaryngology and allied sciences. 2000 Feb;25(1):19-22.
23. Kaliner M. Treatment of sinusitis in the next millennium. Allergy and asthma proceedings: the official journal of regional and state allergy societies. 1998 Jul-Aug;19(4):181-4.
24. Krause HF. Allergy and chronic rhinosinusitis. Otolaryngology-Head&NeckSurgery. 2003;128(1):14-6.
25. Benninger MS. Rhinitis, sinusitis and their relationships to allergies. American journal of rhinology. 1992;6:37-43.
26. Emanuel IA, Shah SB. Chronic rhinosinusitis: Allergy and sinus computed tomography relationships. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2000 Dec;123(6):687-91.
27. Grove R. Chronic hyperplastic sinusitis in allergic patients: a bacteriologic study of 200 operative cases. The Journal of allergy and clinical immunology. 1990(11):271-6.
28. Lane AP, Pine HS, Pillsbury HC, 3rd. Allergy testing and immunotherapy in an academic otolaryngology practice: a 20-year review. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2001 Jan;124(1):9-15.
29. Savolainen S. Allergy in patients with acute maxillary sinusitis. Allergy. 1989 Feb;44(2):116-22.
30. Bousquet J, Van Cauwenberge P, Khaltaev N, et al. Allergic rhinitis and its Impact on Asthma. The Journal of allergy and clinical immunology. 2001;108(5 Suppl):S147-334.
31. Klossek JM, Neukirch F, Pribil C, Jankowski R, Serrano E, Chanal I, et al. Prevalence of nasal polyposis in France: A crosssectional, case-control study. Allergy. 2005;60(2):233-7.
32. Downing E. Bronchial reactivity in patients with nasal polyposis before and after polypectomy. The Journal of allergy and clinical immunology. 1982;69(2):102.
33. Settipane GA, Chafee FH. Nasal polyps in asthma and rhinitis. A review of 6,037 patients. The Journal of allergy and clinical immunology. 1977 Jan;59(1):17-21.
34. Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2000 Sep;16(3):432-6.

35. Larsen K. The clinical relationship of nasal polyps to asthma. Settipane G LV, Bernstein JM, Tos M, editor. Rhode Island: Oceanside Publications; 1997.

36. Settipane GA. Epidemiology of nasal polyps. Settipane G LV, Bernstein JM, Tos M, editor. Rhode Island: Oceanside Publications; 1997.

37. Caplin I, Haynes JT, Spahn J. Are nasal polyps an allergic phenomenon? Ann Allergy. 1971 Dec;29(12):631-4.

38. Chafee FH. Aspirin intolerance. I. Frequency in an allergic population. Allergy Clin Immunol. 1974(53):193-9.

39. Webe r RW, Hof fman M, R a ine DA, Jr., Nelson HS. Incidence of bronchoconstriction due to aspirin, azo dyes, non-azo dyes, and preservatives in a population of perennial asthmatics. The Journal of allergy and clinical immunology. 1979 Jul;64(1):32-7.

40. . Szczeklik A, Gryglewski RJ, Czerniawska- My sik G. Clinical patterns of hypersensitivity to nonsteroidal anti-inflammatory drugs and their pathogenesis. The Journal of allergy and clinical immunology. 1977 Nov;60(5):276-84.

41. Spector SL, Wangaard CH, Farr RS. Aspirin and concomitant idiosyncrasies in adult asthmatic patients. The Journal of allergy and clinical immunology. 1979 Dec;64(6 Pt 1):500-6.

42. Ogino S. Aspirin-induced asthma and nasal polyps. Acta Otolaryngo lSuppl. 1986(430):21-7.

43. May A, Wagner D, Langenbeck U, Weber A. [Family study of patients with aspirin intolerance and rhinosinusitis]. HNO. 2000 Sep;48(9):650-4.

44. Chee L, Graham SM, Carothers DG, Ballas ZK. Immune dysfunction in refractory sinusitis in a tertiary care setting. The Laryngoscope. 2001 Feb;111(2):233-5.

45. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science (New York, NY). 1989 Sep 8;245(4922):1066-73.

46. E l legard EK. The etiology and management of pregnancy rhinitis. Am J Respir Med. 2003;2(6):469-75.

47. Zinreich SJ, Mattox DE, Kennedy DW, Chisholm HL, Diffley DM, Rosenbaum AE. Concha bullosa: CT evaluation. J Comput Assist Tomogr. 1988 Sep-Oct;12(5):778-84.

48. Jones NS. CT of the paranasal sinuses: a review of the correlation with clinical, surgical and histopathological findings. Clinical otolaryngology and allied sciences. 2002 Feb;27(1):11-7.

49. Jones NS, Strobl A, Holland I. A study of the CT findings in 100 patients with rhinosinusitis and 100 controls. Clinical otolaryngology and allied sciences. 1997 Feb;22(1):47-51.

50. Willner A, Choi SS, Vezina LG, Lazar RH. Intranasal anatomic variations in pediatric sinusitis. American journal of rhinology. 1997 Sep-Oct;11(5):355-60.

51. Gordts F, Clement PA, Buisseret T. Prevalence of sinusitis signs in a non-ENT population. ORL J Otorhinolaryngol Relat Spec. 1996 Nov-Dec;58(6):315-9.

52. Ponikau JU, Sherris DA, Kern EB, Homburger HA, Frigas E, Gaffey TA, et al. The diagnosis and incidence of allergic fungal sinusitis. Mayo Clinic proceedings Mayo Clinic. 1999 Sep;74(9):877-84.

53. Sasama J, Sherris DA, Shin SH, Kephart GM, Kern EB, Ponikau JU. New paradigm for the roles of fungi and eosinophils in chronic rhinosinusitis. Current opinion in otolaryngology & head and neck surgery. 2005 Feb;13(1):2-8.

54. Van Crombruggen K, Zhang N, Gevaert P, Tomassen P, Bachert C. Pathogenesis of chronic rhinosinusitis: Inflammation. The Journal of allergy and clinical immunology. 2011.

55. Roca-Ferrer J, Garcia-Garcia FJ, Pereda J, Perez-Gonzalez M, Pujols L, Alobid I, et al. Reduced expression of COXs and production of prostaglandin E(2) in patients with nasal polyps with or without aspirin-intolerant asthma. The Journal of allergy and clinical immunology. 2011 Jul;128(1):66-72 e1.

56. Bachert C, Zhang N, Patou J, van Zele T, Gevaert P. Role of staphylococcal superantigens in upper airway disease. Curr Opin Allergy Clin Immunol. 2008 Feb;8(1):34-8.

57. Bachert C, Gevaert P, Holtappels G, Johansson SG, van Cauwenberge P. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. The Journal of allergy and clinical immunology. 2001 Apr;107(4):607-14.

58. Tieu DD, Kern RC, Schleimer RP. Alterations in epithelial barrier function and host defense responses in chronic rhinosinusitis. The Journal of allergy and clinical immunology. 2009 Jul;124(1):37-42.

59. Kern RC, Conley DB, Walsh W, Chandra R, Kato A, Tripathi-Peters A, et al. Perspectives on the etiology of chronic rhinosinusitis: an immune barrier hypothesis. American journal of rhinology. 2008 Nov-Dec;22(6):549-59.

60. Foreman A, Holtappels G, Psaltis AJ, Jervis-Bardy J, Field J, Wormald PJ, et al. Adaptive immune responses in Staphylococcus aureus biofilm-associated chronic rhinosinusitis. Allergy. 2011 Aug 11;66(11):1449-56.

61. Ohlrich EJ, Cullinan MP, Seymour GJ. The immunopathogenesis of periodontal disease. Aust Dent J. 2009 Sep;54 Suppl 1:S2-10.

62. Dykewicz MS. 7. Rhinitis and sinusitis. The Journal of allergy and clinical immunology. 2003 Feb;111 (2 Suppl):S520-9.

63. Damm M, Quante G, Jungehuelsing M, Stennert E. Impact of functional endoscopic sinus surgery on symptoms and quality of life in chronic rhinosinusitis. The Laryngoscope. 2002 Feb;112(2):310-5.

64. Ling FT, Kountakis SE. Important clinical symptoms in patients undergoing functional endoscopic sinus surgery for chronic rhinosinusitis. The Laryngoscope. 2007 Jun;117(6):1090-3.

65. West B, Jones NS. Endoscopy-negative, computed tomography-negative facial pain in a nasal clinic. The Laryngoscope. 2001 Apr;111(4 Pt 1):581-6.

66. Aaseth K, Grande RB, Kvaerner K, Lundqvist C, Russell MB. Chronic rhinosinusitis gives a ninefold increased risk of chronic headache. The Akershus study of chronic headache. Cephalalgia : an international journal of headache. 2010 Feb;30(2):152-60.

67. Litvack JR, Fong K, Mace J, James KE, Smith TL. Predictors of olfactory dysfunction in patients with chronic rhinosinusitis. The Laryngoscope. 2008 Dec;118(12):2225-30.

68. Craig TJ, Ferguson BJ, Krouse JH. Sleep impairment in allergic rhinitis, rhinosinusitis, and nasal polyposis. Am J Otolaryngol. 2008 May-Jun;29(3):209-17.

69. Rombaux P, Liistro G, Hamoir M, Bertrand B, Auber t G, Verses T, et al. Nasal obstruction and its impact on sleep related breathing disorders. Rhinology. 2005 Dec;43(4):242-50.

70. Bousquet J, Bachert C, Canonica GW, Casale TB, Cruz AA, Lockey RJ, et al. Unmet needs in severe chronic upper airway disease (SCUAD). The Journal of allergy and clinical immunology. 2009 Sep;124(3):428-33.

71. Storms W, Yawn B, Fromer L. Therapeutic options for reducing sleep impairment in allergic rhinitis, rhinosinusitis, and nasal polyposis. Current medical research and opinion. 2007;23(9):2135-46.

72. Poetker DM, Mendolia-Loffredo S, Smith TL. Outcomes of endoscopic sinus surgery for chronic rhinosinusitis associated with sinonasal polyposis. American journal of rhinology. 2007 Jan-Feb;21(1):84-8.

73. Meltzer EO, Hamilos DL, Hadley JA. Rhinosinusitis: establishing definitions for clinical research and patient care. *Otolaryngol Head Neck Surg* 2004;131:S1 S62.

74. Benninger MS, Anon J, Mabry RL. The medical management of rhinosinusitis. *Otolaryngol Head Neck Surg* 1997;117:S41–S49.

75. Lund VJ. Maximal medical therapy for chronic rhinosinusitis. *Otolaryngol Clin North Am*2005;38:1301–1310.

76. Grzincich G, Capra L, Cammarata MG, Spaggiari C, Pisi G. Effectiveness of intranasal corticosteroids. *Acta Biomed.* 2004;75:22–25.

77. Gillespie MB, Osguthorpe JD. Pharmacologic management of chronic rhinosinusitis, alone or with nasal polyposis. *Curr Allergy Asthma Rep* 2004;4:478–485.

78. Badia L, Lund V. Topical corticosteroids in nasal polyposis. *Drugs* 2001;61:573–578.

79. Langrick AF. Comparison of flunisolide and beclomethasone dipropionate in seasonal allergic rhinitis. *Curr Med Res Opin* 1984;9:290–295

80. Dingsor G, Kramer J, Olsholt R, Soderstrom T. Flunisolide nasal spray 0.025% in the prophylactic treatment of nasal polyposis after polypectomy. A randomized, double blind, parallel, placebo controlled study. *Rhinology* 1985;23:49–58.

81. DeMarcantonio MA, Han JK. Systemic therapies in managing sinonasal inflammation. *Otolaryngol Clin North Am* 2010;43:551–563, ix.

82. Lennard CM, Mann EA, Sun LL, Chang AS, Bolger WE. Interleukin-1 beta, interleukin-5, interleukin-6, interleukin-8, and tumor necrosis factor-alpha in chronic sinusitis: response to systemic corticosteroids. *Am J Rhinol* 2000;14:367–373.

83. Van Camp C, Clement PA. Results of oral steroid treatment in nasal polyposis. *Rhinology* 1994;32:5–9.

84. Harvey RJ, Schlosser RJ. Local drug delivery. *Otolaryngol Clin North Am* 2009;42:829–845

85. Talbot AR, Herr TM, Parsons DS. Mucociliary clearance and buffered hypertonic saline solution. *Laryngoscope* 1997;107:500–550.

86. Yu C, Chen FDY, Wang J, Gu YJ, Gao X. Effect of Pulmicort Respule on rehabilitation after functional endoscopic sinus surgery. *Acta Chimi Sin* 2007;21:100–102.

87. Leonard DW, Bolger WE. Topical antibiotic therapy for recalcitrant sinusitis. *Laryngoscope*1999;109:668–670.

88. Kennedy DW. Functional endoscopic sinus surgery. Technique. *Arch Otolaryngol* 1985;111:643–649.

89. Dalziel K, Stein K, Round A, Garside R, Royle P. Systematic review of endoscopic sinus surgery for nasal polyps. Health Technol Assess. 2003;7(17):iii, 1-159.

90. Wynn R, Har-El G. Recurrence rates after endoscopic sinus surgery for massive sinus polyposis. The Laryngoscope. 2004 May;114(5):811-3.

91. Bhattacharyya N. Influence of polyps on outcomes after endoscopic sinus surger y. The Lar yngoscope. 2007 Oct;117(10):1834-8.

92. Hopkins C, Browne JP, Slack R, Lund V, Topham J, Reeves B, et al. The national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. Clin Otolaryngol. 2006 Oct;31(5):390-8.

93. Ragab SM, Lund VJ, Scadding G, Saleh HA, Khalifa MA. Impact of chronic rhinosinusitis therapy on quality of life; A prospective randomized controlled trial. Rhinology. 2010;48(3):305-11.

94. Article title: Complications of Sinus Surgery. Website title: American Rhinologic Society. Taken on 25.5.2018. Link:http://care.american-rhinologic.org/complications_ess.

95. Brown S. Anatomy of nose and paranasal sinuses. In: Lund VJ, H Stammberger, Scott Brown Otolaryngology, Basic Sciences; 5, Butterworth-Heinemann; oxford, 7th edn; 2008:1318.

96. Lanza DC, Kennedy DW. Adult rhinosinusitis defined. Otolaryngol. Head Neck Surg. 1997;117:S1–S7. doi: 10.1016/S0194-5998(97)70001-9

97. . Fokkens W, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps. Rhinol Suppl 2007;20:1–36.

98. Bugten V, Nordgård S, Romundstad P, Steinsvåg S. Chronic rhinosinusitis and nasal polyposis; indicia of heterogeneity. Rhinology. 2008;46(1):40-44.

99. Dursun E, Korkmaz H, Eryilmaz A, Bayiz U, Sertkaya D, Samim E. Clinical predictors of long-term success after endoscopic sinus surgery. Otolaryngol Head Neck Surg. 2003;129:526-531.doi: 10.1016/S0194-5998(03)01576-6.

100. Chen B, Shaari J, Claire SE, et al. Altered ciliary dynamics in chronic rhinosinusitis. Am J Rhinol 2006;20:325–9.

101. Davis SS, Illum L. Absorption enhancers for nasal drug delivery. Clin Pharmacokinet 2003;42:1107–28.

102. Houser SM, Keen KJ. The role of allergy and smoking in chronic rhinosinusitis and polyposis. Laryngoscope 2008;118:1521–7.

103. Tan BK, Zirkle W, Chandra R, et al. Atopic profile of patients failing medical therapy for chronic rhinosinusitis. Int Forum Allergy Rhinol 2011;1:88–94.

104. Asero R, Bottazzi G. Hypersenstivity to molds in patients with nasal polyposis: a clinical study. J Allergy Clin Immunol 2000;105:186–8.

105. Asero R, Bottazzi G. Nasal polyposis: a study of its association with airborne allergen hypersensitivity. Ann Allergy Asthma Immunol 2001;86:283–5.

106. Pumhirun P, Limitlaohapanth C, Wasuwat P. Role of allergy in nasal polyps of Thai patients. Asian Pac J Allergy Immunol 1999;17:13–5.

107. Rosati MG, Peters AT. Relationships among allergic rhinitis, asthma, and chronic rhinosinusitis. *Am J Rhinol Allergy 2016; 30:44-47.*

108. Dixon AE. Rhinosinusitis and asthma: the missing link. *Curr Opin Pulm Med 2009; 15:19-24.*

109. Habib AR, Javer AR, Buxton JA. A population-based study investigating chronic rhinosinusitis and the incidence of asthma. Laryngoscope 2016; 126:1296-302.

110. Ek A, Middelveld RJ, Bertilsson H, et al. Chronic rhinosinusitis in asthma is a negative predictor of quality of life: results from the Swedish GA(2)LEN survey. Allergy 2013; 68:1314-1321.

111. Schleimer RP, Kato A, Peters A, et al. Epithelium, inflammation, and immunity in the upper airways of humans: studies in chronic rhinosinusitis. *Proc Am Thorac Soc* 2009; 6:288–294.

112. Tint D, Kubala S, Toskala E. Risk factors and comorbidities in chronic rhinosinusitis. *Curr Allergy Asthma Rep* 2016; 16:16.

113. Bachert C, Wagenmann M, Hauser U, Rudack C. IL-5 is upregulated in human nasal polyp tissue. J Allergy Clin Immunol. 1997;:99:837-842. Doi: 10.1016/S0091-6749(97)80019-X.

114. Min YG, Lee CH, Rhee CS, Hong SK, Kwon SH. Increased expression of IL-4, IL-5, IFN-gamma, IL-6, IL-8, and TGF-beta mRNAs in maxillary mucosa of patients with chronic sinusitis. Am J Rhinol. 1999;13(5):339-343. doi: 10.2500/105065899781367546.

115. Loehrl TA, Ferre RM, Toohill RJ, et al. Long-term asthma outcomes after endoscopic sinus surgery in aspirin triad patients. *Am J Otolaryngol* 2006; 27:154–160.

116. Chen FH, Zuo KJ, Guo YB, et al. Long-term results of endoscopic sinus surgery-oriented treatment for chronic rhinosinusitis with asthma. *Laryngoscope* 2014; 124:24–28.

117. Alexiou A, Sourtzi P, Dimakopoulou K, Manolis E, Velonakis E. Nasal polyps: heredity, allergies, and environmental and occupational exposure. J Otolaryngol Head Neck Surg. 2011;40:58–63.

118. Cohen NA, Widelitz JS, Chiu AG, Palmer JN, Kennedy DW. Familial aggregation of sinonasal polyps correlates with severity of disease. J Otolaryngol Head Neck Surg. 2006;134:601–604. doi: 10.1016/j.otohns.2005.11.042.

119. Rugina M, Serrano E, Klossek JM, Crampette L, Stoll D, Bebear JP, Perrahia M, Rouvier P, Peynegre R. Epidemiological and clinical aspects of nasal polyposis in France; the ORLI group experience. Rhinology. 2002;40:75–79.

120. Jani AL, Hamilos DL. Current thinking on the relationship between rhinosinusitis and asthma. J Asthma. 2005;42:1–7. doi: 10.1081/JAS-200044744.

121. Kountakis SE, Arango P, Bradley D, Wade ZK, Borish L. Molecular and cellular staging for the severity of chronic rhinosinusitis. Laryngoscope. 2004;114:1895–1905. doi: 10.1097/01.mlg.0000147917.43615.c0.

122. Regnis JA, Robinson M, Bailey DL, et al. Mucociliary clearance in patients with cystic fibrosis and in normal subjects. Am J Respir Crit Care Med 150:66–71, 1994.

123. Gentile VG, Isaacson G. Patterns of sinusitis in cystic fibrosis. Laryngoscope 106:1006-1009, 1996.

124. Gysin C, Alothman GA, Papsin BC. Sinonasal disease in cystic fibrosis: Clinical characteristics, diagnosis, and management. Pediatr Pulmonol 30:481–489, 2000.

125. Robertson JM, Friedman EM, Rubin BK. Nasal and sinus disease in cystic fibrosis. Paediatr Respir Rev 9:213–219, 2008.

126. Adrian Drake-Lee “the physiology of the Nose and Paranasal sinuses” Scott Brown’s Otolaryngology. 6th edition, Volume 1, Basic sciences 1,6,11-15.

127. Sebin Scaria. Radiological evidence of the frequency of involvement of paranasal sinuses in chronic rhinosinusitis. Website Rroij.com. taken on 25.5.2018. Link: http://www.rroij.com/open-access/-radiological-evidence-of-frequency-of-involvement-of-paranasal-sinuses-in-chronic-rhinosinusitis.php?aid=34907.

128. Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A. Chronic rhinosinusitis in Europe - an underestimated disease. A GA(2) LEN study. Allergy. 2011;66(9):1216–1223. doi: 10.1111/j.1398-9995.2011.02646.x

129. Reh DD, Higgins TS, Smith TL. Impact of tobacco smoke on chronic rhinosinusitis: a review of the literature. Int Forum Allergy Rhinol. 2012;2:362–369. doi: 10.1002/alr.21054.

130. Lieu JE, Feinstein AR. Confirmations and surprises in the association of tobacco use with sinusitis. Arch Otolaryngol Head Neck Surg. 2000;126:940–946.

doi: 10.1001/archotol.126.8.940.

131. Houser SM, Keen KJ. The role of allergy and smoking in chronic rhinosinusitis and polyposis. Laryngoscope. 2008;118:1521–1527. doi: 10.1097/MLG.0b013e31817d01b8.

132. Kennedy DW. Prognostic factors, outcomes and staging in ethmoid sinus surgery. Laryngoscope. 1992;102:1–18.

133. Krzeski A, Galewicz A, Chmielewski R, Kisiel M. Influence of cigarette smoking on endoscopic sinus surgery long-term outcomes. Rhinology. 2011;49:577–582.

134. Willes SR, Fitzgerald TK, Permutt T, Proud D, Haley NJ, Bascom R. Acute respiratory response to prolonged, moderate levels of sidestream tobacco smoke. J Toxicol Environ Health A. 1998;53:193–209. doi: 10.1080/009841098159330.

135. Fokkens W.J., Lund V.J., Mullol J., Bachert C., et al. European position paper on Rhinosinusitis and Nasal polyps. Rhinology. Official journal of the European and international societies. 2012:55-196. http://ep3os.org/EPOS2012.pdf

136. Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe Allergy. 2012;67(1):91–98. doi: 10.1111/j.1398-9995.2011.02709.x

137. Kim YS, Kim NH, Seong SY, Kim KR, Lee GB, Kim KS. Prevalence and risk factors of chronic rhinosinusitis in Korea. Am J Rhinol Allergy. 2011;25(3):117–121. doi: 10.2500/ajra.2011.25.3630.

138. Hamilos DL. Chronic rhinosinusitis: Epidemiology and medical management. J Allergy Clin Immunol. 2011;128(4):693–707. doi: 10.1016/j.jaci.2011.08.004.

139. Pilan RR, Pinna FR, Bezerra TF, Mori RL, Padua FG, Bento RF, Perez-Novo C, Bachert C, Voegels RL. Prevalence of chronic rhinosinusitis in Sao Paulo. Rhinology. 2012;50(2):129–138.

140. Slavin RG, Spector SL, Bernstein IL, Kaliner MA, Kennedy DW, Virant FS. American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology The diagnosis and management of sinusitis: a practice parameter update. J Allergy Clin Immunol. 2005;116(6 Suppl):S13–S47. doi: 10.1016/j.jaci.2005.09.048.

141. Rosenfeld RM. Clinical practice guideline on adult sinusitis. Otolaryngol Head Neck Surg. 2007;137(3):365–377. doi: 10.1016/j.otohns.2007.07.02.

142. Endoscopic Sinus Surgery in Chronic Rhinosinusitis and Nasal Polyposis: A Comparative Study Satish Nair, Angshuman Dutta, Ramakrishnan Rajagopalan, Sapna Nambiar Indian J Otolaryngol Head Neck Surg. 2011 Jan; 63(1): 50–55. Published online 2011 Jan 18. doi: 10.1007/s12070-011-0119-8.

10. Biography

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