sinusitis

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Review

Medical Management of Chronic Rhinosinusitis in Adults

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Abstract: Chronic rhinosinusitis can be refractory and has detrimental effects not only on symptoms, but also on work absences, work productivity, annual productivity costs, and disease-specific quality of life measures. The pathophysiology of chronic rhinosinusitis continues to evolve. There is evidence that it is driven by various inflammatory pathways and host factors and is not merely an infectious problem, although pathogens, including bacterial biofilms, may certainly contribute to this inflammatory cascade and to treatment resistance. Given this, medical management should be tailored to the specific comorbidities and problems in an individual patient. In addition to treating acute exacerbations of chronic rhinosinusitis with amoxicillin-clavulanate, second or third generation cephalosporins, or fluoroquinolones, one must consider if nasal polyps are present, when symptoms and disease severity correlate to mucosal eosinophilia, and there is the best evidence for intranasal corticosteroids and saline irrigation. Asthma worsens severity of chronic rhinosinusitis and it is felt to be mediated by increased leukotrienes, when leukotriene antagonists may be utilized. Cystic fibrosis has a genetic defect and increased mucin, which are potential treatment targets with dornase alfa showing efficacy. Other comorbidities that may impact treatment include allergies, ciliary dyskinesia, immunodeficiency, and possibly allergic fungal rhinosinusitis.

Keywords: treatment; medical; management; chronic; sinusitis; rhinosinusitis; adult; polyps

1. Introduction

Chronic rhinosinusitis affects all races to a significant extent. Prevalence within the United States in one study was 13.8% in African Americans, 13% in Caucasians, 8.8% in Hispanics, and 7% in Asians [1]. In another cross-sectional study in the United States, data examining 215 million adults demonstrated the prevalence of chronic rhinosinusitis was approximately 5%. It was associated with one lost workday per year, increased activity limitation (OR 1.54), work limitation (OR 1.50), and social limitation (OR 1.49) [2]. However, when looking at refractory chronic rhinosinusitis, mean lost work days per year was significantly worse at 25 when absent from work and 39 when considering absences from work, in addition to reduced performance at work. Overall, reduced annual productivity cost from refractory chronic rhinosinusitis was $10,077 per patient and it increased with worsening disease-specific quality of life measures [3]. This emphasizes that chronic rhinosinusitis has a significant impact on all ethnicities and has a large economic impact. Furthermore, the total annual cost of chronic rhinosinusitis in the United States was estimated to be $22 billion in 2014 (both direct and indirect costs) [4]. This highlights the importance of effective treatment. Unfortunately, it is evident that there are substantial disparities in the volume of research published on chronic rhinosinusitis over the past forty-five years when compared to other prevalent problems, such as asthma or diabetes mellitus [5]. Thus, we must carefully examine the currently available literature to enhance our treatment approach.

2. Definition and Classification

Rhinosinusitis is defined as inflammation of the paranasal sinuses and nasal cavity that causes symptoms. It may be classified as acute rhinosinusitis (ARS) when it lasts less than four weeks' duration or as chronic rhinosinusitis (CRS) when it lasts more than 12 weeks. During this time, patients may have acute exacerbations, superimposed on their chronic rhinosinusitis. Rhinosinusitis may be caused by viruses, bacteria, fungi, and noninfectious causes, although primary emphasis has recently been placed on noninfectious and bacterial causes [6].

3. Diagnosis and Assessment

Clinicians should assess for nasal obstruction, facial pain/pressure/fullness, purulent nasal discharge, and hyposmia, with two or more symptoms for greater than 12 weeks being highly sensitive for CRS. However, since these symptoms are also nonspecific, it is also recommended that patients have objective evidence of sinonasal inflammation, which can be visualized during anterior rhinoscopy, nasal endoscopy, or on computed tomography. Inflammation is documented when one visualizes purulent rhinorrhea or edema in the middle meatus or anterior ethmoid region, polyps in the nasal cavity or middle meatus, and/or radiographic findings of inflammation. These findings and the patient's symptoms should be persistent for greater than 12 weeks despite adequate treatment for ARS, in order to diagnose CRS [6–9].

In addition, clinicians should assess for other factors that may affect treatment in CRS: the presence or absence of nasal polyps, asthma, cystic fibrosis, ciliary dyskinesia, and an immunocompromised state. One may also consider obtaining testing for allergy and immune function [6,10–14].

4. Treatment

4.1. Acute Exacerbations of CRS and Biofilms

It is widely accepted that acute exacerbations of CRS should be treated with oral antibiotics and this is recommended by American, European, and Canadian guidelines/position papers [15–18]. It is well accepted that bacteria trigger ARS and there has been concern that inadequately treated ARS could cause CRS but this is currently unclear. Many reports show increased rates of *Staphylococcus aureus*, Gram-negative rods, and anaerobes in CRS [19–27]. However, some studies have not shown differences in microbiology between patients with CRS and controls, and it has also been shown that there are similar bacteria in the diseased and non-diseased contralateral sides of the same patient, which raises the question of bacterial colonization *versus* pathologic involvement in CRS [28–30]. It is also possible that these studies may have methodological differences, including performing cultures after antibiotic treatment, patients may have comorbidities affecting these patients' symptoms that were not identified (*i.e.*, allergies), and there is some evidence that bacterial biofilms and bacteria within epithelial cells contribute to inflammatory cascades, but these are not readily detected via standard techniques [31–33].

Biofilms including *Streptococcus pneumonia*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *S. aureus*, and *Pseudomonas aeruginosa* have been commonly identified in CRS patients both with and without nasal polyps [34–38]. There is evidence that epithelial disruption can be present in CRS and this may contribute to biofilm formation [39]. It is clear that bacteria causing an acute exacerbation should be treated, but eradication of possibly colonizing bacteria is not advocated at this time. However, bacterial biofilms raise the concern that pathologic bacteria are present and evading host defenses that are not identified in traditional cultures. These are not felt to be colonizing bacteria. Furthermore, they have shown to be involved in both Th1 and Th2 immune responses [40,41]. In addition, patients with biofilms have more severe preoperative sinus disease, persistence of postoperative symptoms after sinus surgery, ongoing mucosal inflammation, and infections [42–45]. Effective treatments targeting biofilms merit further study. *In vitro*, photodynamic therapy has shown promise at eradicating *P. aeruginosa* and methicillin-resistant *S. aureus*, without causing abnormalities of the epithelium

or respiratory cilia [46–48]. Clinical studies of this therapy are needed to determine if it is efficacious in patients.

In general, empiric oral antibiotics are used to treat acute exacerbations and antibiotic coverage can potentially be narrowed when positive cultures are available. Empiric antibiotic coverage targets common bacteria found in CRS: *S. pneumonia, H. influenzae, M. catarrhalis, S. aureus, P. aeruginosa*, and anaerobes [27]. Antibiotics should be prescribed after considering local antibiotic sensitivity patterns. In general, some effective options include amoxicillin-clavulanate, second or third generation cephalosporins, and respiratory fluoroquinolones [49].

4.2. Chronic Rhinosinusitis with Nasal Polyps

There is a lot of evidence emerging that *S. aureus* is implicated in at least a subset of patients with CRS with nasal polyps. There has been a suggestion this may be occurring because colonizing staphylococcal bacteria are producing superantigenic toxins (Sags) that increase eosinophilic inflammation and promote the formation of nasal polyps, in addition to evidence of B and T cell responses in local tissues to these staph superantigens [50,51]. This has not been found uniformly in patients with nasal polyps and it is felt to be a contributor, as opposed to a single etiology. At this time, acute exacerbations in CRS with nasal polyps should include treatment for *S. aureus* [52].

The inflammatory cascade has been demonstrated to be active in a variety of different ways in CRS with nasal polyps. There has been evidence of local eosinophilic infiltration (mediated by increased GM-CSF), mast cell degranulation, interleukin upregulation (*i.e.*, including but not limited to IL-4, IL-5, IL-8, IL-13, IL-32), VPF/VEGF upregulation, increase in T lymphocytes, increase in dendritic cells, and other pro-inflammatory activity [53–60]. Sinus mucosal eosinophilia (>5/hpf) in histologic samples of patients with CRS correlated with worse CRS disease severity on CT, endoscopy, and smell identification test (hyposmia), whereas the total eosinophil counts correlated with the presence of nasal polyps, asthma, and aspirin intolerance [61].

When nasal polyps are present in CRS, patients should be treated with intranasal therapy, including topical intranasal steroids and/or saline nasal irrigation for symptomatic relief, in addition to long-term management of the nasal polyps themselves with intranasal glucocorticoids which decrease polyp size, polyp recurrence, decrease nasal symptoms, and improve nasal airflow [6,62–70]. Glucocorticoids have been shown to impact epithelial GM-CSF and prolong eosinophil survival [71]. Topical intranasal corticosteroids are more effective when administered with correct technique but there does not appear to be a significant difference between corticosteroids. Oral corticosteroids are effective in decreasing polyp size and nasal symptoms in the short term, but this must be balanced with the risks of oral corticosteroids [72,73]. It may be useful for planned short-term improvement. Long-term oral macrolides may be beneficial because of their anti-inflammatory effects, but this needs to be further elucidated through further study of randomized placebo-controlled trials to better assess the benefits *versus* risks [15,74–77]. Intranasal saline irrigation should be used, as opposed to intranasal saline spray because of increased effectiveness on symptom relief and improving quality of life [68,78].

Endoscopic sinus surgery is safe and effective in patients with CRS with nasal polyps and is typically recommended when patients' signs and symptoms are refractory to medical therapy. In one randomized study, endoscopic sinus surgery was shown to have equivalent efficacy to medical management [79,80].

4.3. Chronic Rhinosinusitis without Nasal Polyps

Intranasal steroids and/or nasal saline irrigation have been shown to be beneficial in CRS without nasal polyps with improved symptom scores [81–86]. This improvement did not seem to be significantly related to a specific corticosteroid. Subgroup analysis suggests that sinus delivery methods may be more effective than nasal delivery.

Additions to nasal saline irrigation that have shown benefit include sodium hypochlorite 0.05% in patients with *S. aureus* [87]. This is also felt to have possible effects on *P. aeruginosa* although further

trials need to be done to better evaluate this. Using xylitol in water as a sinonasal irrigation improved symptom control compared to saline irrigation and can potentially be a useful adjunctive treatment [88].

There is inadequate data to promote the use of oral steroids in CRS without nasal polyps [89]. Topical antibiotics do not show benefit in CRS without nasal polyps [90–93]. Long-term antibiotics, primarily macrolides (azithromycin 500 g weekly or roxithromycin 150 g daily), have shown possible therapeutic response after treatment for 12 weeks, but the evidence is very limited and subject to bias [75–77,94–97]. Further study with placebo-controlled randomized controlled trials is needed to make further conclusions. In addition, as in other conditions that use low-dose long-term antibiotics, there is concern for development of antibiotic resistant bacteria with subsequent infections.

Endoscopic sinus surgery in CRS without nasal polyps has been shown to be safe and effective when medical treatment has failed.

4.4. Allergy

Allergic rhinitis is present in 40%–84% of patients with CRS [98,99]. Patients with allergies and CRS are also more symptomatic than those that have CRS without allergic rhinitis, despite similar CT findings [100,101]. Allergy testing is an option for patients with CRS, with allergy skin testing being the preferred method to evaluate for IgE-mediated sensitivity [102]. There is some, albeit limited, evidence that allergen avoidance or immunotherapy improves CRS [15,103]. Intranasal glucocorticoids and/or nasal irrigation can be beneficial. It is felt that allergic rhinitis is a superimposed exacerbating factor of CRS.

4.5. Asthma and Aspirin Sensitivity

There is a high prevalence of CRS in patients with asthma and they have found that asthma severity directly correlates with the severity of sinus disease on imaging [11,12,104]. When CRS is treated (medically or surgically), asthma symptoms improve and the need for asthma medications decreases [105–108].

Some patients may also have aspirin sensitivity (in the presence or absence of asthma) which has been found to be secondary to upregulation of eicosanoids, mediated by oxidative metabolism of arachidonic acid, with a specific increase of leukotrienes (LTB4, LTC4, LTD4, and LTE4). Leukotrienes in airway mucosa are primarily released by mast cells and eosinophils. These leukotrienes bind to receptors CYSLTR1 and CYSLTR2. In aspirin-tolerant patients with asthma or allergic rhinitis, leukotriene inhibitors that antagonize CYSLTR1 can be potentially beneficial (montelukast and zafirlukast). There has been a study that combined treatment with intranasal fluticasone and montelukast and demonstrated decreased peripheral blood eosinophil counts that correlated with improvement of nasal polyp size and CT findings, in addition to others that demonstrate montelukast is better than placebo in CRS with nasal polyps [109,110]. The studies to date do not elucidate how much improvement you get in CRS beyond the effect of intranasal corticosteroids, but its use in patients with concomitant asthma would provide additional benefit in controlling asthma. The strongest association with leukotriene levels, aside from aspirin sensitivity, is present with nasal polyps. Leukotriene levels were found to be highest in aspirin-sensitive polyps, followed by CRS with nasal polyps (without aspirin sensitivity), CRS without nasal polyps, and then normal mucosa [111–115]. In aspirin sensitive patients, aspirin avoidance is an important part of the management plan. One may also consider aspirin desensitization.

4.6. Cystic Fibrosis (CF)

CRS is reported in 30 to 67% of patients with CF (within all age groups) [116–119]. Some studies have suggested that this may be because of genetic mutation, such as the ΔF508 and 394delTT mutation in Finland [120]. It is clearer that similar bacteria occupy the upper and lower airways of these CF patients, suggesting a possible spread from the upper to lower airways [121–124]. In addition, COX-1 and COX-2 are upregulated in CF patients with CRS leading to increased prostaglandin levels and

there is an increase in mucus gland proliferation, surfactant gene expression, and MUC mucin gene expression. These findings suggest that inflammatory pathways may be treatment targets, in addition to gene therapy and treatment of their microbiology. More aggressive combined medical and surgical treatment demonstrates improved control of CRS in CF patients [125–128]. A mucolytic, dornase alfa, once daily (2.5 mg) administered intranasally either one month after endoscopic sinus surgery, or without surgery in another trial, has been found to be improve nasal symptoms, endoscopic appearance, CT findings, forced expiratory volume in 1 s, and quality of life compared to hypotonic saline or normal saline [129,130]. It is also used for lower airway disease in these patients, but with different dosing regimens and administration route (oral inhalation). Reviews of topical antimicrobials show that they should not be first-line therapies in CF patients for CRS [131]. Nasal irrigation or nebulization was more effective than when applied by nasal spray. Initial attempts to use gene therapy via a viral vector (transmembrane conductance regulator) has been tried in CF patients but has not yet been found to be effective, although it was safely administered to the sinuses [132]. There was a case report of successful use of ivacaftor in refractory CRS in a patient that had the related CF gene defect. Ivacaftor, a CF transmembrane conductance regulator (CFTR) potentiator, targets the G55ID-CFTR mutation in CF [133]. Limited data demonstrates that endoscopic sinus surgery results in similar improvement in CF *versus* non-CF patients with CRS. In addition, patients with CF that have endoscopic sinus surgery with serial antimicrobial lavage had better outcomes than surgery alone [126,134].

4.7. Ciliary Dyskinesia

Decreased mucociliary clearance from ciliary dyskinesia impacts a small percentage of patients with CRS (aside from CF). Mucociliary transit time (MTT) is prolonged when patients have underlying genetic-related ciliary dyskinesia [135–137]. However, there are conflicting results regarding decreased ciliary beat frequency as part of the pathogenesis of CRS and it is still not well understood [136]. Effective treatments need to be further elucidated.

4.8. Immunodeficiency

Some immunodeficient states are found in patients with CRS, including selective IgA deficiency, specific antibody deficiency, common variable immunodeficiency, and human immunodeficiency virus infection (HIV) [138]. Testing for these immunodeficiencies is important to consider in these CRS patients, especially in those with refractory CRS to aggressive treatment or if they have associated otitis media, bronchiectasis, or pneumonia. Testing may demonstrate low serum IgA, low serum IgG, functional abnormalities of IgG to polysaccharide vaccines (based on pre-immunization and post-immunization antibody responses to pneumococcal polysaccharide vaccines or tetanus toxoid), abnormal CH50, decreased measurement of T-cell number and function (tested via delayed hypersensitivity skin testing and flow cytometry analysis of T cells), and positive HIV testing [139–142]. Treatment with intravenous immunoglobulins (IVIG) and/or prophylactic antibiotics is indicated in those with immunoglobulin deficiency, which can improve survival and decrease life-threatening infections [143]. However, it does not appear to affect radiologic appearance of CRS and it is unclear that this clinically improves CRS [144]. Those with immunosuppression from HIV infection should be treated for HIV to raise their CD4 count.

4.9. Fungal

Fungi have been found to be prevalent in patients with CRS and local nasal tissue samples exhibit increased eosinophils, but without increased IgE to indicate a mold allergy. There have been concerns that the eosinophilic response in these patients may be secondary to other underlying etiologies. For instance, the majority of these patients had concomitant asthma that could explain the eosinophilic response. It is recommended not to use oral or topical antifungals given greater risk of harm over potential benefit based on systematic reviews of randomized controlled trials, in addition to their high

cost [6,64,69,74,145–147]. One area that remains less clear is allergic fungal rhinosinusitis which appears to be a clinically distinct entity. It demonstrates a Th2 immune response and also has specific IgE in eosinophilic mucin and mucosa [148–150]. Treatment impact of this needs to be further elucidated. Surgery with and without concomitant medical management has been beneficial in allergic fungal rhinosinusitis [151].

5. Conclusions

Chronic rhinosinusitis presents with uniform signs and symptoms, but should be medically managed according to the medical comorbidities and clinical features present in an individual patient. Inflammatory pathways and host factors continue to be elucidated and treatments will likely continue to evolve as these are better understood, including the potential treatment of bacterial biofilms and modification of the inflammatory cascade in subsets of chronic rhinosinusitis patients.

Conflicts of Interest: The author declares no conflict of interest.

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