Treatment Options for Chronic Rhinosinusitis

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Chronic rhinosinusitis (CRS) is defined as persistent symptomatic inflammation of the nasal and sinus mucosa. Although insights into the pathophysiology of CRS have largely expanded over the last 2 decades, the exact etiology is still unknown and is likely due to multiple host and environmental factors. Treatments are aimed at reducing mucosal inflammation, controlling infection, and restoring mucociliary clearance within the sinuses. The principal goal of this article is to outline a rational approach to the treatment of chronic sinus disease on the basis of currently available diagnostic and therapeutic techniques. Emphasis will be placed on the management, therapeutic response, and objective evaluation of therapeutic efficiency.

Keywords: chronic rhinosinusitis; CRS; sinus surgery; management

Chronic rhinosinusitis (CRS) is one of the most common chronic diseases, with a prevalence as high as 15% of the population in some studies. Like asthma, a disease with which CRS has significant etiologic and pathologic relationships, the incidence appears to be increasing. CRS also has significant socioeconomic implications. The direct and indirect costs related to CRS are substantial, resulting in millions of office visits and billions of dollars of health care costs each year (1).

DEFINITIONS

Rhinosinusitis is a group of disorders characterized by inflammation of the mucosa of the nose and the paranasal sinuses. In 2007, the American Academy of Otolaryngology – Head and Neck Surgery published their most recent and revised guidelines on the diagnosis and management of rhinosinusitis (2). Rhinosinusitis is traditionally classified by duration as acute (<4 wk), subacute (4–12 wk), or chronic (>12 wk, with or without exacerbations) (2). Briefly, the diagnosis of CRS requires that inflammation be documented on physical examination, in addition to persistent symptoms that usually include at least two of the following: nasal obstruction (81–95%), facial congestion/pressure/fullness (70–85%), discolored nasal discharge (51–83%), and hyposmia (61–69%) (2, 3). Nasal endoscopy is an office procedure used to augment the physical examination to better evaluate the nasal cavity and paranasal sinuses. Endoscopy is used to assess sinonasal mucosal inflammation, polyps, or purulence, and can confirm the diagnosis of CRS when symptoms are nonspecific. CRS often coexists with other medical conditions, such as allergic rhinitis, asthma, and cystic fibrosis, and with less common conditions, such as sarcoidosis, Churg-Strauss, and Wegener granulomatosis (2).

PATHOPHYSIOLOGY

There has been an evolution of our understanding of the pathophysiology of CRS. Historically, CRS was believed, perhaps simplistically, to arise from sinus ostium obstruction leading to bacterial infection. Currently, CRS is believed to arise primarily from persistent inflammation of the mucosa and perhaps the underlying bone, caused by a number of factors (Table 1) (1–3). Perhaps the most appropriate broad classification of predisposing factors for chronic sinusitis is into environmental factors (e.g., pollution, allergens, viruses, bacteria, and molds), general host factors (genetic, granulomatous disorders, immune deficiency, cystic fibrosis, and ciliary defects), and local host factors (chronic localized inflammation, anatomic obstruction, polyps, and tumors) (2, 4).

The most common conditions that predispose patients to CRS include allergic and nonallergic rhinitis, nasal polyps, and occasionally anatomic factors, such as a deviated nasal septum (2, 4). The inflammatory process appears to be at least exacerbated by the presence of bacteria and fungi. Therefore, reducing bacterial and fungal contamination, whether by improving sinus drainage, improving mucociliary clearance, antimicrobial therapy, or reducing mucosal edema, has a positive effect. It is clear that CRS is not one disease, but rather is a spectrum of symptoms and signs arising from multiple different causes. To better classify the disorder, a division into polypoid and nonpolypoid CRS has been recommended, based on some significant differences in cytokine profile (3). However, the clinical significance of this finding is not clear, as many patients without nasal polyps will actually have polypoid changes of the sinus mucosa.

Thus, treatment of CRS is aimed at reducing mucosal inflammation, controlling infection, and restoring mucociliary clearance within the sinuses (Figure 1). Eosinophilic inflammation is one of the frequent hallmarks of CRS, and reducing mucosal eosinophilia is one of the therapeutic goals (3). However, there is no one regimen for the management of CRS, and treatments should be individualized. Environmental control is obviously an important part of the management in those patients for whom allergy, pollution, or mold exposures appear to be significant predisposing factors. Sinus surgery is generally reserved for patients who remain symptomatic despite maximal medical therapy. This article discusses the various treatment options for CRS.

STEROIDS

Background

Topical corticosteroids constitute first-line therapy in the medical management of CRS. Long-term treatment with topical nasal steroid sprays has been shown to reduce sinus inflammation and nasal polyp size and improve symptoms associated with CRS (5–7). Short courses of oral steroids are used in the treatment of CRS with nasal polyps but may also be used in cases of severe CRS when rapid symptomatic improvement is needed (6, 8). Topical and systemic steroids reduce mucosal eosinophil chemotaxis and increase eosinophil apoptosis. Corticosteroids also decrease white blood cell migration, production of inflammatory mediators, antibody production, histamine release, and swelling through a variety of mechanisms (9). The daily use of topical nasal steroids appears to be associated with minimal risks; however, long-term systemic steroid use is associated with significant side effects (7, 8). Therefore, a tapered regimen of oral steroids is most commonly given during severe

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TABLE 1. FACTORS IN THE PATHOPHYSIOLOGY OF SINUSITIS

Infectious	Viral, bacterial, fungal
	Biofilms
Local factors	Nasal obstruction
	Allergic and nonallergic rhinitis
	Polyps
	Foreign bodies, nasogastric tubes
	Adenoid infection
	Tumors
	Trauma
	Dental infection
	Prior surgery
	Anatomic variations/aberrations
	Septal deviation
	Concha bullosa
	Haller cells
	Ciliary dyskinesias
	Gastroesophageal reflux
	Sinus osteitis
	Bacterial superantigens
Systemic factors	Asthma
	Cystic fibrosis
	Granulomatous diseases
Immune deficiencies	Congenital
	Selective antibody deficiency
	IgA deficiency
	IgG subclass deficiencies
	Common variable immune deficiency
	C4 deficiency
	X-linked agammaglobulinemia
	Acquired
	HIV/AIDS
	Organ transplant/cancer chemotherapy
Environmental factors	Air pollution
	Cigarette smoke, exhaust fumes
	Swimming

Adapted with permission from Reference (95).

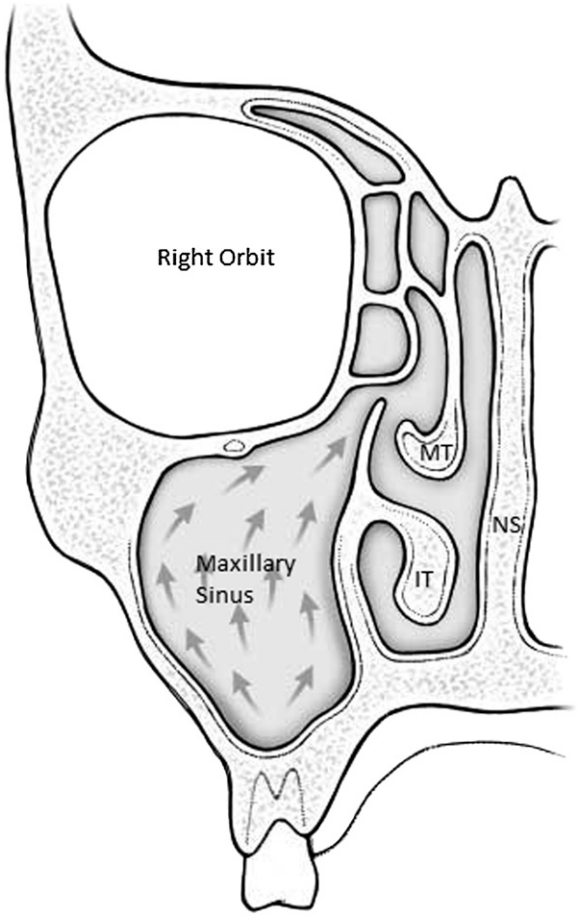

Figure 1. Mucociliary clearance. The mucociliary stream is propelled from the inferior portion of the maxillary antrum upward and around the walls of the sinus toward the primary ostium of the maxillary sinus. IT = inferior turbinate; MT = middle turbinate; NS = nasal septum. Adapted with permission from Reference (95).

CRS flare-ups or in the postoperative period after sinus surgery.

Topical Nasal Steroids

The use of topical nasal steroids has been widely advocated in the treatment of CRS. Several studies have demonstrated that topical corticosteroids are beneficial in the treatment of small to medium-sized polyps and for rhinitis symptoms (10, 11). When combined with antibiotic use, efficacy in symptom reduction was also found during acute exacerbations (12). Corticosteroid nasal sprays have been shown to delay the recurrence of polyps after surgery (13); however, the benefit for nonpolypoid CRS has been harder to demonstrate (14). Common adverse effects with nasal steroids include nasal irritation, mucosal bleeding, and crusting (7, 8).

Systemic Steroids

Oral corticosteroids have been effective in treating allergic rhinitis, reducing nasal polyps and allergic fungal sinusitis (6, 8, 15). Years of clinical practice support their effectiveness in providing rapid relief of facial pressure and nasal blockage by reducing mucosal edema, especially in patients with nasal polyps. Lennard and colleagues (16) demonstrated the effects of steroids in inflammatory cytokines for patients with CRS by nasal biopsy before and after treatment. The authors found significant decreases in IL-6 levels after treatment, with tumor necrosis factor-α trending toward significance. In a study of 25 patients with CRS with massive nasal polyps, treatment with high-dose oral prednisolone was associated with both subjective and objective improvement and involution of nasal polyps (17). Effects were best in the frontal and sphenoid sinuses; however, recurrence was seen after 5 months. Woodworth and colleagues (18) treated 21 patients with CRS with nasal polyps with 60 mg oral prednisone tapered over 3 weeks. The study found that oral steroids decreased all measured chemokines and cytokines compared with placebo and improved Sino-Nasal Outcome Test-20 (SNOT-20; a widely used, disease-specific, health-related quality-of-life measure for rhinosinusitis [19]) scores and the endoscopic examination for the patient population.

However, despite widespread use of oral corticosteroids for CRS, there are few randomized trials. A double-blind placebo-controlled trial of prednisolone 50 mg daily for 14 days versus placebo demonstrated improvement of sinonasal polyposis and symptoms as measured by the 31-item rhinosinusitis outcome measure (RSOM-31) questionnaire, nasal endoscopy, and pre- and post-treatment MRI scans (20). With the available data, it seems reasonable to recommend the judicious use of corticosteroids in CRS as part of a multifaceted treatment regimen, particularly in patients with nasal polyps.

NASAL IRRIGATION

Background

Saline nasal irrigation has been advocated as an adjunct therapy for CRS (1, 5, 6, 21). A recent Cochrane Review reviewed eight randomized clinical trials on the use of nasal saline irrigation for CRS, and included studies demonstrated improvement in symp-

toms, quality of life, and endoscopy findings (21). The procedure involves rinsing the nasal cavity with saline to promote mucociliary clearance by flushing out mucus, crusts, and irritants. Nasal irrigation is well tolerated by patients, without any evidence of significant harmful side effects (22). Other suggested benefits of nasal saline irrigation include enhanced ciliary beat activity, removal of antigen, biofilm, or inflammatory mediators, and a protective role on sinonasal mucosa (23). Nasal irrigation is also particularly useful after endoscopic sinus surgery to clear crusts and thick mucus that are common postoperatively (5).

Daily saline irrigation may also be useful in the secondary prevention of rhinosinusitis exacerbations. In a prospective, randomized trial, Rabago and colleagues (24) used daily saline nasal irrigation and found that patients using irrigation had fewer 2-week blocks with nasal congestion, sinus headaches, and frontal pain and pressure, and used fewer antibiotics and nasal sprays than the control group. In a 12-month follow-up study, the patients using irrigation reported continued improvement of sinonasal symptoms and quality of life (25).

Hypertonic and Isotonic Saline

Several different saline tonicities have been described for use in nasal irrigation. Talbot and colleagues (26) showed that buffered hypertonic saline nasal irrigation improved mucociliary clearance, whereas buffered physiological saline had no effect on mucociliary clearance. The authors also suggested that hypertonic saline might have the added benefit of decongesting the nose through an osmotic mechanism. Hauptman and Ryan (27) looked at nasal patency and mucociliary clearance time in 80 patients treated with either physiological or hypertonic saline. The authors found that both solutions improved saccharine clearance times and improved nasal stuffiness and nasal obstruction. In this study, hypertonic saline caused increased burning and irritation compared with buffered saline. Tomooka and colleagues (28) evaluated the use of pulsatile hypertonic saline nasal irrigations for patients with sinonasal disease and found statistically significant improvements in 23 of 30 nasal symptoms. Patients in this study reported improvements in nasal congestion, postnasal drip, allergies, and nasal discharge. However, other studies have raised questions about the longer-term effects of hypertonic nasal irrigation on the cilia and the potential for cilia damage.

Steroid Nasal Irrigation

Budesonide Respules (Pulmicort; Astra Zeneca, Wilmington, DE) have been added to nasal irrigation as an adjuvant method of treating sinus inflammation. Budesonide, as an aqueous nasal spray, has been shown to be beneficial for those with CRS and allergic rhinitis (29). The theory behind use of the budesonide Respules in irrigation is that much higher concentrations of steroids can be topically delivered to sinus mucosa than what is available as a prescription nasal steroid spray. In a pilot study involving 18 patients over 8 weeks, the addition of budesonide suspension to twice-daily nasal saline irrigations provided significant improvements in sinus symptoms, including the sense of smell (30). There were also improvements in both radiographic and nasal endoscopy objective measures. Seventy-five percent of patients in this small study had complete regression of nasal polyps, and there were trends toward improvement in asthma symptoms. In a separate study to evaluate for systemic absorption of the steroid, Bhalla and colleagues (31) found no suppression of the hypothalamic-pituitary-adrenal axis after 8 weeks of budesonide nasal irrigation. Yu and coworkers (32) studied the use of topical budesonide Respules after functional endoscopic sinus surgery and found decreased mucosal inflammation, shortening the stage of epithelization and accelerating the recovery of mucosa after functional endoscopic sinus surgery. The available literature suggests that steroid nasal irrigation with budesonide as a promising new therapy for select patients with CRS.

Topical Antibiotic Therapy

The goal of topical antibiotic therapy is to deliver high concentrations of antibiotics directly to the site of infection with low systemic absorption and side effects (23, 33). *Pseudomonas* or methicillin-resistant *Staphylococcus aureus* (MRSA) exacerbation of CRS after endoscopic sinus surgery can be seen in up to 30% of endoscopically guided cultures (34, 35). These infections are notoriously difficult to treat and can lead to chronic mucosal inflammation, altered sinonasal ciliary function, and nasal polyp formation. Topical therapy with antibiotics such as gentamicin or tobramycin for patients with CRS can be effective in reducing pain, mucosal edema, secretions, and postnasal drip, especially after endoscopic sinus surgery (35, 36). Vaughan and Carvalho (37) used 3-week courses of culture-directed antibiotics via nebulizer and demonstrated improvements in sinus endoscopic examinations, posterior nasal discharge, facial pain/pressure, and had longer infection-free periods. The literature to date suggests that topical antibiotic therapy is a reasonable treatment option for patients with recalcitrant sinus disease. However, additional studies regarding optimal dosing schedules, treatment duration, delivery mechanisms, and efficacy are needed.

Chemical Surfactant

Chiu and colleagues (38) have demonstrated the efficacy of 1% baby shampoo nasal irrigations for patients with CRS. In this prospective, nonrandomized study, 18 patients with CRS were treated with twice-daily sinus irrigation with 1% baby shampoo in saline for 4 weeks. Baby shampoo irrigations led to subjective improvement in SNOT 22 scores for 46.6% of patients who were previously symptomatic despite medical and surgical management. Greatest improvements were in reducing thickened nasal secretions and postnasal drainage. Baby shampoo nasal irrigation holds promise as an inexpensive, well-tolerated adjuvant therapy to conventional medical therapies for symptomatic patients after functional endoscopic sinus surgery (FESS).

ANTIBIOTICS

Introduction

This section examines the use and effectiveness of antibiotics in the treatment of CRS. Antibiotics are usually one component of medical therapy and should be used when purulence is identified, in conjunction with a combination of topical nasal steroids, nasal irrigation, mucolytic agents, or other adjuvant therapies. A recent survey found that 94% of otolaryngologists prescribed oral antibiotics in the treatment of CRS (39). Systemic steroids are often included in cases of CRS with nasal polyps or when there is significant mucosal edema identified on endoscopy.

Microbiology

The microbiology of CRS differs from that of acute rhinosinusitis. In addition to standard sinus pathogens, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, there is an increased prevalence of *S. aureus*, *Pseudomonas aeruginosa*, and various anaerobic bacteria in CRS. Mixed populations of bacteria and fungus are not uncommon (Figure 2). Antibiotic choice should be made based on current culture and sensitivity results when possible. Klossek and colleagues (40) evaluated the bacteria present in chronic mucopurulent secretions of 394 patients with the diagnosis of CRS. *Hemophilus influenzae*, streptococci, *streptococcus pneumoniae*, *Prevotella*,

and *Fusobacterium* were considered to be causative pathogens. Anaerobes were isolated from 25% of these patients. Betalactamase producers represented 27.5% of *H. influenzae* and 38% of *Prevotella* species isolates. Thirteen percent of *S. pneumonia* isolates had decreased sensitivity to penicillin. Amoxicillin-clavulanate was the most active antibiotic *in vitro*. After sinus surgery, the bacterial flora found from cultures often changes and should be taken into consideration when determining the choice of antibiotic therapy. In one study by Bhattacharyya and Kepnes (41) looking at 203 sinus cultures in patients with a history of endoscopic sinus surgery, gram-positive cocci were found in 37.9% of isolates; gram-negative rods, such as *Enterobacter* species and *Escherichia coli* in 14.8%; and yeast and fungal forms in 1.7%.

Antibiotics for Chronic Rhinosinusitis

No antibiotic has been approved by the U.S. Food and Drug Administration for the treatment of CRS. Most recommendations on antibiotic use have been based primarily on historical practice rather than levels of evidence (42). Most experts agree that antimicrobials for treatment of CRS should provide broad-spectrum coverage. Commonly used agents include amoxicillin-clavulanate, clindamycin, sulfamethoxazole/trimethoprim, and levofloxacin or ciprofloxacin. Antibiotics play a role in the management of CRS to decrease bacterial load and to treat acute bacterial exacerbations of CRS. Acute exacerbations of CRS represent sudden worsening or new symptoms in a patient with CRS and are typically associated with purulence draining from the sinuses visualized on nasal endoscopy (43). As discussed in the previous section, the bacterial flora cultured from purulence in cases of CRS tends to demonstrate increased antibiotic resistance and different species when compared with simple acute rhinosinusitis. Typically, the acute (not chronic) symptoms return to baseline after treatment.

Antibiotics are typically used for at least 3 to 4 weeks, so as to maximize the antiinflammatory effect and effectively lower bacterial loads in the sinuses. In a study with 251 adults with CRS, Legent and colleagues (44) found patients treated with ciprofloxacin for 9 days had significantly higher cure rates than those treated with amoxicillin/clavulanic acid ($P = 0.04$) and fewer side effects ($P = 0.01$). Namyslowski and coworkers (45) compared the efficacy of amoxicillin/clavulanic acid and cefuroxime for 14 days in the treatment of 206 patients with CRS and found similar rates of bacterial eradication and adverse events between the two groups. However, patients treated with cefuroxime had a significantly higher rate of disease relapse ($P = 0.005$).

Figure 2. Electron micrograph demonstrating mixed fungal and *Pseudomonas* biofilm. *Indicates *Pseudomonas*; = indicates fungus. Photo courtesy of Noam Cohen, M.D., Ph.D.

Treatment of Sinonasal MRSA

In a national study by the Centers for Disease Control, MRSA nasal carriage doubled between 2001 and 2004 (46). Recent literature also points to an increasing prevalence of MRSA-positive cultures in CRS (47). Bhattacharyya and Kepnes (48), in a study of 392 cultures on sinonasal infections, found that 19% of isolates were *S. aureus*, with 19% of those being MRSA. Multiple studies have demonstrated *Staphylococcus* species in cases of acute exacerbations of CRS (47, 49).

Patients with MRSA can be divided into two groups: those who are colonized in the sinuses and those with infection. The presence of a positive culture does not necessarily imply treatment in the absence of symptoms or purulence on endoscopy or anterior rhinoscopy. Sudden worsening of symptoms or the presence of new symptoms with purulence on physical examination implies an acute exacerbation of CRS, which should be treated (43). These patients are managed by microbiological culture, determination of antibiotic sensitivities, and appropriate antibiotic therapy.

Treatment options for MRSA sinonasal infections include oral antibiotics, intravenous antibiotics, and topical antibiotics (50). Topical antibiotics have the theoretical advantage of high local levels of drug with minimal systemic absorption, lower costs, and decreased morbidity.

Solares and colleagues (51) have shown encouraging data supporting the use of topical mupirocin nasal irrigations as an alternative to intravenous antibiotics in the treatment of acute exacerbations of CRS due to MRSA. Patients using mupirocin in sinus irrigations showed improved symptoms and reduced MRSA recovery on subsequent cultures. A more recent study found that twice-a-day nasal irrigation with 0.05% mupirocin in Ringer solution improved endoscopic findings in 93% of patients, whereas 75% had symptom improvement (52). For MRSA rhinosinusitis, topical antibiotic therapy with mupirocin appears to be both safe and effective, and may replace oral and intravenous treatments in some patients.

In theory, patients who have had sinus surgery with large antrostomies should be better candidates for widespread delivery of topical antimicrobials than nonsurgical patients. Grobler and coworkers (53) found that 3.95 mm was the minimum ostium diameter to guarantee penetration of topical therapies into the maxillary sinus. A study by Kobayashi and Baba (54) demonstrated that nonsurgical patients did not achieve sufficient concentrations of topical antibiotics in the maxillary sinus after irrigation. However, in a review of topical antimicrobials for chronic sinusitis, Lim and colleagues (55) found that topical therapies were effective for both surgical and nonsurgical patients, but with higher levels of evidence for postsurgical patients.

Macrolide Therapy for CRS

The use of long-term macrolide therapy originated in Japan, where it reduced the mortality rate of diffuse panbronchiolitis and concomitantly improved sinus symptoms (56). Use of erythromycin in the treatment of diffuse panbronchiolitis was eventually attributed to the drug's antiinflammatory and immunomodulatory effects. Macrolides have been found to inhibit inflammatory mediators such as IL-1B, IL-8, and intercellular adhesion molecule-1 (57). Other effects include protecting bioactive phospholipids, reducing the number of neutrophils by accelerated apoptosis, and increasing mucociliary transport (6). In a double-blind, randomized, placebo-controlled clinical trial of low-dose roxithromycin or placebo for 3 months in 64 subjects with CRS, there was a statistically significant improvement in the SNOT-20 score, nasal endoscopy examination,

saccharine transit time, and IL-8 levels in lavage fluid in the macrolide group. In another study, erythromycin or clarithromycin was given to patients with chronic rhinosinusitis with nasal polyps. After 3 months, the IL-8 levels were significantly decreased, which corresponded to a decrease in size of the nasal polyps (58). Available evidence suggests that low-dose, long-duration macrolide therapy is safe and can result in improvements in both subjective and objective measures of CRS in select patients.

ANTIFUNGAL THERAPY FOR CRS

Background

There has been considerable controversy in the literature regarding the role of fungus in the etiology of CRS. Ponikau and coworkers (59) hypothesized that fungal colonization is an important stimulus for persistent inflammation in patients with CRS, including those with or without nasal polyps. The group isolated fungal organisms in 96% of patients with CRS. However, in the same study, 100% of healthy control subjects also had positive fungal cultures. It has also been found that immune cells from patients with CRS react to common airborne fungi with the production of IL-13 and IL-5, which are crucial for eosinophilic inflammation (60). Another study by the Mayo Clinic reported that *Alternaria alternata* induced eosinophil degranulation *in vitro* (61). The authors concluded that certain environmental fungi may be important in the exacerbation of inflammation in asthma and allergic diseases. The potential association between fungal elements and inflammation in CRS has generated interest in the use of topical or systemic antifungal agents.

Topical and Systemic Antifungal Therapy

Despite initial enthusiasm for the use of topical antifungal agents, subsequent studies have not confirmed benefit over that provided by saline irrigation (62, 63). Similarly, a multicenter high-dose double-blind study of terbinafine (Lamisil) in the treatment of CRS performed by Kennedy and colleagues (64) failed to demonstrate any significant benefit either in terms of symptomatic or radiographic resolution. On the other hand, oral itraconazole has been used as an adjunctive treatment of allergic bronchopulmonary aspergillosis (ABPA), and there is significant anecdotal evidence that this may also be helpful in some patients with CRS and nasal polyposis. In patients with APBA, itraconazole has been shown to lower the need for oral steroids, decrease IgE levels, and improve pulmonary function, exercise tolerance, and symptoms. Oral antifungals have been proposed as a treatment option for select patients with allergic fungal sinusitis (65–67) (AFS) and nonallergic eosinophilic fungal sinusitis (66), diseases considered to be similar to ABPA (Figure 2). There are also anecdotal reports of efficacy in patients with Samter triad, a condition associated with severe nasal polyposis, asthma, and aspirin sensitivity.

Patients with AFS are characterized by severe nasal polyposis and thick allergic mucin. Aggressive surgery is usually necessary to remove the bulk of sinus disease; however, in some patients the mucosa remains inflamed unless patients are treated with prolonged courses of oral steroids postoperatively. Clinically, itraconazole has been used for select patients as a steroid-sparing agent, either reducing the dose of oral steroids necessary to control sinus inflammation and polyps or replacing them completely (68). Similar to ABPA (69), it is hypothesized that the response to itraconazole in the sinuses is due to a decrease in the overall fungal load and possibly due to the drug's antiinflammatory effects (65, 66, 68).

Seiberling and Wormald (66) recently reviewed a series of 23 patients with AFS and nonallergic rhinitis with eosinophilia syndrome (NARES) treated with a 6-month course of itraconazole 100 mg twice daily. Nineteen patients (83%) responded to treatment with improvements in symptoms and endoscopic examinations. Eleven patients (48%) had complete response to treatment at a mean follow-up of 15.7 months. Three patients (13%) developed transient elevation of liver function tests (LFTs) that returned to baseline after ceasing therapy. In another study, Rains and Mineck (67) looked at the use of high-dose itraconazole (400 mg/d for 1 mo, 300 mg/d for 1 mo, 200 mg/d for 1 mo, or until clear by endoscopy) started after sinus surgery in 137 patients with AFS. Aspergillus was the most common fungus isolated in this study. After treatment, 69 patients (50.3%) had recurrence at an average of 10.8 months and 17 patients (20.5%) required revision sinus surgery. The authors concluded that itraconazole was safe and reduced the need for oral steroids and further revision surgery. Side effects included edema (7.9%), nausea (5.8%), elevated LFTs (4.3%), fatigue (2.2%), rash (2.2%), headache (0.7%), and malaise (0.7%). Patients started on itraconazole therapy should be monitored closely for side effects, and LFTs should be checked every 4 to 6 weeks. Although data from these studies support the use in itraconazole as an adjuvant therapy in select patients with CRS, larger prospective trials are needed to develop guidelines for dose and duration and to determine which patients would benefit most from therapy.

OTHER TREATMENTS

Decongestants

There are no randomized clinical trials evaluating decongestant use for CRS. Decongestants are α-adrenergic agonists that induce the release of norepinephrine from sympathetic nerves leading to vasoconstriction of the nasal vasculature (5). They are used for relief of nasal congestion, but no studies have demonstrated quicker resolution of sinusitis. Symptoms are improved with topical decongestants, but reduced mucosal blood flow may increase inflammation (70) and increase ciliary loss (71). Despite these reservations, topical decongestants will usually reduce symptoms and speed recovery in patients with rhinosinusitis. However, topical decongestants, such as oxymetazoline or Neo-Synephrine, should not be used for longer than 3 days to avoid rebound nasal congestion and rhinitis medicamentosa.

Mucolytics

Mechanical drainage can also be improved with a mucolytic. Guaifenesin is the most commonly used medication to thin mucus secretions. In a double-blind study involving HIV-positive patients, Wawrose and colleagues (72) reported less nasal congestion and thinner postnasal drainage at doses of 2,400 mg/d at 3 weeks. Nausea was the major reported side effect in doses greater than 1,200 mg/d.

Antihistamines

Antihistamines work by competitive inhibition of histamine receptor sites on respiratory mucosal cells. Histamine type 1 blockers are most effective for atopic patients with symptoms of watery rhinorrhea, sneezing, and facial itching (5, 8). Antihistamines are first-line therapy for allergic rhinitis (73). Second-generation antihistamines have a higher affinity for the histamine receptor, with less of the sedating anticholinergic effects. Azelastine, a topical nasal second-generation antihistamine, has also demonstrated antiinflammatory and mast cell–stabilizing properties (74, 75).

The anticholinergic effects of the first-generation antihistamines can cause excessive drying, which can impair mucus clearance by thickening mucus. At this time, there is no evidence to

support the use of antihistamines for treatment of patients with acute bacterial rhinosinusitis or chronic rhinosinusitis (5).

Leukotriene Inhibitors

Leukotriene inhibitors are systemic medications that are used for the treatment of asthma and allergic rhinitis. The drugs block leukotrienes that cause contraction of smooth muscle, chemotaxis, and increased vascular permeability (5, 8). The observation that leukotriene levels are increased in the nasal secretions of people with asthma with aspirin sensitivity and nasal polyposis raised the possibility that antileukotriene therapy could benefit patients with CRS with nasal polyps (8). Some studies have demonstrated some effect on reducing sinonasal symptoms and nasal polyps (76). Jung and colleagues (77) demonstrated increased leukotrienes as well as other arachidonic acid metabolites in nasal polyps from patients with aspirin sensitivity, nasal polyposis, and asthma. At this time, more research is required to determine which subset of patients with CRS will benefit most from leukotriene inhibitors.

SURGICAL TREATMENT OF CRS

In general, the incidence of patients with CRS requiring surgery is very low, and surgery is reserved for patients who fail medical management. However, in selected patient populations, up to 50% of patients with CRS (not acute sinusitis) will ultimately require surgical intervention (78). The most common reasons for surgical intervention are CRS that does not respond to medical intervention, and symptomatic nasal polyp disease that is not adequately managed on medical therapy alone. However, many other medical problems may require surgical intervention, including complicated acute sinusitis, allergic fungal sinusitis, and mucoceles (Figures 3, 4 and 5) (79, 80). Recently, the indications for this sinus surgery have extended well beyond inflammatory causes to include intranasal, sinus, and skull base tumor removal; closure of skull base defects; orbital decompression; dacryocystorhinostomy; and resection of medially placed intraorbital lesions.

Whereas surgical intervention for CRS used to primarily involve open surgery aimed at mucosal stripping within the maxillary or frontal sinuses, or ethmoidectomy performed with the limited visualization, such surgery has almost completely been replaced by endoscopic intranasal intervention. FESS is associated with significantly lower morbidity and higher success rates than previous surgical approaches, and the techniques for such surgery continue to evolve (81). More recent work has demonstrated the efficacy of extended approaches to the frontal sinus, using angled drills and instrumentation intranasally to create a partial septectomy and one large bilateral intranasal opening. (Figures 6 and 7).

Meticulous surgical dissection using mucosa-sparing techniques has allowed surgeons to treat sinus disease while preserving the natural function of the sinus mucosa. Mucosal integrity is maximally preserved so that healing occurs quickly and normal mucociliary transport is restored (79, 80). However, surgery alone is rarely curative and needs to be combined with intensive medical therapy in the postoperative period. Persistent asymptomatic disease is common after surgical intervention and the goal of therapy has shifted away from short-term symptomatic improvement toward long-term disease resolution. This requires continued medical therapy after surgery, endo-

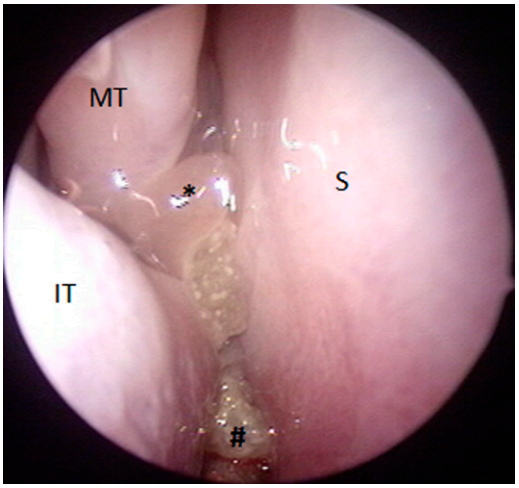

Figure 4. Polyps and allergic mucin in the nasal cavity. *Indicates nasal polyp; #indicates allergic mucin. IT = inferior turbinate; MT = middle turbinate; S = septum.

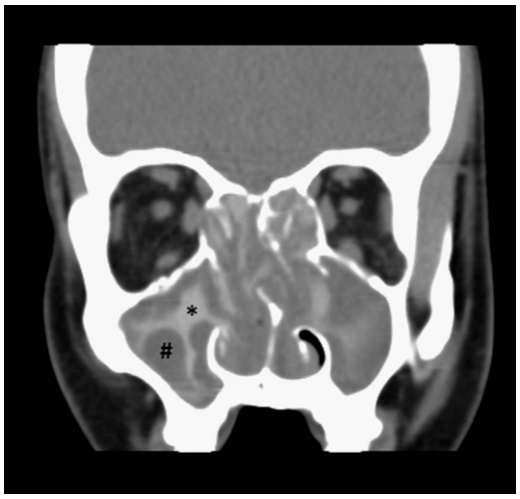

Figure 3. Coronal computed tomography scan demonstrating areas of increased density strongly suggestive of allergic fungal sinusitis. *Indicates hyperdense area; #indicates hypodense area.

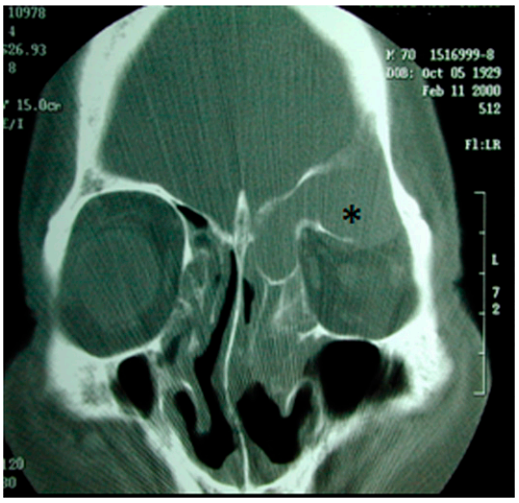

Figure 5. Coronal computed tomography scan demonstrating left frontal sinus mucocele with expansion into the left superior orbit and displacement of the orbital contents. *Indicates area of mucocele.

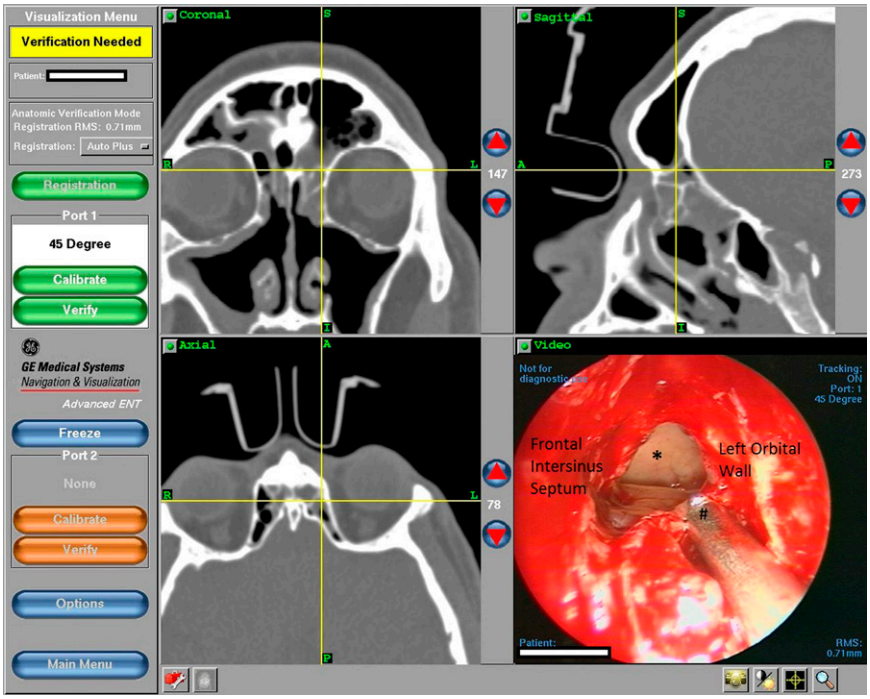

Figure 6. Intraoperative view with computed tomography (CT) image guidance of the left frontal sinus. *Indicates roof of left frontal sinus; #indicates tip of image guidance probe, which corresponds to cross-hairs on triplanar CT images.

scopic surveillance, and management of environmental and general host factors that may predispose to disease.

With the advent of delicate instrumentation, angled telescopes, mechanical microdebriders, and an improved understanding of the pathogenesis of CRS, open surgical intervention is rarely required (82). However, there are still occasional indications for an open osteoplastic approach to the frontal sinus in patients with unusual pathology or neoplasia. In recent years, there has also been a suggestion that merely dilating the sinus ostia (balloon sinuplasty) may be sufficient for disease resolution in CRS (83). However, the evidence for this, at this point in time, remains controversial and seems at odds with some of our understanding of the pathogenesis of this disease. However, it is possible that in the future, when combined with drug-eluting stents and other local therapy to resolve residual inflammation, such therapies may indeed provide an alternative less-invasive therapy to those currently available. Studies suggest that balloon dilation is both safe and well tolerated, with the potential benefit of minimizing collateral damage to surrounding sinus tissue and bone (83). Studies have also demonstrated the use of balloon catheter dilation under local anesthesia, which raises the possibility for use in the office setting (84, 85). However, limitations of the technique include the inability to address ethmoid sinus disease and to remove nasal polyps (86).

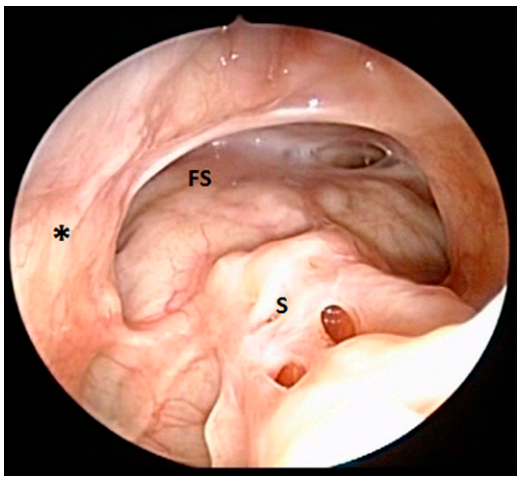

Figure 7. Postoperative endoscopic view in a different patient of the frontal sinuses after removal of the frontal intersinus septum creating a common frontal sinus cavity (Draf III or endoscopic modified Lothrop). FS = frontal sinus; S = nasal septum; *Indicates right orbital wall.

The combination of careful surgical intervention (FESS) and postoperative medical therapy can have profound long-term benefits on both CRS and asthma, with significant long-term reductions in medical therapy. Khalid and coworkers (87) examined 150 postoperative patients and found that functional endoscopic sinus surgery was effective at maintaining a significant improvement ($P < 0.05$) in overall general health status of patients more than 3 years after surgical intervention. Furthermore, overall scores on the SF-36 quality-of-life questionnaire returned to a range of normative values for the general population. A prospective study by Gliklich and Metson (88) reviewed 108 patients undergoing ethmoidectomy and found that after 1 year, significant improvements were noted in 82% of patients. In these patients symptoms improved, and medication usage decreased. Others have shown that endoscopic sinus surgery improves postoperative olfactory function (89) and reduces bodily pain (90), asthma (91), and fatigue (92).

Bradley and Kountakis (93) reported on 113 adult patients with 1 year of clinical follow-up after ESS. They found that a significant reduction in SNOT-20 symptom scores was achieved after endoscopic sinus surgery as early as 3 months after surgery, with an effect that remained significant after 1 year. Similar studies by Levine (94), Cohen and Kennedy (79), and Stammberger and Posawetz (80) revealed significant improvements after FESS as well, even as long as 10 years after surgery.

CONCLUSION

CRS remains a highly prevalent disease with a major impact on overall quality of life. Significant advances in medical and

surgical therapy have not only reduced morbidity and improved the overall results of intervention but also provided long-term benefit when effectively combined. Current treatments aim to reduce inflammation with the goal of restoring normal sinus physiology. However, there remains significant work to be done to better understand the pathogenesis of the spectrum of disorders currently considered as CRS. Ongoing study in this common disorder will undoubtedly provide greater insight into the pathophysiology of this disease and improve outcomes.

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