
1. INTRODUCTION

Rhinosinusitis (RS) is characterized by inflammation of nasal and paranasal sinuses mucosa, which is one of the most prevalent upper airways affections, leading to high social cost. Owing to its high prevalence, RS is recognized and treated by many medical professionals in addition to otorhinolaryngologists, from general practitioners who work with primary health care to pediatricians, pneumologists and allergologists.

After the publication of I Brazilian Consensus on rhinosinusitis in 1999, the term RS was preferred over sinusitis, which was more commonly used. This choice followed the global trend because there is almost no case of paranasal sinuses inflammation without affection to nasal mucosa.

RS is a consequence of infectious, viral, bacterial or fungal processes and may be associated with allergy, nasosinusal polyposis and mucosa vasomotor dysfunction. However, when we use the isolated term RS, we are normally referring to bacterial infectious cases. The remaining types are followed by the main term, reason why it is preferred to use viral RS, fungal RS or allergic RS.

Viral RS is the most prevalent form. It is estimated that adults have on average 2 to 5 episodes of cold per year and children have 6 to 10. However, it is difficult to precisely define this prevalence because most patients who have flu or cold do not go to the doctor. Out of viral episodes, about 0.5% to 10% progress to bacterial infections, which explains the high prevalence of this affection in the general population. As to chronic rhinosinusitis (CRS), it is estimated that 14% of the population in the United States have the disease. In Canada, the prevalence is 3.4% in men and 5.7% in women, whereas a Korean study showed prevalence of 1.01%. These differences are due to different methods used by epidemiological studies. The North-American study was carried out with interviews using standardized questionnaires, the Canadian study included subjects with confirmed diagnosis of CRS, and the Korean one included patients submitted to nasoendoscopy and had mucopurulent secretion in middle meatus. Brazil does not have statistics on prevalence and incidence of RS. There is still controversy on the topic, especially concerning chronic presentations. Acute rhinosinusitis (ARS) is infectious by nature, whereas CRS is considered multifactorial. There is increasing evidence that CRS is an immune and inflammatory response from the host in addition to the initial infection. Obstruction of drainage ostia of paranasal sinuses seems to be less important for the pathophysiology than in the acute cases.

Another major question that remains concerns CRS pathogenesis associated with nasal polyposis (NP). Why

do some patients with RS develop polyps whereas others do not? Are they different diseases? Is CRS to be managed clinically or surgically? Considering its multifactorial nature, is RS a disease or a syndrome?

These and other issues are discussed by the present publication, which will also try to define practical guidelines to managing RS by all medical professionals who see these patients.

2. DEFINITION

RS is defined as mucosal inflammatory process of nose and paranasal sinuses characterized by:

- two or more of the following symptoms: nasal obstruction, anterior or posterior rhinorrhea, facial pain or pressure, reduction or loss of olfaction;
- one or more of the following endoscopic findings: polyps, mucopurulent secretion from middle meatus, mucosa obstructive edema of middle meatus;
- and/or mucosa affection of ostiomeatal complex (OMC) or paranasal sinuses visualized by computed tomography scan (CT).

3. CLASSIFICATION

The most common classification of RS is based on duration of symptoms and frequency of onset.

- acute rhinosinusitis (ARS): symptoms last for up to 4 weeks;
- subacute rhinosinusitis (SRS): symptoms last for over 4 weeks and less than 12 weeks;
- chronic rhinosinusitis (CRS): symptoms last for more than 12 weeks;
- recurrent rhinosinusitis (RRS): four or more episodes of ARS within one year, with complete resolution of symptoms between them;
- chronic rhinosinusitis with periods of agudization (CRSA): lasts longer than 12 weeks with mild symptoms and periods of intensification.

Some issues should be discussed about this classification. Is there pathophysiological basis to support this merely temporal criterion? From a histopathological standpoint, ARS is characterized by exudative process associated with necrosis, hemorrhage and/or ulceration, with predominance of neutrophils. CRS is a proliferative process associated with fibrosis of lamina propria, in which lymphocytes, plasmocytes and eosinophils are the most prevalence cells. SRS does not have histopathological definition. Similarly, from a practical standpoint, it is very difficult to differentiate RRS from CRSA.

Another practical method to assess severity of disease is to use visual analog scale (VAS).



There is still controversy on the classification of RRS with and without polyposis in the same group. Is RRS with polyposis a continuum of RRS without polyposis or are they different diseases? Histologically, NP causes frequent epithelial damage, thickened basal membrane, edematous or fibrotic stroma, with reduced number of vessels and glands. There is inflammatory infiltrate with predominance of eosinophils. RRS with polyposis is characterized by thickened basal membrane, edematous and sometimes fibrotic stroma, with reduced number of vessels and glands. There is inflammatory infiltrate with predominance of eosinophils. RRS without polyposis is characterized by thickened basal membrane, globous cell hyperplasia, subepithelial edema, fibrosis and mononuclear infiltrate. Another difference between the diseases is at molecular level. Without polyposis, there is polarization of T-helper 1 lymphocytes (Th1), with high levels of interferon (INF) and beta transforming growth factor (TGF- β). Nasal polyps have Th2 polarization, with high concentrations of interleukin 5 (IL-5) and immunoglobulin E (IgE).

Based on such discussion, the proposed classification (Chart 1) is similar to that developed by the work group on Allergic Rhinitis and its Impact on Asthma (ARIA).

Chart 1 - Classification of rhinosinusitis

<ul style="list-style-type: none"> • Acute/ intermittent Rhinosinusitis 	Symptoms for up to 12 weeks
<ul style="list-style-type: none"> • Symptoms for up to 12 weeks - CRS without NP - CRS with NP 	Symptoms for more than 12 weeks
<ul style="list-style-type: none"> • Recurrent acute Rhinosinusitis 	4 or more annual episodes of ARS
<ul style="list-style-type: none"> • Mild Rhinosinusitis 	VAS scores 0 to 4
<ul style="list-style-type: none"> • Rinossinusite moderada/acentuada 	VAS scores 5 to 10

4. PREDISPOSING AND ASSOCIATED FACTORS

Etiopathogenesis and pathophysiology of RS are associated with multiple factors that may be either local or systemic. Awareness of such factors is essential for appropriately managing and controlling the disease. Any factor that obstructs sinus ostia (causing difficulty to drain and to oxygenate them), mucociliary transport (MCT) dysfunction and patient immune deficit, resulting in pathogen growth, may predispose the patient to RS.

4.1. ACUTE RHINOSINUSITIS

Viral upper airways infections (UAI)

Many studies have shown that UAI - cold, flu - lead to inflammatory impairment of paranasal sinuses. Bacterial or purulent ARS develop as complications in 0.5% to 10% of UAI. The main mechanisms through which viral infection predisposes to bacterial infection are: nasal epithelial damage (high virulence pathogens such as influenza and adenovirus), increase in adherence of potential pathogenic bacteria to rhinopharynx, increase in production of histamine, bradykinin and many cytokines, and suppressant effect of virus to the functions of neutrophils, macrophages and leukocytes.

Allergic Rhinitis

Coexistence of allergic rhinitis and RS, both in adults and children, have been documented by many studies. High prevalence of allergic rhinitis in patients with ARS has also been demonstrated. Allergic rhinitis is shown as a predisposing factor to RS because it causes nasal mucosa edema, especially around drainage ostia, which lead to sinus hypoventilation and retention of secretion, favoring colonization of nasosinus mucosa by virus and bacteria. Other implied mechanisms are release of mediators by mast cells and exposure of ligation sites of *Streptococcus pneumoniae* by inflammatory mediators secreted by eosinophils. The higher frequency of allergic rhinitis in patients with acute maxillary RS is a given, but the number of previous episodes of RS among allergic and non-allergic subjects does not show significant differences. Thus, despite the suspicion that allergic rhinitis has a key role in the genesis of RS, the literature is still controversial and lacks sufficient evidence (prospective studies) to confirm its real role as predisposing factor of RS.

Smoking

A Canadian study has demonstrated increase in incidence of RS in smoking patients, but another one from Korea did not confirm these results. The topic is still controversial.

Structural affections

Anatomical anomalies to nasal septum (septal deviation) and/or middle meatus structures (middle bullous concha, uncinata process and ethmoidal bulla hypertrophy, paradoxical middle concha and presence of Haller cells) are referred as causes of narrowing of sinus drainage paths, characterized as RS predisposing factors. However, there are few studies that show the prevalence of these diseases among healthy people and patients with ARS or CRS. Evidence does not lead to the conclusion that anatomical affections play a role in the origin and progression of infectious RS.

Foreign body

Presence of foreign bodies in the nasal cavity may provide accumulation of secretion and consequent bacterial superinfection. Despite being more common in children, it may also occur in adults, including after nasal or dental surgical procedures. Suspicion should be investigated in presence of RS with unilateral fetid secretion in patients with compatible clinical history.

Barotrauma

In cases of sinusal barotrauma (plane, diving) there is accumulation of blood in the sinuses in addition to inflammatory process resulting from mucosa lesion. These combined factors may lead to subsequent bacterial RS.

4.2. CHRONIC RHINOSINUSITIS

4.2.1 Factors associated with chronic rhinosinusitis without polyposis

Mucociliary transport (MCT) affection

Ciliary function has an important role in paranasal sinuses clearance, preventing chronic inflammation. Secondary ciliary dyskinesias are observed in patients with CRS, but they are probably reversible. Primary ciliary dyskinesias, such as in Kartagener's syndrome or cystic fibrosis (CF) patients, who have increased mucus viscosity, leads to chronic RS presentations.

Allergy

Despite the association observed by some authors between CRS and allergy, the role of allergy in CRS pathophysiology is uncertain. Karlsson et al. did not observe increase in incidence of RS in pollen seasons and Hinriksdottir et al. did not identify differences in prevalence of CRS in patients with and without allergic rhinitis. Nasosinusal radiological affections observed in allergic patients should be carefully interpreted given that 24.7% to 49.2% of CT scans performed in subjects without symptomatology may be abnormal.

Asthma

Rhinosinusitis and asthma are frequently coexistent, but their interrelation is not very well understood. It is known that clinical and/or surgical treatment of CRS reduces the need to take asthma medication.

Gastroesophageal reflux disease (GERD)

There are few studies about the influence of acid reflux on pathogenesis of bacterial RS, but owing to the potential impact on ciliary activity, reflux should be considered as a potential predisposing factor until new studies are completed.

Immune status

The presence of congenital or acquired immunodeficiency may favor the onset of CRS. There are studies indicating high rate of immunodeficient patients who have difficult to treat CRS. Common variable immunodeficiency may be diagnosed in 10% of these patients, whereas selective immunoglobulin A (IgA) deficit may be detected in 6%. Some authors have observed that RS may be considered among the most prevalent diseases in subjects with acquired immunodeficiency syndrome (AIDS). Therefore, immune tests should be part of diagnostic investigation in patients with CRS.

Genetic factors

Genetic affections have not been associated with CRS to present.

Pregnancy

The incidence of RS among pregnant women is approximately 1.5%. During pregnancy, women may have nasal congestion. However, the correlation between gestational rhinitis and development of RS is not clear.

Local factors

Despite the fact that many studies have shown anatomical variations in patients with CRS, none has correlated CT scan as predisposing factor to RS. In addition, other studies have shown the presence of similar anatomical affections in CT studies of subjects with RS and in controls.

Microorganisms

Bacteria: Some authors think that CRS results from ARS, which is a hypothesis that has never been confirmed. The role of bacteria in CRS is not clear, and despite the presence of some pathogens described in the middle meatus and in paranasal sinuses of some patients, their pathogenicity has never been confirmed.

Environmental factors

Some studies have shown that smoke from cigarettes and low income may be associated with CRS. However, there are no convincing studies that associate pollutants and toxins such as ozone to CRS.

Iatrogenic factors

Iatrogenia that may occur during nasosinusal endoscopic surgeries may predispose to CRS episodes, such as the accidental perforation of a new ostium in an attempt to access the natural ostium of maxillary sinus, promoting the phenomenon of recirculation or, in cases of mucoceles.

4.2.2 Factors associated with chronic rhinosinusi- tis with nasal polyposis

Allergy

It is known that 0.5-4.5% of patients with allergic rhinitis have NP, and approximately 25% of the patients with NP are allergic. Recently, it has been concluded that there is increase in eosinophil and total IgE in nasal polyps, associated with negative skin allergic tests. Thus, allergy may be associated and exacerbate symptoms of CRS with NP, but it is not the cause of polyposis.

Asthma

It is known that asthma is reported in 26% of patients with NP, whereas 7% of patients with asthma have NP. Late asthma development is associated with nasal polyps in 10-15% of the patients. In approximately 69% of the patients with NP and asthma, asthma preceded the presentation, whereas polyps appeared 9 to 13 years later. However, not all patients with NP have lower airway affections.

Aspirin sensitivity

It is known that among all patients with aspirin (AAS) intolerance, 36-96% have NP. Normally, these patients do not have atopy and prevalence increases after the age of 40 years.

Genetic factors

Some studies have suggested the existence of associated hereditary factor to NP. This is explained by the fact that patients who have RRS with NP have increase incidence of NP in the family. Rugina et al. observed that more than half of 224 patients with NP had positive family history. Some studies have shown the association between HLA-A74, HLA-DR7-DQA1*0201, HLA-DR7-DRB1*0202 and HLA-DRB1*03 and *04.

Environmental factors

The role of environmental factors in pathophysiology of CRS has not been established yet.

5. INFLAMMATORY MECHANISMS IN RHINOSINUSITIS

The term CRS comprises a heterogeneous and broad group of diseases that affect the nose and paranasal sinuses involving cells and chemical mediators that lead to formation of chronic inflammatory process. It is still not clear whether CRS results from RRS, which lead to formation of nasal polyps, or whether they have different physiopathogenesis and develop independently.

NP and CRS are frequently classified as one single disease owing to the fact that it is very difficult to differentiate them. Currently, NP is considered as a subgroup of CRS. As not all subjects with CRS develop nasal polyps, it is suggested that there are different physiopathogenic mechanisms and properties in the mucosa of NP and CRS subjects.

5.1. INFLAMMATORY MECHANISMS IN ACUTE RHI- NOSINUSITIS

Sinusal mucosa of patients with ARS is seldom submitted to histopathological analysis unless in cases of complications that result in emergency surgeries. As a consequence, there are relatively few studies with cytokines and inflammatory mediators in ARS. They show inconsistent results, especially in studies made in animal models or with cadavers, when compared to CRS, in which there is increase in IL-5 mediator.

Inflammatory mediators

In one of the first studies performed with 10 patients operated on due to complications, samples of maxillary sinus mucosa showed significant increase in protein concentration of IL-8 compared to 7 controls. Similar results (not significant) were obtained from IL-1 β and IL-6, whereas other cytokines such as GM-CSF, IL-5 and IL-4 were not increased. A recent study has shown that IL-8 and TNF-alpha and total proteins increased in nasal lavage with patients with ARS, compared to controls and patients with allergic rhinitis.

Proinflammatory cytokines such as IL-1 β , IL-6 and TNF have a prominent role in the progression of inflammatory reaction because they activate endothelial cells, lymphocytes T and others, inducing the expression of cell adhesion molecules and release of other cytokines such as IL-8. IL-8 belongs to the group of CXC-cytokines and it is a potent chemotactic protein of neutrophils,

constantly synthesized at the nasal mucosa. The cytokine pattern found in ARS reminds us of the viral rhinitis naturally acquired.

Inflammatory process triggering factors

Environmental factors such as allergens, virus or air pollutants stimulate mucous epithelium inducing local inflammation of sinus mucosa. In narrow channels, the inflammation causes approximation of mucosa surfaces, inducing ostial obstruction and accumulation of sinus secretion that drain at the site. Bacteria find the conditions to proliferate within the paranasal sinuses. There is metaplasia, with reduction of quantity and quality of cilia responsible for movement of secretion and particles of fragmented material to the outer part of paranasal sinuses, creating additional inflammation.

Local factors that reduce MCT of paranasal sinuses may contribute to the development of ARS. During acute viral rhinitis, about 80% of the patients have reduction of permeability of maxillary sinus ostium. Therefore, ostia are considered key to inflammatory response of paranasal sinuses. Sinus MCT acts as a mechanical cleaning system and removes secretion and its contents from the sinuses and nose towards the rhinopharynx. MCT in many sinuses is directed to the ostium, and it is not modified with the surgical creation of an accessory opening within the sinus. When there is obstruction, there is a convenient pathological environment to bacterial growth. Tissue congestion worsens as the immune system responds to infection. pH becomes acid and it favors anaerobiosis.

When mucosa and cilia are damaged, there is the opportunity of transforming the process into chronic. Ostium obliteration induces development of intrasinus negative pressure owing to reabsorption of air into the sinus cavity. Thus, obstruction gives rise to a vicious cycle of ciliary dysfunction, retention of secretions, lymphatic drainage obstruction, edema and mucosa hyperplasia, which generates chronic disease. Regardless of the etiological factor, if the ostium is obliterated, ventilation and transport of secretions become inefficient and promote sinusitis. This theory is supported by the investigation of patients with RRS, which have ostia smaller than normal subjects.

5.2. INFLAMMATORY MECHANISMS OF CHRONIC RHINOSINUSITIS

Inflammatory mechanisms of CRS without formation of polyps are described based on histopathology, inflammatory pattern, cytokine profile, and remodeling process.

Histopathology

Histopathological abnormalities of nasosinus mucosa of CRS are well documented and are characterized by significant affections of ciliary pseudo-stratified columnar epithelium: goblet cell hyperplasia, cilia loss, epithelial metaplasia, subepithelial edema, mononuclear cell infiltrate, basal membrane thickness, submucous gland hyperplasia, and presence of fibrosis.

Goldwyn et al., in a quantitative study of inflammatory cells in CRS, observed increase in number of lymphocytes, neutrophils and eosinophils when compared to control group. Berger et al. found two different groups in a histopathological and immunohistochemical study of subjects with CRS. The first study showed macroscopic edema of sinus mucosa and microscopically it showed polypoid mucosa, massive edema, with many eosinophils infiltrated into the lamina propria. Next to the mucosa, the mucous was filled with inflammatory cells, including eosinophils. In some samples, the epithelium was intact, in others there was complete desquamation or low epithelium comprising one single layer of cells. Basal membrane had considerable thickness and lamina propria showed lymphocytes, plasmocytes, in addition to many eosinophils. In the second group, the mucosa had less edema, and microscopically the submucosa showed marked hyperplasia of serous mucous glands, which formed continuous layers and occupied wide regions of lamina propria, without connective tissue interposition.

Ethmoidal bone assessment in CRS showed histopathological affections, such as bone remodeling. It is suggested that nasosinus mucosa inflammatory process is involved in the stimulation of osteoblastic and osteoclastic activity.

Lee et al. have also observed osteitis and bone remodeling in subjects with CRS and suggested that the bone below nasosinus mucosa is involved in the pathogenesis of persistent inflammation found in CRS.

The comparison of inflammation cells and collagen deposits in nasosinus mucosa of adults and children with CRS showed that the number of T lymphocytes, eosinophils, basophils and subepithelial collagen deposits is increased in both groups when compared to normal mucosa. The number of mast cells is higher in children, whereas the number of eosinophils, neutrophils and collagen deposit in submucous layer is greater in adults.

Sinus mucosa of children with CRS has higher density of lymphocytes in the submucosa, less density of eosinophils, finer and intact epithelium, thinner basal membrane and fewer submucosa glands than sinus mucosa of adults with CRS.

Poelzehl et al. observed more round cells, eosinophils, plasmocytes and greater edema in the stroma,

ethmoidal mucosa of subjects with CRS and NP compared to patients without NP. Basal membrane thickness, goblet cell and submucous gland hyperplasia, number of neutrophils, lymphocytes and mast cells did not show any difference between the groups. The authors assumed that CRS with NP and without NP are different diseases, with different etiologies and discrepant management approaches.

Immunohistochemical studies have demonstrated that the number of eosinophils, activated T lymphocytes and plasmocytes are increased in CRS, but when compared to nasosinusal mucosa of subjects with NP, we can observe greater amount of these inflammatory cells. As to neutrophils and macrophages, there was no statistical difference between CRS with and without NP.

Inflammatory pattern, cytokine profile, remodeling

Interleukin 8 (IL-8) has power activity in chemotaxis and activation of neutrophils and expression of messenger RNA are enhanced in CRS, which is a findings suggesting contribution of neutrophils to CRS pathogenesis.

Upon studying the concentration of IL-3, IL-4, IL-5, IL-8 and GM-CSF, we observed increase in IL-3 in CRS and IL-8 in the mucosa of ARS. IL-3 is responsible for local defense and repair of chronically inflamed mucosa, because it regulates many cell populations and indirectly contributes to fibrosis and mucosa thickness.

Concentration of many cytokines such as IL-1, IL-6, IL-8, TNF-alpha, IL-3, GM-CSF, ICAM-1, neutrophil markers (MPO) and eosinophilic cationic protein (ECP) are increased in CRS. VCAM-1, a molecule involved in selective recruiting of eosinophils and IL-5, key cytokine to survival and activation of eosinophil, is not increased in CRS. Such cytokines and the profile of mediators are similar to that of viral rhinitis and ARS, except for the small amount of ECP.

The study about type of inflammation of nasosinusal mucosa in subjects with NP and CRS without NP showed quantitative and qualitative differences. Authors suggested a subdivision in the classification of CRS into two different diseases. Whereas in NP the predominant type of inflammation is eosinophilic, IL-5 and albumin (inflammatory marker of vascular permeability), in CRS without NP lymphocytes and neutrophils are the predominant cells. In this study, concentration of IL-8 was similar in both groups.

The correlation between clinical parameters and molecular, cellular and histological markers shows that the presence of polyps (clinical parameters) and tissue eosinophilia (histological marker) is correlated with severity of CRS. Concentration of cysteinyl-leukotriene-4 (molecular marker) is increased in all groups, representing a general

marker of inflammation that does not show correlation with disease severity.

In the study by Lee et al. they observed increase in messenger RNA that codified gene MUC8 and marked expression of protein MUC8 in sinusal mucosa of subjects with CRS. It is suggested that MUC8 may be related with the mechanism of overproduction of mucus in CRS.

Overproduction of mucus in CRS is followed by histopathological affections, such as presence of goblet cell and submucosa gland hyperplasia. Kim et al. demonstrated that expression of messenger RNA to codify mucus MUC5AC and MUC5B is increased, respectively, in the cytoplasm of goblet cells and in mucosa cells of submucous glands.

There is high concentration of TGF- β in CRS in comparison to NP. TGF- β in extracellular matrix is related with fibrosis and may differentiate CRS from NP.

Metalloproteinase matrix (MMP) cells are endopeptidases capable of degrading extracellular matrix and are regulated by cell inhibitors (TIMPs). In CRS and NP, there is increase of MMP-9 and TIMP-1, whereas MMP-7 is increased only in NP. CRS and NP have different characteristics of MMP-9, MMP-7 and TIMP-1, suggesting that regulation of enzymes is related with tissue remodeling observed in both diseases.

Bhattacharyya identified aerobic and anaerobic bacteria in affected and non-affected paranasal sinuses of subjects with CRS. This finding questioned the etiological role of bacteria in CRS and suggested that other agents or factors may be involved in the pathogenesis of CRS.

Watelet et al. demonstrated that the concentration of MMP-9 in nasal secretion and in extracellular matrix, after sinusal surgery, is increased. Inflammatory cells represent the major source of MMP-9 increase, which is related with low quality of healing.

The study of biomarkers in nasal secretion of subjects with ARS and CRS with and without NP shows that, regardless of type of RS, all biomarkers are increased in relation to the control group. Nasal IL-5 and IgE are specific markers of CRS with NP.

Analysis of interleukins IL-4, IL-6, IL-8, IL-11 and TGF- β in CRS with and without NP shows that IL-6, IL-8 and IL-11 are non-specific markers of sinusal inflammation and are present in CRS with and without NP. However, in cases of CRS with NP, there is increase in transcription of TGF- β in response to use of IL-4, which suggests the participation of IL-4 in the mechanism of stromal proliferation, in the formation of nasal polyp.

Bacterial biofilm is a three-dimensional structure of aggregated bacteria that has special properties of resistance to antibiotics. In the study by Sanderson et al., bacterial biofilm was present in 14 out of 18 studied

subjects and provided a possible explanation to failure in antimicrobial therapy in CRS.

Eicosanoid receptors (leukotrienes and prostaglandins) are proteins that regulate immunomodulation in respiratory inflammatory diseases. Perez-Novó et al. observed increase in leukotriene receptors in nasal polyps and correlation with eosinophilic inflammation. Receptors of prostaglandins EP1 and EP3 are reduced in NP, whereas prostaglandins EP2 and EP4 are increased, both in NP and in CRS without NP. It is suggested that these receptors are not directly related with the pathogenesis of eosinophilic inflammation and may be related with other inflammatory cells.

It is known that innate immune recognition of pathogens by nasosinusal mucosa epithelial cells plays an important role in the pathogenesis of CRS. The expression of TLR-9 protein (receptor toll-like) is present both in normal epithelial cells and in CRS, but the level of expression is reduced in CRS with NP. This finding suggested that inappropriate immune response to pathogens via TLR9 in epithelial cells of nasosinusal mucosa may represent the critical point in inflammatory mechanism of CRS.

The presence of fungi may also be related with the pathogenesis of CRS with eosinophilic mucus owing to the fact that surfactant proteins (Sp-D) play a key role in immune response to *Aspergillus fumigatus* in the lungs. Ooi et al., upon studying healthy and diseased nasosinusal mucosa, showed for the first time the expression of SP-D. In subjects with CRS, expression of SP-D was increased, which is regulated by fungal allergens.

The profile of cytokines in CRS without NP has abundant expression of INF- γ (cytokine Th1) and TGF- β , whereas in CRS without NP there is predominance of IL-5 (cytokine Th2), ECP and IgE. There are higher concentrations of MPO and IL-8 observed in the nasal polyp of subjects with CF. As a result of these observations, authors have determined the sensitivity and specificity of all cytokines and inflammatory mediators, and revealed that ECP, IgE and IL-5 contribute to differentiate NP from CRS and NP with CF, presenting sensitivity and specificity above 80%. It confirms that eosinophils and their inflammatory products represent a marked characteristic of NP, when compared to CRS without NP and NP associated with CF. Finally, NP with CF may be differentiated from CRS using MPO, IL-8 and ECP, which are increased in NP with CF.

5.3. INFLAMMATORY MECHANISMS OF CHRONIC RHINOSINUSITIS WITH POLYPS AND EOSINOPHILIC INFLAMMATION

Many studies have detected the action of eosinophi-

lic mediators in nasal polyp tissues and have demonstrated the different types of cells produced by these mediators. Initial studies by Denburg et al. showed that the culture of epithelial cells of nasal polyps presented powerful eosinophilic stimulating colony activity, as well as similar activity of interleukin-3. Authors have suggested that accumulation of eosinophils in polyps should be in part due to differentiation of stem cells stimulated by factors that derive from mucosa cell populations. Later, other mechanisms such as enhanced synthesis of GM-CSF by epithelial cells, fibroblasts, monocytes and eosinophils were suggested. According to Hamilos et al. polyps of patients with and without allergy have different cytokine profiles. "Allergic" polyps present higher tissue density of GM-CSF, IL-3, IL-4, and IL-5 than controls, and polyps of non-allergic patients have higher tissue density of GM-CSF, IL-3 and IFN. Other studies of proteins in homogenized tissue did not confirm these results. However, authors have found IL-5 at significantly increased levels in nasal polyps when compared to controls and the increase was independent from the existence of allergy. The highest levels of IL-5 were related to patients with non-allergic asthma and intolerance to AAS. Eosinophils were positively stained for IL-5, suggesting an autocrine mechanism of this cytokine in the activation of eosinophils, and strong correlation between concentration of IL-5 and ECP was later demonstrated. The key role of IL-5 was confirmed by the fact that treatment with monoclonal antibodies anti-IL-5 of polypoid tissue with eosinophilic infiltrate resulted in apoptosis of eosinophils and reduction of tissue eosinophilia. The combination of these studies has suggested that increased production of IL-5 influences predominance and activation of eosinophils in nasal polyps, regardless of atopy. However, many other studies have not found differences in amount of cytokines found in polyps of allergic and non-allergic patients. Wagenmann et al. have demonstrated that Th1 and Th2 cytokines are increased in NP, regardless of the results of skin allergic tests. Recently, some authors have studied the regulation of IL-5 receptor, which is divided into two isoforms: soluble (antagonist effect) and transmembrane (signal transducer). In NP, the former is increased and the later is reduced. However, the first study using anti-IL5 antibodies in patients with NP confirmed the role of IL-5 in this disease, showing that local concentration of IL-5, and not its receptor, could predict clinical response to treatment. The study has confirmed previous descriptive and in vitro studies suggesting that anti-IL5 antibodies represent a new approach in NP management.

Recent studies have shown that nasal polyps express high levels of RANTES and eotaxin, two of the main chemotaxins. Bartels et al. have shown that expression

of mRNA, eotaxin and RANTES was increased in allergic and non-allergic nasal polyps, compared to normal nasal mucosa.

Similarly, Jahnsen et al. found enhanced expression of mRNA to eotaxin, eotaxin-2 and MCP-4. Other studies have indicated that eotaxin and not RANTES, in cooperation with IL-5, play a key role in chemical attraction and activation of eosinophils in nasal polyp tissue. These data are in accordance with findings of a recent study with 950 allergic and non-allergic patients with NP, who have also suggested that attraction and activation of eosinophils are correlated with enhanced expression of eotaxin genes and not with expression of RANTES. Increased production of eotaxin in nasal polyps was recently confirmed by comparing it to controls and patients with CRS.

Studies of cell adhesion molecules are relatively scarce. Initial studies by Symon et al. have demonstrated that ICAM-1, E-selectin and P-selectin are well expressed by nasal polyp endothelium, whereas expression of VCAM-1 is poor or absent. In an elegant study by Jahnsen et al., using three-color immunofluorescence staining, it was demonstrated that the number of eosinophils and proportion of positive vessels to VCAM-1 was significantly higher in nasal polyps than in the turbinate mucosa of the same patients. Moreover, treatment with glucocorticoids had reduced density of eosinophils and expression of VCAM-1 in polyps. Interaction between VLA-4 in eosinophils and VCAM-1 in endothelial cells is essential not only to transendothelial migration of eosinophils, but it may also modify its activation and functions.

Regulation of extracellular matrix

Expression of TGF- β 1 and TGF- β 2, predominantly by eosinophils, and their effects in activities of fibroblasts and pathogenesis of NP were suggested in many different studies. Authors have compared levels of these proteins in homogenized tissue of patients with NP treated or not with oral corticoids and controls. Patients with untreated NP and controls presented significantly higher levels of IL-5, eotaxin, ECP and albumin, and significantly lower levels of TGF- β 1. Conversely, treatment with corticosteroids significantly reduced concentrations of IL-5, ECP and albumin, and increased concentration of TGF- β 1. These observations suggested that IL-5 and TGF- β 1 are cytokines with contrary activities, with low concentrations of TGF- β 1 in IL-5-rich polyps. Moreover, they support the theory that albumin deposits and other plasma proteins take part in the pathogenic mechanism of forming nasal polyps, caused by reduction of TGF- β 1 production. TGF- β 1 is a powerful cytokine that stimulates formation of extracellular matrix, has chemotactic action to fibroblasts, but inhibits synthesis of IL-5 and reduces the effect of

prolongation of eosinophil survival produced by IL-5 and GM-CSF. Edema and formation of pseudocysts with only some areas of fibrosis characterizes NP. Imbalance between metalloproteinases and increase in MMP-7 and MMP-9 in NP has recently been demonstrated, which may contribute to the formation of edema and accumulation of albumin.

Role of enterotoxins in Staphylococcus aureus (SAEs)

Initial studies have shown that tissue concentration of IgE and number of positive cells for IgE may be increased in NP, suggesting the possibility of local production of IgE. The local production is a characteristic of NP, and the number of IgE producing plasma cells may be 10 times greater than in controls. The analysis of IgE specific revealed a multiclonal response to nasal polyp tissue, and anti-SAE IgE antibodies in approximately 30% to 50% of the patients and 60% to 80% of those with NP associated with asthma. A recent prospective study confirmed that colonization of middle meatus by Staphylococcus aureus is more frequent in NP (63.6%) than in CRS (27.3%), and it is related with prevalence of anti-classical enterotoxin IgE antibodies (27.8%) in NP and in CRS (5.9%). In cases of NP association, intolerance to AAS and asthma, colonization of middle meatus by Staphylococcus aureus reached 87.5%, anti-enterotoxin IgE antibodies were found in 80% of the cases. Classical SAEs, especially TSST-1 and Staphylococcus protein A (SPA), are inducers of synthesis of multiclonal IgE, based on release of IL-4 and expression of CD40 in T cells, and B7.2 in B cells. Moreover, enterotoxins stimulate T cells binding to variable beta chain receptors of these cells, inducing to production of cytokines IL-4 and IL-5, which activates directly the epithelial cells, leading to release of cytokines. SAEs activate antigen presenting cells and enhance their function. Animal models have confirmed the important role of Staphylococcus enterotoxins in upper airways affections, with SAEs inducing eosinophilic inflammatory responses in sensitized mice with their application in upper and lower airways.

Thus, Staphylococcus enterotoxins induce eosinophilic inflammatory reaction in addition to multiclonal IgE synthesis with high tissue concentrations of total IgE suggesting that SAEs are at least modifiers of NP disease. Similar findings were recently reported for asthma, which is known to be associated with NP, in chronic obstructive pulmonary disease (COPD), defining a correlation between upper and lower airways.

Conclusion

Inflammatory mechanisms of CRS without NP cause histopathological, cellular and molecular affections that

differentiate it from CRS with NP. Many factors contribute to activation of these mechanisms: mucociliary system dysfunction, viral infections, bacterial or fungal infection, allergy, mucosa edema, obstruction caused by anatomical variations of nasal cavity or paranasal sinuses, environmental factors and cell receptors of the subject.

Despite the overlapping of affections found in CRS and NP, most studies about histopathological characteristics of CRS describe the main findings as: goblet cell hyperplasia, thickened basal membrane, submucous gland hyperplasia in stroma, chronic inflammatory cell infiltrate, with predominance of lymphocytes and neutrophils.

We have observed some disagreeing issues concerning type of inflammatory cells. Goldwyn et al. e Van Zele et al. have demonstrated increase in lymphocytes, eosinophils, plasmocytes and neutrophils in CRS, whereas Poelzehl et al. have not observed statistical difference in quantity of lymphocytes and neutrophils between the groups.

In general, chronic inflammatory process of CRS without NP shows predominance of lymphoplasmocytic characteristic with increase in secretory cells, but in CRS with NP the main characteristic is in the presence of eosinophil with stromal edema.

The bone tissue that supports the nasosinusal mucosa in CRS also shows abnormalities such as remodeling and neosteogenesis, suggesting the involvement in the pathogenesis of CRS.

Concerning the profile of cytokines and inflammatory mediators, it is observed that in CRS there is a standard type Th1 and increase in inflammatory mediators related with neutrophils, plasmocytes and lymphocytes such as INF-, TGF- β , IL-8, MPO. Conversely, Th2 standard is predominant in NP and key inflammatory mediators are related with presence of eosinophils such as ECP, IL-5, IgE. According to Van Zele et al., to differentiate entities based on such small numbers and concentrations is at least intriguing. Authors have suggested that studies with larger samples of patients may increase the sensitivity and specificity of these markers.

The concept of airway remodeling refers to the anatomical consequence of the chronic inflammatory action on the airways and it is spread to other affections resulting from the inflammatory process itself, such as epithelial hyperplasia, increased deposit of extracellular matrix, degradation and accumulation of plasma proteins, in addition to lack of repair appropriate to chronic lesion. It is believed that the understanding of pathogenic mechanisms involved in remodeling of the airways may support classification and management of CRS.

Inflammatory mechanisms are activated and maintained by a number of factors such as infection, irritant

agents, pollutants (physical and chemical agents) and the site where there is these inflammation and their consequent structural changes (histopathological) and functional changes (inflammatory mediators and cytokines) need genetic predisposing. Recent studies have shown that innate immune recognition of pathogens by epithelial nasosinusal mucosa cells plays an important role in pathogenesis of CRS. The expression of TLR9 protein is present both in normal epithelial cells and in CRS, but the level of expression is reduced in CRS with NP. This finding suggests that there is inappropriate immune response to pathogens via TLR9 in nasosinusal mucosa epithelial cells and it may represent the critical point to the inflammatory mechanism of CRS.

6. DIAGNOSIS

6.1. SIGNALS AND SYMPTOMS

6.1.1 Acute rhinosinusitis

Most cases of RS are viral. In some cases, there may be bacterial superinfection and more rarely RS starts from the beginning as a bacterial affection. The suspicion of bacterial RS after viral episode should be considered if symptoms remain for over 10 days, or if there is worsening of symptoms after 5 days. However, there is no specific symptom for etiological diagnosis of RS (viral x bacterial). The most frequently observed symptoms are:

Nasal obstruction and facial congestion: Despite the fact that they are non-specific symptoms, they are present in most of the patients with ARS, in viral or bacterial presentations, in addition to being present also in allergic episodes. Assessment of nasal obstruction is subjective and it varies from subject to subject but there are tests that try to assess objectively these symptoms. Objective tests that have better correlation with clinical complaints are those that measure flow (rhinomanometry, nasal peak flow), and not those that measure area (acoustic rhinometry).

Rhinorrhea: Presence of nasal secretion, anterior or posterior, which is a symptom suggestive of ARS, despite the fact that in many occasions the level of nasal congestion is high and patients have difficulty to eliminate such secretions. There is no specific test that objectively assesses the amount of nasal secretion in a satisfactory way. In most cases, when secretion is aqueous or mucoid, we may assume that it is initial viral or allergic presentation. As bacteria presence increases, secretion is transformed into mucopurulent, purulent and finally, if there is some level of mucosa destruction, secretion may have signs of bleeding. However, this is the classical situation and we should not forget that we may observe purulent secretion in viral infections as well.

Facial pain or pressure: Pain may be present in viral and bacterial RS. In viral episodes it tends to be diffuse, but it is very intense. Pain caused by bacterial RS is classically characterized by weight, it is non-pulsatile and worsens when the head is moved forward. There may be referred dental pain, which worsens with mastication. Despite the popular belief that headache and sinusitis episodes are related, this symptom is frequent but not specific to diagnosis. Studies that tried to relate the pain to objective findings of infection (aspirate, CT scan) or to the affected sinus had no convincing results.

Hyposmia or anosmia: Olfaction abnormalities in bacterial RS may occur by nasal obstruction, hindering the access of odor particles to olfaction areas or the influence of purulent secretions present in nasal cavity (cacosmia). Moreover, both viral and bacterial infections may cause direct lesions on the olfactory epithelium.

Others: Other symptoms that may be present in bacterial RS episodes are: ear fullness, caused by drainage of secretions in the pharyngeal ostium region of auditory tube. Cough (dry or productive) because of secretions draining posteriorly through the rhinopharynx. Laryngeal, pharyngeal and tracheal irritation causing sore throat and hoarseness, in addition to other distant symptoms such as lower airways affections, fever, dizziness and malaise, which depends on severity of infection and predisposition of each patient.

Subjective assessment of these symptoms should take into account their intensity, duration and to what extent they affect patients' quality of life. To scientific studies, assessment of intensity is normally made using questionnaires and it may include terms such as mild, moderate and severe, numeric or visual analog scale. To assess duration, we may use the terms symptomatic or asymptomatic in a specific period of time (hours per day, days of the week, etc).

Signals

The most suggestive signs of bacterial RS (Chart 2) are:

Upon inspection and palpation: Periorbital edema, without hyperemia or infectious signs that would lead to suspicion of complication. Halitosis, caused by presence of purulent secretions in nasal fossa and drained by rhinopharynx. Pain upon facial palpation corresponding to sinus region (maxillary, frontal and ethmoidal).

Anterior rhinoscopy: Presence of edema and nasal concha hyperemia. After vasoconstriction (not necessarily) we may observe presence of secretion in middle meatus region or nasal fossa and the characteristic of the secretion may suggest possible etiology (viral or bacterial). Drainage of secretion may also be visualized through anterior rhinoscopy.

Chart 2 - Suggestive signs of bacterial rhinosinusitis.

- Periorbital edema, without hyperemia or infectious signs that would lead to suspicion of complication.
- Halitosis caused by presence of purulent secretion.
- Pain upon facial palpation corresponding to sinus region (maxillary, frontal and ethmoidal).
- Secretion in the region of middle meatus or nasal fossa.
- Posterior drainage of mucopurulent secretion.
- Hyperemia of oropharynx posterior wall.

Oroscopy: Posterior drainage of mucopurulent secretion is suggestive of bacterial RS. Hyperemia of posterior oropharyngeal wall may be present in viral and bacterial episodes.

Despite the fact that it is an initial evaluation, we should bear in mind that even in experienced hands, clinical examination has sensitivity and specificity of 69% and 79%, respectively, which is many times may require use of diagnostic tools.

6.1.2 Chronic rhinosinusitis

The main differential between episodes of ARS and CRS is duration of symptoms (> 12 weeks). Despite the fact that most symptoms found in patients with CRS are similar to those found in ARS, some characteristics are different and should be pointed out. However, it is important to bear in mind that in cases of agudization of chronic cases, we may find the same symptoms of acute cases.

In CRS, the presence of nasal obstruction and congestion is less frequent, and when present it is normally associated with other factors, such as septal deviations, allergic rhinitis and others.

Rhinorrhea tends to be less abundant in chronic cases and it may be characteristically aqueous, mucoid or mucopurulent. It may be evident by the nostril or be perceived only as retronasal drainage.

Cough is a common symptom, specially in children and it is normally non-productive. Sometimes, it may be the only symptom present in cases of CRS. It has periods of exacerbation at night and it is associated with retronasal rhinorrhea that causes secondary inflammation in the pharynx. Cough may also result from release of inflammatory mediators in the inflamed nasosinusal mucosa, which stimulates tracheobronchial mucosa and nasopulmonary reflexes.

Facial pain is an infrequent symptom in chronic

pictures and when present it suggests episodes of re-augmentation.

Olfactory affections may occur primarily due to the presence of pathological secretions or destruction of olfactory epithelium due to prolonged infectious presentation.

6.1.3 Chronic rhinosinusitis with polyposis

In cases of CRS associated with polyposis, symptoms are very similar to those cases without the association. However, depending on the amount of polyps present in nasal cavity, the symptom of nasal obstruction may be exuberant. Moreover, patients who have ethmoidal polyposis may present constant nasal congestion and facial pressure.

Polyposis cases normally have high level of olfactory affections as well, especially anosmia and hyposmia. It occurs because the polyps obstruct the passage of odors dissolved in the air to the regions of olfactory epithelium.

6.2 EXAMS

Diagnosis and management of RS are difficult if based exclusively on clinical history. Thus, objective exams are becoming increasingly more necessary to precisely determine presence of RS. The two most used objective methods of assessment by ENT physicians are nasal endoscopy and paranasal sinuses CT scan.

Rhinoscopy: It is an exam routinely used before and after application of topical vasoconstrictor over the nasal mucosa. Anterior rhinoscopy provides definition of nasal mucosa aspect, especially at the level of inferior concha and nasal septum, as well as the presence and aspect of secretions inside the nasal cavity. The exam is not appropriate to carefully assess the middle meatus and the upper and posterior regions of the nose.

Endoscopy Nasal endoscopy enables the examination of all portions of nasal cavity and the detailed macroscopic analysis of nasal and sinus mucosa, if the patient had been previously operated on. To help identify erythema, edema, polyps, crusts, synechia, scars, and nasal mucus the aspect and presence of mucous pus or clearly purulent secretion in any region of the nasal cavity or rhinopharynx is helpful. Semi-quantitative scores may be applied to abnormalities noticed in endoscopy to stage polyposis, for example.

It is a mandatory exam to assess and manage patients with persistent, recurrent or chronic symptoms. In addition to supporting diagnosis, the technique provides material for bacteriological exams collected using non-

invasive methods. However, it is important to point out that normal endoscopic test does not exclude RS.

Imaging: Despite the fact that RS may be diagnosed by most patients based only on clinical history and physical examination (endoscopy), patients with persistent or recurrent disease normally require imaging exams.

- Simple x-ray - It is a technique that is getting less attention from otorhinolaryngologists. In acute cases, simple X-ray is dispensable, and clinical history and physical otorhinolaryngological exam are enough. If required, they should be performed at orthostatic position. In recurrent or chronic cases, it does not correctly assess middle meatus, OMC, frontal recess, sphenoidal recess, nor the upper 2/3 region of the nasal cavity.

- Computed Tomography scan (CT) - it is the imaging of choice to assess RS. It is specially indicated in cases of poor response to clinical treatment, in recurrent or chronic cases, in the presence of complications and for surgical planning. Traditionally, only coronal and axial sections are ordered. As a result of top generation multislice tomographers, 3D reconstructions at coronal and axial sections provide careful analysis of anatomy of all paranasal sinuses and their drainage ports, in addition to the possibility of sagittal visualization.

Despite high sensitivity, the specificity of affections at CT scan and other imaging tests should be carefully interpreted. In many cases, differentiation between mucosa thickness, presence of secretions and presence of fibrous scars, for example, is difficult to make. Another factor to be considered is that not always is there correlation between CT and clinical findings with trans and/or postoperative findings.

Moreover, CT scan is used as standard method for RS staging. There are many staging systems and most are based on presence and quantity of inflammatory disease in the paranasal sinuses. The most widely accepted system to classify RS is Lund-McKay (Table 1).

Table 1 - Lund-McKay staging system.

Paranasal sinuses	Right	Left
Maxillary0, 1, 2		
Anterior Ethmoid0, 1, 2		
Posterior Ethmoid0, 1, 2		
Sphenoid0, 1, 2		
Frontal0, 1, 2		
Ostiomeatal complex0* or 2*		
Total points to each side		

0 = no abnormalities; 1 = partial opacification; 2 = total opacification

0* = not occluded and 2* = occluded

One of the problems of Lund-McKay classification is the broad spectrum of patients that may be classified as grade 1. Partial opacification ranges from 10% to 90% of the affected sinus. A patient with 10% (grade 1) that improves with clinical or surgical treatment may go to grade 0 (no abnormalities). However, a patient with 90% opacification (also grade 1) that improves 70% with clinical or surgical treatment goes down to 20% opacification and, thus, despite the substantial improvement, it is still classified within the same group, grade 1 (partial opacification). Therefore, Meltzer et al. proposed a modified Lund-McKay staging system. It is basically the same system, but grade 1 is divided into 3 subgroups 1A, (1-33% opacification), 1B (34-66% opacification) and 1C (67-99% opacification).

It is important to emphasize that the exam should be ideally requested at acute stages of the disease (except if there is suspicion of complications).

- Magnetic resonance imaging (MRI) - MRI provides important information about mucosa and other soft tissues. It is superior to CT in showing spreading of nasosinusal processes beyond the limits of paranasal sinuses, such as into the orbits and intracranial compartment. The technique is used to diagnose and stage tumors and can differentiate infectious inflammatory disease by bacteria and virus from fungal diseases.

- Others - Both transillumination and ultrasound are not widely used by otorhinolaryngologists because of the high rate of false positive and false negative results, considered to have low specificity and low sensitivity.

Bacteriology: To determine the microbiology of RS and/or its response to treatment, samples of sinusal secretion should be collected without contaminating the normal respiratory or oral flora. Bacteriology is indicated preferentially in cases of recurrence or in chronic cases or in cases that do not respond to conventional treatment (for ex. immunodepressed patients, among others). The two most widely used techniques are maxillary sinus puncture and endoscopy. Maxillary sinus puncture provides aspiration of secretions that may be performed through the canine fossa or inferior meatus. Nasal endoscopy provides staining of microswab of the middle meatus or even collection of aspiration material, which is less invasive and morbid than a puncture. A recent meta-analysis has shown accuracy of 87% in culture of middle meatus assisted by endoscopy in relation to puncture and aspiration through the canine fossa in cases of acute maxillary RS. Quantitative analysis is important because it shows the likelihood that the revealed organism is the agent responsible for the local infection and not simply that contamination increases if density of bacteria is high ($\geq 10^3$ - 10^4 cfu/mL).

Nasal cytology and biopsy: The presence of eosinophils in nasal secretion may indicate the presence of allergy, whereas presence of neutrophils indicate infectious process. However, nasal cytology is not normally used for diagnosis of RS and in isolation it can not diagnose allergic rhinitis. Anatomic pathological exam may be indicated to exclude the presence of neoplasm, vasculitis or autoimmune diseases (Wegener's granulomatosis, nodular polyarthritis, recurrent polychondritis) and to study nasal polyps.

Mucociliary function

- Mucociliary clearance: For general assessment of mucociliary clearance we may use saccharin or radioisotope. Despite the fact that assessment using radioisotopes is more objective, saccharin test is more used because of its simplicity, safety and low cost. However, abnormal saccharin test results (> 30 minutes) do not differentiate between primary or secondary ciliary dysfunction.

- Others: Assessment of frequency of ciliary beating with microscopy with phase contrast or other culture techniques and assessment of ciliary ultrastructure using transmission electron microscopy or scan microscopy are also used to have more detailed definition of architecture and ciliary function and may take to more specific diagnosis, such as primary ciliary dyskinesia.

Specific tests of nasal permeability:

Rhinomanometry (airflow verification) and **acoustic rhinometry** (verification of area and nasal volume) quantify the magnitude of "nasal obstruction" symptom at a given time, but they do not contribute to diagnosis of RS.

Olfaction: Olfaction may be qualitatively and/or quantitatively checked. However, these tests are not used for diagnosis of RS, but rather to determine olfaction function itself and to follow up its response to employed treatments, both clinical and/or surgical. The most popular test, especially in North America, is the one from University of Pennsylvania, named University of Pennsylvania Smell Identification Test - UPSIT (Sensonics, Inc.) They are plates soaked with different micro-encapsulated odors that the subject scratches and smells.

Others test olfaction threshold, presenting to patients serial dilutions of specific pure odors, such as for example, pm carbinol. There are many other tests and exams including assessment of olfactory evoked potentials, but their review goes beyond the objectives of the present guidelines.

Laboratory tests: Many lab tests may be important to diagnose and to follow-up responses to treatment. Reactive C protein may be important, plus clinical history and physical examination, to exclude the diagnosis of

bacterial infection. Others are chlorine level in sweat (CF), total and specific immunoglobulins (immunodeficiency, RS allergic to fungi), complement (CH50, CH100), anti-neutrophil cytoplasmatic antibodies (c-ANCA, Wegener's granulomatosis), angiotensin converting enzyme (sarcoidosis), among others.

7. IMPACT OF RHINOSINUSITIS ON QUALITY OF LIFE

To study quality of life in patients with RS, it is important to differentiate three basic concepts: health, health status and quality of life. Health is defined as physical, mental and social wellbeing, according to the World Health Organization. Health status refers to physical, social and emotional limitations and disabilities of the patient that may be determined by physicians and health-related professionals. Quality of life is assessed based on personal experience and reflects other circumstances of patients' life in addition to health status.

To assess quality of life, we use validated questionnaires with health measurements of physical, mental and social aspect, which show impact of the disease, management or environment on patient's life. These questionnaires are important in the development of health policies for the area of prophylaxis and/or disease treatment.

Pre-defined questionnaires may assess general and specific aspects of diseases. This concept was mentioned by Lembcke, who stated that the best quality of life measurement is the one that intends to prolong life, relieve stress, restore function and prevent disability.

Non-specific questionnaires to assess impact on quality of life

Medical Outcomes Study Short Form 36 (SF-36)

It is the most widely used and better validated questionnaire available. It may be applied to any disease, including RS, gathering general information (non-specific). It comprises 8 aspects: physical limitation, health status, body pain, limitations of activities, vitality, social limitation, mental health and emotional limitation. It has been validated in many languages (France, Spain, German, Australia). It is self-applicable to people over the age of 14. Higher scores indicate better quality of life (0-100). It has been applied in RS to assess pre and postoperative status (evidence level B).

Specific questionnaires

There are specific questionnaires to analyze quality of life in nasosinusal diseases, especially RS and allergic rhinitis. In addition to specific nasosinusal symptoms, it

includes assessment of physical, functional, emotional and social aspects. Some analyze the duration of symptoms, others their severity. These questionnaires check the impact of RS on quality of life and efficacy of clinical and surgical treatment. In Brazil, we used translated questionnaires because specific RS questionnaires have not been validated in Portuguese yet (consistency, applicability and reliability).

The disease-specific questionnaires related with quality of life are:

Rhinosinusitis Outcome Measure (RSOM): 31 items divided into 7 domains; 20-Item Sinusnasal Outcome (SNOT-20) was a modification validated by RSOM-31, to primarily assess RS treatment.

Sinusnasal Outcome Test 16 (SNOT 16) and 11 Point Sinusnasal Assessment Questionnaire (SNAQ-11) are other questionnaires modified from RSOM that address quality of life of people with RS.

Chronic Sinusitis Survey (CSS): 6 items assessing severity and duration of symptoms and treatment (medication), validated, indicated to assess CRS (high sensitivity to clinical changes after long periods); higher scores indicate better quality of life.

Rhinosinusitis Disability Index (RSDI): 30 items about specific nasosinusal symptoms and functional limitation, similar to RSOM 31; does not allow indication of most important symptom; has some general questions similar to SF-36.

The Chronic Rhinosinusitis Type Specific Questionnaire: 3 forms (nasosinusal symptoms before and after treatment and clinical classification of RS); it is time-demanding.

Rhinoconjunctivitis quality of life questionnaire (RQLQ): it is validated but specifically designed to assess allergic rhinitis and conjunctivitis, with no relevance to RS.

Rhinosinusitis Quality of Life Survey (Rhino QoL): validated, it has 17 items (frequency, disturbance and impact of symptoms); applicable to CRS but not consistent for ARS.

Sinus and Nasal Quality of Life Survey (SN-5): 5 items (nasosinusal infection, nasal obstruction, allergic symptoms, emotional stress and limitation of activities); it is indicated for children with persistent nasosinusal symptoms; validated.

Questionnaire by Damm: 7 items about nasosinusal symptoms and their severity and impact (nasal obstruction, retropharyngeal discharge, headache, hyposmia, respiratory dry syndrome, asthma complaints); the test has not been validated; it is the only one that assesses symptom intensity.

Results

- General

CRS has worse impact on quality of life when compared to rheumatoid arthritis, insulin-dependent diabetes and chronic obstructive pulmonary disease (COPD), with worst impact on body pain and social limitation, according to Gliklich and Metson. SF-36 showed significant differences in 8 domains, when compared to normal subjects (evidence level B).

There is variation in the impact of RS on quality of life in different populations, probably due to cultural influences. In Taiwan, it has been demonstrated that women were more impacted by it than by migraine or initial stage breast cancer. Application of SF-36 in the Taiwanese population showed worse scores than the results of the questionnaire in the American population studied by Gliklich and Metson, with high deterioration of emotional aspect, even though it did not cause physical limitation (evidence level B).

The study analyzed the impact of depression in patients with CRS. Depressive patients had pain and negative impact on physical activity. These patients presented poorer response to surgical treatment via endoscopic approach.

- Specific

Assessment by SNOT-20 showed that higher impact symptoms on quality of life of patients with RS are: thick nasal secretion, posterior discharge, fatigue, poor sleep quality, and tiredness upon waking up. Damm showed that CRS influenced quality of life of 94% of the patients and 74% of them characterized it as severe or intolerable owing to nasal obstruction, posterior discharge, headache, hyposmia and/or dry syndrome (evidence level B). In children, the most impacting symptoms on quality of life are nasal obstruction, sinus infection, medication use, emotional stress, allergic symptoms and limited activities.

Studies using TyPE and SF-36 have shown that RS associated with asthma and allergy cause greater impact on vitality and overall health perception of patients than isolated rhinosinusitis.

Radenne et al. used questionnaire SF-36 to compare allergic rhinitis and RS with NP. Both reduce quality of life, but NP has greater impact, especially on vitality, general health and pain. Mental health is more affected than physical health and there is change to emotional health. Association with asthma reduces vitality, pain and physical function, but in isolation, NP has more impact than asthma.

NP associated with bronchiectasia does not worsen SF-36 scores, according to Guilemani et al; therefore, it does not cause additional impact on quality of life.

A prospective randomized study involving patients with CRS and NP has compared 3-month clinical treatment with macrolide and nasosinusal endoscopic surgery. During 3, 6, 9 and 12-month follow-up they analyzed nasal symptoms, SNOT-20, SF-36, expired nitric oxide, acoustic rhinometry, saccharin test and nasal endoscopy. Ninety patients were randomized and there were 40 surgical cases and 38 clinical cases to be analyzed in the end. There was significant improvement in all objective and subjective parameters in both groups, without differences between treatment except for nasal volume (rhinometry) that was greater in operated cases. The study conformed the reliability of subjective measurement of quality of life with objective parameters (evidence level B).

Many studies have confirmed quality of life improvement in patients with CRS and NP submitted to endoscopic surgery, with 3-year follow-up. Damm et al. demonstrated improvement in 85% quality of life and the best clinical improvement occurred in 76.4% of the cases, whereas hyposmia was the symptom that persisted the most after surgery. A study using isolated RS has demonstrated that endoscopic surgery caused less impact on symptoms of hyposmia, fever, dental pain, halitosis and cough. Moreover, there was reduction in use of antihistaminic (AH) and antibiotics and increase in use of topical corticoids. Radenne et al. noticed that nasal endoscopic surgery in massive nasal polyposis was associated with asthma and improved nasal obstruction and quality of life, reducing the need to use asthma medication, but did not modify objective pulmonary parameters. Application of SF-36 and CSS to assess the benefit of nasosinusal endoscopy surgery at 3, 6, and 12-month follow-up showed significant improvement in quality of life, but there was no difference during the follow-up. Patients that had lowest preoperative scores maintained the lowest postoperative scores, showing the low impact of surgery when the patient has few symptoms.

Quality of life of osteoplastic surgery with obliteration of frontal sinus improved in only 48.7% of the patients. Patients were assessed after the treatment with conventional sinus surgery (Dencker access), using SF-36 and McGill Pain Questionnaire-Dutch Language Version (MPQ) and there was improvement of pain and physical limitation, but the other 6 domains remained unaltered.

Wabnitz et al. carried out a prospective study to check the correlation between the symptoms with SSC and SNOT-20 and staging of paranasal sinuses CT scan (Lund/MacKay classification) in patients with CRS. There was no statistically significant difference between scores of the quality of life questionnaire and staging of CT scan, suggesting a deficit in the questionnaires that assess RS severity.

Assessment of quality of life in RS is a way of quantifying disease impact and efficacy of treatment on patient's life. However, these questionnaires have to be validated in the Brazilian population and new randomized multicenter studies have to be carried out to transform them into important instruments to determine the best management of patients with RS.

8. TREATMENT

8.1. ANTIMICROBIAL TREATMENT IN RHINOSINUSITIS

8.1.1 Acute Rhinosinusitis

The main purpose of using antibiotics in ARS is to eradicate bacteria from the infection site, making the affected sinus restore its normal status, reducing symptoms and, preventing complications to avoid a chronic process.

Antimicrobial treatment of both acute and chronic RS is normally empirically based, supported by microbiological data (cultures and sensitivity to in vitro antimicrobials) and studies published in the literature. Especially in acute maxillary sinusitis, antibiotic therapy has shown efficacy in moderate to severe cases, reducing the time required to resolve symptoms. In previously healthy patients with mild ARS general and supportive therapeutic measurements may suffice to quickly solve the symptomatology without requiring use of antibiotics.

In ARS in adults and children, the most common etiological agents, which amount to over 70% of the cases, are *Streptococcus pneumoniae* and *Haemophilus influenzae*; less frequently, there is also *Moraxella catarrhalis*, *Staphylococcus aureus* and *Streptococcus beta hemolytic*. Thus, antimicrobial treatment should necessarily be effective against pneumococcus and *Haemophilus influenzae*.

Use of antibiotics, especially in RS, has been object of literature review and comparative studies using the many antimicrobials available and amoxicillin has shown the equal efficacy.

In bacterial RS, the selection of antibiotic should take into account severity of the disease, its progression and exposure to recent antibiotic therapy. Patients are divided into two categories: those with mild symptoms who had not used antibiotics for the past 4 to 6 weeks and those with mild symptoms but who had used antibiotics in the past 4 to 6 weeks, with or without moderate to severe disease regardless of previous antibiotic use.

The recommendation of initial therapy in adults with mild disease who need antibiotic therapy and had

not used antibiotics in the past 4-6 weeks include:

amoxicillin, amoxicillin-beta lactamase inhibitors, second-generation cephalosporin (axetil cefuroxime, cefprozil, cefaclor). Trimethoprim-sulfamethoxazole, doxycycline, and new macrolides (azithromycin, clarithromycin, or roxithromycin) may be considered for patients with allergy to beta-lactamic antibiotics, but there is estimated treatment failure of 20 to 25% of the cases (Table 2).

Table 2 - Acute rhinosinusitis.

Antibiotics	Adults	Children
Amoxicillin	1.5- 4 g/day TID or BID	45-90 mg/kg/day
Amoxicillin + beta lactamase inhibitor	1.5- 4g / 250 mg/ day TID or BID	45-90 mg/6.4 mg/kg/day
2nd generation Cephalosporin	500 mg-1g /day BID	15-30 mg/kg/day
Macrolides	500 mg /day BID or qd	10-15 mg/kg/day- qd or BID
Trimethoprim-sulfamethoxazole	1600 mg + 320mg /day BID	30 mg/kg + 6 mg/kg/day
Doxycycline	200 mg /day BID, 1st day, after 100 mg qd	
Ceftriaxone	1 g/day / 5days qd	50 mg/kg/day / 5days
Levofloxacin	500 mg /day qd	
Moxifloxacin	400 mg /day qd	
Gemifloxacin	320 mg qd	

The recommendation of initial therapy in adults with mild disease who had used antibiotics for the past 4-6 weeks, adults with moderate-severe disease, regardless of recent antibiotic use, include: high doses of amoxicillin-clavulanate, respiratory fluoroquinolones: levofloxacin, moxifloxacin and gemifloxacin. Ceftriaxone 1 g/day IM or IV for five days.

The recommendation of initial therapy in children with mild disease who had not used antibiotics in the past 4-6 weeks include: amoxicillin, amoxicillin- beta lactamase inhibitors, second-generation cephalosporin (axetil cefuroxime, cefprozil, cefaclor). Trimethoprim-sulfamethoxazole, macrolides (azithromycin, clarithromycin and roxithromycin) may be considered if the patient has allergy to beta-lactamic agents. It is important to bear in mind that the latter has limited action over most pathogens, leading to possible treatment failure (Table 3).

The recommendation of initial therapy in children with mild disease who had used antibiotics in the past 4-6 weeks, or children with moderate-severe disease in-

Table 3 - Chronic Rhinosinusitis

Antibiotics	Adults	Children
Amoxicillin + clavulanate	1.5 - 4 g/250 mg/day TID or BID	90 mg/6.4 mg/ kg/day
Clindamycin	900-1.800 mg/day TID	10-30 mg/kg/day
Metronidazole + cefalexin	1.2 g + 1.5 g/day TID	15 mg/kg/day + 25-50 mg/kg/day
Metronidazole + cefuroxime	1.2g + 500 mg-1 g/ day	15 mg/kg/dia + 25-30 mg/kg/dia
BID	15 mg/kg/day + 25- 30 mg/kg/day	15 mg/kg/dia + 15 mg/kg/dia
Metronidazole + cefprozil	1.2g + 500 mg-1 g/ day	
BID	15 mg/kg/day + 15 mg/kg/day	
Moxifloxacin	400 mg/day qd	
Levofloxacin	500 mg/day qd	
Metronidazole + 1st and 2nd generation cephalosporin		

clude high doses of amoxicillin-beta lactamase inhibitors and second-generation cephalosporin (axetil cefuroxime, cefprozil and cefaclor). Trimethoprim-sulfamethoxazole, azithromycin or clarithromycin are recommended if the patient has history of Type I allergic reaction to beta-lactamic antibiotics. Ceftriaxone, at 50 mg/kg dose per day IM or IV for five days.

Antibacterial resistance to predominant pathogens in ARS, such as *Staphylococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, has increased at variable rates in the whole world. The choice of antibacterial agent may differ from region to region and the choice depends on local resistance level and etiology of the disease.

Duration of recommended treatment is 10 to 14 days, depending on severity and progression of clinical case.

8.1.2 Chronic Rhinosinusitis

It is significantly more difficult to assess efficacy of antibiotics used in treating CRS compared to ARS owing to the conflict in terminology and definition of CRS clinical presentation in the literature.

Even though the exact etiology of inflammation associated with CRS is still unknown, the presence of bacteria in the nose and paranasal sinuses has been well documented. Thus, is it possible to assume that bacteria may perform a direct or indirect role in the development

or maintenance of CRS? Despite the fact that this issue is not totally clarified, antibiotic therapy has been the most common approach to treat CRS. Studies have shown efficacy of antibiotics in the treatment of CRS. However, it is important to emphasize that to present, there is no randomized placebo controlled study in the literature about efficacy of antibiotics in treating CRS.

For CRS, antimicrobial therapy is normally supportive, with effective coverage against the aerobic microorganisms mentioned above, in addition to strict anaerobic bacteria. Considering the higher prevalence of *Staphylococcus aureus* and *Staphylococcus coagulase negative* in chronic cases and the association with positive anaerobic bacterial, clindamycin or the combination Amoxicillin - potassium clavulanate are good therapeutic options. The use of metronidazole associated with first-generation cephalosporin (cefalexin) or second-generation cephalosporin (cefprozil, axetil cefuroxime, cefaclor), active against *Staphylococcus aureus*, may be considered. Respiratory fluoroquinolones may also be used in CRS. In children with higher likelihood of having *Haemophilus influenzae* resistant to beta-lactamic agents or pneumococcus with mutation in the penicillin receptor protein, use of amoxicillin at usual doses (45 mg/kg) should be avoided in chronic cases. Amoxicillin is normally given in higher doses (90 mg/kg/day) and preferably associated with beta-lactamase inhibitors (Table 3).

Treatment duration will depend on other therapeutic measures, such as surgical management, but it lasts on average 3 to 6 weeks.

In immunocompromised patients, especially those granulocytopenic, patients with AIDS and CF, the possibility of infection by aerobic gram-negative rods should be considered, specially by *Pseudomonas aeruginosa*. The use of cephalosporin with anti-pseudomonas activity, such as ceftazidime (1-2 g IV TID/BID), or even better, a fluoroquinolone, such as ciprofloxacin (400 mg BID) associated or not with aminoglycoside, such as amycacin (15 mg/kg/day IV or IM TID), depending on severity, are excellent options. In nosocomial infections by oxacillin-resistant *Staphylococcus aureus* (0.5-2 g QID), vancomycin (40-60 mg/kg/day IV QID) should be considered in the therapeutic regimen.

Treatment of chronic rhinosinusitis with long-term antibiotics

Many studies have demonstrated that use of long-term low dose macrolides is effective in treating CRS, which is incurable both by surgical approach and using glucocorticoids, with improvement rates of symptoms that range from 60% to 80%.

There is increasing evidence that in vitro macrolides have antiinflammatory effect. Many studies have

confirmed that macrolides inhibit the gene of interleukin expression for IL-6 and IL-8 and inhibit the intercellular adhesion molecule essential for recruitment of inflammatory cells. However, this mechanism has not been defined as a clinical relevant mechanism yet.

There are in vitro evidences, as well as clinical experiences, that macrolides reduce virulence and tissue damage caused by chronic bacterial colonization, without eradicating the bacteria. Moreover, treatment with long-term antibiotics has shown increase in ciliary beating frequency.

A prospective randomized study with ninety patients with CRS without polyposis treated them either with erythromycin for 3 months or endoscopic surgery, followed up for one year. Both groups had significant improvement (evidence level 1B), and there was no difference between the two groups nor between the groups with and without nasal polyps except for total nasal fossa volumes, which was higher in the group submitted to surgical management.

Treatment with low doses of macrolides for prolonged periods of time should be considered only in selected cases and after failure of corticosteroid management.

However, to present, there are no placebo-controlled studies to determine the real efficacy of macrolides and whether this type of treatment may be beneficial to patients with CRS.

Acute exacerbation of chronic rhinosinusitis: treatment with oral antibiotics

In clinical trails, oral antimicrobials have proven to be effective in the symptomatology of acute exacerbation of CRS, which may be caused by the same organisms responsible for ARS, in addition to other pathogens present in this type of disease.

The combination of topical corticoid and oral antibiotic has positive effect in managing acute exacerbation of CRS, confirmed by double blind studies. However, no study has shown efficacy of antibiotics in treating the acute phase of CRS by placebo controlled double blind design.

Acute exacerbation of chronic rhinosinusitis: treatment with topical antibiotics

Some studies have compared the effects of topical antibiotics in CRS and in acute exacerbation.

Desrosiers, in a randomized double blind controlled study compared the use of saline solution with tobramycin as opposed to only saline in 20 patients with CRS refractory to clinical and surgical management, studied for 4 weeks, and observed no differences between the groups, concluding that the method is safe and effective, which makes it an alternative to treating these patients,

regardless of the addition of antibiotic.

Sykes has not found any additional effect of neomycin added to spray with dexamethasone and tramazoline QID for two weeks.

Schienberg et al. studied the effectiveness of using antibiotics in paranasal sinuses, through nebulation, in 41 patients with RRS refractory to clinical and surgical treatment and obtained excellent and good results in 82.9% of the cases.

Evidence-based scheme to treat acute and chronic rhinosinusitis with antibiotics

Treatment should be based on symptom severity.

Antibiotics used in acute rhinosinusitis

Treatment	Level	Level of recommendation	Relevance
Antibiotics	Ia	A	Yes: after 5 days, or in severe cases

Antibiotics used in chronic rhinosinusitis

Treatment	Level	Level of recommendation	Relevance
Short-term antibiotics - 2 weeks	III	C	No
Long-term antibiotics ± 12 weeks	III	C	Yes
Topical antibiotics	III	D	No

Antibiotics used post-operatively for chronic rhinosinusitis

Treatment	Level	Level of recommendation	Relevance
Short-term antibiotics - 2 weeks	IV	D	Early postop if there is pus during surgery
Long-term antibiotics ± 12 weeks	III	C	Yes

Antibiotics in nasal polyposis

Treatment	Level	Level of recommendation	Relevance
Short-term antibiotics - 2 weeks	No available data	D	No
Long-term antibiotics ± 12 weeks	III	C	Yes
Topical antibiotics	No available data		No

Antibiotics in nasal polyposis postoperative setting

Treatment	Level	Level of recommendation	Relevance
Short-term antibiotics - 2 weeks	No available data	D	Early postop if there is pus during surgery
Long-term antibiotics \pm 12 weeks	III	C	Yes
Topical antibiotics	No available data	D	No
Antibióticos tópicos	Sem dados disponíveis	D	Não

Level of evidence:

Ia: metaanalysis and controlled studies

Ib: at least one controlled randomized study

IIa: at least one controlled study without randomization

IIb: at least one quasi experimental study

III: descriptive non- experimental study

IV: opinion of committees or clinical practice

Level of recommendation:

A: evidence I

B: evidence II or extrapolates evidence I

C: evidence III or extrapolates evidences I or II

D: evidence IV or extrapolates evidences I, II or III

8.2 CLINICAL MANAGEMENT OF RHINOSINUSITIS: SUPPORTING THERAPEUTIC MEASURES

Treatment of RS includes therapeutic alternatives to reduce intensity and morbidity of symptoms, which should be indicated depending on the needs and limitations of each patient. Classically and parallel to antibiotic therapy, we may use short-term corticosteroids and/or decongestants, in addition to nasal lavage.

Other drugs and management options, which have lower level of scientific evidence and level of recommendation are still under investigation.

Systemic and topical corticosteroids

Systemic and topical corticosteroids are very useful as supporting tools in treating RS, contributing to the success of antibiotic therapy, as shown in the literature. Hormonal antiinflammatory action of corticosteroids promotes reduction of edema, facilitating drainage and maintaining permeability of ostia, which facilitates clinical cure of RS. Corticoid therapy is especially useful when there is RS associated with allergy, in non-allergic eosinophilic RS and in CRS with nasal polyposis. Effectiveness of corticoids is limited only by the long list of contraindications and adverse reactions, which are well known and explicit in the package insert.

Topical or systemic drugs inhibit the action of chemokines, which are produced by nasal mucosa cells and polyp epithelium. They reduce feasibility and activation of eosinophils, among other antagonistic effects to inflammatory reaction. Biological action of corticoids depends on the activation of intracellular receptors of glucocorticoids (GR α and β). Such receptors enhance antiinflammatory gene transcription or repress pro-inflammatory response.

Oral corticosteroids (prednisone, prednisolone, dexamethasone, betamethasone, deflazacort) are largely indicated, but surprisingly there is little evidence about their use in RS in the literature.

In ARS, oral corticoids control inflammatory process that leads to more marked symptomatology such as pain and congestion. They should be recommended for short periods of time (about one week), considering the adverse events present in prolonged use. Injectable corticosteroids are quickly and present easy dose format, but they are not safe in controlling adverse reactions, in addition to having scarce scientific evidence.

In persistent RS without polyposis, there are good results with oral corticoid therapy, especially in improving nasal obstruction. In the literature, there is no more evidence about predisposition to infection. Use of oral corticosteroids is less frequently documented in CRS with nasal polyposis than intranasal formulations. They reduce the size of polyps and have better effect over olfaction. It is important to point out that despite the effective improvement, results of corticoid therapy are reversible. In CRS, another option is joint indication of systemic and topical corticoid therapy.

The use of nasal topical corticoids has improved inflammatory upper airways diseases (rhinitis, CRS with nasal polyposis). Topical corticoids are well indicated when we prioritize local action and low systemic absorption. Mometasone and fluticasone, budesonide, triamcinolone and beclomethasone are the ones that have lower bioavailability, by increasing order.

The literature has shown good evidence of use of topical corticoids in episodes of ARS, exacerbated or not by allergy. This action is also acknowledged in CRS with and without polyposis and in postoperative treatment. Presentation in spray is traditionally used, but formulations in drops have proven to be useful in CRS with NP, according to European studies. The use of solutions based on other topical corticosteroids, with or without antibiotics and vasoconstrictors, and specially used for long periods of time, may lead to higher likelihood of adverse events, such as anosmia.

Despite greater safety of intranasal corticoid therapy, it is always necessary to prevent adverse events and

guide the use, in addition to scheduling periodical visits for nasal cavity examination.

Adverse events of corticoids are reason for concern of physicians and patients, especially those with CRS that require more frequent or prolonged courses of treatment to CRS. Suppression of hypothalamus-pituitary axis, osteoporosis, failure to thrive in children, cataracts and glaucoma are well known adverse events, whereas the best known contraindications are dyspeptic diseases, hypertension and diabetes. Adverse events are more marked after oral than topical management, and the higher the dose and duration of treatment, the worse the effects.

In addition, topical corticosteroids used by inhalation, taken by many asthmatic patients who have CRS with NP, predispose to more adverse events than through nasal route, and increase the risks if there is concomitant use of intranasal corticosteroids.

Non-steroidal antiinflammatory drugs (NSAID)

There is no reference to the use of different NSAID in international consensus, nor there are studies that support their indication to RS. This drug class is especially contraindicated in patients that have CRS with NP, related with intolerance to salicylate.

Antihistaminic drugs

Allergic rhinitis is a predisposing condition to all forms of RS. Antihistaminic drugs (AH) may be supportive in managing ARS and RRS with exacerbation of allergic presentation. AH are available in isolated presentations or associated with decongestants and corticoids. Classical AH, such as dexchlorpheniramine, cause adverse reactions such as sleepiness and loss of reflexes, but they are effective and are common in associations. Non-sedative AH, frequently used and widely accepted are loratadine, desloratadine, cetirizine, epinastine, fexofenadine, ebastine, and rupatadine.

Studies have supported the use of loratadine in symptomatic control of patients with ARS. Desloratadine has been subject of experimental studies with positive results. In CRS with NP, cetirizine has proven to reduce coriza, sneezing, and obstruction, but it did not affect polyp size. AH are frequently prescribed to CRS, even without scientific basis.

Topical and systemic decongestants

Decongestants: they are alpha-adrenergic agonist drugs that act as vasoconstrictors. Upon causing constriction of nasal vascular bed and consequent limitation of blood flow, they reduce edema and obstruction, resulting in relief of nasal congestion. They are normally indicated for few days and intermittently in ARS, to improve ventilation and drainage of paranasal sinuses.

Systemic decongestants: they are normally safe in therapeutic dosages and may lead to adverse reactions due to concomitant stimulation of cardiovascular system or central nervous system. They should not be used in liable hypertensive patients, in prostate hypertrophy, glaucoma, patients that take antidepressants and MAOI. They are not appropriate to adult patients that operate machines, drive any vehicles, fly aircrafts, or in athletes.

Presented always in association with AH, many of these products are over-the-counter and have blister presentations without package insert, which means that patients do not have access to information about adverse events and contraindications. Among the drugs indicated to respiratory diseases, systemic and topical decongestants are the main causes of drug intoxication, based on data from recent studies.

The literature indicates that the association between decongestants and AH does not produce better results than isotonic saline solution, together with antibiotic therapy, in a study of children with ARS. The use of decongestants in CRS with and without polyposis is not based on scientific literature support.

Topical decongestants: owing to their vasoconstrictor effect, they may be used in ARS for a short period of time (3 to 5 days), reducing the risk of rebound effect. Such proposition is accepted in the literature based on clinical experience. Topical decongestants are effective in the control of nasal obstruction, acting over the mucosa of lower and middle conchae mucosa, and they do not act over the sinusal mucosa, as demonstrated in radiological studies with CT scan and MRI. The effect of decongestants over MCT has always been controversial and recent studies have suggested that it improves mucociliary clearance in vivo after 2 weeks, similarly to saline solution at 3%, but not better than in the control group. Use and prescription should be well instructed by the physician, considering the risk of intoxication in children, drug-related rhinitis, arrhythmia, glaucoma and other severe systemic complications.

Nasal lavage / saline solution

Mucociliary system is the main mechanism of non-specific defense of upper airways forming a barrier to microorganisms and particles. Mucus, formed by water (95%), proteins (3%), lipids (1%) and minerals (1%) adsorbs particles and microorganisms from air current. MCT acts based on viscoelasticity of mucus, ciliary beating (in metachronic waves) and coupling of cilia and mucus.

In airway diseases, there is mucosa damage, affected viscoelasticity of secretions and failure of MCT, favoring bacterial colonization, which leads to destruction of epithelium. MCT is abnormal in conditions such

as Kartagener's syndrome, primary ciliary dyskinesia, CF, among others, leading to predisposition to RS.

Irrigation of nasal mucosa with isotonic saline solution (0.9%) is a classical and safe measure, very useful in mobilizing secretions and hydrating the mucosa as supportive and preventive treatment in inflammatory and infectious nasosinusal diseases. Hypertonic saline solutions (up to 3%) increase frequency of ciliary beating and reduce edema of nasal mucosa, with improvement of MCT and reduction of nasal obstruction. Nasal lavage with saline solution is indicated as supportive therapy in allergic rhinopathies, ARS, as preventive measure in intermittent RS and CRS, and postoperatively in nasosinusal surgeries.

The best way to hydrate or clean the nose depends on the amount and viscosity of secretions to be removed. There are physiological solutions (isotonic) and hypertonic solutions, with and without preservatives, in liquid or gel, drops or spray, available in the market. Homemade solutions are economical, but the preparation should be carefully instructed by the physician, because they are potentially harmful if using random amounts of salt, without proper hygiene care, storage or validity period. The use of saline solutions is easier in children if we use formulations at room temperature or body temperature.

Worsening of MCT due to action of preservatives in topical medication is a controversial issue. In adverse climatic conditions in presence of environmental pollution, cold temperature or dry season, patients with RS may benefit from preventive oral or nasal hydration.

Hypertonic saline solution is effective, but it causes the sensation of mucosa irritation when applied and some patients do not tolerate its use. It provides easy removal of crusts and epithelial debris, and it is especially useful in postoperative periods. It also removes interstitial edema caused by tissue dehydration and consequently, it temporarily unclog the nose. Recent studies have demonstrated improvement in MCT.

Isotonic Formulation:

- 1,000ml Lukewarm boiled water
- 1 tablespoon (10cc) sea or coarse salt
- 1 tablespoon (10cc) sodium bicarbonate

Hypertonic Formulation:

- 1,000ml Lukewarm boiled water
- 2 tablespoons (20cc) sea or coarse salt
- 1 tablespoon (10cc) sodium bicarbonate

Mucolytic agents

It is a group of drugs whose main purpose is to modify consistency of secretions from the respiratory system, facilitating transport and clearance. The literature

is controversial, but the beneficial effects of mucolytic agents does not seem to overcome the advantages of using water, which continues to be a fluidizing agent of mucus in the airways.

Appropriate water intake, steam inhalation and nasal lavage with isotonic saline solution are satisfactory approaches as supportive management of most airways diseases, without potential risks and inconveniences of drug use, in addition to comfort and low cost.

The literature mentions studies with specific and inconsistent results of mucolytic use, acting on the reduction of persistent ARS and CRS.

Phytomedicine

Phytomedicines are standardized extracts made of purified vegetable principles that are industrialized under ideal conditions of hygiene and stored under strict quality control.

Fresh medicinal plants are used in Brazil with the mistaken notion that they never cause adverse events, but there is the risk of intoxication and drug interaction. Many herbs are used without appropriate conditions of hygiene or guarantee of origin. Non-standardized extracts, owing to variability of concentration of active principles, may lead to inconsistent results. It is essential to question patients about the use of phytotherapeutic agents so that they may be discontinued 2 to 3 weeks before nasosinusal surgical procedures. To avoid intraoperative bleeding, suspension of "4G" is recommended: garlic, ginkgo biloba, ginseng and ginger.

In Brazil, the medicinal plant most commonly used in informal treatment of RS is *Luffa operculata*, known as "buchinha-do-norte" or "cabacinha", which has shown deleterious effects over the respiratory mucosa in experimental studies. There is relief of symptoms after profuse release of secretion, which is in part intracellular liquid, after rupture of mucosa cells. There is also risk of bleeding showing that this and other medicinal plants have to be further studied.

Available in Brazil, EPs7630 extract of *Pelargonium sidoides*, with antiviral and mucokinetic properties, may be used in viral RS. Extract Ze339 of *Petasites hybridus*, which acts as AH and anti-leukotriene, such as this pharmacological class, may be supportive in the treatment of CRS and intermittent allergic patients. In both situations, though, there is still lack of RS-specific studies.

Bacterial lysates / immunostimulating agents

Some patients have repetitive RS owing to affection to local or systemic immunity. Among them, it has also been observed increase in bacterial resistance to antimicrobials and more patients that are refractory to

Table 4 - Indication of supporting therapeutic measures.

Therapy	Indication	Note
Intranasal and oral corticosteroid	ARS;	Indicação individualizada; observar risco de reações adversas
Antihistaminic	Prophylaxis of recurrent ARS; CRS	In allergic patients
Topical and systemic decongestants	ARS and RRS	Use for 3 to 5 days
Nasal lavage with saline solutions	ARS; RRS prophylaxis; CRS without NP; CRS with NP; CRS postoperative	Customize indication of isotonic or hypertonic solution; appropriately guide use of homemade solution; observe the need to have further hydration or hygiene
Mucolytic	ARS, CRS	Elderly, ciliary dyskinesia
Bacterial lysate	RRS prophylaxis; CRS	RRS prophylaxis; CRS
Phytomedicine	ARS	In natura plants are not recommended
Leukotriene antagonist	Prophylaxis and post of CRS with NP	Prophylaxis and postoperative
Proton inhibitor pump	CRS	Gastroesophageal reflux
Complementary therapies, homeopathy, acupuncture	Insufficient data to make recommendations	

long courses of antibiotics or even surgeries. Expecting that abnormal immune response would be responsible for repetitive infections, preventive or supportive treatments have been proposed using immunomodulators or immunostimulating drugs, such as bacterial lysates in different compounds.

The literature presents some studies referring to reduction of number of treatment courses and duration of antibiotic therapy in ARS and RRS, among other infectious presentations. These drugs are effective in reducing score and severity of symptoms, including cough in CRS.

Anti-leukotriene

Leukotrienes are inflammatory mediators present in many respiratory tract diseases. Anti-leukotriene drugs are safely indicated in rhinitis and severe asthma, corticoid-dependent patients and those with intolerance to salicylates. Owing to its antiinflammatory action, they are better indicated in CRS with NP. Open label studies have shown good results, but there are still few controlled studies to confirm efficacy.

The drugs available for use in Brazil are montelukast and zafirlucast. The former has been used in studies with patients with CRS with NP, which is an option for oral corticosteroid use, associated with topical corticosteroids.

8.3 SURGICAL INDICATIONS

Functional endoscopic sinus surgery has been widely communicated in the 80's and assessed by many clinical trials. Functional surgery intends to recover mucosa sinus disease by improving nasosinus ventilation

and restoring mucociliary clearance, preserving as much as possible the mucosa and removing only what is necessary to restore physiological functions of the nose and paranasal sinuses. As the century went by, many discussions exposed the opinions of conservative and radical professionals about the best surgical treatment approach to the paranasal sinuses. Modifications of the technique proposed by Messerklinger have come into place and others are still suggested all over the world.

Minimum trauma during surgical procedure and the diagnostic accuracy that endoscopy provides has given otorhinolaryngologists the possibility of improving diagnosis and treatment of RS. Technological development has brought to market new equipment to be used in the surgical bed, such as microdebrider, which speeds up the surgical procedure, or navigation CT system, which provides greater accuracy and safety to surgeons.

The videoendoscopy system allowed greater exchange of knowledge between surgeons, which facilitated teaching of new physicians. Surgical clamps have also been enhanced and enable more delicate endoscopic access to sphenoid and frontal sinuses.

However, despite the whole technological development, there is still high risk of potential complications during surgical approach of the nose and paranasal sinuses. Regardless of the type of material used, under microscopy, naked eye or endoscopy, the surgeon should be knowledgeable about the surgical anatomy, and should practice before the surgical act.

Many factors have influenced the result of nasosinus surgery, such as age, extension and duration of disease, previous surgery, presence or not of polyposis,

concomitant diseases (AAS intolerance, CF, allergy, asthma) and specific etiologies (odontogenic origin, autoimmune disease, immunodeficiency). Relevant surgical factors include type of access (external or endonasal), surgical technique (functional or conventional), extension of surgical intervention, type of visualization and lighting (photophore, endoscope, microscope) and used instrument. Postoperative medication is also considered a factor that influences surgical results (Chart 3).

Chart 3 - Factors that influence the result of nasosinusal surgery.

- age, extension and duration of disease
- previous surgery
- presence of polyposis
- concomitant diseases (intolerance to AAS, CF, allergy, asthma), specific etiologies (odontogenic origin, autoimmune disease, immunodeficiency) and type of access (external or endonasal)
- surgical technique (functional or conventional);
- extension of surgical intervention;
- type of visibility and lighting (light, endoscope, microscope) and instrument used;
- postoperative drug therapy

Access routes

After a specific surgical indication, we should select the access, which may be by endonasal, external approach or combined access. Reoperation of paranasal sinuses normally presents greater technical difficulties, especially owing to loss of anatomical repair. The type and extension of surgical access should not be based on paranasal sinuses CT findings, but rather take into account the combination of these findings with the clinical presentation and endoscopic findings.

Endonasal access

It is the surgical preferred access especially in inflammatory affections. Technological advancement of diagnostic media and sophisticated surgical instruments have enabled conservation of mucosa and healing of minimum fibrosis, expanding the indication of this access.

External access

Despite the main preponderance of endonasal access, there are situations in which the external access is indicated as the most appropriate solution to solve the patient's problem. Lateral location of maxillary or frontal sinus disease may prevent endonasal access as route of main access. Lack of reliable anatomical repair point to prevent orbital and intracranial complications indicates the use of external route.

Surgery in ARS

To present, there are no data to assess the role of surgery in uncomplicated ARS.

CT scan is a mandatory imaging test to preoperatively assess patients with CRS, and it should necessarily be present in the operating room during intraoperative procedures. However, surgical indication should not be based on CT scan findings but rather in its correlation with clinical presentation. Paranasal sinuses CT scan represents a true guided surgical map that instructs the surgeon to make the procedure safer and avoiding possible complications.

Surgery of CRS refractory to clinical treatment

Terris and Davidson analyzed 10 large trials (1 level III and 9 level IV studies) comprising a total of 1,713 patients who showed on average 91% improvement (73% to 97.5%). About 60% of the patients reported very good results (complete resolution of symptoms), 28% had good results (improved, but without complete resolution) and 9% did not have satisfactory results (without improvement or even getting worse). About 12% of the patients required surgical review and major complications were detected in 1.6% of the patients.

In 2001, surgical studies in patients with CRS were reviewed in the context of evidence based medicine. Good results with 80 to 95% improvement were reported.

a) Comparison between endonasal surgery and external access.

No comparative study between endonasal surgery and external frontoethmoidectomy was found. In some studies, endonasal surgery was compared to Caldwell-Luc access. Caldwell-Luc access was described between 1893 and 1897 by Caldwell in the USA and Luc in France. The most common complication of this kind of access is anesthesia or paresthesia of the gums, teeth and/or face, resulting from damage or stretching of infraorbital nerve which is solved within 3 to 6 months. Other complications include damage to orbital floor, infra-orbital nerve damage, damage to dental apex, hemorrhage, oroantral fistula and epiphora.

Penttila et al. carried out a randomized study with 150 patients with diagnosis of maxillary CRS that did not respond to treatment after antibiotic therapy and antral irrigation. Half of the patients (n = 75) were submitted to endonasal surgery and the other half (n = 75) was submitted to Caldwell-Luc access (level IB). The rate of complications has significantly favored endonasal access, as well as nasal obstruction, hyposmia and rhinorrhea.

These patients were reassessed 5 to 9 years later with a questionnaire, and 85% of the patients responded. Both in the groups of endonasal access and in Caldwell-Luc access, about 80% of them were asymptomatic or had improved, but with no relevant differences between the groups. However, postoperative facial pain and sensitivity abnormalities concerning temperature changes were detected in 23% of the patients submitted to Caldwell-Luc access.

Despite improvement in clinical symptomatology in maxillary CRS it may be obtained by endonasal access and Caldwell-Luc access, Caldwell-Luc access presents a greater risk of affections related with trigeminal nerve damage.

b) Comparison between functional endonasal surgery of paranasal sinuses and conventional endonasal surgery

Conventional endonasal surgical techniques include irrigation of maxillary sinus, simple polypectomy, inferior meatus antrostomy, and radical transnasal sphenoidectomy with or without middle concha resection.

Eighty-nine patients with maxillary CRS were enrolled in a controlled randomized study. Forty-five patients were submitted to maxillary sinus irrigation and 44 patients were submitted to maxillary sinus irrigation followed by functional endoscopic sinus surgery (FESS), and all patients were periodically followed up for up to 1 year. Second surgical intervention due to treatment failure was required in 13 patients in the group that had only irrigation and 2 patients in the group with FESS and irrigation (Level IB).

In a controlled randomized trial, 25 patients submitted to FESS were compared to 25 patients submitted to conventional endonasal surgery. Conventional surgery included antral puncture, intranasal ethmoidectomy and Caldwell-Luc access. Postoperative follow-up ranged from 15 to 33 months, mean of 19 months; 76% of the patients in the endoscopic surgery group had complete remission of symptoms, 16% had partial improvement and 8% had experienced no improvement, compared to 60%, 16% and 24%, respectively, in the conventional endonasal surgery group.

In a prospective controlled study, Arnes et al. performed inferior meatus antrostomy on one side and

middle meatus antrostomy on the opposite nasal cavity in 38 patients with maxillary CRS. Laterality for performance was randomized. After a follow-up period that ranged from 1 to 5 years, no significant difference was observed between the two sides using symptom scores and imaging tests. These data go against the study by Lund (level III) that analyzed nasal symptom score for a long period of time for both types of antrostomy, which showed superiority of middle meatus antrostomy.

Surgery should be reserved to RS refractory to conservative clinical management or RS associated with complications. As a conclusion, the consistency of results in a large number of patients suggested that selected CRS patients, with or without NP, may benefit from nasosinus surgery, which represents a safe therapeutic option.

8.4. CLINICAL X SURGICAL MANAGEMENT OF CHRONIC RHINOSINUSITIS WITH NASAL POLYPO-SIS

Despite the fact that all cases of NP seem to be similar, they have different clinical and histological characteristics that may be classified into 5 distinct groups, according to Stammberger:

1. antrochoanal polyps;
2. large and isolated choanal polyps;
3. polyps associated with chronic rhinosinusitis, without predominance of eosinophils;
4. polyps associated with chronic rhinosinusitis, with predominance of eosinophils;
5. polyps associated with specific diseases such as CF, malignant tumors and foreign bodies.

Choanal polyps and polyps associated with specific diseases have unknown etiology, whereas polyps associated with CRS are still a major challenge to otorhinolaryngologists. Among polyps associated with CRS, about 80-90% belong to the group with predominance of eosinophils with diffuse NP, which is in many situations associated with history of asthma or hyperreactivity of the airways, and hypersensitivity to aspirin.

Therefore, the term nasosinus polyposis is used to describe the presence of multiple and bilateral polyps, of softened consistency, which may be glossy, transparent, pale, slightly grayish or pink, and pediculated, normally originating from middle meatus region, which may expand to nasal cavity, nasopharynx, nostrils and paranasal sinuses, leading to presentation of nasal obstruction and hyposmia.

It is a chronic disease that is difficult to treat and has high recurrence rates. Some studies have shown re-

currence rates of about 60% after 2 years from the surgical procedure.

To present, it is a poorly defined clinical condition of unknown etiology. Theories try to explain abundant eosinophils present in it.

It is believed that nasosinusual polyposis is an inflammatory, multifactorial, non-allergic (not IgE mediated) disease that has eosinophil infiltrate as the main histological characteristic in most cases. Recent studies have shown the role of super-antigens to *Staphylococcus aureus*, fungi and biofilm activating the exacerbated inflammatory response whose main final route is eosinophil (discussed in a later section).

For some years, as of 1933, allergy was considered the main cause for NP formation, a theory that started to be questioned in 1977 when Settipane and Chafee showed in a retrospective study that most patients with NP were atopic. Even though prick test is less positive in patients with NP when compared to the population in general, it is known that tissue concentration of IgE is increased regardless of the result of prick test, which may suggest local production of IgE. In addition, prevalence of NP in the general population is 2-4%, whereas among allergic rhinitis cases the prevalence is about 15-20%. Allergic rhinitis tends to specially affect children and young adults, whereas NP affects mainly adults. Prevalence of NP in allergic patients is low, normally below 5%, which is similar to the prevalence in the general population. In addition, specific allergic therapy in patients with NP has not proven to be effective.

Staging of the disease is made by endoscopic study, complemented by paranasal sinuses CT scan and confirmed by surgery. The association of staging based on CT scan (Chart 4) and endoscopy (Chart 5) may be useful in following up disease progression because it allows subdivision of the patients according to extension of the process, which leads to better assessment of disease severity.

Strategies used to treat nasal polyposis are clinical management, surgical management or a combination of both.

Chart 4. Staging of nasosinusual polyposis (Stamm, 1992).

Stage Location
I ostiomeatal complex/middle concha
II ostiomeatal complex/middle concha/ethmoidal sinus
III Stage II + 1 paranasal sinus
IV Stage II + 2 paranasal sinuses
V All paranasal sinuses

Chart 5. Endoscopic staging of nasosinusual polyposis (Meltzer et al., 2006).

Stage Location
0 absence of polyps
1 small polyps in middle meatus/ edema
2 middle meatus obstruction
3 polyps extend beyond middle meatus without complete nasal obstruction
4 massive nasal polyposis

Chart 6. Clinical treatment approaches proposed to chronic rhinosinusitis with and without nasal polyposis.

Controlled studies - confirmed effects on reducing polyp size, symptomatology and recurrence of polyposis
CORTICOSTEROIDS
There are few studies that confirm efficacy
ANTIBIOTICS
ANTIFUNGAL
Effect on lower conchae but not on polyp size
DECONGESTANTS
Effect on symptomatology of patients with associated allergy
ANTIHISTAMINIC
There are no controlled studies – reduce symptomatology and recurrence of polyposis (patients with AAS intolerance and/or associated pulmonary affection)
ANTI-LEUKOTRIENES
ASPIRIN DESENSITIZATION
Open-label studies – reduce recurrence of polyposis
CAPSAICIN
FUROSEMIDE
There are no clinical trials correlating medication and polyposis
MUCOLYTIC
BACTERIAL LYSATE
IMMUNOMODULATORS
NASAL/ ANTRAL IRRIGATION
PROTON INHIBITOR PUMPS
PHYTOTHERAPIC AGENTS

CLINICAL TREATMENT

Many clinical treatment options are proposed by different authors to address chronic rhinosinusitis with and without NP (Chart 6). This section will address chronic rhinosinusitis with NP, which corresponds to a subgroup of chronic rhinosinusitis. Chart 7 shows level of clinical evidence concerning drug treatment.

Chart 7. Clinical evidence of drug treatment to chronic rhinosinusitis with nasal polyposis.

Medication	Level of evidence	Recommendation	Relevance
Topical Corticosteroid	1b	A	Yes
Oral corticosteroid	1b	A	Yes
PO antibiotic < 2 weeks	There are no studies	D	No
PO antibiotic > 12 weeks (macrolides)	There are no studies	D	Yes to late recurrence
Nasal lavage	1b (There are no studies with isolated use)	A	Yes (to symptomatic cases)

CORTICOSTEROIDS

Clinical efficacy of systemic and topical corticosteroids is associated with direct action on reducing eosinophilic infiltration present in the airways, preventing its increase and activation, and indirect action on reducing release of chemotactic cytokines by the nasal mucosa and epithelial cells of nasal polyps. However, it is known that the potency of these effects is greater in the nasal mucosa than in the nasal polyp, suggesting reduced inflammatory resistance enhanced by corticosteroids in subjects with chronic rhinosinusitis and nasal polyposis. In fact, alpha corticosteroid receptors (pro-inflammatory receptors) are reduced in subjects with NP, whereas beta corticosteroid receptors (inhibit the role of alpha receptors) are enhanced in these patients.

Upon observing the studies referring to treatment of nasal polyposis, it is important to assess separately the effect of rhinitis symptoms associated with polyposis and the effects of polyp size.

In general, topical corticosteroids have well documented symptoms relief associated with nasal polyposis such as nasal obstruction, secretion, and sneezing, but its effect over hyposmia is not that good. There is a high level of clinical evidence about the effect of polyp size

and associated nasal polyposis symptoms. Topical corticosteroids are effective in improving nasal obstruction, but not in improving hyposmia.

However, oral corticosteroids present better results in relation to hyposmia. Despite the fact that there are no placebo-controlled or dose/effect studies concerning systemic corticosteroid, the use of this drug class in NP may be based on some open-label studies that have observed improvement in reduction of polyp volume, improvement in radiological pattern, nasal obstruction and hyposmia. Systemic corticosteroids may delay the need for surgical management, as well as facilitate it. In general, beneficial effects are observed within two weeks from start of use. There is no standardization of dose and/or oral corticosteroid to be used. Some authors associate oral and topical drugs with good results (Chart 8).

The use of systemic and/or topical corticosteroids isolated or in combination is effective to reduce recurrence of postoperative polyps after polypectomies.

There are no studies showing efficacy of corticosteroid injection in nasal polyps or inferior nasal concha. These procedures are considered obsolete and have high risk of amaurosis or fatty necrosis on injection site.

In view of recent discoveries about physiopathogenesis of NP - inflammatory disease with excessive production of eosinophils, it is easy to assume that treating the underlying disease with corticosteroids may be a rational option, even if surgical procedure will be performed. Therefore, topical and systemic corticosteroids are first choice medication in approaching nasal polyposis.

ANTIBIOTICS

It is significantly more difficult to assess efficacy of antibiotics in chronic rhinosinusitis in comparison with acute rhinosinusitis, given that there is conflict of terminology and definition of chronic rhinosinusitis presentations. There are few studies that have specifically analyzed antibiotic therapy in chronic rhinosinusitis with nasal polyposis.

DECONGESTANTS

The effect of decongestants occurs specifically over the inferior concha, confirmed by endoscopic and CT scan exams, but they have no effect over nasal polyp.

MUCOLYTICS

There are no clinical trials trying to correlate the use of mucolytics and improvement in NP.

ANTI-HISTAMINIC

They may be useful in subjects with nasal polyposis and associated allergy, in improving symptoms related

Quadro 8. Tratamento com corticoesteróide sistêmico na rinosinusite crônica com polipose nasal.

Study	Medication	N	Dose/ Time	Effect on symptoms	Effect on polyps	Level of evidence
Lildholt,1997	Betamethasone Budesonide	16	14mg/ 52 week	Yes	Yes	III
Lildholt,1988	Betamethasone beclometasone	53	?/ 52 week	Yes	Yes	III
Van Camp, 1994	Prednisolone	25	60mg/2 week	72%	Yes 10/22	III
Damm,1999	Budesonide Fluocortolone	20	?	Yes	?	III
Benitez, 2006	Prednisone Budesonide	84	2 week/10 week	Yes	Yes	Ib
Hissaria, 2006	prednisolone	41	50mg/2 week	Yes	Yes	Ib

Key: N: sample number

with rhinitis (nasal obstruction, rhinorrhea and sneezing), without affecting polyp size.

ANTIFUNGAL AGENTS

In open-label, not placebo-controlled studies in patients with chronic rhinosinusitis with and without NP, Ponikau has observed significant subjective improvement in 75% of the symptoms and in 74% of the endoscopic exams of patients submitted to application of topical nasal amphotericin. However, other placebo-controlled studies did not observe differences in reduction of nasal polyposis in subjects submitted to topical nasal antifungal before and placebo later.

BACTERIAL LYSATE

There are no clinical data that correlate the use of bacterial lysates and improvement of nasal polyposis.

IMMUNOMODULATORS

There are no clinical trials that correlate the use of immunomodulators and improvement of nasal polyposis.

NASAL/ANTRAL IRRIGATION

Even though some studies have shown that nasal irrigation are beneficial to relieving symptoms, improving endoscopic findings and in quality of life questionnaires of patients with chronic rhinosinusitis, there are no studies showing its efficacy in nasal polyps. It is known that hypertonic solution is preferred to isotonic solution, given that it improves mucociliary transport.

CAPSAICIN

Capsaicin is the active substance of red pepper. It is a neurotoxin that depletes substance P. Substance P is

effective in reducing nasal symptoms of patients with non-allergic rhinitis when applied topically. For this reason, some authors have used it topically and have observed reduction in size of polyps, as well as protective effect of their recurrence after surgical procedure, when compared to the placebo group.

FUROSEMIDE

The use of topical furosemide may play a protective role, reducing the recurrence of polyps after surgery; it may also be used preoperatively to reduce nasal polyp edema. The literature does not have any placebo-controlled study with prolonged use of this medication.

PROTON PUMP INHIBITORS

Some authors have tried to correlate chronic rhinosinusitis with presence of extraesophageal reflux. However, there are no studies correlating reflux and presence of nasal polyposis.

ANTI-LEUKOTRIENES

Improvement in symptoms of patients with chronic rhinosinusitis, with or without nasal polyposis, has been observed in patients submitted to anti-leukotriene treatment associated with conventional approach. AAS intolerant patients were also benefited from treatment. However, further controlled studies are required to study improvement in nasal polyposis and use of anti-leukotrienes.

ASPIRIN DESENSITIZATION

Systemic desensitization to aspirin or topical application of lysine-aspirin may be involved in protection of chronic rhinosinusitis and nasal polyposis. In general,

AAS is used in high doses (>600mg/d), thus treatment should be performed by experienced physicians, at hospital setting, because the risk of anaphylactic reaction is high. It is normally indicated in cases of nasal polyposis associated with AAS intolerance, but it may also be used in patients with asthma associated with nasal polyposis refractory to clinical and surgical treatment. However, further controlled randomized studies are required.

PHYTOMEDICINES

There are no clinical trials that have correlated use of phytotherapeutic agents and improvement in nasal polyposis.

CLINICAL TREATMENT X SURGICAL TREATMENT IN PATIENTS WITH CHRONIC RHINOSINUSITIS AND NASAL POLYPOSIS

Few studies in the literature have tried to correlate clinical and surgical treatment in nasal polyposis patients.

In 1988 and 1997, Lildholdt et al. developed two open label studies in which nasal polyposis patients were divided into 2 specific treatment groups: one group was treated with 14 mg injection of betamethasone and topical corticosteroid nasal spray (beclomethasone in 1988 and budesonide in 1997) and the other group underwent simple polypectomy followed by nasal spray of the same topical corticosteroid. After 12 months, both groups answered a questionnaire related to nasal symptoms and olfaction. Results were the same in both groups, concluding that corticosteroid acted similarly to surgical polypectomy, leading to a so-called clinical polypectomy.

Blomqvist et al. followed up 13 patients with nasal polyposis. All patients were treated with oral prednisolone for 14 days and nasal topical budesonide for 4 weeks. Next, only one nasal fossa of 32 patients was submitted to paranasal sinuses functional endoscopic surgery and postoperatively all patients were treated with bilateral nasal topical corticosteroid for 12 months. After this period, patients performed specific olfaction tests in each nasal fossa and answered a nasal symptom questionnaire. Authors observed that olfaction of patients had improved within 12 months, with no additional improvement in the operated nasal fossa. Surgical procedure had reduced the complaints of nasal obstruction and secretion. The authors concluded that surgical management should be indicated after clinical treatment, especially if there is persistence of obstruction and nasal secretion, but not if hyposmia is the primary complaint of the patient.

In 2004, Ragab et al. performed a prospective study with 90 patients with chronic rhinosinusitis with and

without NP. They separated two groups of patients – one referred to clinical management and the other to surgical management. Patients in the clinical management group were treated with oral erythromycin, nasal topical corticosteroid and nasal lavage with alkaline solution for 12 weeks. In turn, the surgical group was submitted to FESS depending on disease extension. Postoperatively, they were treated with two weeks of oral erythromycin, tramazoline nasal spray and nasal lavage with alkaline solution, plus nasal topical steroids for 3 months. Both groups were assessed at 6 and 12 months using SNOT-20, SF-36, nitric oxide nasal dosage and acoustic rhinometry. Both groups presented similar results and there were no statistically differences between the groups ($p>0.05$), except for total nasal volume, measured by acoustic rhinometry, in which patients submitted to surgery had higher values compared to those that were treated only clinically.

Even though the four studies have suggested that clinical and surgical treatment have similar results, some observations should be taken into account:

1. Studies by Lildholdt et al. were open-label and not controlled studies, with low level of evidence.

2. None of them described the extension of nasosinusoidal polyposis. Thus, a patient with extensive polyposis could have been matched to a patient with disease restricted to middle meatus edema, which would have led to different baseline diagnosis.

3. Efficacy of nasosinusoidal surgery to improve nasal polyposis has proven to be effective in all studies that compared it with clinical management and therefore, surgery may be considered a therapeutic option to treating nasal polyposis.

4. In the studies by Blomqvist et al. and Ragab et al, surgical treatment associated with clinical treatment was more effective than clinical treatment concerning nasal obstruction.

Long-term adverse events of medications should be taken into consideration when they are being prescribed. Systemic corticosteroids, for example, have severe adverse events and for this reason they should be used for 2 to 3 weeks in diseases, in the morning, for a maximum of 4 times a year. The likelihood of adverse events occurrence increases with dose and duration of use and, therefore, only the minimum dose required for treatment should be prescribed. Topical corticosteroids may present minor adverse events when used in the long run, such as nasal bleeding and septal perforation, in addition to major adverse events such as effects on growth, ocular effect, bone affection and adrenal-pituitary-hypothalamus axis affections, given that systemic bioavailability ranges from <1 to more than 40-50%. Chronic use of antibiotics, in turn, may lead to malaise, diarrhea and vaginal fungal

infections in women. Allergic presentations may also be triggered, in addition to Stevens-Johnson syndrome and irreversible ototoxicity generated by aminoglycosides.

SURGICAL TREATMENT

Among the objectives of treating nasal polyposis we can include improvement of nasosinusal symptoms – nasal obstruction, congestion, hyposmia, anosmia and hypersecretion, in addition to reducing number of infection episodes and recurrences, improving lower airway symptoms, if present.

Aware of the fact that long-term clinical treatment is efficient but may trigger significant adverse events, this is the time to indicate nasal polyposis surgery.

In general, clinical treatment should be administered at least for three months and if there is no improvement in symptomatology, characterizing therapeutic failure, the surgery should be indicated.

Surgical treatment should be indicated when primary complaint of the patient is nasal obstruction and/or nasal secretion. Ragab et al. used rhinometry to ob-

jectively observe improvement in nasal flow of patients submitted to surgery compared to those undergoing clinical treatment.

Improvement of hyposmia with surgical procedure is reason for controversy. On the one hand, Blomqvist et al. have not observed differences in olfaction of nasal fossae of patients submitted to clinical and surgical treatment. Alobid L et al., in turn, have observed that patients submitted to surgical management had better rates in quality of life questionnaire relative to hyposmia when compared to the group submitted to clinical treatment.

Some studies in the literature have demonstrated improvement in pulmonary presentation after surgical treatment of nasal polyposis and thus presence of pulmonary disease associated with difficult to treat nasal polyposis is also an indication for surgical procedure in the presence of clinical treatment.

According to Bachert et al., surgery should be indicated in therapeutic failures, presence of adverse events, low compliance to clinical treatment and rhinosinusitis complications. Chart 9 shows the main indications of surgery in treating nasosinusal polyposis.

Chart 9. Surgical indication in treating nasosinusal polyposis.

Failure in clinical treatment administered for at least 3 months
Adverse events in clinical management
Low compliance to drug treatment
Primary complaint of nasal obstruction, hypersecretion and/or olfaction disorders, without improvement with clinical treatment
Presence of persistent lower airway symptoms without improvement with drug treatment
Rhinosinusitis complications

When surgery is considered, preoperative treatment with systemic corticosteroids may facilitate surgical procedure because it reduces the size of polyps. Preoperative antibiotic therapy is indicated in the presence of associated infectious process to reduce intraoperative inflammatory process, which reduces bleeding during the procedure. Clinical pathology of nasal polyps, either pre or intraoperatively, may be useful in identifying possible eosinophilia, which leads to the diagnosis of difficult to control disease. Previous use of corticosteroids may prevent the detection of eosinophilic finding.

Many surgical modalities have been described to treat chronic rhinosinusitis with NP, including their advantages and disadvantages. Surgical techniques are based on exclusive removal of nasal polyps (simple polypectomy) to extraction of polyps associated with radical sphenoidectomy, such as those described in the specific section. Therefore, depending on disease staging, some specific surgical procedures may be performed. In some

cases, the association of external techniques, such as external sphenoidectomy, osteoplastic surgery of frontal sinus or even external maxillary sinusotomy may be associated with intranasal sphenoidectomy and/or intranasal frontal sinusotomy.

Surgical results depend on many factors: surgical technique, patient age, comorbidities, systemic diseases associated with nasal polyposis, surgical instruments, among others.

There are no literature reports comparing efficacy of external frontoethmoidectomy and endonasal access. However, studies that have compared Caldwell-Luc surgery and endonasal maxillary antrostomy have shown that the external approach is more likely to cause comorbidities such as orofacial edema and trigeminal nerve branch damage. Paranasal sinuses endoscopic surgery has nasosinusal symptom resolution rate of 73-97.5%, with complication rate of about 1%.

Among surgical instruments that may be used,

there are no statistical differences between the use of cutting or non-cutting clamps. The use of microdebrider considerably reduces surgical time, intraoperative bleeding and postoperative crusts when compared to conventional methods. The use of intraoperative laser reduces postoperative crusts.

Recurrence of nasosinus polyposis is high and may be present in nearly 60% of the patients two years after the surgery. Therefore, even maintaining clinical management after surgical procedure, revision surgery may be required. Bhattacharyya observed in a controlled prospective study that improvement of symptoms in patients with chronic rhinosinusitis refractory to clinical treatment after endoscopic surgery to drain paranasal sinuses is similar to improvement rate of patients submitted to the former, reinforcing the importance of revision surgery.

In revision surgery cases, as well as in massive polyposis, in which nasosinus anatomy is impaired, the use of CT navigation system may be instrumental to avoid complications.

9. COMPLICATIONS OF RHINOSINUSITIS

Acute complications of paranasal sinuses diseases are more frequent in children than in adults and are directly related with the close anatomical relations that exist between the paranasal sinuses and other head, neck and chest structures (Chart 10).

Chart 10. Complications of rhinosinusitis.

Orbital	Intracranial	Bone
	Meningitis	Brain bone osteomyelitis
Diffuse orbital cellulitis	Sub and extradural abscesses	
Subperiosteal abscess	Cerebral abscess	
Orbital Abscess	Cavernous sinus thrombophlebitis	

There are many literature studies that show the decline of this type of complication after the advent of antibiotic therapy and, more recently, thanks to the breakthrough of modern imaging techniques. However, we should bear in mind that in developing countries, in which one can still find poor nutrition, poverty and inappropriate health care, this is a prevalent problem that leads to high mortality rate. It is important to point out that RS may turn into a severe disease, which has many complications that require quick multidisciplinary approach, because delay in diagnosis may lead to patient's death.

9.1. ORBITAL COMPLICATIONS

According to the experience of most authors published in the literature, the most common complications of ARS are orbital complications. Ognibene et al. reported a prevalence of 83.1% of orbital complications in 65 patients studied within a 10-year period. Mortimore and Wormald found 80% complication rate in a 5-year follow-up study. In the findings by Mekhitarian Neto et al., male children were more affected than female patients. Before the development of antibiotic therapy, prevalence of orbital complications resulting from RS was very high.

Some series reported mortality rates of 17-19% and prevalence of amaurosis of 20-33%. Fortunately, those rates rarely go over 5% in our days.

Frontal and sphenoid sinuses may be source of orbital infection during late childhood, given that pneumatization of sinus starts at the age of 6 years. Conversely, ethmoidal labyrinth and maxillary sinuses are already pneumatized at neonates. OMC is the key area for the development of paranasal sinuses infections and, in most cases, they progress to the orbit. Some factors may explain this correlation:

- the close relation between orbital contents and ethmoidal labyrinth, which is separated from the orbit by a thin bone layer, papyraceous lamina;
- presence of many neurovascular foramens and sutures on the orbital medial wall, especially in children whose sutures are still opened, foramens are enlarged and bones are more porous, facilitating disease dissemination;
- occurrence of congenital dehiscence on the orbital floor and papyraceous lamina.

Avalvular venous system, which implies free communication between the face, nasal cavity, paranasal sinuses, orbit and pterygoid region, also facilitates dissemination of paranasal sinuses infections. In the genesis of orbital complications, the most important vessels to the system are upper and lower ophthalmic veins, which communicate with vessels inside the orbit and directly with the cavernous sinus, leading to free blood flow between ethmoidal veins and orbit veins. Therefore, complications of rhinosinus infections may result in directly extension. Purulent secretion in the ethmoidal labyrinth may interrupt blood flow to the periosteum, causing avascular necrosis of papyraceous lamina. The expansion of paranasal disease to the orbit by contiguity or through blood vessels will produce signs and symptoms that should be properly analyzed.

Staging and orbital classification of RS are extremely important to correctly decide on the best therapeutic option. Since 1937, when Hubert published the first

classification of sinusitis complications, up to 1997 when Mortimore & Wormald proposed the new classification based on CT, there has been huge confusion on the terminology of orbital infections given by the fact that many authors have used the words pre-septal and periorbital, which by definition describe the extra-orbital conditions to different infectious stages into the orbit.

The original classification by Chandler, published in 1970, has since then been used to divided orbital cellulitis into the following categories:

- 1) periorbital edema;
- 2) orbital cellulitis;
- 3) subperiosteal abscess;
- 4) orbital abscess;
- 5) cavernous sinus thrombosis.

This classification was designed in pre-CT scan era and its terminology does not take into account anatomical parameters that characterize orbital compartment. Technically, the orbit starts after the orbital septum. This structure is a reflex of the orbital periosteum (named periorbit) and at the level of the orbit rim adopts a vertical direction, forming orbit compartments and separating the orbital content from the palpebral one. Thus, no orbital pathological finding may be named pre-septal. The term pre-septal is used to describe palpebral pathology and should no longer be used to characterize orbital pathologies. There are similar problems with designations “peri-orbital cellulitis” and retro-orbital cellulitis”, commonly used in clinical practice to name intraorbital infections, which are not exact either. The last category in Chandler’s classification (cavernous sinus thrombosis) does not refer to orbital pathology, but rather mentions one of the most feared intracranial complications of cellulitis, and thus, should not be considered as a sub-type of orbital cellulitis either.

Therefore, Chandler’s classification, the most used one, has a number of problems. To make things easier, we will use the one proposed by Velasco-Cruz et al., which is based on more specific terms to help physicians define the best approach to each case (Table 5).

Table 5. Orbital complications of acute rhinosinusitis according to Velasco and Cruz.

I	Orbital cellulitis
II	Subperiosteal abscess
III	Orbital abscess

Diffuse orbital cellulitis: There is diffuse edema of orbital contents with enlargement of rectus muscle adjacent to infected sinus. The patient has axial proptosis (forward protrusion of eyeball), chemosis (conjunctival

edema), enhanced sensitivity, pain with extra-ocular muscle movement, edema and palpebral hyperemia. There may be mild abnormality of ocular motility. Visual acuity, pupil reflexes and eye fundus are normal.

Subperiosteal abscess: It is defined by presence of liquid (frequently collection of purulent material) between the periorbit and orbit bone wall. There are also palpebral edema, chemosis, non-axial proptosis (eyeball protrusion inferiorly, superiorly and laterally). There is inflammation of conjunctiva, pain and restriction of eye mobility. There is no reduction of visual acuity and eye fundus and pupil reflexes are normal.

Orbital abscess: It represents an extreme and immediately dangerous presentation because the infection has disseminated into the orbital contents. There is proptosis, chemosis, significant pain that never increases with bulb pressure or movement and ocular movement limitation. There may also be ophthalmoplegia, congestion of retina veins, papilledema, visual loss caused by ischemia or optical neuritis. As worsening of the picture, the disease extension may affect the cavernous sinus.

We should bear in mind that in many situations these presentations may be associated; for example, a typical case of subperiosteal abscess may present a halo of infiltration in the adjacent orbital fat.

Considerations and treatment

New modalities of imaging such as CT scan and MRI, as well as nasosinus endoscopy, have contributed enormously to early diagnosis in such cases and have also enabled identification of the grade of complication, providing to physicians the chance to start the appropriate management approach.

Therefore, after detailed history, careful physical examination (ENT, ophthalmologic, and sometimes neurological, if necessary), and laboratory tests, radiology prevails.

CT scan shows three-dimensional location of size of abscess and clear relations with eyeball, extra-ocular muscles and optical nerve. In children, the differentiation between orbital cellulitis and subperiosteal abscess is critical. According to Clary et al., the correlation between radiological and surgical findings, even though not absolute, supports the use of CT scan as a therapeutic guide and this is undisputable in our days.

In cases of subperiosteal abscess, CT scan reveals detachment of periorbit of one of the walls related to paranasal sinuses (roof, papyraceous lamina and orbital floor). The detachment is shown by presence of homogeneous opacification between the orbital wall and displaced periorbit. There is edema of extra-ocular muscle related to the abscess and non-axial displacement of eyeball. In

orbital abscess, CT reveals obliteration of extra-ocular muscles and optical nerve, and homogeneous mass compatible with abscess. Differential diagnosis of orbital cellulitis includes palpebral infection, idiopathic orbital inflammation (pseudotumor) and neoplasm.

Healy is absolutely correct when he states that the main principle described by Chandler remains valid up to present: patient hospitalization, ophthalmic assessment and aggressive management using intravenous broad spectrum antibiotics that cross the blood-brain barrier, always focusing on the most commonly found agents, which include *Haemophilus influenzae* (especially in children below the age of 5), *Streptococcus pneumoniae* and *Staphylococcus aureus*. Anaerobes are occasionally isolated in children. Treatment should be promptly started and modifications are made right after the result of culture, which may be performed in the outpatient center, directly into the middle meatus using nasal optical fiber. Total management time should be considered based on clinical progression of patient (Table 6).

Table 6. Treatment of rhinosinusitis complications in adults and children with normal renal function.

Adults	Children
Oxacillin- 2 g IV QID + Ceftriaxone	Oxacilina - 200 mg/kg/dia EV de 8/8 h + Ceftriaxone - 100 mg/kg/dia EV de 12/12 h
- 2 g IV BID	Oxacilin - 200 mg/kg/day IV TID + Ceftriaxone - 100 mg/kg/day IV BID
Amoxicillin clavulanate – 1 g IV TID	Amoxicillin clavulanate – 100 mg/kg/day IV TID
Levofloxacin- 500 g/day IV + Clindamycin – 600 mg IV TID	Chloramphenicol – 100 mg/kg/day IV QID

Surgical indication is essential in cases of abscess. In some cases, the decision to operate is related with two situations. On the one hand, the patient has not progressed well with antibiotic therapy after 24-48 hours. The parameters used to assess the progression of the patients are: phlogistic signs, ocular motility, proptosis, and visual function. In the presence of visual deterioration or absence of improvement as a whole, surgery should not be postponed. Alternatively, the patient improves but there are persisting unacceptable visual abnormalities. In this case, drainage of abscess plus paranasal sinuses surgery should be performed.

The decision about the best surgical technique depends on the individual experience and technical mastery of surgeon. Currently, and increasingly more frequently, surgeons have preferred nasosinusal endoscopic surgery. Many advantages have been reported.

1) Treatment of baseline disease (cleaning of infected cavities, removal of narrowed structures and widening of space limited to drainage and ventilation of the whole OMC) and, concomitantly, drainage of orbital abscess;

2) Easy access to typical sites of superiosteal and intraorbital abscesses on the medial wall of the orbit using endoscope;

3) Diagnostic technique: it is possible to make more precise examination of the nasal fossae (to assess the presence of foreign bodies, polyps and tumors) and appropriate collection of material for culture;

4) Procedure safety: it is an extremely safe technique in experienced hands that provides to patients shorter recovery time, reducing the length of stay in hospital;

5) There are no scars and it has low surgical complication rate. External frontoethmoidectomy, widely used, in our opinion should be reserved to revision cases or to situations in which the orbital abscess is lateral after frontal sinus infection. In the presence of localized abscess in regions difficult to reach using an endoscope, other surgical approaches routinely used by specialists in orbital surgery may be employed. Transconjunctival access to the orbit floor and medial wall (infracaruncular access) is an excellent option for orbital drainage. The same may be said about access through the superior palpebral sulcus that provides broad exposure of orbit roof.

9.2. INTRACRANIAL COMPLICATIONS

They are rare complications, but potentially more dangerous because they have significantly higher rate of mortality (20-40%), despite all modern diagnostic and therapeutic resources. Kraus & Tovi presented a study of 58 cases of central nervous system complications in 39 children in which 20% of the cases had RS as the main cause. Lerner et al., studying 443 children admitted to Children's National Medical Center, found 3% of rhinosinusal-based central nervous system complications.

Because of their location, ethmoidal, sphenoid and frontal sinuses are prone to causing intracranial problems. Acute processes, in addition to acutely worsened chronic problems, amount to the highest number of complications. This type of complication is more commonly caused by retrograde thrombophlebitis through avascular diploic veins. They are extensively in communication with dura veins and emitting veins, which are interconnected with upper sagittal and cortical veins. In adolescence, diploic system vascularization is enhanced, and it coincides with the expansion of frontal sinuses, both predisposing factors to development of post-RS frontal complications.

Focal inflammation (frontal bone osteitis) may take to avascular necrosis and osteomyelitis of anterior and

posterior frontal bone plates. When dissemination is made towards the anterior plate, there may be skin edema over the frontal sinus, protruded as a mass, characterizing the edematous tumor of Pott. When dissemination is backwards, there may be meningitis and abscesses.

Meningitis

It is the most common intracranial condition. It is a pia mater and arachnoid inflammation mainly caused by sphenoid RS.

Singh et al. found 22 cases of meningitis (10%) in 219 studied children with intracranial complications; 59% of the cases had associated orbital inflammation; 46% of the cases died. Unfortunately, this type of complication still has alarming high mortality rate.

Patients presented high temperature, lethargy, neck rigidity, photophobia, and headache. Pain is diffuse and severe owing to meningeal involvement. After neurological examination, cerebrospinal fluid investigation is essential.

Sub and extradural abscesses

Singh et al. found 144 cases of abscesses (127 subdural and 17 extradural cases) among 219 studied children. They were normally found in older children and amounted to 50-70% of all subdural empyemas.

Clinical presentation is not very well known and diagnosis is frequently delayed by one to three weeks, when symptoms progress with signs of intracranial pressure increase: worsening of headache, vomiting, lethargy, behavior disorders, and palpebral edema. Mortality rate ranges from 18% to 40%.

Brain abscesses

Singh et al. found 38 cases of brain abscesses among 219 studied children. Gallagher et al. found 14% of brain abscesses in 176 patients. This type of abscess is not common in childhood, comprising less than 25% of brain abscesses in the general population. ENT disease is the most common source of abscesses, and rhinosinusal origin is responsible for nearly 2/3 of the cases. However, when the abscess is formed, the mortality rate is 10-20% despite aggressive and early management. Classical neurological presentation, frequently seen in adults, is mild or absent in children. Focal symptoms and increase in intracranial pressure is sometimes late, leading to progressive deterioration of general conditions, coma and cranial nerve palsy.

Cavernous sinus thrombophlebitis

Formation of orbital abscess may in some occasions migrate to the cavernous sinus, leading to retrograde

thrombosis. The most important signs and symptoms are fever, lack of activity, severe and profound pain behind the orbit, bilateral involvement leading to visual loss and ophthalmoplegia. Prognosis is poor and mortality rate is high, reaching nearly 30%.

Considerations and treatment

Brain, orbit and paranasal sinuses CT scan, with and without contrast, should be performed to confirm the presence and determine extension of the complication. MRI may be more sensitive to detect early stages and it is more indicated to study cerebral parenchyma abnormalities.

High doses of intravenous antibiotic should be promptly started, even before the causal agent is determined. Definite adjustment of treatment is guided by the results of culture and duration is determined by clinical response. In general, there is association of two or more antimicrobial agents, especially in cases of infection caused by more than one etiological agent. The most commonly found pathogens are Streptococcus, Staphylococcus and anaerobes. Most of the cases require craniotomy and surgical drainage to ensure successful treatment result.

Bone complications

Cranial bone osteomyelitis is a complication that may be fatal due to the absence of anatomical barrier from diploic brain veins. The incidence of this type of complication is higher in adolescent years. It may be presented by high fever, local and severe pain, headache and conscious affections that present slow and gradual worsening. Recommended management is intravenous antibiotic. Surgery is indicated only in cases of bone sequestration.

9.3. COMPLICATIONS OF RHINOSINUSITIS SURGICAL TREATMENT

Similarly to the onset of complications, the close relation between paranasal sinuses, cranial fossa and orbit expose the orbital and cranial contents to the risk of damage during paranasal sinuses surgery, especially of ethmoidal sinuses. Despite the fact that complications are rare, they may result in severe morbidity, including the most severe one, which is permanent visual loss.

Currently, paranasal sinuses endoscopic surgery has been the procedure of choice in treating CRS and NP, because it is relatively safe especially when performed under the supervision of modern ENT training programs.

The incidence of these complications varies a lot in the literature, regardless of external, intranasal or endoscope-assisted intranasal approach. To some authors, the

Table 7. Postoperative complications of paranasal sinuses surgery.

	Major Complications	Minor Complications
Orbital	Hematoma	Orbital emphysema
	Loss of sight	Palpebral ecchymosis
	Diplopia	
	Lachrymal pathway trauma	
Intracranial	CSF fistula	Uncomplicated CSF fistula
	Pneumoencephalus	
	Encephalocelle	
	Cerebral Abscess	
	Meningitis	
	Intracranial hemorrhage	
	Brain damage	
Hemorrhage	Severe (requires large packing and blood transfusion)	Mild
	Damage to anterior ethmoidal artery	
	Damage to sphenopalatine artery	
	Damage to internal carotid artery	
Others	Severe exacerbation of preexisting asthma	Mild exacerbation of preexisting asthma
	Toxic shock syndrome	Anisocoria
	Anosmia	Sinechya
	Death	Hyposmia
		Local infection (osteitis)
		Atrophic Rhinitis
		Temporary irritation of infraorbital nerve
		Hyperesthesia of lips or teeth

rate of post-endoscopic surgery is lower, whereas others disagree. However, according to Bolger & Kennedy, we have been operating much better and completely reaching the paranasal sinuses. Complications may be divided into major and minor and are shown in Table 7.

Meta-analyses of these data have suggested that major complications occur in approximately 1% of the cases and minor complications in 5-6% of the cases, that is, low incidence even in teaching institutions, probably owing to the advance of videoendoscopic monitoring, neuronavigation surgery and improvement of teaching and training methods of surgical techniques. In 1995 Stamm, among 420 operated cases between 1983 and 1993, reported five cases of CSF fistula, three cases of orbital lesion, six cases of hemorrhage, five cases of facial pain and one case of meningitis. Voegels et al. described the presence of 66 cases of synechiae, five cases of papyraceous lamina damage, one case of anterior ethmoidal artery damage, and one case of subcutaneous periorbital emphysema in 706 cases operated between 1995 and 2000.

The surgeon should be familiarized with anatomy

and physiology, basic surgical techniques, risk areas and significant strategies to early identify and manage these complications. Appropriate training using laboratory tests, endoscopes and imaging exams (CT and MRI) may help prevent and minimize such complications. According to European Guidelines on Rhinosinusitis 2007, special attention should be given to risk factors for post-surgical paranasal sinuses complications:

- Extension of the pathology, which require infundibulotomy or complete surgery to all sinuses;
- First or revision surgery, in which there is loss of anatomical landmarks, papyraceous lamina dehiscence;
- The most affected side of sinuses: the right side is more frequently affected and it is the most difficult to be operated on;
- Hemorrhage present during surgery: use of microdebrider and systematic continuous use of intravenous anesthetic drugs with plasma metabolism - Propofol may significantly reduce the rate of hemorrhage;
- Experience of surgeon: a specific training program, including cadaver dissection, surgical technique

courses, video studies, supervision in the first surgeries, gradual progression towards complexity is always recommended.

Another important point is the obligation the surgeon has to discuss the procedure and its risks with the patient. Informed consent is the process of explaining the procedure and its risks, benefits and alternative treatments, including their implications if the surgery is not performed, which enables the patient to make the decision of undergoing the surgery or not. According to Wolf et al., this is key to reduce patients' dissatisfaction. In addition to medical-legal aspects, appropriate patient-physician relationship contributes to safer and confident performance by the surgeon.

10. CHRONIC RS AND LOWER AIRWAYS

The purpose of this presentation is to correlate CRS and bronchial hyperreactivity.

Respiratory inflammatory chronic syndrome has broad spectrum of clinical manifestations. In severe cases, there is commitment of the whole respiratory tract - CRS in the upper respiratory airways and bronchial hyperreactivity in the lower airways. The correlation between upper and lower airways affection has strong evidence: both non-allergic and allergic CRS are risk factors for bronchial asthma. The assumption that the nose is the core of inflammatory chronic syndrome is justified by the fact that it is the preferred site for air allergen deposits, including bacterial and fungal allergens. Pathophysiology of bronchial hyperreactivity involves different airways: nasal obstruction and mouth breathing, nasal-sinusal-bronchial reflex, release of inflammatory mediators (cytokines and interleukins), microaspiration of lower airways - all these factors together facilitate bronchial asthma.

Incidence of allergy in the CRS is extremely variable. This variability is probably consequence of the characteristics of the analyzed sample. Friedman found 94% of allergic cases among hyperplastic CRS patients submitted to sinusectomy. More recent studies in patients with CRS undergoing FESS showed incidence of allergic patients that ranged from 14% to 60%; in children submitted to FESS, allergy ranged from 49% to 60%.

Comments on Clinical Practice and Epidemiology of CRS and Bronchial Hyperreactivity

Imaging diagnostic studies of CRS in a population of asthmatic patients showed radiological findings suggestive of CRS in 88% of the patients with mild asthma and in 100% of the patients with severe asthma. Upon comparing the control group (not asthmatic) with the asthma group, it was concluded that ethmoidal sinus was the most affected in the asthma group. It is important to point

out that imaging abnormalities should not be dissociated from clinical presentation, because they may give rise to false positive results.

Clinical and epidemiological studies are positively correlated with CRS and bronchial affection. In a sample of CRS, 40% of the patients had healthy lower airways (LA); 60% had bronchial hyperreactivity, and out of these, 36% had positive bronchoprovocation caused by histamine and 24% were asthmatic. In a sample of patients with bronchiectasia, 70% had CRS; in a population of non-allergic asthma patients there was "high incidence" of CRS.

In a study dedicated to bacteriology of upper and lower airways in CRS, the authors confirmed positive culture in 71% of sinusal secretion and in 8% of bronchial lavage, and they never mentioned the agreement of biota. These results suggested that in CRS microaspiration of secretions through the lower airways has secondary importance.

Bachert et al., in a current study, correlated CRS without NP, CRS with NP and lung affections. They concluded that different inflammatory mediators and different types of tissue regeneration in both forms of CRS determine different bronchial affections. In CRS without NP bronchial asthma is prevalent and in CRS with NP, COPD is prevalent.

Comments about histopathology and immunopathology

Histopathological and immunohistochemical studies in people with CRS and bronchial asthma have detected similar characteristics of sinusal and bronchial asthma: basal membrane thickness, eosinophilic infiltrate, proliferation of myofibroblasts and increased expression of IL-1, IL-3, IL-5, IL-6 and IL-8 and cytokines Th-2. CRS with NP has exuberant eosinophilic infiltrate and different concentrations of interleukins and cytokines when compared to CRS without NP, which determines different forms of tissue repair. CRS and bronchial asthma are part of a systemic disease that involves the respiratory tract as a whole.

Recently, research studies have suggested that the symptomatic triad AAS intolerance, bronchial asthma and naso-sinusal polyposis is related with immune-allergic response to super-antigen *Staphylococcus aureus* (enterotoxin). Conversely, in asthmatic patients, Lee et al. have observed significant increase in specific IgE to superantigen in *S. aureus* and have suggested that this IgE is correlated with bronchial hyperreactivity.

CRS treatment and its repercussion in bronchial hyperactivity

Surgical approach of CRS, be them maxillo-ethmoidal sinusectomies or FESS, suggests improvement of asthma both in children and in adults, which may occur in

80% of the subjects submitted to FESS. Conversely, Smith et al. stated that FESS improves quality of life of patients with CRS, but in the triad of AAS intolerance, results of the surgery are disappointing. Kim et al. reported clinical and endoscopic presentation of people with CRS with and without asthma submitted to FESS; in the group of CRS with asthma, post-surgical results were worse. Ragab et al. demonstrated that both clinical and surgical treatment for CRS improved subjective and objective parameters of asthma (VEF1). Clinical treatment proved to be more long lasting than surgical treatment.

The use of anti-leukotrienes in AAS intolerance triad controls CRS; clinical treatment of CRS improves symptoms of asthma and quality of life in children.

Studies have shown conflicting results in relation to surgical treatment, especially in cases of AAS intolerance triad. Clinical and surgical treatment of CRS with asthma suggests beneficial results but randomized studies and objective analyses of the studies are still required.

Conclusion

The role of CRS in asthma is still only partially understood, especially owing to the deficiency in clinical classification and knowledge of pathogenic mechanisms.

Existing clinical epidemiological and immune evidences point to the concept of a single inflammatory disease involving the upper and lower airways. This concept suggests that CRS and asthma are not localized diseases, but rather part of an inflammatory systemic disease that involves the whole respiratory tract. Therefore, we should consider combined treatment strategies for CRS and asthma.

11. FUNGAL RHINOSINUSITIS

Fungi, bacteria and viruses, are well defined as one of the etiologies of RS, specifically in chronic presentations (CRS). Viable or not, they may be found in the nasal fossae both in patients with CRS and in normal subjects right from birth, which makes it difficult to differentiate these microorganisms as colonizers or infectious agents. All explanations about what really determines the modifications in behavior of fungi and inflammatory responses of host and their presence in the airways are still not fully understood at all. In the meantime, it is clinically essential to define whether the respiratory mucosa has fungal invasion or not.

The classification has three new entities: benign fungal ball on one extreme of the spectrum, and invasive fungal RS on the other extreme, with high morbidity and mortality, but both have clear clinical and laboratory diag-

nostic presentations. Finally, allergic fungal rhinosinusitis (AFRS), more prevalent than the others, but presenting terminology, diagnostic confirmation methods and therapeutic possibilities widely questioned in the literature - it is questioned whether it is really a fungal pathology and whether it is more prevalent than what has been described to present.

Classically, different types of AFRS are differentiated into invasive and non-invasive. Both fungal ball and AFRS are considered non-invasive processes, in which signs and symptoms are originated from local and/or systemic inflammatory response and there is time to discuss different treatment options. Invasive processes are considered resultant from a specific fungal infectious process. Morbidity of invasive processes may vary in different subjects, depending on the level of immunosuppression of the host and aggressiveness of the involved fungus. These differences lead to subdivision of invasive processes into acute or fulminating invasive fungal RS and chronic invasive fungal RS (indolent), with prognosis that depends on patient's immunity (which is in generally good). The nomenclature chronic granulomatous rhinosinusitis is used to address a specific group of North-African patients.

Saprophyte infestation is a phenomenon in which fungi are visibly close to nasal and paranasal sinuses crusts in an asymptomatic form. It is more frequent postoperatively in nasosinusal surgeries and not specifically as an entity among fungal RS.

Classification (Table 8)

- Fungal ball
- Allergic fungal rhinosinusitis
- Invasive fungal sinusitis

- Acute invasive fungal rhinosinusitis (fulminating)

- Chronic invasive fungal rhinosinusitis (indolent)
Fungal ball

In the case of fungal ball, there is accumulation of mycelium resulting from deposit and deficient germination of spores from different inhaled fungi (*Aspergillus fumigatus*, *Aspergillus flavus*, *Alternaria* sp., *Rhizopus microsporus* and *Pseudallescheria boydii*) over the respiratory mucosa of one isolated paranasal sinuses without invading the mucosa. Even though it is not characterized by the presence of marked inflammatory response, there are local inflammatory reactions with identification of purulent secretion drained to the affected paranasal sinus. Treatment is directed to complete removal of fungi regardless of the chosen surgical technique (endoscopic, combined or external).

Table 8. Classification of fungal rhinosinusitis

Classification	Fungal Ball	AFRS	Acute Invasive FRS	Invasive FRS (Fulminating) Chronic (Indolent)
Sings and Symptoms	Intermittent and non specific nasosinusual symptoms, with purulent occasional sinus detected by endoscopy	Chronic nasosinusual symptoms (congestion). Nasal polyps. Always mucin. Positive Prick/ specific IgE.	Nasosinusual symptoms were initially not specific with fulminating progression, with symptoms that depended on impaired areas (CNS, eyes, palate, skin). White areas, ischemic or dark crusts at endoscopy, with minimum bleeding upon manipulation.	Non-specific and chronic nasosinusual symptoms that may determine impairment of vision at orbital apex area. Immunocompetent patients.
Immunity	Immunocompetent patients.	Immunocompetent patients	Immunosuppressed patients (< 500 leukocytes)	Mild immunosuppression or immunosuppressed
Radiology	Isolated paranasal sinus is affected (maxillary sinus is the most common). Isolated radiopaque image.	Asymmetry in both sides. Variation of density of secretions. MRI - hypersignal of mucosa; hyposignal of secretion. Bone redefinition.	Images may be initially normal with mild edema of mucosa and/or nasal vestibule skin, progressing to lesions that invade neighboring tissues MRI is important in cases of suspicion of CNS invasion because of differences in prognosis	Images similar to AFRS or eosinophil mucin
Histology	Mucosa without invasion with no specific mild inflammation. Cluster of hyphae (Aspergillus sp. is the most common one).	Mucosa without invasion with marked eosinophilic inflammation and mucin with necrotic eosinophils and fungi (hyphae).	Invasion of mucosa, submucosa, vessels and bone by fungi.	Characteristic mucin and mucosa and/or submucosa invasion by fungi.
Treatment	Surgical extraction (external and/or endonasal access).	Endonasal surgery. Long postoperative systemic corticoid and topical corticoid during upper airways infection.	Endonasal and/or external surgery trying to maintain oncological principles. Intravenous systemic antifungal agents	Endonasal surgery. Oral systemic antifungal agents (intravenous agents if immunosuppressed patient ≤ 500 leukocytes).
Prognostic	Cure	Improves quality of life Frequent recurrences	High mortality Short term	Chronic presentations/ frequent recurrence Immunocompetent. Morbidity and mortality to be considered in immunosuppressed.

Allergic Fungal Rhinosinusitis (AFRS)

AFRS was described for the first time more than 20 years ago and the most common diagnostic criteria were described by Bent and Kuhn in 1993, including the history of type 1 hypersensitivity, skin tests or positive serology tests to fungi, nasosinus polyposis, characteristic CT scan findings, eosinophilic mucin without mucosa invasion by fungi, and direct or positive culture to fungi of material extracted through surgical exploration. Currently, there are some convictions and some uncertainties about the role of fungi in RS.

In some sporadic situations, patients may present dramatic clinical pictures owing to compression and displacement of key structures and/or acute nasal obstruction, but in general clinical presentations are subclinical and slow.

Radiological findings strongly suggest the diagnosis by symmetrical impairment of many paranasal sinuses showing central hyper attenuation, occasional isolated mucocoeles, as well as narrowing and/or erosions of bone limits (papyraceous lamina and skull base) in the CT scan and reduction of sign in center of affected paranasal sinuses in MRI, both at T1 and T2, which corresponds to mucin areas (high protein and low water content, in addition to heavy metal deposits) and peripheral hypersignal of inflamed mucosa.

Immune assessment of these patients show significant positive results in both skin and serology tests to fungal and non-fungal antigens. Responsiveness to different fungi by the same subject has raised the hypothesis of a common element among these microorganisms with significant antigen power. High serum IgE is also a frequent finding in patients with AFRS.

Macroscopic identification of thick and persistent secretion owing to its high viscosity, with color that ranges from light brown to brown or dark green, is considered pathognomonic of AFRS. In other words, in this disease the characteristics of mucin are more important to final diagnosis than the history of respiratory mucosa. This fact should not exclude the need to make histopathological assessment of polyps and mucosa, because we have to rule out the possibility of an invasive process. In most cases, the mucosa has chronic inflammation with predominance of eosinophils, whereas mucin is described as laminations, such as onion peel, with necrotic eosinophils or degranulation areas, amidst mucin, with occasional hexagonal crystals of lysophospholipase, named Charcot-Leyden crystals, and rare fungal hyphae.

Regardless of the discussion about the true role of fungi, one of the main obstacles to diagnosis of AFRS is the difficulty to cultivate and identify involved fungi.

It is a consensus that in addition to having a laboratory with mycological experience, there should be a routine logistic to enable transport of collected material as soon as it is collected from patients. Despite the fact that the use of collection techniques with irrigation seems to enable collection of more material coming from inaccessible areas than by swabs and brushes, we should be careful to interpret results of a possible inclusion of material coming from rhinopharynx, vestibule and even the skin. Endoscopy-guided aspiration of different regions of paranasal sinuses in a sequential and independent way may minimize the risk of confusion. Therefore, similarly to investigation of bacteria causing RS, it is possible that endoscopy-guided middle meatus lavage present the same results as direct collection from the paranasal sinuses. Even using the same techniques, percentages of positivity are still widely varied among different authors. DNA identification of different fungi through polymerase chain reaction (PCR) has been interpreted as a confirmation of studies that cultivate fungi in most of the patients and an indication that the problem of high percentage of negative cultures in the other studies result from the logistics employed by such centers.

The presence of hypersensitivity inflammatory response mediated by IgE and IgG in the respiratory mucosa in view of presence of fungi, or especially of its proteins, with significant recruiting of eosinophils and its consequences (formation of mucin) is responsible for triggering and maintaining the signs and symptoms of patients. Fungal morphology has close relation with the intensity of immune response by patients. For example, whereas spores and yeasts can be entirely phagocytized, hyphae require support of more than one inflammatory cell. The search for identification of specific immunoglobulins to different fungi in this group of patients is pointed as a possibility to make a correct differential diagnosis with other CRS in which there is also formation of mucin, but in which there is no identification of fungi and/or presence of atopy. These patients are classified as having mucin eosinophilic rhinosinusitis (MERS). The recent comparison of genes contained in patients diagnosed as having AFRS and MERS did not show any significant differences between the two groups.

Treatment still includes surgery as an important support in managing AFRS, even though it has high recurrence. There are no evidences in the literature to define what is the best technique to approach these patients: minimally invasive surgery (MIST) or FESS or nasalization. If topical antifungal agents are shown to be useful in treating these patients, it is likely that techniques with exposure of cavities are more indicated. To present, there is no definite support to the use of topical or systemic antifungal agents in AFRS.

Topical and systemic corticosteroids are the base of treatment, but they may require prolonged use since immediate postoperative setting, usually in regressive doses. The use of systemic corticosteroids is also indicated at high initial doses for a short period of time during airway infections owing to the high level of recurrence of the disease. Endoscopic surgery to remove polyps, hyperplastic mucosa and accumulation of mucin are still the best signs and symptoms of improvement. Postoperative immunotherapy has shown results in preventing recurrence together with other short-term therapies. Other drugs, including anti-leukotrienes, antibiotics with associated antiinflammatory action are not supported by any literature data to present. Definitive results are not available for the use of topical or systemic antifungal agents.

From a practical perspective, to present, laboratory identification of fungi in paranasal sinuses material seems to determine no difference in prognosis, management and quality of life of these patients. However, while there are questions, at least from an academic perspective, complete study of these patients valuing the search for fungi and other elements that may be part of the pathogenesis of CRS should be encouraged, including the differentiation of these patients to better target possible new therapeutic options that require correct classification. To that end, systematic approach of material collection methods, type of medium and quick transport to a laboratory with experience in the study of fungi is essential to successfully identify these microorganisms. The contents of lavage or collection by secretion aspiration with sterile solution of areas under endoscopic vision should be quickly gathered and sent to the laboratory where trained staff can manipulate the sterile secretion using the accepted technique to avoid contamination (under laminar flow) with substances that dissolve the mucus and release possible fungi. Out of the collected material, 0.5ml are cultivated in medium of Sabouraud/glucose (4%) with chloramphenicol (0.4 gl-1) and gentamicin (0.04 gl-1) and incubated for 30 days at 37° and 30° C, respectively. Other 0.5 ml should be analyzed, if available, by PCR under strict technique to avoid false positive results by sample contamination. Material may also be submitted to microscopy for direct identification of fungal hyphae. The use of techniques such as PCR may serve to confirm that there are fungal particles inside the nose and paranasal sinuses which may be a response to the difficulties found in studies that use the culture as the main investigation medium. However, it should not be used in the attempt to differentiate colonization and infection by fungi in the upper airways. Taking it for granted that it is necessary to investigate the presence of fungi, likewise we should perform skin and serological tests to confirm whether the patient is allergic

in general and, if possible, to the cultivated fungus.

Other entities in process of definition with very similar clinical presentation to AFRS, especially owing to the presence of mucin and eosinophils, are fungal eosinophilic rhinosinusitis without atopy and eosinophilic rhinosinusitis in atopic cases, but without fungi.

Invasive fungal rhinosinusitis (fulminating and indolent)

Invasive rhinosinusitis diseases are infectious forms commonly identified in patients with underlying diseases such as diabetes, induced immunosuppression such as in transplanted cases, or immunosuppressant diseases. In diabetic patients, the most common agent is *Mucor* sp, which benefits from the acid medium that these patients are exposed. In other cases, there is variation in type of fungi, with high frequency of *Aspergillus* sp. Even though not all acute invasive processes are fulminating, the name warns to the need of early diagnosis, which increases the chance of treating the patient before his death. Immunosuppressed patients (<500 leukocytes) or uncontrolled diabetic patients with nasosinusal symptoms should always be assessed, regardless of normal result of imaging exams. The presence of light ischemic lesions or dark necrotic lesions at nasal endoscopy should be promptly submitted to biopsy to confirm the diagnosis of fungi (hyphae) invading the mucosa or bone, in addition to perivascular and endovascular impairment and microvessel thrombosis. Studies have pointed to the middle concha as a frequently affected area, which can be possibly used for biopsies in these patients. In many situations, ischemic lesions or significant edemas may be detected close to the nasal vestibule, including nasal skin. CT scan may confirm the presence of inflammation with or without lesions that compromise bone limits of nasal fossa and/or paranasal sinuses and/or hard palate, which also confirms the diagnosis and supports the definition of surgical procedure extension. MRI may be useful in cases of doubts concerning invasion of central nervous system or large vessels, because in case of confirmation, mortality gets close to 100% and major deforming surgical procedures may be dully weighted against the real benefits. In addition to surgery, the use of systemic antifungal agents is indicated. High doses of amphotericin B are used by adding liposomal release when there is renal failure caused by monotherapy. In cases of infections by *Aspergillus* sp comparative studies indicate higher efficacy of the use of Voriconazole in relation to Amphotericin B. New antifungal agents such as Caposfungin still need definite results in comparison to the available antifungal agents. Surgery should be as broad as possible, as oncological surgery would be, to try to reach the limits of the disease.

In addition to acute invasive form (fulminating), there may be chronic presentations (indolent) in patients with less significant immune affections or even in some undiagnosed cases or immunosuppressed patients. The subdivision into non-granulomatous and granulomatous has not proven to have any use for prognosis and management. The granulomatous form is found in the North of African continent, including bone necrosis due to the pressure caused by fungal agents, orbital proptosis or even brain invasion. In chronic invasive form in immunocompetent cases, presentation is similar to any case of chronic nasosinusal affection, with NP, mixed cell infiltrate, and thick mucus and pus. In immunodepressed patients, morbidity is higher and it may affect orbital apex, with reduced visual acuity and ocular mobility, in addition to ocular proptosis and intracranial invasion. Prognosis and aggressiveness of treatment depend on status of immunity of the patient, which may vary from minor endonasal surgery to major procedures, comprising no systemic antifungal to intravenous treatment with these drugs. In addition to the reported fungi, other common etiological agents are *Mucor* sp. and *Basidiobolus* sp.

Diagnostic suspicion of fungal rhinosinusitis

- Isolated impairment of one paranasal sinus (maxillary, sphenoid) or asymmetric impairment (significant percentage of unilateral disease), with opacification and calcification of its inside and/or different density in CT scan and hyposignal in secretion and hypersignal in the mucosa shown by T2 section of MRI.
- Facial pain with exacerbation, non-specific signs and symptoms of RS (congestion, headache, rhinorrhea, etc), nasal and facial edema.
- Thick brownish secretion (mucin) and/or caseous by diagnostic endoscopy or during surgical act.
- Ischemic or necrotic areas found by endoscopy.
- Direct examination of secretion with eosinophils in degranulation and/or necrotic appearance (Charcot-Leyden crystals).
- Direct fungi identification (hyphae); if negative, positive culture (Sabouraud/Micosel); if both are negative, positive PCR (considering clinical and radiological findings described above).
- Mucous cover with nonspecific inflammation; if fungi are present in the epithelium, submucosa and/or bone, invasive presentation (correlate with clinical findings and immune status of the patient).
- Similar clinical and radiological presentation as in eosinophilic mucin; there are no methods available to identify positive fungi that may indicate non-fungal eosinophilic CRS (mucinic, atopic or non-atopic).

- Presence of fungi by direct examination, culture and/or PCR may be found in normal subjects.

12. RHINOSINUSITIS IN CHILDHOOD

Rhinosinusitis in childhood is an affection that brings significant repercussions to quality of life of children and parents. A study by Cunningham et al. has shown that parents and children with CRS perceived it as causing more physical limitation than bronchial asthma or juvenile rheumatoid arthritis.

RS in children has many peculiarities that should be considered for management. The first difference concerns anatomy. Upon birth, the subject has only maxillary sinus and 2 or 3 ethmoidal cells. Sphenoid sinuses are present at the age of 2 years, even though some rudimentary structure may be seen in neonates. Frontal sinuses start to develop at the age of 6 years. At about 7 years, maxillary sinuses reach the height of nasal fossa floor.

Children immune immaturity makes them present a higher number of episodes of upper airway infections of viral etiology (6 to 10 per year, as opposed to 2 to 5 in adults). Thus, if 0.5% to 10% of viral upper airway infections progress to bacterial infection, incidence of RS in children is higher than in adults. There is clear reduction of prevalence after 6 to 8 years, probably owing to maturation of immune system.

An MRI study in school-aged children evidenced that 50% of them had some paranasal sinuses mucosa affection. Half of the patients had resolution of the process 6 to 7 months later, without any intervention. Another MRI study showed prevalence of 45% sinusal affections in children. The prevalence increased to 50% if at the time there was nasal obstruction complaint, 80% when mucosa edema was present at rhinoscopy, 81% to tests performed after recent upper airways infection, and 100% in the presence of purulent rhinorrhea.

The most commonly isolated bacteria in children with ARS are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catharralis*. In CRS, in addition to these pathogens, there is predominance of *Haemophilus influenzae*, alpha-hemolytic *Streptococcus*, coagulose-negative *Staphylococcus*, *Staphylococcus aureus* and anaerobes. In children with CF, there is the possibility of having infection by *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Viral upper airways infections that do not improve after the fifth day, or whose symptoms persist beyond day 10, indicate bacterial infection. Symptoms are less specific than in adults. Rhinorrhea seems to be the most frequent symptom in all forms of RS (70% to 100%). Other prevalent symptom in children is cough (50% to 95%),

dry or productive, which may worsen at night, but is manifested during the day. Nasal obstruction and mouth breathing are also highly prevalent, especially in CRS (70% to 100%). Fever, halitosis and lack of appetite may be the only symptoms in children. Headache and facial pressure are uncommon symptoms.

In 1996, the Brussels Consensus proposed a classification of ARS in children concerning symptom severity (Chart 11). The classification intended to guide the type of initial therapeutic approach used, with more conservative approaches in mild cases.

Chart 11. Classification of rhinosinusitis in childhood based on severity.

Mild ARS	Severe ARS
Any type of rhinorrhea	Purulent Rhinorrhea
Nasal obstruction	Nasal obstruction
Cough	Facial pain or headache
Headache, facial pain, irritability (present or absent)	Periorbital edema
Low or absent temperature	High temperature ($\geq 39^{\circ}\text{C}$)

Adapted from Clement et al., 1998.

The physical examination of these children by anterior rhinoscopy is extremely important. It may be performed by raising the nose tip with the thumb or using a nasal speculum or an endoscope. The use of rigid nasal endoscopes or preferably flexible instruments enhances sensitivity of physical examination owing to direct visualization of the whole nasal fossa, including the middle meatus and sphenoid-ethmoid recess. The presence of mucopurulent secretion in these regions confirms the diagnosis of RS. It is useful to study predisposing anatomical factors, such as adenoid hyperplasia, nasal polyps and septal deformities. Presence of NP in children should lead to investigation of systemic diseases, such as CF and primary ciliary dyskinesia.

Exams should be carefully interpreted. Simple x-ray may under or over diagnosed the disease. There is 75% discrepancy between simple x-ray findings and CT scan, considered the gold standard to study paranasal sinuses. However, CT scan may not be interpreted independently from the clinical presentation of the patient. Glassier et al. evidenced that 97% of the children submitted to CT scan for reasons not related with nasosinus disease that had had colds 2 weeks before the exam presented paranasal sinuses mucosa affections. Conversely, there is advantage in assessing in details the OMC. CT scan is indicated in

cases of children that present complications of bacterial ARS, RS resistant to habitual clinical treatment, recurrent RS and surgical treatment considerations. MRI is reserved to cases of complex disease or in the investigation of intracranial complications.

Anatomical variants of OMC perform a controversial role in the pathophysiology of RS. Prevalence of these variants in asymptomatic patients with CRS is similar, or close to 40%. In children, anatomical variations of OMC are even less important. In those that have presented recurrent ARS or CRS, other factors such as allergy, immunodeficiency, laryngopharyngeal reflux, CR, primary ciliary dyskinesia, adenoid hyperplasia, day care attendance, parental smoking, should be investigated. Pharyngeal tonsillitis and pharyngeal tonsil hypertrophy are considered risk factors for RS in children: both pharyngeal tonsil hyperplasia causing ventilation disorder and obstructing mucus passage through the nasal cavity, and pharyngeal tonsillitis, acting as a bacterial reservoir in the nasal portion of the pharynx.

Pediatric RS is primarily treated with non-surgical management. Surgery should be considered if symptoms persist despite appropriate medical treatment for at least 3 months. Investigation and treatment of predisposing factor are significant elements in managing these children. To illustrate this statement, Bothwell et al. studied 25 (89%) out of 28 children with CRS and there was no surgical indication after laryngopharyngeal reflux management.

Some authors question the use of antibiotics in children with ARS because this affection has spontaneous cure rate of 40 to 45% of the cases. Those that advocate its use want to reach quick clinical cure, eradicate etiological agents, prevent suppurative complications and chronification of disease, reduce tissue edema, restore normal drainage of paranasal sinuses and recover sinus function. Treatment duration ranges from 10 to 14 days or 7 days after symptom remission.

In CRS, the use of antibiotics is even more controversial, but it still remains as first line treatment. Because there is high likelihood of having *Haemophilus influenzae* resistant to beta-lactamic agents and *Pneumococcus* with mutations of penicillin-receptor protein, the use of amoxicillin in usual doses (45 mg/kg) should be avoided in chronic cases. This antibiotic may be used in higher doses (90 mg/kg/day) and preferably associated with clavulanate. To patients allergic to penicillin, second generation cephalosporin is an alternative. The duration of treatment should be 3 to 6 weeks. If there is therapeutic failure with oral antibiotic therapy, we may administer it intravenously, based on cultures of maxillary sinus aspirate, before indicating functional endoscopic surgery.

Intravenous ceftriaxone or amoxicillin/clavulanate

are the preferred antibiotics in RS with orbital or intracranial complications.

Differently from adults, paranasal sinuses surgery in children with rhinosinusitis is still controversial, and it is always indicated in very specific situations. Procedures that do not approach the paranasal sinuses per se, such as for example adenoidectomy, have been used as initial procedure to control sinus disease. However, its effectiveness is highly controversial, especially owing to the difficulty in differentiating chronic rhinosinusitis from pharyngeal tonsil hyperplasia. Nasal obstruction, snoring and speech affections are more frequent in children with pharyngeal tonsil hyperplasia, whereas symptoms such as rhinorrhea, cough, headache, mouth breathing and anterior rhinoscopy findings are more frequent in children with chronic rhinosinusitis. Conversely, there seems to be no correlation between size of adenoid and presence of purulent secretion in the middle meatus. Recent studies have demonstrated that adenoidectomy is effective suggesting that it should be a previous surgical option to functional endoscopic surgery, especially in smaller children with obstructive symptoms.

No study has been able to demonstrate efficacy of continuous irrigation or inferior antrostomy. Possible indications for punch or inferior antrostomy would be for primary ciliary dyskinesia and cystic fibrosis, hoping that it would promote gravitation drainage.

However, the main controversy still concerns the indications of paranasal sinuses endoscopic surgery in children. Based on the Consensus on Rhinosinusitis in Children held in Belgium in 1998, the Brazilian Consensus on Rhinosinusitis - 1999 recommended surgical management of rhinosinusitis in children in the following situations:

1. Presence of extensive polyposis
2. Orbital complications with abscess and intracranial complications
3. Fungal rhinosinusitis
4. Chronic rhinosinusitis resistant to clinical treatment.

It is important to emphasize that in children, surgical procedures for chronic rhinosinusitis resistant to clinical treatment or with frequent flare should be indicated as exceptions. They are normally limited to conservative procedures, such as for example partial ethmoidectomy, that is, total or partial removal of unciform process, with or without maxillary antrostomy. Simple opening of ethmoidal bulla is normally enough. In cases of extensive polyposis, more extensive procedures may be necessary.

The results of most existing studies about surgical treatment in children should be assessed through symptom

improvement and they do not include images or endoscopic tests, and many of them have been consistent in showing high success rates.

Metaanalysis studies showing number of patients per study, postoperative follow-up, retrospective or prospective design, inclusion and exclusion criteria, have shown positive progression rates in 84 to 92% of the cases. Moreover, studies with follow-up over 10 years have not demonstrated affections to facial development after sinus surgery. Based on these data, it was concluded that functional endoscopic surgery could be considered safe and effective in treating children with chronic rhinosinusitis refractory to clinical treatment in children.

13. DIRECT AND INDIRECT COSTS OF RHINOSINUSITIS

13.1. DIRECT COSTS

Because of its high prevalence, RS generates direct and indirect impact on overall economy. Most available data about the topic portray the North American and European realities and few studies report information about Latin America.

In 1994, there were approximately 35 million people with RS, with prevalence of 134.4: 1,000 inhabitants in the United States of America. The prevalence was higher than for arterial hypertension, diabetes mellitus and allergic rhinitis. In 1995, RS was the 11th most frequent outpatient diagnosis in the USA, amounting to a total of 11,898,000 cases and 2% of all medical visits in the year. The cost of treating ARS and CRS, as estimated by National Medical Expenditure Survey, was 3.4 billion dollars in 1996.

Ray et al. analyzed the coexistence of RS and other pathologies such as asthma, otitis media and allergic rhinitis and noticed that 10% to 15% of the cost of these diseases was attributed to RS, increasing the economic impact to approximately US\$5,78 billion. The authors used data by National Centre for Health Statistics and did not distinguish types of RS.

Murphy et al. observed 43% more hospital visits, 25% more emergency visits, and 43% more prescriptions, but 29% less admissions to hospital. As to cost, it was 35% higher for serving patients with RS and drug use increased significantly (28%), because of antibiotics (60%), corticoids (21%) and AH and decongestants (19%). Overall, it had 6% cost increase compared to the mean of adults seen, which cost US\$2,609 per year, including radiology, hospitalization and medication. In 1994, 20,9 million patients with rhinosinusitis were seen, with estimated cost of US\$206 per person, which corresponds to total cost of

US\$4.3 billion. Considering the current prevalence of 32 million patients with RS/year, the cost would climb up to US\$6.39/ year.

Owing to improvement in diagnostic methods and technological innovations, especially with the development of CT scan and nasosinus endoscopy, there has been increase in the cost of RS diagnosis. Stankiewicz et al. suggested that it would be cheaper to treat only with clinical diagnosis, without CT or endoscopy, but 52% of the patients would be inappropriately medicated. Specific diagnosis with CT and endoscopy might lead to higher cost, but treatment is more appropriate and effective.

As to cost of surgical management, a Chinese study carried out in 2004 showed that the expenditures with rhinosinusitis amount to 65.6%, followed by radiological and laboratory exams (13.8%) and admission services (6.6%). Every year, \$40,829,43 Taiwanese dollars are spent with patients undergoing endoscopic surgery and the authors have suggested indication of endoscopic surgery only to severe RS cases. In this study, surgeries were made under local anesthesia and there was no reference to costs of non-surgical patients.

Gliklich & Metson observed that the annual cost with medication to treat RS is equal to U\$1,220, distributed between nasal topical corticoid (U\$250), antibiotics (U\$772) and other drugs (U\$198). They have demonstrated that the cost of these drugs decreased significantly after nasosinus endoscopic surgery.

The European study performed at Netherlands hospital, in 2001, demonstrated that direct cost of patients with severe CRS was Euro 1,861 per year.

It was concluded that direct cost with clinical and surgical management of CRS ranges from U\$200 to U\$6,000, which amounts to approximately R\$420 to R\$13,200. Enhanced and more updated analyses are required to guide management, especially in surgical approach of CRS with NP.

13.2. INDIRECT COSTS

In addition to direct costs, RS causes indirect damage, because affected subjects have decrease in performance or inability to work. High frequency of RS generates major social-economic impact, considering that 85% of the patients who have RS are aged 18-60 years. According to Murphy et al., between 1986 and 1988, CRS was responsible for 51,651,000 days of leave from work and 16,144,000 days of disabling disease every year.

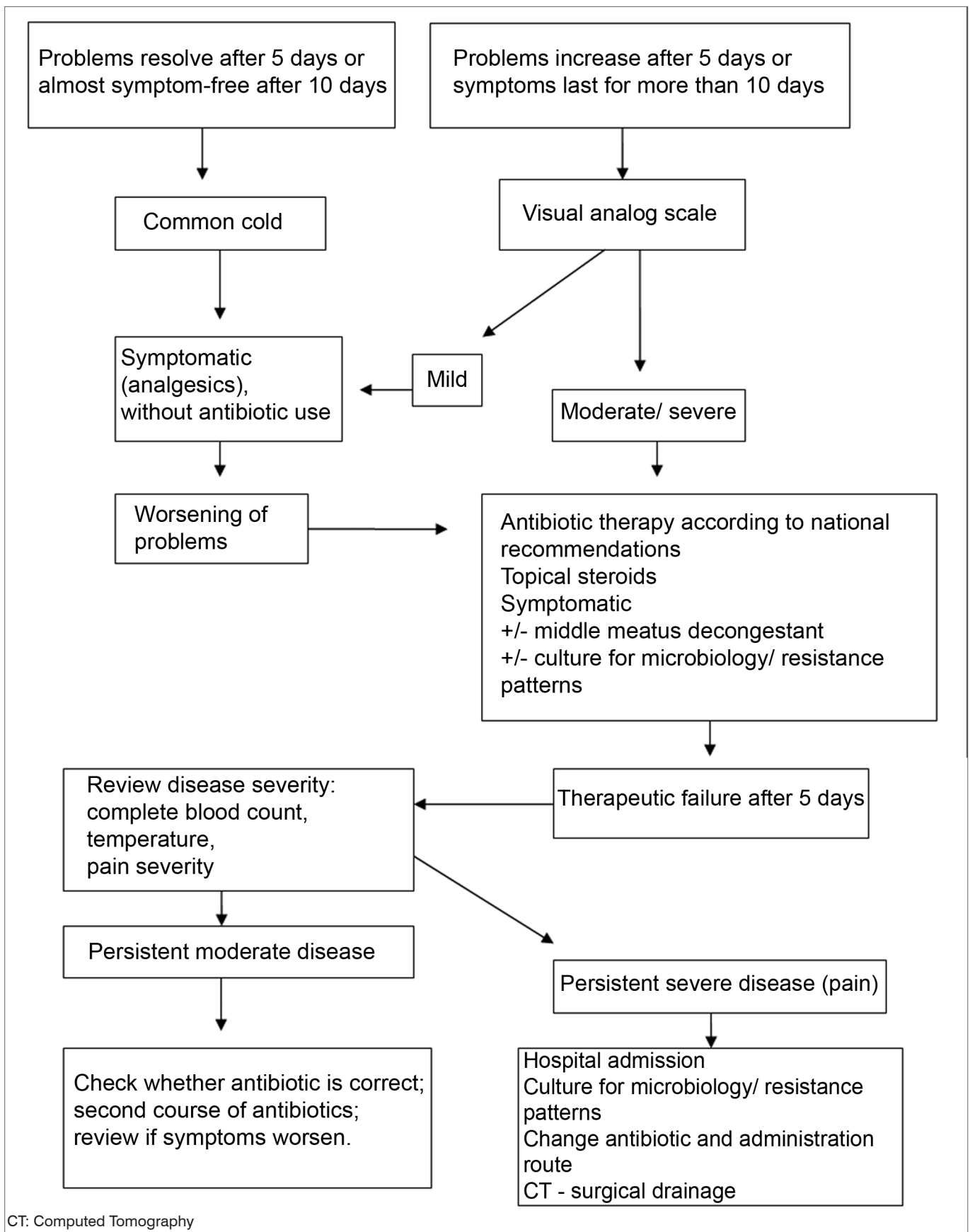
Gliklich & Metson have observed that in addition to direct savings and direct economy related with medication expenses, after nasosinus endoscopy there has been indirect gain from fewer disabling days (18.3% to 15.3%) and work leaves (5% to 3%), generating savings of U\$430 per patient. These savings will eventually payoff the cost of endoscopic surgery within 7 years.

RS generated expenses of U\$60,17 per employee per year, within a universe of 375,000 workers. It amounted to U\$22,563,750, and 40% was attributed to indirect costs of work leave or disabling status.

Bhattacharyya, in 2003, determined the direct and indirect economic impact of RS in workers, analyzing symptoms, drugs and leaves. The total cost per worker per year was U\$1,539, and 40% referred to lost days at work (average 4.8 days). The author concluded the study estimating that 32 million American workers are affected every year, generating expenses equivalent to U\$47 billion. In this study, data were based on ENT visits. In the United States costs of medical visit and management by specialists is more expensive and the referred patients are only severely affected cases.

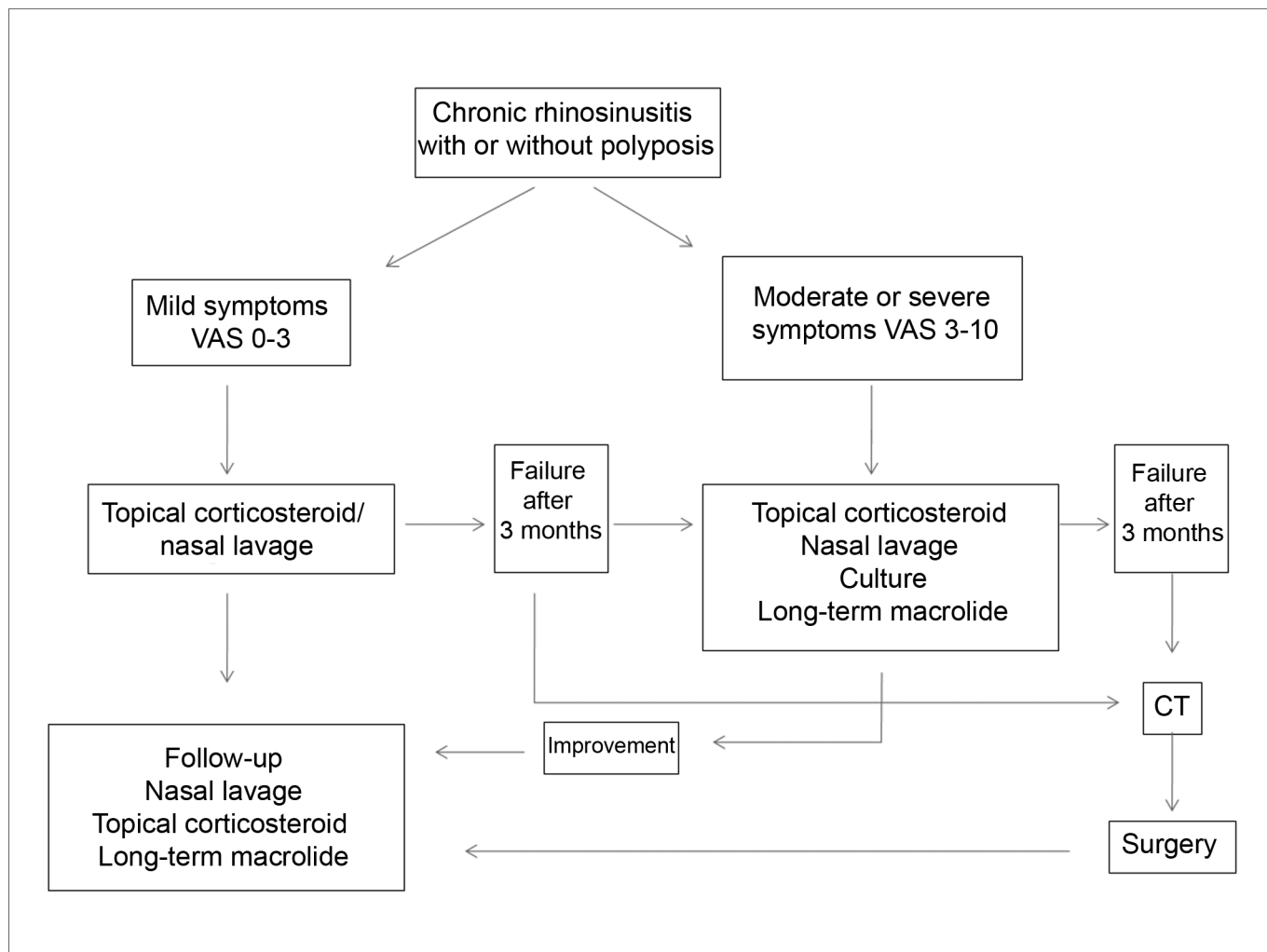
RS causes significant impact on quality of life, including limitation of occupational activities, as described in the literature. Costs related with decreased productivity and absenteeism are high and frequently underestimated.

14. TREATMENT ALGORITHM FOR ACUTE RHINOSINUSITIS IN ADULTS



CT: Computed Tomography

15. TREATMENT ALGORITHM FOR CHRONIC RHINOSINUSITIS IN ADULTS



Key:

VAS: visual analog scale

CT: Computed Tomography

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