Prevalence of septal deformities in patients with chronic rhinosinusitis

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Abbreviations

ARS- Acute rhinosinusitis

ESR- Erythrocyte sedimentation rate

CRP- C reactive protein

CT- Computerized tomography

CRS- Chronic Rhinosinusitis

CRSwNP- Chronic Rhinosinusitis with nasal polyposis

CRSsNP- Chronic Rhinosinusitis without nasal polyposis

GA2LEN- The Global Allergy and Asthma Network of Excellence

ENT- Ear, Nose and Throat

CF- Cystic Fibrosis

NP- Nasal Polyps

AIDS- Acquired Immunodeficiency Syndrome

INCS- Intranasal Corticosteroids

ESS- Endoscopic Sinus Surgery

NSD- Nasal Septal Deviation

CI- Confidence Interval

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Summary

Title: Prevalence of septal deformities in patients with chronic rhinosinusitis

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Objectives: The aim of this study was to assess the prevalence of septal deviations in CRS patients who underwent ESS treatment for sinonasal disease at the Department of ORL and HNS, Sisters of Charity University Hospital in Zagreb and compare the results to other studies.

Methods: 108 CRS patients who underwent endoscopic sinus surgery in 2018 were retrospectively reviewed. We analyzed demographics, CRS phenotypes, septal deviation and types of surgical procedures.

Results: From the 108 reviewed patients, 85 were diagnosed with chronic rhinosinusitis with nasal polyposis (CRSwNP) and 21 were diagnosed with chronic rhinosinusitis without nasal polyposis (CRSsNP). 38% (41) of patients had a diagnosed septal deviation at the time of surgery. No difference was found when comparing the prevalence of nasal septal deviations NSD in patients with CRSwNP and the general population; however a statistically significant result was shown for patients with CRSsNP (52.38% as opposed to 32.70%).

Conclusion: We concluded that NSD could represent an etiological factor in a subset of CRS.

Key words: Chronic rhinosinusitis, nasal septal deviations, endoscopic sinus surgery

Sažetak

Naslov: Prevalencija septalnih deformacija u pacijenata s kroničnim rinosinusitisom

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Cilj: Cilj ovog istraživanja bio je utvrditi prevalenciju devijacija nosne pregrade u bolesnika koji su podvrgnuti endoskopskoj operaciji sinusa kao dio liječenja sinonazalne bolesti na Klinici za otorinolarigologiju i kirurgiju glave i vrata, KBC Sestre milosrdnice, i usporediti rezultate s drugim studijama.

Metode: Retrospektivno smo analizirali 108 pacijenata operiranih metodom endoskopske sinusne kirurgije u 2018. Analizirali smo demografiju, fenotipove KRS-a, devijaciju nosne pregrade i tipove operacije.

Rezultati: Od 108 pacijenata, 85 je imalo dijagnozu kroničnog rinosinusitisa s nosnom polipozom (KRSsNP), 21 je imalo kronični rinosinuitis bez nosne polipoze (KRSbNP). 38% (41) pacijenata je imalo devijaciju nasne pregrade u vrijeme operacije. Nije pronađena razlika u prevalenciji DNP-a u pacijenata s KRSsNP i opće populacije. Utvrdili smo statistički značajnu u prevalenciji DNP-a u pacijenata s KRSbNP (52,38% nasuprot 32,70%)

Zaključak: Zaključujemo da bi devijacija nosne pregrade mogli predstavljati etiološki čimbenik u podgrupi pacijenata s KRS-om.

Ključne riječi: Kronični rinosinuitis, devijacija nosne pregrade, endoskopska sinusna kirurgija

1. Introduction

Rhinosinusitis represents a very common problem that is encounterered by a broad range of different specialties including, but not limited to primary care physicians, allergologists and otorhinolaryngologists. In the adult population, it 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/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) accompanied by:

- facial pain/pressure
- reduction or loss of smell
- endoscopic signs of: nasal polyps, and/or mucopurulent discharge primarily from middle meatus and/or oedema/mucosal obstruction primarily in middle meatus
- CT changes: mucosal changes within the ostiomeatal complex and/ or sinuses (1)

The definition of rhinosinusitis in children substitutes the reduction or loss of smell for cough, all other criteria being equivalent. Rhinosinusitis is divided into acute and chronic forms of the disease, a cutoff value of 12 weeks is used to distinguish between the two. ARS is further subdivided into the common cold, post-viral rhinosinusitis and acute bacterial rhinosinusitis. The common cold is caused by rhinoviruses and is diagnosed when symptoms and signs of acute rhinosinusitis are present for <10 days without an increase in severity. Acute post-viral rhinosinusitis is defined as an increase of symptoms after 5 days or persistent symptoms after 10 days with less than 12 weeks duration. Acute bacterial rhinosinusitis, the least common of the three entities, is suggested by unilateral pain, purulent discharge, fever (>38ºC), elevated ESR/CRP, ‘double sickening’ (i.e. a deterioration after an initial milder phase of illness). Chronic rhinusinusitis is defined by having a duration that exceeds 12 weeks and is further subdivided into forms with and without nasal polyposis. It's a complex disease with multifactorial pathogenesis which is incompletely understood. Through the years, various theories have been proposed to explain its natural history some of which will be discussed later on. This paper deals with the possible role of septal deviation in the pathogenesis of chronic rhinosinusitis. Deviations of the nasal septum due to developmental abnormalities or trauma are common but often are asymptomatic and require no treatment. Symptomatic septal deviation causes nasal obstruction and epistaxis due to drying air currents. Other symptoms may include facial pain, headaches, and snoring.

2. Epidemiology of chronic rhinosinusitis and septal deformities

It is difficult to ascertain the exact prevalence of CRS because of different definitions being used in the literature and varying technical possibilities for diagnosis in different specialties. it was estimated that CRS, defined as having ‘sinus trouble’ for more than 3 months in the year before the interview, affects 15.5% of the total population in the United States(2).However, the prevalence of doctor-diagnosed CRS is much lower reaching 2%. The majority of primary care physicians 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. 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 was 10.9% (range 6.9-27.1)(3). Septal deformities are extremely common. In an international multi-centre study Mladina et al. showed through examination by anterior rhinoscopy that almost 90% of the ENT patients in the various geographic regions of the world had 1 of the 7 types of septal deformities(4).

3. Factors associated with CRS

3.1. Ciliary impairment

The cilia play an important role in the clearance of foreign matter in the respiratory tract, they help keep the sinuses clean and curb chronic inflammation. The connection between ciliary function and CRS is readily illustrated in patients with Kartagener syndrome and primary ciliary diskinesia who often have problems with respiratory infections and CRS. Similar problems occur in CF patients, due to the increased viscosity of mucous secretions the cilia are unable to perform their function adequately, and consequently CRS develops. Nasal polyposis is present in 40% of patients with CF(5). Thus, ciliary malfunction likely plays a role in the development of CRS.

3.2. Allergy

Both allergy and CRS share an increase in prevalence. 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 (6). Among CRS patients undergoing sinus surgery, the prevalence of positive skin

testing ranges from 50% to 84%, of which the majority (60%) has multiple sensitivities.

3.3. Aspirin sensitivity

CRSwNP is common in patients with aspirin sensitivity, the prevalence is reported to be 36-96% (7). 96% of patients have radiographic changes affecting their sinuses (8) .Patients with aspirin sensitivity, asthma and NP are usually non-atopic and the prevalence increases over the age of 40 years. The children of patients with asthma, NP, and aspirin sensitivity had NP and rhinosinusitis more often than the children of controls (9). Bearing this in mind it seems there is a connection between the two entities; however, the mechanism remains to be elucidated.

3.4.Immunocompromised state

There is some evidence linking the development of CRS with immunodeficient states of both the acquired and congenital variety. A retrospective review of refractory sinusitis patients found an unexpectedly high incidence of immune dysfunction. Of the 60 patients with in vitro T-lymphocyte function testing, 55% showed abnormal proliferation in response to recall antigens. Low immunoglobulin (Ig), IgA and IgM titers were found in 18%, 17%, and 5%, respectively, of patients with refractory sinusitis. Common variable immunodeficiency was diagnosed in 10% and selective IgA deficiency in 6% of patients(10). The prevalence of CRS in AIDS patients is higher than in the general population (36%) and is correlated with the CD4+ count (11). It is possible that atypical organisms (e.g. P. Aureginosa, Aspergillus sp.) isolated from the nasal mucosa of AIDS patients contribute to the development of their sinonasal pathology (12). Immunological testing should be an integral part of the diagnostic pathway of patients with CRS.

3.5. Biofilms

The polyps in CRSwNP are colonized with different strains of bacteria which form biofilms rendering them more adapted to the environment of the nasal cavity. Although they are not thought to be the main etiologic factors in the development of CRSwNP, but their presence is correlated with a more severe clinical picture and worse surgical outcomes(13). Mucosal inflammation in nasal polyps is orchestrated by Th2 cytokines amplified by S. aureus

enterotoxins is characterized by an increased eosinophilic inflammation and the formation of IgE antibodies(14). It is likely that biofilms modulate the immune environment and have a role to play in the development of CRS.

3.6.Environmental factors

Cigarette smoking was associated with a higher prevalence of CRS in Canada (15) and exposure to secondhand smoke is common and significantly independently associated with CRS. The GA(2)LEN study demonstrated that smoking was associated with having CRS in all parts of Europe(16). One study found that a significantly smaller proportion of the population with polyps were smokers compared to an unselected population (15% vs. 35%) (17), whereas this was not confirmed by others (18). One study reports on the association between the use of a woodstove as a primary source of heating and the development of NP (19). There are many contradictions and failures of replication within the literature dealing with the association of environmental factors and CRS, it is not yet clear to which extent the environment is involved in its pathogenesis.

4. Pathogenesis of CRS

CRS can be described as a dysfunctional host-environment interaction occurring in the nose and paranasal sinuses. Many hypotheses have been put forward as an attempt to unravel its pathogenesis and open the doors to more successful clinical management, although the true pathophysiological underpinnings of CRS continue to be elusive, we will discuss some of the current thinking in the field in the hope of providing a more complete picture. Namely: the fungal hypothesis, the staphylococcal superantigen hypothesis, the immune barrier hypothesis and lastly the biofilm hypothesis.

4.1 The fungal hypothesis

One of the first theories to address CRS hypothesized that its development is related to an excessive immune response to Alternaria antigens through a non IgE mediated mechanism (20).The use of sensitive detection techniques has indicated that fungi are a ubiquitous intranasal presence, identified in close to 100% of both CRS patients and controls (21). As opposed to controls however, patients with CRS also exhibited eosinophils in the nasal tissues and lumen, with no increase in IgE mediated mould allergy (22). Interest in fungi

spawned a series of drug trials. An extensive, multi-centre, blinded, randomized trial using intra nasal amphotericin failed to show any evidence of efficacy, however (23). More significantly, a follow up study indicated that amphotericin had no significant effect on any pro-inflammatory chemokine, cytokine or growth factor in the CRS lavage samples. Thus, reducing the initial enthusiasm for the fungal hypothesis.

4.2.The staphylococcal superantigen hypothesis

It is thought that S. aureus contributes to the development of CRS. The purported mechanism for this effect begins with epithelial damage i.e. barrier dysfunction which results in colonization. Thereafter, S.aureus alters the functioning of the immune system through superantigens in order to survive in the nasal cavity. The effects on the host include Th2 skewing (24), changes in eicosanoid metabolism (25) and generation of IgE auto-antibodies locally. All these effects are thought to modulate disease severity, especially in CRSwNP (26).

4.3.The immune barrier hypothesis

One other idea about the pathogenesis of CRS approached the problem from the standpoint congenital deficiencies in immune barrier function. The hypothesized defect would cause inadequate function of the sinonasal mucosa resulting in colonization with various microbial species and a compensatory adaptive immune response which would manifest as CRS. One potential molecular mechanism for this hypothesis would include local defects in the STAT 3 pathway, which has been identified in some forms of CRS (27). Systemic defects in STAT 3 have been identified in Job's disease, a disorder with some striking similarities to CRSwNP (28).

4.4. 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.

The symptomatology can be further subdivided into local, distant and systemic manifestations of the disease. The local signs and symptoms are the ones previously discussed and form the backbone of CRS diagnosis. Distant symptoms occur within the head and neck region e.g. tracheal and pharyngeal irritation causing sore throat and cough. Systemic symptoms are those of malaise, fever and drowsiness. We can see that the presentation is similar to the acute form of the disease; however the picture in ARS is usually clearer and more severe, in CRS there is a broad variation in the symptoms that present in individual patients and the symptoms are commonly of lesser intensity.

Most commonly the diagnosis is reached in the primary care setting based on symptoms alone, however there are additional tests and procedures that are helpful in assessing disease severity and should be applied in order to be objective, notably these include CT scans and nasal endoscopy. These methods can be used to stratify the disease and provide guidance in the context of therapeutic response.

The assessment of symptom severity can be guided by the visual analog scale or generally by using a grading system such as 0 to 10, it is best to use one of the validated questionnaires to assess the quality of life.

4.5. Complications of CRS

Complications of CRS occur mostly in the surrounding bone. They are generally a result of disordered resorption, remodeling and regeneration and are far less common than those arising from acute infection. Some of these processes may be considered elements of the natural history of the disease. Complications include:

1. Mucocele formation

2. Osteitis

3. Bone erosion and expansion

4. Metaplastic bone formation

5. Optic neuropathy

If compression of adjacent structures is an issue complications can be managed surgically. CRS is not associated with and increased risk of malignant or benign neoplasia.

7. Therapeutic modalities in CRS

The goal of therapy in CRS is control of the disease by reducing inflammation and mucosal swelling and ensuring adequate mucociliary clearance. Management of acute infections also plays an important role. Since there are broad individual differences in the natural history of the disease there is no all-encompassing treatment algorithm which would be adequate for every case. Treatment of CRS must be individually tailored for each patient. The therapeutic options can be divided into pharmacological and surgical modalities. Generally, therapy is initiated pharmacologically whereas sinus surgery is reserved for patients who show no improvement in symptoms despite maximal medical management. Lastly, in patients in whom mould exposure, pollution and allergy influence the course of disease, environmental measures offer another therapeutic possibility.

7.1. Pharmacological therapies

7.1.1. Corticosteroids

The use of glucocorticoids has led to improvements in the treatment of upper and lower airway disease. The clinical efficacy of glucocorticoids may depend in part on their ability to reduce airway eosinophil infiltration by preventing their increased viability and activation(29).Both topical and systemic glucocorticoids may affect the eosinophil function by both directly reducing eosinophil viability and activation or indirectly reducing the secretion of chemotactic cytokines by nasal mucosa and polyp epithelial cells(30). Intranasal corticosteroids constitute the first line therapy in CRS. It is interesting to note the relationship of ESS to the bioavailability, and therefore efficacy of INCS. Pre-surgery, the distribution to the sinuses is extremely limited regardless of device. Post-surgery distribution is superior with high

volume positive pressure devices. Simple low volume sprays and drops have very poor distribution and should be considered a nasal cavity treatment only, especially prior to ESS (31). 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 (32).In addition, corticosteroids have been shown to delay recurrence of polyps after surgery (33). Common side effects with intranasal steroid use include nasal irritation, mucosal bleeding, and crusting (34). 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 (35). 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 (36). Daily usage of topical nasal steroids appears to be associated with minimal risks, however, long-term systemic steroids is associated with significant side effects (37). Therefore, a tapered regimen of oral steroid is given during severe flare-ups of CRS or in the postoperative period after sinus surgery.

7.1.2. Antibiotics

Antibiotics have been used with varying success in CRS. They may be applied systemically and topically, short term (less than 4 weeks) or long term (more than 4 weeks). Short term antibiotics should be used for the management of acute exacerbations of CRS with positive culture. 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. There has been success in the use of low-dose, long-term macrolides for the treatment of airway inflammatory disease. Long term erythromycin treatment changed the 10 years survival rate from 25% to over 90 % and simultaneously cleared the CRS in diffuse panbronchilitis (38). From the available studies on macrolides in CRSAll studies show a response rate (reduction in symptoms) that varies between 60 and 80 %. Most studies also show a reduction of inflammatory markers and some an increased ciliary beat frequency indicating less sticky secretions (39, 40). One study compared surgery with 12 weeks of erythromycin. Both treatment modalities improved symptoms significantly, except for nasal volume, which was better in the surgery group (41).

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 who also have a problem with inflammation of the sinus lining (mucous membrane 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, nebulizers) 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.

7.2. Surgical Modalities

Surgical interventions used for CRS used to involve open approaches; 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 (42) ESS may be done under local or general anesthesia it involves the use of nasal endoscope that is inserted through the nostril to view the nose and sinuses. The goal of the surgery is to 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.

7.2.1. Surgery for CRSwNP

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 (43). 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.

7.2.2. 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 (42). 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. Even though there is some evidence that a significantly higher rate of recurrent surgery is required in patients with nasal polyposis than those without polyps, patients with polyps may have more improvement following sinus surgery than CRSsNP patients (44, 45).

7.2.3. 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 that are worth mentioning;

· Bleeding: It is normal to have some degree of bleeding after surgery on the nasal septum or turbinate. Rarely does this require additional intervention and extremely rarely does it require blood transfusion. 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: because of the proximity of floor of the anterior cranial fossa a CSF leak may occur. 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.

7.2.4. 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.

8. The nasal septum

8.1. Anatomy and development

The nasal septum (Lat. septum nasi) separates the left and right nasal cavities. It extends from the nares anteriorly to the choanae posteriorly and is covered by squamous epithelium. The vertical midline nasal septum is comprised primarily of a single nasal cartilage from the external nose and two bones. Anteriorly the septal cartilage (or quadrangular cartilage) which approximates a quadrilateral shape. Posteriorly it meets the concave anterior margins of the ethmoid and vomer. Superoposteriorly is the perpendicular plate of the ethmoid, inferoposteriorly is the vomer; these two bones have a diagonal articulation running in a superoposteriorly-anteroinferiorly direction. Occasionally the nasal septal cartilage extends more posteriorly interposing itself between the ethmoid and vomer which in some cases never meet (46).The greater alar cartilages which form part of the cartilaginous scaffolding of the external nose each have two crura, lateral and medial. The two medial crura are tenuously joined in the midline and together with some intervening soft tissue forms the septum mobile nasi at the most anteroinferior margin of the septal cartilage. Anteriorly, the columella is the visible soft tissue portion of the nasal septum that separates the two nares (nostrils) and incorporates the septum mobile nasi. The nasal septum is supplied is by the sphenopalatine artery and the anterior and posterior ethmoidal arteries in addition to the superior labial artery anteriorly and the greater palatine artery posteriorly. The posterosuperior part of the septum is innervated by the anterior ethmoidal nerve, the posteroinferior part by the nasal branches of the greater palatine nerve and the anterior cartilaginous septum by the nasopalatine nerve. Around the fourth week of gestation, neural crest cells begin to migrate caudally toward the midface. These develop into two symmetrical nasal placodes. Each placode is divided by a nasal pit into a medial and lateral nasal process. The septum develops from the medial processes, along with the premaxilla and philtrum.

8.2. Deviations and deformities

Deviations of the nasal septum are a common problem and may take various forms and degrees. Some studies show that the incidence of septal deformities to increase slowly from childhood to adulthood, finally becoming very high, reaching close to 90% of the population in the world (47). It is useful to classify them in accordance with the plane in which the deviation occurs. Mladina types of septal deformities (SD) are divided in two main groups: so called “vertical” deformities (types 1, 2, 3 and 4), and “horizontal” ones (types 5 and 6) and an

additional type 7 which is a combination of the aforementioned types (48). One should distinguish between deviations and deformities, deviations signify a declination in a certain plane whereas a deformity signifies a more general change in shape. Type 1 means a mild unilateral vertical ridge in a valve area which slightly interferes with the function of the nasal valve; thus, in most cases, this has mild clinical importance. Type 2 means a unilateral vertical ridge, which is much more emphasized, i.e. it stays in close contact with the anterior nasal valve and thus, from the physical point of view, remarkably narrows or even totally blocks the air passage on the related nasal side. Type 3 means unilateral vertical deformity, i.e. unilateral convexity next to the anterior edge of the head of the middle turbinate. The nasal cavity is very narrow on this side and very wide on the opposite one. From a clinical point of view, it must be stressed that type 3 is the most frequent septal deformity in the general population and very frequently found in all cases of chronic rhinosinusitis (CRS). Type 4 is a bilateral vertical deformity, consisting of previously mentioned types, i.e. type 2 on one side, and type 3 on the other (so called "S- shaped" septum, or "reverse S-shaped" septum). Clinically, it summarizes all clinical implications of both types. Type 5 is a unilateral deformity, which is known in the literature as a "septal spur". It causes a unilateral horizontal deformity, discretely ascending from anterior to posterior, appearing as a crest which juts out more laterally than deeper in the nose, resulting in most cases in the impaction of its tip to the region of the sphenopalatine foramen. Type 6 is also a so-called horizontal deformity, consisting of two separate components: an anteriorly positioned basal septal crest on one side and more or less massive wing of the inter-maxillary bone on the opposite side. Between the intermaxillary bone wing and the septum there is a horizontal groove. The groove is a strict characteristic which determines type 6. Type 7 ("crumpled septum") is very variable and presents a combination of previously mentioned types with all of their clinical implications. In fact, it always involves a combination of one of two horizontal deformities (type 5 and/or type 6) with one of those belonging to so-called vertical deformities (types 1, 2, 3 or 4).

8.3. Nasal septal deviations as a possible etiologic factor in CRS

In light of the current understanding of the multifactorial pathogenesis of CRS, it is appropriate to reconsider anatomical deviations as contributing factors. Historically, it has been thought that nasal septal deviations play a role in the development of CRS by either causing ostiomeatal obstruction or by dysregulating the flow of air trough the nasal cavity. The literature on this topic is conflicted and burdened by varying definitions of both CRS and NSD. A systematic analysis of 13 articles found that septal deviation is associated with an

Increased prevalence of rhinosinusitis, although the impact is limited (49). In a correlational study of 120 cases it was found that there is no correlation between NSD and sinusitis in general, however when taking into account the type of NSD it was shown that horizontal deviations (type V) are more prone to sinusitis and vertical deviations (type I and type II) predispose to sinusitis due to involvement of nasal valve area (50).The incidence of type 3 NSD in CRS patients was 21.63% (51). It seems that the morphology of NSD impacts its association with CRS.

9. Hypothesis

We hypothesized that there is an association of nasal septal deformities with the development of CRS. The aim of this study was to investigate the prevalence of NSD in patients who were operated for CRS and to see how many of them had a correction of the NSD simultaneously with ESS.

10. Materials and methods

This study is a randomized retrospective study done on the Department of Otorhinolaryngology & Head and Neck Surgery, University Hospital Center Sestre milosrdnice. Characteristics of 108 patients who were diagnosed with CRS and who underwent ESS were taken from the medical data. The patient medical record collected also included disease phenotype, age, sex, septal deformation and type of surgery. For views and statistical calculations, Microsoft Excel Office was used. We looked at age and sex distributions, analyzed how many patients with CRSwNP and CRSsNP had concomitant NSD, and how many underwent FESS only or FESS with septoplasty.

11. Results

A total of 108 patients records were analyzed

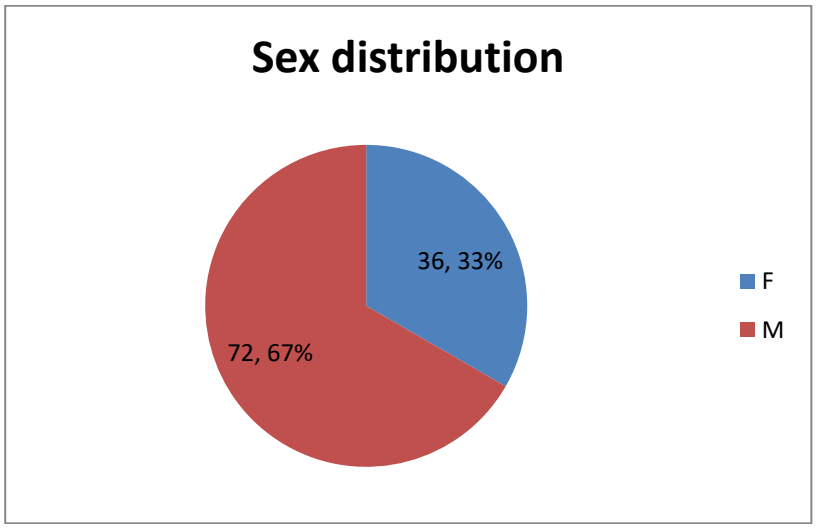

Figure 1. Sex distribution of patients

72 (66.66%) were male, 36 (33.33%) were female, male to female ratio was 1.5:1.

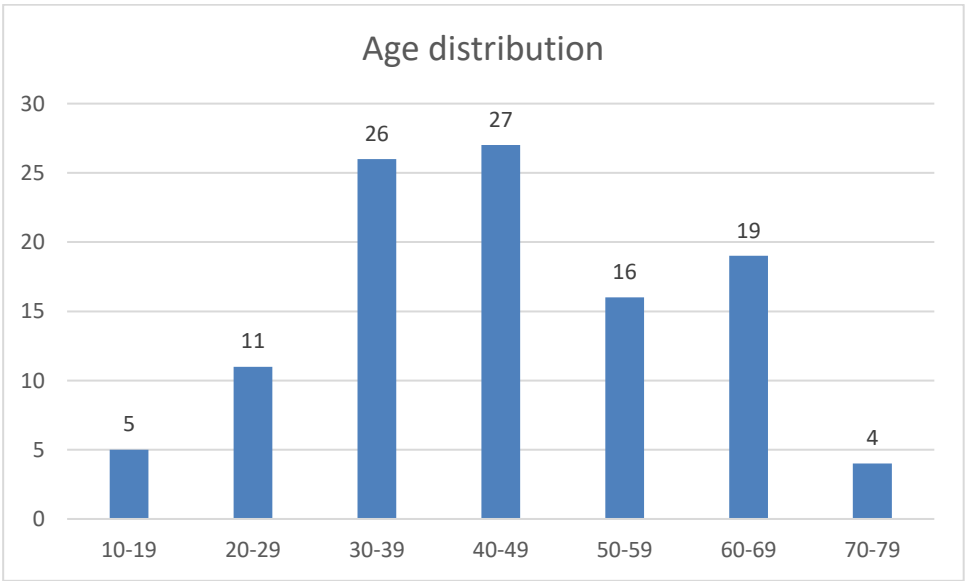

Figure 2. Age distribution of patients

The age distribution approximately follows a bell curve with only 5 (4.62%) in the second and 4 (3.7%) in the seventh decade of life. The bulk of patients is concentrated in the thirty and forty year olds, 26 (24.07%) and 27 (25%), respectively. 11 (10.18%) were in their twenties, 16 (14.81%) in their fifties and lastly 19 (17.59%) in their sixties.

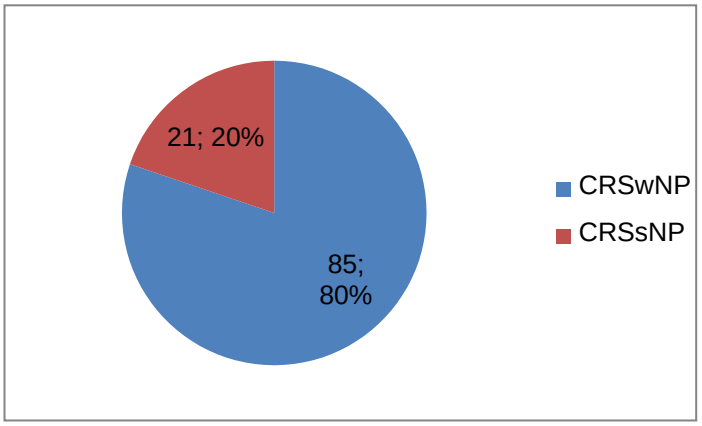

Figure 3. Disease phenotypes

The preceding figure shows the distribution of disease phenotypes, 80% of the analyzed patients had CRSwNP, 20% had CRSsNP.

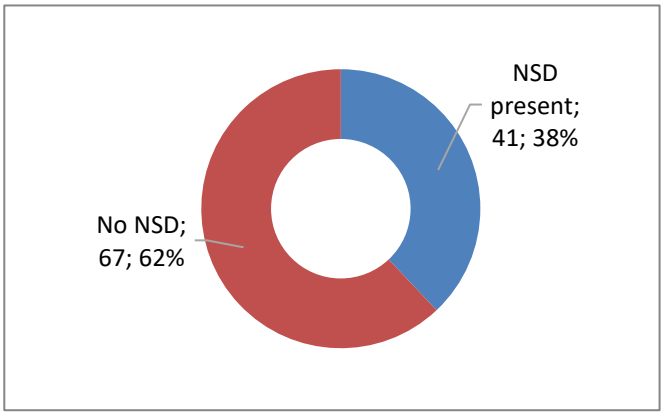

Figure 4. Distribution of nasal septal deviations

This figure shows the number and percentage of patients who had a diagnosed septal deformity regardless of disease phenotype, 38% (41) of patients had deviations at the time of surgery.

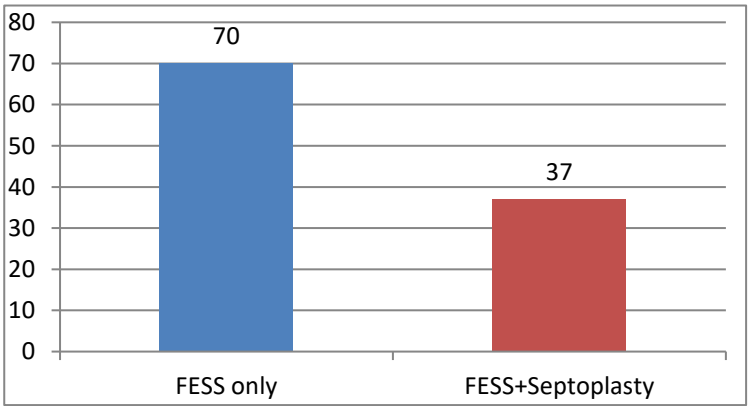

Figure 5. Comparison of FESS only and FESS together with septoplasty

70 (65.42%) patients had FESS only, whereas 37 (34.57%) had concomitant correction of septal deviations; one patient was not included in this graph since he had a maxillectomy due to comorbid cancer. The following figures show this comparison by disease phenotype.

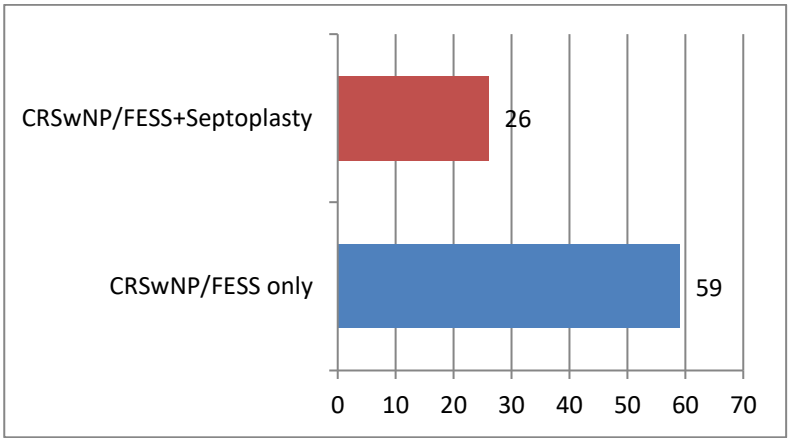

Figure 6. Types of procedures in patients with CRSwNP

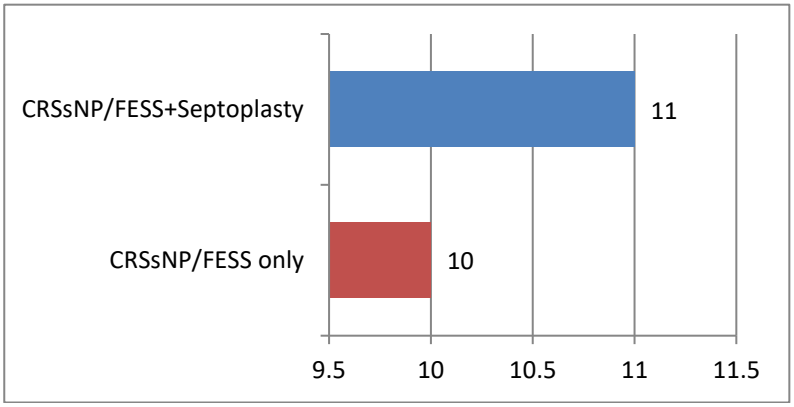

Figure 7. Types of procedures in patients with CRSsNP

Out of 85 patients with CRSwNP 59 (67.81%) had FESS without septoplasty, the remaining 26 (32.18%) had a concomitant septoplasty. In patients with CRSsNP 11 (52.38%) had septoplastay the remaining 10 (47.62%) had only FESS.

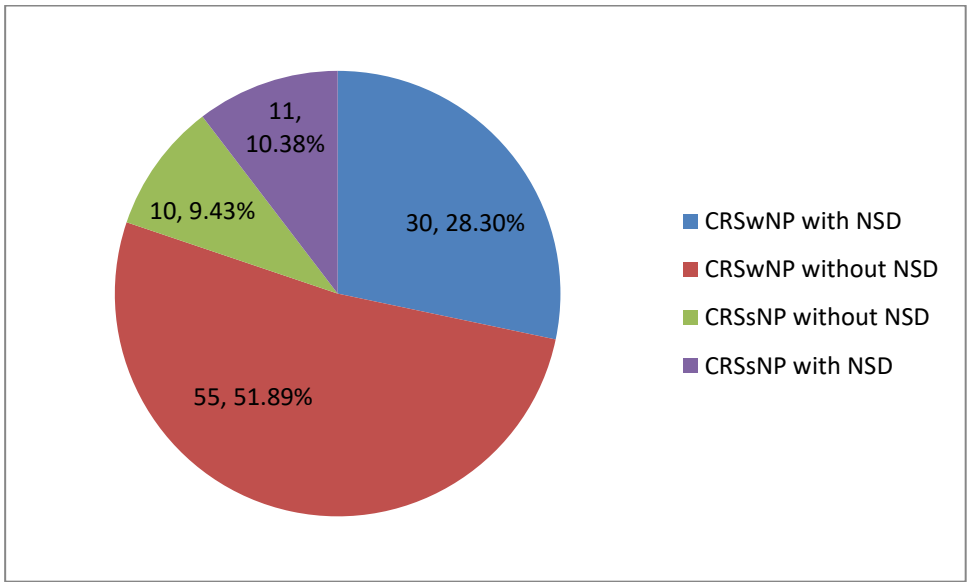

Figure 8. NSD in relation to disease phenotype

This graph shows all the patients together according to the presence of NSD in relation to the phenotype of the disease. All of the patients with CRSsNP and with a NSD had a concomitant septoplasty, whereas 4 of the patients with nasal polyposis and deviation did not have their septum repaired at the same time as FESS.

12. Discussion

Chronic rhinosinusitis is one of the most common otorhinolaryngological problems in the population; epidemiological studies show that it is present in 5-15% of people (52). It is managed by a wide variety of different clinicians and has a substantial influence on the quality of life of patients. Economically speaking, it was estimated that the direct cost of treating severe CRS was 1861$ per year in a study done in the Netherlands (53). National health care costs in the US remain very high for CRS, at an estimated 8.6 billion dollar per year (54). Factors contributing to this high expenditure are: the high prevalence of the condition, chronicity with acute exacerbations, and the use of radiological methods to aid diagnosis, often incomplete symptom resolution and finally the lack of a universal cure (55). CRS can be further subdivided into two phenotypes; CRSwNP and CRSsNP, the main difference being the presence nasal polyps (CRSwNP) defined as pedunculated lesions as opposed to cobblestoned mucosa, endoscopically visualized in middle meatus (56). CRSsNP is frequently associated with facial pain/pressure/fullness whereas CRSwNP is frequently characterized by hyposmia. The etiology of CRS is varied; 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 (57). The pathogenesis of CRS is still incompletely understood, there have been several theories describing the pathogenetic mechanism in terms of a dysfunctional host-environment interaction and immune modulation brought about by either staphylococcal superantigens, fungi or barrier dysfunction, as well as aerodynamic changes as a consequence of posterior nasal septal deviation (Bechert's pressure theory) (58). Anatomical variations have been suggested as a possible contributing factor in the development of CRS. A review article of CT studies of anatomical variations showed that there is no consistent difference in the prevalence of anatomical variations between a symptomatic group and a control group, with the possible exception of a septal deviation (59). Our hypothesis was that NSD is more prevalent in patients with CRS. It is problematic to ascertain the exact prevalence of NSD in the population, one recent study has shown that the number of cases of nasal septum deviation increases steadily with age, from 15% in children aged 7-8 years to 39.7% in adults (60) Taking this adult data into account would provide us with an odds ratio of 0.68-0.76 (CI=95%) for the CRSwNP group, rejecting the hypothesis. However when the same data is applied to the CRSsNP group it strongly supports the hypothesis with an odds ratio of 1.58-1.76 (CI=95%). The smaller number of patients in the CRSsNP group should be taken into account when interpreting the findings. The extent and type of the NSD could also modulate its effect on the development of CRS. Two separate studies showed mild to moderate degree of NSD was not a risk factor for chronic sinus disease (61.62). Only gross deviation of the nasal septum (more than 21%) was shown to be a statistically significant risk factor for the development of CRS ($p=0.035$). The purported mechanism is compression of the middle turbinate and obstruction in the normal mucus flow, leading to secondary inflammation and infection. Our study design did not gather information about the degree of septal deviation, but results are in line for the CRSwNP group, showing no correlation. There have been other studies that have analyzed the connection between CRS and NSD. In a large Korean study of 9069 persons Min et al. found and odds ratio of 0.88-2.21 thus refuting the association (63). However, their design did not account for disease phenotype, making an accurate comparison with our results difficult in regards to CRSsNP. In a high resolution CT study on variants in sinonasal anatomy Kayalioglu et al. found septal deviation in 20 patients (22.22%) who had symptomatic sinus disease and 10 (12%) who had gotten a CT scan for other reasons (64). These results show a lower incidence of septal deviations in general and in patients with sinus disease (not exclusively CRS) then the one we have observed. One other factor to consider in the interpretation of the literature is the

variability of the populations that have been studied; genetic and environmental differences could influence the mechanisms that lead to CRS development as well as the prevalence of NSD. The literature at the moment leaves the question of about the precise relation between CRSwNP, CRSsNP and NSD unclear. This problem could be circumvented by performing studies with a standardized methodology that would include data about the degree of deviation and the disease phenotype of CRS.

13. Conclusion

We hypothesized that nasal septal deviations are more common in patients with chronic rhinosinusitis. The hypothesis was rejected for the CRSwNP group and proven a statistically significant for the CRSsNP group, meaning that NSD could be an etiological factor in a subset of CRS.

14. Acknowledgments

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15. References

1. Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps 2007. Rhinol Suppl. 2007(20):1-136.

2. 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.

3. 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.

4. Mladina, Ranko, et al. "Nasal septal deformities in ear, nose, and throat patients: an international study." *American journal of otolaryngology* 29.2 (2008): 75-82.

5. 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.

6. Benninger MS. Rhinitis, sinusitis and their relationships to allergies. American journal of rhinology. 1992;6:37 43.

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

8. Szczeklik A, Stevenson DD. Aspirin induced asthma : advances in pathogenes is and management .The Journal of allergy and clinical immunology. 1999 Jul;104(1):5-13.

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

10. 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.

11. Garcia-Rodriguez JF, Corominas M, Fernandez-Viladrich P, Monfort JL, Dicenta M. Rhinosinusitis and atopy in patients infected with HIV. The Laryngoscope. 1999 Jun;109(6):939-44.

12. Sabini P, Josephson GD, Reisacher WR,Pincus R. The role of endoscopic sinus surgery in patients with acquired immune deficiency syndrome. Am J Otolaryngol.1998 Nov-Dec;19(6):351-6.

13. Sun Y, Zhou B, Wang C, Huang Qian, Zhang Qi, Han Ye-hua et al. Clinical and histopathologic features of Biofilm associated chronic rhinosinusitis with nasal polyps in Chinese patients. Chinese Medical Journal 2012;125, 6:1104-1109.

14. Bachert C, Zhang N, Holtappels G, De Lobel L, van Cauwenberge P, Liu S, et al. Presence of IL-

5 protein and IgE antibodies to staphylococcal enterotoxins in nasal polyps is associated with comorbid asthma. The Journal of allergy and clinical immunology. 2010 Nov;126(5):962-8, 8 e1-6.
15. Tomassen P, Newson RB, Hoffmans R, Lotvall J, Cardell LO, Gunnbjornsdottir M, et al. Reliability of EP3OS symptom criteria and nasal endoscopy in the assessment of chronic rhinosinusitis--a GA(2) LEN study. Allergy. 2011 Apr;66(4):556-61.
16. 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.
17. Rugina M, Serrano E, Klossek JM, Crampette L, Stoll D, Bebear JP, et al. Epidemiological and clinical aspects of nasal polyposis in France; the ORLI group experience. Rhinology. 2002 Jun;40(2):75-9.
18. 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.
19. Kim J, Hanley JA. The role of woodstoves in the etiology of nasal polyposis. Archives of otolaryngology—head & neck surgery. 2002 Jun;128(6):682-6.
20. Ponik au 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.
21. Braun H, Buzina W, Freudenschuss K, Beham A, Stammberger H. 'Eosinophilic fungal rhinosinusitis': a common disorder in Europe? The Laryngoscope. 2003 Feb;113(2):264-9
22. Ebbens FA, Scadding GK, Badia L, Hellings PW, Jorissen M, Mullol J, et al. Amphotericin B nasal lavages: not a solution for patients with chronic rhinosinusitis. The Journal of allergy a n d c l i n i c a l i m m u n o l o g y. 2 0 0 6 Nov;118(5):1149-56.
23. Ebbens FA, Georgalas C, Luiten S, van Drunen CM, Badia L, Scadding GK, et al. The effect of topical amphotericin B on inflammatory markers in patients with chronic rhinosinusitis: a multicenter randomized controlled study. The Laryngoscope. 2009 Feb;119(2):401-8.
24. 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.
25. Okano M, Fujikura T, Haruna T, Kariya S, Makihara S, Higaki T, et al. Prostaglandin E2 suppresses staphylococcal enterotoxininduced eosinophilia-associated cellular responses dominantly through an E-prostanoid 2-mediated pathway in nasal polyps. The Journal of allergy and clinical immunology. 2009;123(4):868-71.
26. 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.
27. Peters AT, Kato A, Zhang N, Conley DB, Suh L, Tancowny B, et al. Evidence for altered activity of the IL-6 pathway in chronic rhinosinusitis with nasal polyps. The Journal of allergy and clinical immunology. 2010 Feb;125(2):397-403 e10.

28. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, et al. STAT3 mutations in the hyper-IgE syndrome. The New England journal of medicine. 2007 Oct 18;357(16):1608-19.
29. Mullol J, Lopez E, Roca-Ferrer J, Xaubet A, Pujols L, Fernandez-Morata JC, et al. Effects of topical anti- inflammatory drugs on eosinophil survival primed by epithelial cells. Additive effect of glucocorticoids and nedocromil sodium. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 1997 Dec;27(12):1432-41.
30. Pujols L, Mullol J, Roca-Ferrer J, Torrego A, Xaubet A, Cidlowski JA, et al. Expression of glucocorticoid receptor alpha- and betaisoforms in human cells and tissues. Am J Physiol Cell Physiol. [Research Support, Non-U.S.Gov't]. 2002 Oct;283(4):C1324-31.
31. Harvey RJ, Goddard JC, Wise SK, Schlosser RJ. Effects of endoscopic sinus surgery and delivery device on cadaver sinus irrigation. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2008 Jul;139(1):137-42.
32. Badia L, Lund V. Topical corticosteroids in nasal polyposis. Drugs 2001;61:573–578.
33. 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.
34. Gillespie MB, Osguthorpe JD. Pharmacologic management of chronic rhinosinusitis, alone or with nasal polyposis. Curr Allergy Asthma Rep 2004;4:478–485
35. 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.
36. Van Camp C, Clement PA. Results of oral steroid treatment in nasal polyposis. Rhinology 1994;32:5–9. 38
37. Gillespie MB, Osguthorpe JD. Pharmacologic management of chronic rhinosinusitis, alone or with nasal polyposis. Curr Allergy Asthma Rep 2004;4:478–485.
38. Kudoh S, Kimura H, Uetake T, et al. Clinical effect of low-dose, long-term macrolide antibiotic chemotherapy on diffuse panbronchiolitis. Jpn J Thorac Dis. 1984;22:254-54.
39. Nishi K, Mizuguchi M, Tachibana H, Ooka T, Amemiya T, Myou S, et al. [Effect of clarithromycin on symptoms and mucociliary transport in patients with sino-bronchial syndrome]. Nippon Kyobu Shikkan Gakkai Zasshi. 1995;33(12):1392- 400.
40. Scadding GK, Lund VJ, Darby YC. The effect of long-term antibiotic therapy upon ciliary beat frequency in chronic rhinosinusitis. J Laryngol Otol. 1995 Jan;109(1):24-6.
41. Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomised, controlled tr ial. The Laryngoscope. 2004;114(5):923-30.
42. 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.
43. Wynn R, Har-El G. Recurrence rates after endoscopic sinus surgery for massive sinus polyposis. The Laryngoscope. 2004 May;114(5):811-3.

44. 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.
45. 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
46. Navarro, João Adolfo Caldas, João de Lima Navarro, and Paulo de Lima Navarro. *The nasal cavity and paranasal sinuses: surgical anatomy*. Springer Science & Business Media, 2001.
47. Šubarić M, Mladina R. Nasal septum deformities in children and adolescents: A cross sectional study of children from Zagreb, Croatia. Int J Ped Otorhinolaryngol. 2002;63:41–8.
48. Mladina, R., Skitarelić, N., Poje, G., & Šubarić, M. (2015). Clinical implications of nasal septal deformities. *Balkan medical journal*, *32*(2), 137.
49. Orlandi RR, A systematic analysis of septal deviation associated with rhinosinusitis. Laryngoscope. 2010 Aug;120(8):1687-95.
50. Sumit Prasad, Saurabh Varshney,corresponding author S. S. Bist, Sarita Mishra, and Namita Kabdwal, Correlation Study Between Nasal Septal Deviation and Rhinosinusitis, Indian J Otolaryngol Head Neck Surg. 2013 Dec; 65(4): 363–366.
51. Poje G, Zinreich JS, Skitarelić N, Đuríc Vuković K, Passàli GC, Passàli D, et al. Nasal septal deformities in chronic rhinosinusitis patients: clinical and radiological aspects. Acta Otorhinolaryngol Ital. 2014;34:117–22.
52. Hamilos DL. Chronic rhinosinusitis: Epidemiology and medical management. J Allergy Clin Immunol. 2011;128(4):693–707. doi: 10.1016/j.jaci.2011
53. Agthoven v. Cost analysis of regular and filgrastim treatment in patients with refractory chronic rhinosinusitis. Rhinology. 2002;40(2):69-74.
54. Bhattacharyya N. Incremental health care utilization and expenditures for chronic rhinosinusitis in the United States. The Annals of otology, rhinology, and laryngology. 2011 Jul;120(7):423-7
55. Bhattacharyya N, Orlandi RR, Grebner J, Martinson M. Cost burden of chronic rhinosinusitis: a claims-based study. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011 Mar;144(3):440-5.
56. Bugten V, Nordgård S, Romundstad P, Steinsvåg S. Chronic rhinosinusitis and nasal polyposis; indicia of heterogeneity. Rhinology. 2008;46(1):40-44.
57. 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.
58. 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.
59. Jones, N. S. "CT of the paranasal sinuses: a review of the correlation with clinical, surgical and histopathological findings." *Clinical Otolaryngology & Allied Sciences* 27.1 (2002): 11-17.
60. Wojas, O., et al. "Nasal Septum Deviation by Age and Sex in a Study Population of Poles." *Journal of Rhinolaryngo-Otologies* 7 (2019): 1-6.
61. Yasan, Hasan, et al. "What is the relationship between chronic sinus disease and isolated nasal

septal deviation?." *Otolaryngology—Head and Neck Surgery* 133.2 (2005): 190-193.
62. Gregurić T, Baudoin T, Tomljenović D, Grgić M, Štefanović M, Kalogjera L. Relationship between nasal septal deformity, symptoms and disease severity in chronic rhinosinusitis. *Eur Arch Otorhinolaryngol*. 2016;273(3):671-677. doi:10.1007/s00405-015-3615-8
63. Min YG, Jung HW, Kim HS, Park SK, Yoo KY. Prevalence and risk factors of chronic sinusitis in Korea: results of a nationwide survey. European archives of oto-rhino-laryngology : official journal of the European Federation of OtoRhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 1996;253(7):435-9
64. Kayalioglu, Gulgun, Orhan Oyar, and Figen Govsa. "Nasal cavity and paranasal sinus bony variations: a computed tomographic study." *Rhinology* 38.3 (2000): 108-113.

16. Biography

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