

# Anti-Inflammatory and Anti-Allergy Drugs in Rhinosinusitis

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**Abstract:** Rhinosinusitis constitutes one of the most common respiratory tract diseases affecting up to 15% of the adult population in the Western world.

Sinusitis is almost always accompanied by inflammation of the contiguous nasal mucosa, thus the correct terminology is now rhinosinusitis. It can be classified into acute and chronic form by duration, or into acute bacterial rhinosinusitis or viral rhinosinusitis, by symptoms.

This paper describes some aspects about epidemiology, pathophysiology, and predisposing factors in rhinosinusitis and nasal polyps, offering evidence based recommendations on diagnosis and first line and second line treatment.

The medical management of rhinosinusitis is related to the duration and severity of symptoms and a variety of general and topical pharmacologic interventions are available, for eliminating causative factors and controlling the inflammatory and infectious components. The Authors make a review of the literature to describe the most useful anti-allergy and anti-inflammatory drugs in the management of rhinosinusitis.

**Keywords:** Rhinosinusitis, nasal polyposis, medical management.

## INTRODUCTION

Sinusitis is symptomatic inflammation of the paranasal sinuses, which is almost always accompanied by inflammation of the contiguous nasal mucosa [1] so it is better to use the term rhinosinusitis, as recommended in both the European Academy of Allergology and Clinical Immunology position paper on rhinosinusitis and nasal polyps and the latest American rhinosinusitis classification [2,3].

Rhinosinusitis constitutes one of the most common respiratory tract diseases affecting up to 15% of the adult population in the Western world [4] and may present to a wide range of clinicians from primary care to accident and emergency, pulmonologists, allergists, otorhinolaryngologists and even intensivists and neurosurgeons when severe complications occur, such as meningitis, brain abscess, orbital cellulitis, orbital abscess.

The incidence of acute viral rhinosinusitis (common cold) is very high. It has been estimated that adults suffer 2 to 5 colds per year, and school children may suffer 7 to 10 colds per year but the exact incidence is difficult to measure because most patients with common cold do not consult a doctor. The annual incidence of rhinosinusitis in the European country is about 4 million people in Spain, 5 million people in Italy, 7 million individuals in France, 8 million in the United Kingdom, 12 million in Germany [3].

Also in the United States sinusitis is one of the most common health care problems, and it is increasing in prevalence and incidence [5]. Estimates suggest that sinusitis is more widespread than arthritis or hypertension and affects

approximately 31 million Americans annually [6] causing significant physical symptoms and negatively affecting quality of life.

## CLASSIFICATION

Rhinosinusitis (including nasal polyps) is defined as inflammation of the nose and the paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip),  $\pm$  facial pain/pressure,  $\pm$  reduction or loss of smell; and either endoscopic signs of polyps and/or mucopurulent discharge primarily from middle meatus and/or; oedema/mucosal obstruction primarily in middle meatus, and/or CT changes showing mucosal changes within the ostiomeatal complex and/or sinuses [3].

Rhinosinusitis can be divided into acute and chronic form, the first is a condition in which inflammation and infection of the nasal and sinus mucosa last less than 4 weeks. Although these infections can recur, the mucosa does recover between episodes with complete resolution of symptoms.

In the immunocompetent person living in the general community, acute rhinosinusitis is typically believed to be induced by viruses and does not require antibiotics for the first 10 to 14 days unless complicating features are present, at which point bacteria are presumed to be involved and antibiotics are often employed. These complicating features include severe headache or facial pain, high fever, and impending or actual complications to the eye, lung, or brain. Without any complicating feature present, after 10 to 14 days of symptoms consistent with rhinosinusitis and objective findings, bacteria are presumed to predominate, and the patient might benefit from initiating appropriate antibiotic therapy. Patients with acute rhinosinusitis typically present with varying degrees of the following symptoms: anterior puru-

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lent drainage, posterior purulent drainage, or both plus nasal obstruction, facial pain-pressure-fullness, or both. Relative to nasal inflammation, hyposmia can be present. Purulence arising from the sinonasal passages must be present to ensure this diagnosis. The nature of predominating organisms (viruses, bacteria, or fungi) in the immunocompromised host and intensive care unit patient are considered to be more variable, and these patients are not the target population of these definitions and clinical trial recommendations [2].

The definition of chronic sinusitis is more nebulous and continues to evolve: it lasts longer than 12 weeks and often causes residual damage to the sinus mucosa, which can lead to long-term symptoms.

Chronic rhinosinusitis (CRS) is divided into two subclasses: CRS without nasal polyposis (Chronic Rhinosinusitis sine Nasal Polyposis, CRSsNP) and CRS with nasal polyposis (CRSwNP). This subclassification is supported by the fact that CRSsNP differs from the polypoid form in histologic factors, inflammatory profiles and clinical outcome, indicating possible different pathogenic processes involved in these subclasses [7].

In the European position paper CRS is considered as a major finding and nasal polyposis represents a subgroup of this entity [8]. From this definition it follows that nasal polyposis does not exist without concurrent chronic inflammation in the paranasal sinuses. The American consensus conference on rhinosinusitis differs from the European version also in CRS classification. They suggested a classification scheme for CRS based on the presence or absence of three distinguishing features: 1) nasal polyps; 2) eosinophilic or other inflammatory features; and 3) fungal hyphae in sinus mucus [2].

Chronic rhinosinusitis with or without nasal polyps is often taken together as one disease entity, because it seems impossible to clearly differentiate both entities [9-12]. The question remains as to why "ballooning" of mucosa develops in polyposis patients and not in all rhinosinusitis patients.

Nasal polyps have a strong tendency to recur after surgery even when aeration is improved [13]. This may reflect a distinct property of the mucosa of polyp patients which has yet to be identified. Some studies have tried to divide chronic rhinosinusitis and nasal polyps based on inflammatory markers [13-18].

Although these studies point to a more pronounced eosinophilia and IL-5 expression in nasal polyps than that found in patients with chronic rhinosinusitis, these studies also point to a continuum in which differences might be found at the ends of the spectrum but at the moment no clear cut division can be made.

Nasal polyps appear as grape-like structures in the upper nasal cavity, originating from within the ostiomeatal complex. They consist of loose connective tissue, oedema, inflammatory cells and some glands and capillaries, and are covered with varying types of epithelium, mostly respiratory pseudostratified epithelium with ciliated cells and goblet cells. Eosinophils are the most common inflammatory cells in nasal polyps, but neutrophils, mast cells, plasma cells, lymphocytes and monocytes are also present, as well as fibroblasts. IL-5 is the predominant cytokine in nasal poly-

posis, reflecting activation and prolonged survival of eosinophils [19].

The reason why polyps develop in some patients and not in others remains unknown. There is a definite relationship in patients with "Samter triad": asthma, NSAID sensitivity and nasal polyps. However, not all patients with NSAID sensitivity have nasal polyps, and vice-versa. In the general population, the prevalence of nasal polyps is 4% [20]. In patients with asthma, a prevalence of 7 to 15% has been noted whereas, in NSAID sensitivity, nasal polyps are found in 36 to 60% of patients [21,22].

It had long been assumed that allergy predisposed to nasal polyps because it may alter the normal physiology of the paranasal sinuses by obstructing the sinus ostia facilitating the development of acute bacterial rhinosinusitis [6,23]. However, epidemiological data provide no evidence for this relationship: polyps are found in 0.5 to 1.5% of patients with positive skin prick tests for common allergens [21,24].

Although its contribution in CRS is controversial, there is evidence that allergic rhinitis might be IgE-mediated rhinitis patients have been demonstrated to have more severe sinus changes in CT scans during a common cold than non-allergic subjects, indicating perhaps a greater risk for development of acute bacterial rhinosinusitis [6].

From a symptomatic point of view, we can define acute rhinosinusitis as an inflammation of the nose and the sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/ congestion or nasal discharge (anterior/posterior nasal drip) associated or not with facial pain/pressure or with reduction or loss of smell. Generally endoscopic signs are mucopurulent discharge primarily from middle meatus and/or edema/mucosal obstruction primarily in middle meatus. CT scan shows the mucosal changes within the ostiomeatal complex and/or sinuses.

## CAUSATIVE FACTORS IN RHINOSINUSITIS

Chronic rhinosinusitis is a multifactorial disease [25]. Factors contributing can be mucociliary impairment [26,27], (bacterial) infection [28], allergy [29], swelling of the mucosa for another reason, or rarely physical obstructions caused by morphological/anatomical variations in the nasal cavity or paranasal sinuses [30,31] such as deformities of the uncinate process, pneumatization or paradoxical curvature of the middle turbinate, bulla ethmoidalis, Haller's cells and agger nasi cells [32]. A role in the pathogenesis of rhinosinusitis is certainly played by the ostiomeatal complex, a functional unit that comprises maxillary sinus ostia, anterior ethmoid cells and their ostia, ethmoid infundibulum, hiatus semilunaris and middle meatus. The gradual obstruction due to increased tissue formation in the ostiomeatal complex, leading to impaired sinus ventilation and drainage [33]. As a consequence the oxygen levels inside the sinus decrease, resulting in impaired phagocytosis by decreased opsonization of bacteria, which in turn leads to increased virulence of micro-organisms [34]. Hypoxia can also enhance the production of proteolytic enzymes, which in turn decrease the mucociliary. Thus the key element is the maintenance of the ostial patency.

Viral infection has been detected in over 80% of patients with common cold and radiological abnormalities in the paranasal sinuses [35].

The role of viral and bacterial infections in the pathogenesis of rhinosinusitis is not completely clarified and the microorganisms of CRS are different from those in acute rhinosinusitis.

In immunocompetent patients with the common cold rhinovirus has been the major causative viral agent found in maxillary sinus aspirates, sinus brushing samples or mucosal biopsies in over 50% of patients [36-39]. Other viruses detected from maxillary sinuses include coronavirus, influenza virus A and B, parainfluenza virus and adenovirus and in children also respiratory syncytial virus (RSV) [39-41].

Criteria to define a case of viral rhinosinusitis are lacking. However, attention has been given to trying to define situations in which viral agents are not the sole cause; that is, the 0.5% to 2% of cases of viral rhinosinusitis that are estimated to be complicated by secondary bacterial infections [42,43]. However, it should be recognized that no studies have ever been conducted in which the sensitivity and specificity of various clinical findings have been evaluated and the comparison standard is a positive viral or bacterial sinus aspirate culture [43]. The current clinical diagnostic criteria for a large proportion of the cases of acute community-acquired bacterial rhinosinusitis and for the use of antimicrobial treatment that is the most widely accepted today include a cold that is no better or worse after 10 to 14 days. Conversely, the current clinical diagnostic criteria for viral rhinosinusitis include a cold that is beginning to resolve after a few days and is better by a week to 10 days after onset. For purposes of research, the criteria standards for diagnosis of viral rhinosinusitis are a positive virus culture or detection of viral nucleic acid in cells of the sinus epithelium, indicating active viral replication [44].

Further, RSV infection significantly enhances non-typeable *Haemophilus influenzae* attachment to respiratory epithelial cells, thus providing an example of mechanisms other than ostial obstruction by mucosal swelling by which viral infection results in secondary bacterial infection in acute rhinosinusitis [45]. However, it is estimated that only 0.5-2% of acute viral rhinosinusitis develops into acute bacterial infection [46].

Although the paranasal sinuses are believed to be sterile under normal circumstances, the upper respiratory tract, specifically the nose and nasopharynx, are heavily colonized with normal flora [42]. Normal nasal flora in adults and children include coagulase-negative staphylococci (CNS), *Corynebacterium* species, and *S. aureus*. In children the organisms frequently cultured from the nasal cavity include *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae*. Normal nasal-sinus flora in patients with CRS and the role of bacterial pathogens in CRS are poorly defined. In CRS the mucosal response to bacterial colonization or bacterial infection in an otherwise normal host is likely to be different than that in acute rhinosinusitis. Given this possibility, different criteria to define colonization and infection are probably needed but have not been established [2].

Recent studies suggest that some bacteria might play an important role in the onset of rhinosinusitis through the production of exotoxins that are able to activate T lymphocytes by cross-linking the MHC (Major Histocompatibility Complex) II molecule on antigen-presenting cells with the variable beta (V<sub>b</sub>) region of the T-cell receptor. These exotoxins are termed superantigens because they activate subpopulations representing up to 30% of T lymphocytes in contrast to classical antigens, which activate less than 0.01% of T lymphocytes.

In addition, superantigens can also act as classical antigens, leading to concomitant generation of anti-superantigen antibodies. These include antibodies of the IgE isotypes [48,49].

Common microbial superantigens include *Staphylococcus aureus* enterotoxin and some fungi, such as *Alternaria* and *Aspergillus*, may have superantigen activity [49-51]. It is hypothesized that CRS patients, especially those with nasal polyposis, could have microbial superantigen production inside the paranasal sinuses with subsequent sinus mucosal immune activation leading to eosinophilic inflammation in genetically susceptible hosts [51]. In fact, Bachert and colleagues demonstrated specific immunoglobulin Ig E to *Staphylococcus aureus* enterotoxins A and B in 50% of altogether 20 patients with eosinophilic nasal polyposis [52]. Moreover, the presence of *Staphylococcus aureus* enterotoxin specific IgE was associated with higher levels of total serum IgE, more severe local disease and increased incidence of systemic manifestations such as asthma, suggesting a possible role of superantigens as disease modifiers.

It is important to consider that the majority of bacteria live in a biofilm, which is a communicating organization of microbes surrounded by glycocalyx that frequently forms on an artificial or damaged biologic surface. Organisms living in a biofilm are relatively impervious to host defenses and antimicrobial agents. Bacterial biofilms have been demonstrated in a rabbit model of otitis media and cholesteatoma. The possibility that a bacterial biofilm could be contributing to CRS has not been formally studied. This possibility is theoretically attractive and might help to explain the clinical situation in which patients frequently have negative cultures, improve symptomatically while receiving antibiotics, and relapse when antibiotics are withdrawn. In a biofilm, planktonic bacteria leave the biofilm, cause symptoms, and are susceptible to host defenses and antibiotics. However, the biofilm itself is relatively impervious to antimicrobial agents and is never eradicated. Mechanical debridement appears to be the only mechanism resolving biofilm, which may explain the improvement of symptoms with surgery and irrigation in some refractory patients.

Some investigators have argued that bone turnover in CRS patients is similar to that in osteomyelitis and trauma. Although bacterial organisms have not been identified in the bone in either human subjects or animal models of CRS, areas of increased bone density and bony thickening are frequently seen on CT scans in areas of chronic inflammation and might be a marker of the chronic inflammatory process [2].

Whether bacteria induce bony remodelling because of associated inflammation or whether they truly infect bone is unknown [53], but it is found that CRS patients have a greater bone remodelling activity. In rabbit studies of experimentally induced *Pseudomonas maxillary sinusitis*, Perloff *et al.* [54] demonstrated that not only does the bone become involved adjacent to the involved maxillary sinus but also that the inflammation typically spreads through the Haversian canals and might result in bone changes consistent with some degree of chronic osteomyelitis at a distance from the primary infection. A study by Khalid *et al.* [53] using both *Pseudomonas* species and *S aureus* in a rabbit study demonstrated similar results. Bone involvement was noted in 92% of the animals on the ipsilateral side to the infection, and in some specimens clear osteonecrosis was identified. Inflammatory bone changes were also noted on the contralateral side in 52% of the animals. The inflammation caused well-defined changes in the bone in rabbits, both adjacent to the infection and at a distance from the primary site of inflammation, which were compatible with a histologic diagnosis of chronic osteomyelitis. The inflammatory spread within the bone appears to occur as a result of well-defined changes in the Haversian canals, leading first to widening of the canals and increased vascularity, then to an inflammatory cellular collection within the canals, and later to fibrosis in the involved area. It is certainly possible that these changes, if further confirmed in patients, might, at least in part, explain why CRS is relatively resistant to medical therapy [2].

Recently a great interest was given to the role that fungi may play in the development and perpetuation of the inflammation in rhinosinusitis: it is known that fungi are capable of invading the paranasal sinuses in both normal and diseased states because of the ubiquitous nature of these organisms. In some circumstances this leads to macroscopic fungal proliferation named fungus balls (formerly referred to as mycetomas) or saprophytic growth of fungus. In these cases, fungal mycelia accumulate and occupy available spaces within the nose and paranasal sinuses in the absence of significant mucosal inflammation. Treatment is simply directed to extirpation of the offending fungal growth. In other forms, however, it is the inflammatory response to the fungus, rather than the mere presence of the fungus, that is the primary manifestation of disease. In these forms, small amounts of fungi result in clinically significant disease, demonstrating the ability of fungal exposure to initiate a cascade of inflammatory events [2, 55].

Fungal rhinosinusitis presents in five distinct clinicopathological forms [56-58]. The invasive forms are acute fulminant, chronic, and granulomatous (also called primary paranasal *Aspergillus* granuloma) invasive fungal rhinosinusitis. The non-invasive variants of fungal infection are sinus mycetoma (fungus ball) and allergic fungal rhinosinusitis (AFRS), in which fungi are found within the sinus cavity without penetration of the mucosal barrier. The exact diagnosis of fungal rhinosinusitis is difficult to establish because they have many common signs and symptoms and only tissue examination, often with specific fungal stains, provides accurate diagnosis and classification [59,60]. The role of fungal culture in the diagnosis of fungal rhinosinusitis is not determined. Culture is insensitive, as only 20-40% of

fungal infections are estimated to be culture positive, but it is often needed for fungal specification [60]. Accurate classification of fungal rhinosinusitis is important, since the treatment and prognosis vary between the disease categories.

Classification of invasive fungal rhinosinusitis into three subcategories is based on the type and intensity of the infection estimated by clinical and histopathologic findings [57]. Acute fulminant invasive fungal rhinosinusitis is characterized by rapid spread of the fungus into the adjacent tissues and intracranially often leading to death. Patients are usually immunocompromised having malignant disease, other cause of neutropenia, diabetes, or taking immunosuppressive drugs [61]. They become acutely ill with fever, sinonasal infection, pale and ischemic mucosa, and headache/facial pain, which is in disproportion to physical findings. Anaesthesia of the nasal mucosa and/or facial skin is suggestive of an invasive process and does not occur in bacterial infections. Necrotic septal ulcers (eschars) are traditionally described as a hallmark of invasive fungal rhinosinusitis but they are a late finding. Affected tissues are necrotic, and histopathology shows fungal invasion to mucosa and blood vessels, haemorrhage, vasculitis with thrombosis and extensive tissue necrosis with neutrophilic inflammation [57]. The vascular fungal invasion is suggested to be responsible for the fulminant course. The saprophytic fungi of order Mucorales, such as *Rhizopus*, *Mucor*, *Rhizomucor* and *Absidia*, and *Aspergillus* species are the most common fungi involved in acute fulminant form [57]. The treatment includes wide surgical debridement, intravenous anti-fungal drugs and correction of the underlying condition. The prognosis depends upon early diagnosis and treatment, and it tends to be poor. The two other subgroups of invasive fungal rhinosinusitis have more chronic course of the disease, but they as well lead to death if left untreated [56,57]. The chronic invasive fungal rhinosinusitis is clinically less aggressive than the acute fulminant form. It may present as proptosis or orbital apex syndrome, otherwise the clinical features are rather similar to the acute fulminant invasive fungal rhinosinusitis. The histopathologic studies show penetrating fungal hyphae, tissue necrosis with low-grade inflammation. *Aspergillus fumigatus* is the most common offending organism [57]. As in the acute fulminant form, patients are usually immunocompromised. The most common underlying condition is diabetes. Treatment is the same as in acute fulminant fungal rhinosinusitis. However, the infection often recurs and the prognosis is poor. Granulomatous invasive fungal rhinosinusitis has mostly been reported in Sudan, but also in Pakistan, India and few sporadic cases in the United States [57,62,63]. It is caused by *Aspergillus flavus* in immunocompetent patients. The clinical result is chronic polypoid rhinosinusitis associated often with proptosis. Typically only one sinus is affected. Histopathology shows profuse fungal growth with regional, superficial micro-invasion of fungal hyphae and noncaseating granuloma with giant cells. Eosinophilic inflammation, necrosis and vasculitis are sometimes noted [64]. A concomitant negative mycobacterial stain must be present [57]. Surgical resection followed by oral antimycotic drugs for months is needed [65]. Relapse rate as high as 80% and mortality is reported in patients treated by surgery alone.

The non-invasive forms of fungal rhinosinusitis are more common accounting for over 90% of cases [60]. In sinus

mycetoma (fungus ball) there is mucopurulent material within the sinus and histological examination reveals a dense conglomeration of fungal hyphae with a chronic inflammatory response in the adjacent mucosa without tissue necrosis or granulomas and no evidence of fungal invasion using special fungal stains [58]. Usually only one sinus is affected. Patients present clinically with polypotic chronic rhinosinusitis. Patients are usually immunocompetent, but may have additional underlying risk factors including previous sinus surgery and trauma [61]. The treatment of choice is surgery with the removal of all fungal material and also obstructing hypertrophic sinus mucosa. The prognosis is excellent and usually only one operation is needed. AFRS is the most controversial form of fungal rhinosinusitis. It was first described in 1983 and termed allergic *Aspergillus* sinusitis because of its histopathologic resemblance to allergic bronchopulmonary aspergillosis [66]. Moreover, it was considered to be caused by a type I immediate hypersensitivity reaction to colonizing fungi leading to allergic inflammation of the sinus mucosa. Since then many other fungal species than *Aspergillus*, mostly dematiaceous fungi such as *Bipolaris*, *Curvularia*, *Alternaria* and *Exserohilum*, have been reported in association with allergic *Aspergillus* sinusitis like conditions and name was changed to AFRS [67]. As also the IgE-mediated mechanism in its pathophysiology is in dispute, the term eosinophilic fungal rhinosinusitis is recommended by some investigators [68]. In AFRS the characteristic feature is allergic mucin, which is a greyish-green material with the consistency of peanut butter containing eosinophils, Charcot-Leyden crystals and sparse non-invasive fungal hyphae. The consensus view of the criteria are lacking, but the latest American rhinosinusitis classification proposed following research criteria: CRS; oedema in the middle meatus or ethmoid area, or nasal polyposis; allergic mucin containing fungal hyphae and no histologic evidence of fungal invasion; CT findings of sinus mucosal disease; and evidence of fungal-specific IgE by means of skin testing or blood testing [2]. The last criterion was excluded from the earlier classification by de Shazo and Swain [69]. The treatment of AFRS is also a matter of controversy. Most reports are from the United States and no international consensus exists. Surgical resection of all mucin and polyps is required [61]. Oral corticosteroids, most commonly prednisone following the modified allergic bronchopulmonary aspergillosis protocol postoperatively for up to one year, has been reported to provide clinical improvement and prolong time to subsequent sinus surgery without significant side effects [67,70]. This is often followed by topical steroids [70]. The role and efficacy of systemic antifungal drugs or antifungal irrigations is also unclear [7,70]. An aggressive allergy management is recommended involving nasal steroid sprays, antihistamines and immunotherapy. In a retrospective analysis of 60 AFRS patients 11.1% of patients receiving immunotherapy were reoperated compared to 33% of patients not receiving immunotherapy, suggesting the potential benefit of immunotherapy in preventing recurrence of AFRS [31]. However, immunotherapy can worsen patients' symptoms if therapy is started before surgery [71]. Recurrence is common and close follow-up for years is recommended [70].

Perennial allergic rhinitis appears to be a predisposing factor for acute bacterial rhinosinusitis as it may alter the

normal physiology of the paranasal sinuses by obstructing the sinus ostia. Although its contribution in CRS is controversial, there is evidence that allergic rhinitis might facilitate development of acute bacterial rhinosinusitis [6,23].

IgE-mediated rhinitis patients have been demonstrated to have more severe paranasal sinus changes in CT scans during a common cold than non-allergic subjects, indicating perhaps a greater risk for development of acute bacterial rhinosinusitis [6].

Several studies have reported an increase in the prevalence of atopic markers and allergy in CRS patients [72-74]. Approximately half of the CRS patients have associated allergies, and the prevalence of positive skin prick tests in patients undergoing sinus surgery has been over 80% in some studies [74,75]. Controversially, the prevalence of CRSwNP was only 0.5% in atopic subjects compared to 4.5% prevalence in non-atopic patients [76,77]. Moreover, nasal polyps are statistically more common in nonallergic asthma than in allergic asthma (13% vs. 5%) [77].

Furthermore, the total IgE levels and concentration of eosinophilic cationic protein (ECP) and interleukin (IL-5) in CRSwNS do not differ between atopic and nonatopic subjects, indicating that the systemic allergic phenotype does not correlate with local inflammatory mechanisms leading to eosinophilic inflammation in the sinus mucosa [33,78-80]. In CRSsNP the allergic patients have a full T helper cell(Th) type 2 cytokine profile compared to mixed Th1/Th2 cytokine pattern seen in non-allergic patients [72]. Also the degree of eosinophilic infiltration is not markedly different between allergic and non-allergic subjects. Thus it seems that local immunological responses are more important in the development of inflammation in CRS than atopic status.

In conclusion, although an attractive hypothesis, we can repeat the statement made a decade ago that there are no published prospective reports on the incidence of infective rhinosinusitis in populations with and without clearly defined allergic rhinosinusitis [81].

CRS is strongly associated with asthma: there is a strong interactions between upper and lower respiratory tract. The nasal airways, the sinus cavities, and lower airways form a continuous structure lined with ciliated columnar epithelium and share a common embryologic origin. There are also several clinical observations supporting this so called integrated airway syndrome model, which has a wide spectrum of severity varying from rhinitis to asthma and possibly rhinosinusitis [82,83]. Both allergic and non-allergic rhinitis are risk factors for asthma and also for acute exacerbations of asthma [84-86]. Epidemiological studies indicate that rhinitis coexists with asthma in 85% to 94% of patients, compared to approximately 20% in general population [83,87]. Moreover, rhinitis in asthmatic patients is often more severe than in non-asthmatic patients. Several studies have demonstrated that the severity of asthma correlates with the severity of rhinitis, and treatment of allergic rhinitis with topical corticosteroids or second generation antihistamines has beneficial effects on the outcome of asthma [86,88-90].

Furthermore, the lack of symptoms in the lower airways in rhinitis patients or the nasal cavity in asthmatic patients does not mean a lack of involvement. Allergic rhinitis pa-

tients with no history of lower airway symptoms have been found to have hyperresponsiveness, inflammation and even tissue remodelling in the lower airways [91,92]. And vice versa, the nasal mucosa of the asthmatic patients shows signs of inflammation even in the absence of nasal symptoms [93].

Approximately 80% of asthmatic patients have allergic rhinitis and 60% have rhinosinusitis [94]. Conversely, up to over 50% of CRSwNP patients have asthma, of whom 30-40% have also ASA intolerance [73,77].

The incidence of rhinosinusitis as identified by radiography in ASA intolerant asthmatics may be over 95% and the frequency of nasal polyps may be as high as 70% [95]. The aspirin-exacerbated respiratory disease is a clinical syndrome defined as a triad of asthma, nasal polyposis and intolerance to ASA and most of the nonsteroidal anti-inflammatory drugs [96]. The onset of the disease occurs typically in the early adulthood [96]. The mechanism activating the underlying respiratory disease is unknown, but the pathogenesis of the respiratory reactions in this disease is in part due to altered arachidonate metabolism [97] thus whether the patients ingests cyclooxygenase 1 inhibitors (aspirin or nonsteroidal anti-inflammatory drugs) it triggers a severe upper and lower respiratory tract reaction.

Other important factors which are involved in the development of rhinosinusitis are humoral immune deficiency (congenital or acquired hypogammaglobulinemia) or congenital defects in mucociliary clearance (primary ciliary dyskinesia or cystic fibrosis) resulting in recurrent or chronic respiratory tract infections with mucus retention leading to rhinosinusitis, serous otitis media, rhinitis, and bronchitis [98].

## DIAGNOSIS

The evaluation of rhinosinusitis is based on history and physical exam. The signs and symptoms predicting of rhinosinusitis were described above (mucopurulent drainage, anterior posterior or both; nasal obstruction; facial pain-pressure-fullness; decreased sense of smell).

Among the physical examinations, the anterior rhinoscopy is the first step to determining the existence of pathology of paranasal sinuses. It is best to evaluate the patient after decongestion with topical decongestants. However, even with this method, examination of the nasal passages beyond the anterior portion can be limited, so it is needed a more accurate assessment: nasal endoscopy helps identify erythema, edema, polyps or polypoid swelling, crusting, eosinophilic mucin, and mucopus or frank pus deep in the nasal cavity. It is most useful in the evaluation and treatment of patients with refractory or chronic symptoms and in patients who have impending or existing complications of rhinosinusitis.

To avoid an improper diagnosis, together with the nasal endoscopy, sinus imaging with CT scan represents a leading method of objective assessment necessary to accurately determine the presence or absence of rhinosinusitis. Infact endoscopy alone cannot be used to determine normalcy because rhinosinusitis can occur in sinus areas that endoscopy cannot detect. Similarly, abnormalities seen in imaging can be present without associated symptoms.

Therefore both subjective and objective assessments have value.

CT has two major roles in rhinosinusitis: to define the anatomy of the sinuses before surgery and to help in the diagnosis and management of recurrent rhinosinusitis or CSR. Although MRI does not display the bony anatomy as does CT, it does provide an excellent display of the mucosa, and it is superior in distinguishing between bacterial-viral inflammatory disease and fungal concretions [47].

## THERAPY

A number of general and topical treatment measures are disposable in the management of rhinosinusitis for eliminating causative factors and controlling the inflammatory and infectious components.

As said above, acute rhinosinusitis (ARS) is characterized by 4 weeks of purulent nasal drainage accompanied by nasal obstruction, facial pain-pressure or both. It is induced by viruses and symptoms resolve within two weeks without antibiotics in 70% of cases. Infact only about 0.5% to 2% of viral rhinosinusitis are complicated by bacterial infections so antibiotics are necessary in those patients with unusually extrasinus manifestations or to prevent them.

Moreover antibiotics have not been shown to decrease the risk of complications or progression to chronic rhinosinusitis and their use implies many risks including possible allergic reaction, potential side effects, and promotion of bacterial resistance. However an empiric treatment of ARS may include as first line antibiotics amoxicillin, amoxicillin-clavulanate, azithromycin, cefpodoxime proxetil, cefprozil, cefuroxime axetil, clarithromycin and trimethoprim/sulfamethoxazole [98]. They are superior to placebo and as effective as other agents that are more expensive, have greater risk of side effects, and/or should be reserved for more serious infections. It should be used first-line alternatives (e.g., doxycycline, azithromycin) only for patients allergic to both first line drugs. The duration of therapy should be between 10 and 14 days. An exception is azithromycin (500 mg daily), which should be prescribed for 3 days. If there is a partial but incomplete resolution after an initial course of antibiotics, the duration of therapy could be extended by an additional 7 to 10 days for a total of 3 weeks of antibiotics. For minimal or no improvement with initial treatment, it might be consider changing to an antibiotic with broader coverage, including resistant strains such as amoxicillin at high dose or amoxicillin/clavulanate [99].

The treatment of ARS is primarily symptomatic, with an analgesic or antipyretic to resolve pain or fever and to allow patients to achieve comfort and rest. Nonsteroidal anti-inflammatory drugs given alone or in combination with an opioid, are the principal analgesic used to fight mild-moderate pain thanks to their convenience, ease of use and cost [100].

Adjunctive treatments for rhinosinusitis that may give a symptomatic relief include decongestants (alpha adrenergic), corticosteroids, saline irrigation and mucolytics.

Nasal congestion is one of the principle symptoms of rhinosinusitis; it is related with an increased blood flow

through the nasal mucosa, which causes an increase in the filling pressure to the venous sinuses and their swelling. Nasal decongestants are applied in the treatment of ARS in order to decrease nasal swelling and obstruction and to improve sinus ventilation and drainage.

Systemic and topical decongestants act through stimulation of  $\alpha$ -adrenergic receptors in the mucosa of the upper airways. Stimulation of these receptors results in vasoconstriction of the mucosal capillaries with decreasing of swollen or edematous mucosa [101].

Topical decongestants, particularly oxymetazoline hydrochloride, generally provide rapid and significant relief of nasal obstruction with minimal systemic effects. Whether the reduction in nasal swelling has a positive effect on rhinosinusitis is debatable. Based on experiments in a rabbit model, Bende *et al.* [102] recently suggested that topical decongestants may actually have a negative effect. In this study histologic sections of rabbit sinuses obtained after the induction of sinusitis and treatment with nasal oxymetazoline were actually found to have a significantly greater degree of inflammation than sections from untreated sinuses on the opposite side. The authors postulated that decongestant nasal sprays may interfere with the normal defense mechanisms during bacterial-induced sinusitis, possibly by decreasing mucosal blood flow. Moreover the use of decongestants for adult CRS has not been evaluated in a randomized controlled trial. Decongestants and sinus drainage did not prove to be superior to saline in chronic paediatric maxillary sinusitis in terms of subjective or x-ray scores [103].

CT studies before and after decongestant application in patients with or without nasal polyposis did not show any densitometric changes in the sinuses or polyps, but only decongestion of the inferior turbinates [104]. A randomized double blind placebo controlled trial did not show any difference between placebo, epinephrine and naphazoline on polyp size at endoscopy and lateral imaging [105].

Despite these observations, topical decongestants will usually reduce symptoms and speed recovery in patients with rhinosinusitis. The rationale for the use of topical decongestants for only short period is that prolonged use can cause nasal irritation and the development of rhinitis medicamentosa with rebound nasal congestion, thus these agents are likely to be most effective in patients with acute rhinosinusitis, acute exacerbation of chronic rhinosinusitis, or recurrent acute rhinosinusitis.

Systemic decongestants are also used to treat many patients with rhinosinusitis. Because rhinosinusitis involves inflammation of the nose and the sinuses, nasal obstruction and drainage are common symptoms. Systemic decongestants help to alleviate these bothersome symptoms. Furthermore, unlike many antihistamines, systemic decongestants have minimal drying side effects and thus are less likely to impede mucus transport. Oral decongestants should be used with caution in patients with medical conditions such as hypertension, ischemic heart disease, hyperthyroidism, and diabetes mellitus and in patients who are taking monoamine oxidase inhibitors. Whether oral decongestants speed the resolution of rhinosinusitis is debatable. Nonetheless, given the low risk, controllable side

effects, relatively low cost, and benefits in symptom reduction, the use of decongestants seems to be warranted in some, if not many, patients with rhinosinusitis [99].

Antihistamines have been used for many years to manage CRS in patients with coexisting allergy [106-109]. However, no studies clearly show a positive effect for antihistamines in this situation [110].

A multicentre randomized double-blind, placebo controlled trial evaluated the beneficial effect of loratadine in terms of symptom reduction for the treatment of ARS in patients with allergic rhinitis. Patients receiving loratadine together with antibiotic treatment had a reduction of sneezing and obstruction on daily VAS scores, and overall improvement was confirmed by their physicians. [111].

Although numerous clinical trials have supported the efficacy of antihistamines in reducing the sneezing and rhinorrhea associated with allergic rhinitis, the mechanism by which these agents act is still not completely understood. It is known that histamine H1-receptor antagonist are highly selective for H1 receptors on nerve endings, smooth muscle cells, and glandular cells and have a little effects at H2 or H3 receptors. In addition, all first generation antihistamines have been shown an anticholinergic (antimuscarinic) action by activating muscarinic and cholinergic receptors with a competitive antagonism. Some also have sedative, local anesthetic, and antiserotonin effects.

In administering antihistamines to patients with sinusitis it is important to consider whether the anticholinergic effects of these drugs, might result in the excessive drying of nasal and sinuses secretions, leading to crust formation and stagnation within the sinuses. Because the newer second-generation antihistamines (desloratadine, levocetirizine, fexofenadine) typically are free of undesirable anticholinergic effects, these agents can be used to relieve symptoms in patients with both allergy and rhinosinusitis [112].

The most commonly reported events during treatment with second generation antihistamines were upper respiratory tract infections, wheezing, vulvitis, cough, headache, migraine, drowsiness, sedation and injury, most of them reported in 1 to 5% of the treated population, however, not necessarily related to medication [3].

Specific studies have been demonstrated that antiallergy and antiinflammatory effects are produced by various antihistamines, these drugs may not be simply antiallergy medications. More studies are required to determine whether these effects are relevant in the treatment of chronic sinusitis. In particular, antihistamines appear to be useful for preventing or treating acute allergic flares in patients with both allergy and chronic rhinosinusitis. Because the allergic reaction results in hypersecretion and local edema, which may lead to stasis within the sinuses, prevention of this situation may avoid the development of a secondary sinuses infection [113].

Many studies make in evidence the importance of using a steroid therapy in management of rhinosinusitis. The introduction of topical nasal steroid revolutionized the treatment of allergic, nonallergic rhinitis and chronic rhinosinusitis: with the same efficacy of oral steroid but

without the adverse systemic effects, intranasal corticosteroid (INCS) by decreasing the inflammatory response, reduce the mucosal swelling, promote drainage and increase aeration of the sinuses.

The clinical efficacy of both topical and systemic glucocorticoids depends on their ability to reduce airway eosinophil infiltration by directly blocking their influx and activation [114-117] or indirectly reducing the secretion of chemotactic cytokines by nasal mucosa and polyp epithelial cells. In fact it seems that an important part of the clinical effects of these drugs is due to a down regulation of T-cell function, that with their humoral products, cytokines, play important roles in the inflammatory reaction [118-121].

It is not known whether INCS penetrate the nasal mucosa or act on target cells. However, their low systemic activity supports the concept of local action on nasal mucosa. This local effect can influence a variety of inflammatory cells and their mediators such as epithelial cells, lymphocytes, basophiles, mast cells and Langerhans cells. Corticosteroid-induced inhibition of the immunoglobulin E dependent release of histamine is a possible but unproved mode of action [122]. The potency of these effects is lower in nasal polyps than in nasal mucosa suggesting an induced inflammatory resistance to steroid treatment in chronic rhinosinusitis/nasal polyposis [117,118]. The biological action of glucocorticoids is mediated through activation of intracellular glucocorticoid receptors (GR) [123], expressed in many tissues and cells [124]. Two human isoforms of GR have been identified, GR $\alpha$  and GR $\beta$ , which originate from the same gene [125]. Upon hormone binding, GR $\alpha$  enhances anti-inflammatory or represses proinflammatory gene transcription, and exerts most of the anti-inflammatory effects of glucocorticoids through protein-protein interactions between GR and transcription factors, such as AP-1 and NF- $\kappa$ B. The GR $\beta$  isoform does not bind steroids but may interfere with the GR function. There may be several mechanisms accounting for the resistance to the anti-inflammatory effects of glucocorticoids, including an over expression of GR $\beta$  or a down expression of GR $\alpha$ . Increased expression of GR $\beta$  has been reported in patients with nasal polyps [126,127] while down regulation of GR levels after treatment with glucocorticoids [128,129] has also been postulated to be one of the possible explanations for the secondary glucocorticoid resistance. The anti-inflammatory effect of corticosteroids could, theoretically, be expected as well in non-allergic (i.e. infectious) as in allergic rhinosinusitis. Tissue eosinophilia is thus also seen in CRS [130].

A variety of investigations suggests the efficacy of INCS used as an additional treatment to antibiotics [131-134]. Only the Meltzer [135] study compares topical corticosteroid as monotherapy to antibiotic: this study demonstrates mometasone furoate nasal spray (MFNS) 200 mg twice daily monotherapy was well tolerated and induced significantly relief of most acute rhinosinusitis symptoms compared with amoxicillin and placebo given alone. Furthermore, there was no evidence suggestive of rhinosinusitis recurrence or predisposition to bacterial infections after MFNS therapy cessation, supporting a recommendation to reduce prescribing of antibiotics for patients presenting with these clinical findings. These data indicate MFNS monotherapy is an effective

treatment option for relieving the symptoms faced by patients of acute, uncomplicated rhinosinusitis in general practice. In EP3OS [3] study it is argued that in Meltzer article objective references of bacterial infection were lacking (sinus aspirates for culture) as well as CT or x-ray. There might be a high number of viral infections but the results are in favour of a more restricted attitude to antibiotics in ARS.

The efficacy of INCS for CRS is evaluated by some investigations and no side effects were seen, including no increased signs of infection, but there are no data showing efficacy of oral corticosteroids in chronic rhinosinusitis without nasal polyps (NP). On the contrary, studies on systemic steroids in chronic rhinosinusitis with nasal polyps have been demonstrated that they are effective after two weeks use in doses acceptable for a majority of patients, giving symptom relief, and MRI changes, reducing polyp size [3].

Topical corticosteroids sprays have a documented effect on bilateral NP and also on symptoms associated with NP such as nasal blockage, secretion and sneezing but the effect on the sense of smell is not high. Intranasal administration of corticosteroids is associated with minor nose bleeding. This effect has been attributed to the vasoconstrictor activity of the corticosteroid molecules, and may lead to the rare occurrence of nasal septal perforation [136]. Thanks to their systemic bioavailability and their systemic safety, INCS eliminate many potential adverse effects on growth, eyes, on bone, and on the hypothalamic- pituitary-adrenal axis [137]; thus there are not contraindications, which are typical of a systemic corticosteroid therapy, to local steroid treatment such as glaucoma, herpes keratitis, diabetes mellitus, advanced osteoporosis, severe hypertension, tuberculosis or other chronic infections. A small effect on growth has been reported in one study in children receiving a standard dosage over 1 year. However, this has not been found in prospective studies with the intranasal corticosteroids that have low systemic bioavailability [138]. In summary, intranasal corticosteroids are very effective, but they are not completely devoid of systemic effects. Thus especially in children, who need long-term treatments, these drug must be prescribed with care.

Systemic steroids may be an additive to a basic treatment with INCS, in same severe cases. The anti-inflammatory effects of corticosteroids cannot be separated from their metabolic effects because all cells use the same glucocorticoid receptor, therefore when corticosteroids are prescribed measures should be taken to reduce their side effects. Obviously, a possible side effect increases with the dose and duration of treatment and so the minimum dose necessary to control the disease should be given. Many other types of preparations have been investigated, but the data demonstrating evidence for their efficacy are poor. These medications include antral washings, isotonic/hypertonic saline, antimycotics, mucolytic agents/phytomedical preparations, immunomodulators/immunostimulants and bacterial lysate preparations.

Saline solution nasal spray have been shown to reduce the symptoms of both allergic and nonallergic rhinitis so they are useful also in rhinosinusitis to decrease dryness and/or the viscosity of mucus and to clear nasal crust after surgery [99].

Immunotherapy (IT) seems to be important in controlling allergies and to prevent recurrence of CRS after surgery. It can be specific (ITS) or not; ITS may be indicated in those patients who do not get advantages by drugs or in whom drugs induced problematic side effects. The usual route of administration of SIT is subcutaneous, which is the most effective in relieving allergy symptoms, but there are also a nasal, an oral and a sublingual way of administration.

What is important to stress is that only high allergen doses should be given in those form of immunotherapy. The mechanisms by which immunotherapy gives its effects is not completely known and remains a matter of study. It produces an allergen-specific immunoglobulin G-blocking antibodies, with an initial increase and then a drop in allergen specific immunoglobulin E antibodies; a decrease in the release of basophil histamine in response to an allergen challenge, an increase in allergen-specific suppressor T cells, and a decrease in the lymphocyte-cytokine response to an allergen challenge [139]. Whether immunotherapy has any direct effect on sinus mucosa has not been studied.

Although no studies support the use of immunotherapy in the treatment of allergy coexisting with chronic sinus disease, however the clinical practise suggests the utility of immunotherapy in improving allergic symptoms [99].

Probably an altered immune response is expected to be responsible for frequent recurrence in some patients difficult to treat or unresponsive in the long-term to medical and surgical treatment. In these cases non-specific immunotherapy could be useful: the most common form of medications used are bacterial lysates. Efficacy of bacterial lysate preparations (*Enterococcus faecalis* autolysate [140], ribosomal fractions of *Klebsiella pneumoniae* (Kp), *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae* and the membrane fraction of Kp [141], and mixed bacterial lysate) [142], have been tested in the treatment of both acute recurrent rhinosinusitis and CRS in terms of the period between the relapses and need for antibiotic treatment; the outcomes measured were the reduced rate of acute episodes and antibiotic treatment in ARS and the reduction in symptoms including cough and expectoration during the treatment period [142] in CRS.

Mucolytics were used together with antibiotic treatment and decongestant treatment in ARS in order to reduce the viscosity of sinus secretion. The benefit of such treatment has not been evaluated in many trials, while a cohort study in a mixed group of 45 ARS and CRS patients suggested beneficial effect of adding mucolytic to standard rhinosinusitis treatment in terms of reducing treatment duration [143]. No clinical trials have tested the effects of mucolytics in nasal polyp treatment [3].

Antimycotics are used as topical and systemic treatment, as an adjunct to sinus surgery, in allergic fungal, and invasive fungal rhinosinusitis, especially in immunocompromized patients [144]. The Surgery is considered the first line treatment for allergic fungal [145] and invasive fungal rhinosinusitis [146]. No studies support the benefits of using these drugs in ARS and/or CRS, but in a cohort of 139 patients with AFS high dose postoperative itraconazole,

combined with oral and topical steroids reduced the need for revision surgery rate to 20.5% [147].

Recent investigations [148,149], suggest the idea of treating CRS patients with and without NPs, with a topical antimycotic, based on the premise of an altered local immune (non-allergic) response to fungal presence in nasal/sinus secretions resulting in the generation of chronic eosinophilic rhinosinusitis and nasal polyposis. Although the presence of fungus in sinus secretions was detected in a high proportion (< 90%) of patients with CRS, as well as in a control disease-free population in a few study centres [148], it cannot be taken as proof of aetiology. Ponikau *et al.*, [150] conducted a study in a group of 51 patients with CRS, including polyposis patients, treated with topical amphotericin B as nasal/sinus washing, without placebo or other control treatment. The treatment resulted in 75% subjective improvement and 74% endoscopic improvement [150]. As the authors concluded, antifungal treatment should be evaluated in a controlled trial to be justified. Possible side effects of a long-term oral antimycotic treatment are nausea, headache, skin rash, vomiting, abdominal pain and diarrhoea. Major adverse events, like serious liver disfunction is rare, and mostly seen in patients at risk and due to drug interactions. Adverse events during 3 to 6 months topical amphotericin B treatment in 3 randomized placebo controlled trials was similar in the active and placebo groups. However, major adverse events were more common in the active treatment group (9% in active vs. 0% in placebo group respectively) although only 1 was judged to be drug-related (asthma attack) [3].

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