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Refractory Chronic Rhinosinusitis: Etiology & Management

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1. Introduction

Chronic rhinosinusitis (CRS) is a common disease with significant morbidity and health care cost. Although the medical and surgical treatments for CRS have improved markedly over the past few decades, a subset of patients remains quite resistant to all forms of therapy.

Such patients end up being over-treated and subjected to numerous unsuccessful surgeries some of which can result in serious complications. The optimal treatment for these patients (an entity referred to as refractory or recalcitrant sinusitis) (RCRS) is complex and challenging.

The true incidence of RCRS is unknown. It is estimated that at least 10 % of patients with CRS continue to be symptomatic after appropriate endoscopic sinus surgery (ESS) with long term follow up. This 10% failure rate translates into 30,000 patients yearly undergoing ESS with poor postoperative outcome. Because these numbers are cumulative over years, approximately 450,000 cases in the United States are currently estimated to have chronic sinusitis that is unresponsive to medical and surgical therapy. Today, these chronic patients form a significant portion of most rhinology practices. (Desrosiers, 2004).

The aims of this chapter are to review the updated possible pathogenesis of RCRS and suggest possible algorithmic management plan for this condition.

2. History and physical examinations

Thorough and detailed history is fundamental in evaluating patients to find out whether optimal treatment has been given, and whether there are any personal or technical predisposing factors.

Current symptomatology should be determined. Detailed questions regarding nasal symptoms: facial pressure, nasal obstruction, anterior or posterior rhinorrhea, and alteration of sense of smell should be asked. Frequency and duration of symptoms exacerbation as well as different modalities of treatments used should be reviewed.

Routine medical questions should also be included. Specific attention should be paid to the symptoms of respiratory system, such as cough, wheeze, and shortness of breath. History

of recurrent infections in the skin, urinary tract or digestive tract may indicate immunodeficiency. Additionally, connective tissue disorders, granulomatous diseases and vasculitis related symptoms need be asked.

Medication should be reviewed and the use of oral immunosuppressive agents determined.

Allergy questionnaires should cover presence of household pets or excess mold in the domestic environment. Work history should be obtained to evaluate occupational causative elements to the disease. Both smoking history and passive exposure to smoke should be assessed.

Previous nasal surgeries reviewed. Type of surgery, recovery, complications and response should all be documented.

Complete ear, nose, and throat examination is followed. Anterior rhinoscopy should assess nasal patency, nasal mucosa condition, inferior turbinates, and the presence of nasal crusting.

Direct visualization using 0 and 30 degree rigid endoscopy is crucial in this group of patients, to look for any evidence of active infection or obstruction to sinus ostium. The presence of polyps, pus, synechiae, stenosis, middle turbinate lateralization should also be evaluated. Pathological looking mucosa can be biopsied under local anesthesia as office procedure to rule out systemic diseases or tumors.



Fig. 1. Coronal CT scan for patient with RCRS, thickened mucosa with patent sinus ostium and Osteitis of the left lateral maxillary wall.

If surgery is not technically adequate and evidence of obstruction noticed revision surgery is offered.

Thin cut CT scan with coronal and sagittal reconstruction should be ordered. CT scan can illustrate detail in lateral wall of sinuses where the endoscopic view cannot reach. Extent of sinus involvement, extent of prior surgery, presence of obstruction to sinus drainage, unventilated cells, development of new bone deposition or neo-osteogenesis, and evidence of previous intraoperative complications can be easily visualized. Figure 1 showed the typical CT scan finding in patients with RCRS.

3. Pathogenesis and treatment

3.1 Immunodeficiency & RCRS

Although the exact role of bacteria and fungus in the etiology of sinusitis is still controversial, we have reasonable evidences to believe they play significant role in this wide spectrum disease. Bacteria and fungus have been detected in endoscopic guided culture, type of organisms identified in acute sinusitis differs from those reported in chronic and in RCRS. In general, patients with sinusitis report improvement in their symptoms while they are on Antibiotics. Additionally, the prevalence & severity of sinusitis in immunocompromised patients correlate with their immunological status. In fact, Antimicrobial therapy is still the most common form of therapy prescribed by physicians for the treatment of CRS.

Various forms of immunodeficiencies predispose to rhinosinusitis, however in RCRS the most important are selective IgA deficiency and systemic subtle humoral immunodeficiencies. These patients are usually diagnosed after being treated with multiple sinus surgeries. Other forms of immunodeficiency, for example, common variable immunodeficiency lymphopenia or neutropenia are more important in the pathogenesis of recurrent acute forms of rhinosinusitis and acute invasive fungal sinusitis.

Immune dysfunction as a risk factor for RCRS has gained attention in recent years. Chee et al studied the incidence of primary immune deficiency in patients with refractory sinusitis. Among a group of 79 patients with refractory sinusitis 17.9% were noted to have low IgG and 16.7% were noted to have low IgA. Common variable immunodeficiency was found in 9.9% and selective IgA deficiency was diagnosed in 6.2%. Although these numbers are interesting, the authors included some patients who didn't fit with the current definition of RCRS, they defined refractory sinusitis as at least one previous sinus surgery and/or three episodes of objectively documented rhinosinusitis in the previous year (Chee et al., 2001).

Vanleberghe et al. reported on a series of cases with RCRS who had undergone immunologic evaluation. Out of 307 (261 adults and 46 children) patients tested, 22% had evidence of humoral immunodeficiency. The majority of these were subtle IgG subclass deficits, low level of major immunoglobulins was reported in 7% for IgA and 3.3% for IgG. Low level of IgM or Common variable immunodeficiency weren't detected (Vanleberghe et al., 2006).

In a recent paper Al-Qudah et al studied the contribution of primary immunodeficiency in 67 patients with RCRS at a large tertiary care medical center. In addition to major immunoglobulin and IgG subclasses blood level, Functional antibody response was assessed by examining the antibody response to the unconjugated pneumococcal

polysaccharide vaccine. Low IgG was detected in 9%, low IgA in 3%, low IgM in 12% of patients, and IgG subclasses in 19%. Common variable immunodeficiency was diagnosed in one case. 67% of patients failed to produce more than a fourfold increase in postimmunization antibody titer for 7 of 14 serotypes being tested and were considered to have functional antibody deficiency. Interestingly there was no statistically significant difference in the incidence of low level of immunoglobulins between patients with normal antibody response and poor response group. They recommended measurement of serum immunoglobulin levels in all patients with RCRS; if these are normal, then functional antibody responses should be evaluated (Alqudah et al., 2010).

Functional antibody responses or selective antibody deficiency syndrome is a condition with normal or near normal serum immunoglobulin concentrations but an inadequate production of specific antibodies response to polysaccharide organisms, which are T-independent type 2 antigens, like *Streptococcus pneumoniae*. Patient with this condition have recurrent respiratory infections such as: sinusitis, bronchitis, and pneumonia. The diagnosis can be reached by taking paired blood sample before and 6-weeks after immunization with pneumococcal vaccine. The consensus recommendation is that a normal response in adults is a fourfold increase in antibody titers to 70% of the 14 serotypes unconjugated pneumococcal polysaccharide and a normal response in children is a fourfold increase in antibody titers to 50% of the serotypes tested (Bonilla et al., 2005).

T cell immunodeficiency patients are unlikely to present with Refractory sinusitis symptoms without other apparent clinical presentation. Primary T cell disorders are rare and usually diagnosed during childhood. Secondary T cell deficiency presents with unusual or severe viral, fungal or protozoal infection.

Food allergy is another possible cause of persistent nasal symptoms after proper medical and surgical therapy especially in patient with nasal polyp. Most common "masked" food allergens in adults are those foods commonly eaten and include: wheat, dairy, soy, corn, and, eggs (Ferguson et al., 2009).

The condition is usually difficult to recognize by the patients as symptoms may show up hours or even a day after food absorption and the fact that common allergic foods are so prevalent in our diet that many patients eat them nearly every day. An elimination food challenging test is a convenient and inexpensive procedure that can be performed by the patient at home. The targeted food is eliminated from the diet for 5 to 7 days and then reintroduced into the diet during this hyperresponsive period of 5 to 10 days following elimination. If the food causes symptoms, then the patient will generally be aware of either nasal or non-nasal symptoms after the food challenge. Those who note symptoms on reintroduction of the food are instructed to eliminate the food from their diet for approximately 3 months, after which time the food may be reintroduced into their diet, although the food should not be eaten on a daily basis (Ozdemir et al., 2009).

Our immune evaluation for patients with RCRS is displayed in Table 1. All patients should have complete blood cell count with differential, measurement of serum IgG, IgA, IgM, IgE and IgG subclasses as well as allergy skin test or radioallergosorbent test. If serum immunoglobulin levels are normal, functional antibody responses should be evaluated by determining specific antibody response to an unconjugated pneumococcal polysaccharide vaccine.

Complete blood cell count with differential
Quantitative immunoglobulins: IgA, IgE, IgM, IgG and IgG subclasses
Allergy Test.
Pneumococcal antibody titers

Table 1. Immune work up in refractory chronic sinusitis

In addition to twice daily nasal irrigations and long term nasal steroid all RCRS patients with immunodeficiency need to be on prophylactic oral antibiotics. Our protocol is to use two different antibiotics rotating every two weeks and so any emerging resistant clones will wipe out with the other antibiotic. For many reasons, Bactrim and Doxycycline are our first option: They are old, cheap, safe antibiotics and prescribed twice daily. Additionally these two antibiotics have a potent anti-inflammatory effect. Cephalexin, Amoxicillin and Clarithromycin are alternative options for those patients who are allergic or can't tolerate Bactrim and Doxycycline. The duration of prophylactic antibiotics use is flexible and depends mainly on patient's symptoms duration and clinical response. Antibiotics can be used all through the year or given in symptomatic season. Acute exacerbation is treated according to endoscopic guided culture. Patients who failed to improve on antibiotics can benefit from intravenous or subcutaneous immunoglobulin replacement. The recommended stander dose is 400-600 mg/kg given every four weeks for 1-2 years. (Shearer et al 1996).

Cessation of treatment is schedule during summer months to avoid allergy season and to avoid the high incidence of infections during winter.

3.2 Biofilm & RCRS

Biofilms are a complex organized community of germs that adhere to the mucosal surface and surrounded by a self-produced extensive extracellular polymeric substance called (glycocalyx) which composed primarily of polysaccharides. The glycocalyx is a mixture of bacterial colonies of different phenotypes with various physiochemical properties. It serves as protection for its bacterial inhabitants while also modulating the microenvironment of the colonies through its numerous water channels. Biofilms intermittently release free floating bacteria (planktonic) that can provide a constant nidus of infection.

Biofilm's life cycle and interactions with the environment can be divided into three stages: attachment, growth, and detachment. During the attachment phase,the substratum has to be adequate for the reversible adsorption and ultimately the irreversible attachment of bacteria to the surface. During the growth phase, as thecells divide and colonize the surface, a polysaccharide matrix is formed, and the biofilm begins to display athree-dimensional structure. During this phase water channels are formed. Once biofilms reach maturity, bacteria slough off and embolize to other areaswhere the process may begin again (Sanclement et al.,2005).

Bacterial biofilms have two microbiological characteristic: first, they are difficult to detect and culture using routine conventional methods and second, they are 10-1000 time resistant to current antimicrobial therapy when compared with genetically identical planktonic bacteria (Kilty & Desrosiers, 2009).

Antibiotics resistance is most likely related to biofilm slow growth and metabolic rate as well as sharing of multiple resistance genes within the members of the biofilm community. Antibiotic treatment will kill bacteria in the periphery where the cells are metabolically active, but doesn't reach the bacteria in the deeper layers of the biofilm. Thus, the biofilm serves as a bacterial reservoir that sheds planktonic forms causing systemic illness, especially when released into the circulation. In these circumstances, antibiotic treatment will eliminate the circulating bacteria but not the biofilm, leading to recurring acute exacerbations (Post et al., 2007).

Biofilm infection theory may offer an explanation of the high rate of negative sinus cavities in CRS and why antibiotic treatment is unable to resolve CRS with bacteria that are sensitive to antibiotics. In 2004, Cryer and his colleagues were first to demonstrate the presence of biofilms in the biopsied mucosa from a number of symptomatic CRS patients who had prior appropriate medical and surgical management (Cryer et al., 2004). One year later Ramadan et al identified biofilms on the mucosa of five patients at the time of ESS. (Ramadan, 2006).

Further studies found significant differences in the rate of biofilms formation between control, CRS and refractory sinusitis (Bendouah et al., 2006; Psaltis et al., 2007; Sanclement et al., 2005).

Another support to the biofilm theory is that pathogenic bacteria most commonly implicated in RCRS have been identified in patients with RCRS to exist in the form of a biofilm. In several studies of bacteriology in RCRS performed with conventional culture methods, *Staphylococcus aureus*, Coagulase negative staphylococci and *Pseudomonas aeruginosa* have been identified as the most common bacteria to colonize the paranasal sinuses and these same species were the most common bacteria identified in the biofilms of refractory sinusitis patients using different invasive laboratory techniques.

The preoperative presence and type of bacteria biofilms in sinus mucosa may correlate with continuous postoperative symptoms and mucosal inflammation after ESS. Bendouah et al took 31 isolates from 19 CRS patients who had undergone ESS a year earlier. 71% of isolates showed biofilm formation. Among the bacteria recovered, *Pseudomonas aeruginosa* and *Staphylococcus aureus* biofilm was shown to have a correlation with poor outcome after ESS, whereas Coagulase negative staphylococci biofilm did not (Bendouah et al., 2006). More recently, Psaltis et al retrospectively studied a group of 40 CRS patients who had undergone ESS. Outcome measures revealed that bacterial biofilms were found in 50 percent of the 40 patients and that the poorer post operation symptoms were correlated with the presence of bacterial biofilms. Interestingly biofilms formation is independent of many common risk factors, (such as allergy, polyps, samter's triad) cited in the etiology of CRS were not found to be of significant in (Psaltis et al., 2008).

Staphylococcus aureus, *Pseudomonas aeruginosa* and Coagulase negative staph. are the most frequent biofilm forming bacteria in RCRS, these bacteria are usually resistant to oral and intravenous antibiotics at minimum inhibitory concentration (MIC). In a study aimed to determine the in vitro activity of moxifloxacin against *Staphylococcus aureus* in biofilm form with samples recovered from patients with at least 1 year post-ESS, the authors found moxifloxacin at 1000 times the known MIC was statistically significant in reducing the number of viable bacteria (Desrosiers et al., 2007).

In another work, authors studied the MIC of different antibiotics to eradicate *Pseudomonas aeruginosa* biofilms, they found The minimum biofilm eradication concentration for

Pseudomonas biofilms has been shown to be 60-fold greater than the MIC for gentamicin and greater than 1000-fold for ceftazidime and piperacillin (Ceri, 1999)

These data and others encourage rhinologists in the past few years toward treating biofilms in RCRS with different delivery methods of topical antibiotics at concentration above the MIC level with minimum systemic side effects, taking advantage of the anatomical and physiological changes after ESS where paranasal sinuses become single large cavity connected with multiple patent ostia.

Antibiotics can deliver into nasal cavity by nasal sprays, irrigations, nebulizers or by direct installation using syringe and large gauge needle. Because nasal sprays rely on mucociliary clearance to transport the drug, and this is often impaired in RCRS, as well as their small surface area deposition many believe this method of delivery is suboptimal (Lim et al, 2008, Richard et al, 2010).

Most of clinical research on topical antibiotics for RCRS is limited with small number of patients, short follow up, different protocols for treatment and inclusions and exclusions criteria, however the conclusion of 2 recent review articles support the use of topical antibiotics in RCRS and recommend the need of larger and better designed randomized double-blinded placebo-controlled studies (Lim et al, 2008, Richard et al, 2010)

3.3 Osteitis and neo-osteogenesis in RCRS

Although CRS begins in the mucosa there are evidences that inflammation can spread and involve underlying bony structures leading to persistent of patients' symptoms following aggressive medical and proper surgical treatment. The mucosa and underlying bone are not separated units and they communicate with each other.

Bolger et al studied the histopathology changes after induce sinus infection in 33 New Zealand white rabbits with *Pseudomonas aeruginosa*. Histologic analysis of the bone 4, 14, 21, and 28 days after bacterial infection showed stromal changes of bone resorption, reactive osteoblasts, and appositional or intra-membranous new bone formation as early as 4 days after bacterial inoculation. Bacteria were present in the sinus lumen, surface of sinus mucosa, mucosal crypts, mucosal abscesses, and ulcers but not in the bone itself. They conclude that although bacteria were limited to the mucosa, the infection induced histopathological changes at the submucosa and bone level (Bolger et al., 1997). Using the same model and pathogen, Perloff and colleagues confirmed these bony changes to be identical to chronic osteomyelitis, interestingly, in all studied specimens some bony changes were found at the non-infected side. They suggested that inflammation may travel along bone to adjacent sinuses without intervening mucosal disease. Properly inflammatory or infectious agents entered the underlying bone, through Haversian canals, and subsequently activated the remodeling process in sites distant or adjacent to the original inoculation site (Perloff et al., 2000).

In another study, 14 rabbits were induced by *Staphylococcus aureus*, chronic osteomyelitis in the non-infected side was found in (43%) (Khalid et al., 2002).

Bony changes had been also reported in studies on patients with CRS. Kennedy et al noted marked activity with features of increased fibrosis, remodeling, and woven bone in ethmoid labyrinth. Ethmoid septations were found to have evidence of marked acceleration in bone

physiology with histologic findings including presence of inflammatory cells, fibrosis, and new bone formation. They also reported inflammation in the bone even when the overlying mucosa was intact (Kennedy, 1998).

Giacchi et al. compared bone from ethmoid septa of 20 patients with CRS and control group. Those with CRS typically showed periosteal thickening and resorption or remodeling. They also found a trend toward more advanced histologic bone stage associated with higher CT score indicating that mucosal and bone pathological changes occurred simultaneously (Giacchi et al., 2001).

In a recent study from Netherlands, the authors used CT scan to report the incidence of osteitis in 102 CRS patients and in an age- and gender matched control group of 68 non-CRS patients. Forty per cent of the CRS group and none of the control group had evidence of clinically significant osteitis. In the CRS group the severity of osteitis was correlated with Lund-Mackay score ($P < 0.001$), duration of symptoms ($P < 0.01$) and previous surgery ($P < 0.001$). The association between osteitis and number of previous surgery remained strong even after adjusting for the disease duration. There was no association between osteitis and age, gender, smoking, co-existing asthma, allergy or Sumter's triad (Georgalas et al. 2010)

Osteitis and neo-osteogenesis may also affect the success rate after sinus surgery. Kim et al studied the correlation between pre-operative bony changes detected in CT scan and postoperative endoscopic signs of healed sinus cavities in 81 patients. Patients with no radiological signs of bony changes showed better healing mucosa compared to those with bony changes (Kim et al., 2006).

Pathological changes described by human histological studies included: the presence of new bone formation, fibrosis, inflammatory cells, periosteal thickening and a varying degree of increased osteoblastic- osteoclastic activity, as shown by the disruption of organised lamellar bone and formation of immature woven bone, these are best to fit under the terms osteitis and neo-osteogenesis. Localized or generalized thickened, irregular, heterogeneous lining of the sinus walls, is the radiological sign observed in CT scan, as illustrated in Figure 2 (Georgalas et al., 2010).

Osteitis and neo-osteogenesis in CRS are probably secondary to inflammatory process rather than direct bacterial invasion. In all animals and human studies, bacteria were not detected in the inflamed bone except in Tovi's study where actinomycosis was found in one patient (Tovi et al., 1992).

Cytokines produced by inflammatory cells such as osteoclast activating factor, interleukins, and tumor necrosis factor as well as prostaglandins such as prostaglandin 2 are known stimulators of bone resorption. These could be important mediators in inflammatory bone resorption and bone loss such as in periodontal disease and arthritis(9). Prostaglandin E is also shown to cause hyperostosis with periosteal osteoblast proliferation, thickened periosteum, and neocortex formation (Kocak et al., 2002; Faye-Petersen et al., 1996).

Mechanical pressure resulting from increased intrasinus pressure caused by inflammation and ostiomeatal unit obstruction may stimulate bone remodeling. This could explain the trend toward more advanced bone stage associated with higher CT stage of mucosal disease observed by Giacchi et al .



Fig. 2. Coronal and axial CT for patient with RCRS showed osteitis in the maxillary wall.

Another possible explanation is bacterial Biofilms may act as a 'depot' for low grade bacterial production and be responsible for the release of soluble bacterial virulence factors that generate local bony changes. The authors of most studies on biofilms and sinusitis didn't specify whether their sinus samples were purely mucosal or with some bony fragments, biofilms have been reported to present in infected bone in orthopedic and dental literature. Indeed, further studies are needed to determine the exact role of biofilms in osteitis in RCRS.

Long therapeutic plan required in management of these patients. Complete removal of crust and sequestered bone is essential first step to provide healthy environment for mucosal regeneration. Topical combination of antibiotic and steroid may also help.

3.4 Granulomatous disease and vasculitis in RCRS

The sinonasal cavity may be the first organ to manifest such a systemic condition. Presenting symptoms and signs may be identical to those of other forms of CRS and thus these patients may have delay diagnosis.

The list of granulomatous diseases that can affect the sinonasal tract is extensive Sarcoidosis, Wegener's granulomatosis, Churg- Strauss syndrome, are the most common. Detailed history, careful systemic examination and local biopsy of any abnormal looking mucosa may be the hint of early identification of these patients.

Sarcoidosis is an inflammatory multisystem disorder of characterized by noncaseating granulomas. Sinonasal cavity is affected in only 0.7% to 6% of cases. Symptoms that may point to sarcoidosis are fatigue, pulmonary symptoms, night sweating, weight loss and fever. Physical signs include mucosal hypertrophy, purple mucosa with nodules (granulomas), and lupus pernio. Diagnosis is based on clinical findings, chest radiography, elevated angiotensin-converting enzyme levels, and findings of mucosal biopsy from affected mucosa (Matthew, 2008; Ferguson et al., 2009).

Wegener's granulomatosis is a rare granulomatous vasculitic disorder, affecting primarily middle age white people. Sinonasal manifestations are very common and occur in up to 89% of patients. Common symptoms include nasal obstruction, bloody rhinorrhea, epiphora, and crusting. Patients may present with, septal perforation, mucocele, orbital pseudotumor, or saddle-nose deformity. Positive cytoplasmic antineutrophil cytoplasmic antibodies and an elevated erythrocyte sedimentation rate suggest the diagnosis. However, definitive diagnosis depends on histopathologic analysis of affected mucosa.

Churg-Strauss syndrome is a multisystem disorder with necrotizing granulomatous eosinophilic tissue infiltration. Nasal involvement can occur in up to 75% of patients. Nasal polyps and rhinosinusitis are early manifestations of the illness, with subsequent development of eosinophilia and systemic involvement. Diagnosis is based on clinical findings, positive perinuclear antineutrophil cytoplasmic antibodies, and biopsy.

Treatment of nasal granulomatous diseases most commonly includes aggressive sinus debridement to remove crust formation, saline rinses and topical, systemic, intralesional steroids and immunosuppressive medications, surgery is reserved for complicated cases. Early consultation with rheumatology and immunology teams is essential for proper management plan (Ryan 2008, Ferguson and Otto 2009).

3.5 Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) has been implicated as a contributing factor in many air way disease processes like: dysphonia, benign vocal cord lesions, vocal laryngospasm, subglottic stenosis, asthma, CRS, post nasal drip and idiopathic cough.

Three mechanisms could explain the effect of GERD on sinusitis: direct exposure of the nasopharynx and nose to gastric acid causing mucosal inflammation and impaired mucociliary clearance, the second possible mechanism is a dysfunction of the autonomous nervous system resulting in vagus nerve stimulation, the third possible mechanism relates to the direct role of *Helicobacter pylori*.

DelGaudio was first to document nasopharyngeal reflux (NPR) in RCRS patients, in prospective study using 24 hour pH study with a specially designed probe with sensors located in the nasopharynx, 1 cm above the upper esophageal sphincter, and the distal esophagus.

He found significant differences in the number of patients with NPR events (pH less than 5) and GERD between patients with RCRS and two control groups, the first consisted of patients who had at least one ESS procedure and had no symptoms of CRS or mucosal inflammation with a minimum of 1 year postoperative follow up. The second control group consisted of subjects with no history of CRS or sinus surgery. Limitation of this paper was that the study and control groups were not matched for age and comorbidities. The study group was older than the control group by approximately 10 years, and also, the study group patients have more comorbid conditions, especially asthma, compared with the control group. This weakness may question the accuracy of the results and conclusions (DelGaudio, 2005).

In prospective study, DiBaise et al treated 11 RCRS patients with proton pump inhibitor, not all patients had frank symptoms of GERD, Individual sinus symptoms (nasal congestion, nasal drainage, sinus pressure, facial headache, malaise) and global satisfaction were modestly improved in 25-89% and 91%, respectively, at 12 week (DiBaise et al., 2002).

Flook and Kumar conducted a recent review analysis for the evidence to link acid reflux with chronic sinusitis or any nasal symptoms; their conclusion was that the evidence of a link is poor with no good randomized controlled trials available. The few adult studies that show any link between acid reflux and nasal symptoms are small case-controlled studies with moderate levels of potential bias. There is not enough evidence to consider anti-reflux therapy for adult refractory CRS and there is no evidence that acid reflux is a significant causal factor in CRS (Flook & Kumar, 2011).

In our practice, we don't referred asymptomatic patients with RCRS for 24-hour Ph monitoring; however we started all RCRS patients on 20mg omeprazole BID for 3 weeks, if patient reports improvement in nasal symptoms or endoscopic score we recommend to continue on this regimen for 12 weeks.

4. Conclusions

A group of CRS patients continue to be symptomatic after appropriate medical and surgical therapy. Detailed history, endoscopic examination, laboratory and immunology tests

required to look for any reversible underlying pathology. Further clinical studies and in vitro research are in great needed to support and validate the current management protocol. The current treatment of RCRS is by nasal toilet, debridement, prophylactic antibiotics and immunoglobulin as well as topical medications.

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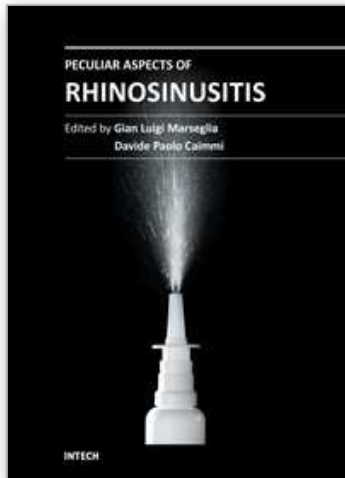
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Peculiar Aspects of Rhinosinusitis

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Rhinosinusitis has both a great practical interest and a broad significance due to the scientific complexity of the pathogenetic problems related to the disease, not yet completely resolved, and their implications for clinical treatment. This book highlights certain specific topics that usually are not clarified in other resources. The first chapter is devoted to the impoverished quality of life experienced by patients suffering from rhinosinusitis. The second chapter focuses on the microbiological aspects of rhinosinusitis, while the two subsequent chapters explain the peculiar aspects of chronic rhinosinusitis and of recurrent chronic rhinosinusitis. The first chapter of the second section of the book is dedicated to the imaging techniques used to visualize the nasal sinuses and the other to a medical topical type of treatment.

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