Pharmacologic Management of Chronic Rhinosinusitis, Alone or with Nasal Polyposis

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Patients with chronic rhinosinusitis (CRS) and chronic rhinosinusitis with nasal polyposis (CRSwNP) commonly present with nasal obstruction, nasal discharge, facial pressure/pain, and hyposmia of prolonged duration. Recent evidence suggests that, despite clinical similarities, CRS and CRSwNP are distinct entities with separate inflammatory pathways and cytokine profiles. Antibiotics and nasal steroids are the mainstay of treatment in CRS, whereas combination systemic and nasal steroids are the foundation of CRSwNP management. Allergy therapy may play a significant role in CRS, whereas antileukotriene therapy has demonstrated promise in CRSwNP. Although prolonged medical therapy is usually necessary with both disorders, surgery may also be required to relieve refractory symptoms, and to improve sinus aeration and nasal access for topical therapy.

Introduction

Chronic rhinosinusitis (CRS) is a widespread disorder that affects approximately 31 million people in the United States each year [1•]. CRS with nasal polyposis (CRSwNP) is less prevalent but is, nevertheless, estimated to produce symptoms in 1% to 4% of the US population in any given year. The total medical and economic impact of these disorders is unclear due to overlap with other rhinologic conditions that produce similar symptoms. It is, therefore, necessary to review current criteria for diagnosis prior to a discussion of the management of these disorders.

Rhinosinustis comprises a variety of disorders that cause inflammation of nasal and sinus mucosa, and may involve bacterial, viral, fungal, allergic, nonallergic inflammatory, pharmacologic, neural, genetic, and/or hormonal causes.

Rhinosinusitis is usually a clinical diagnosis based largely on patient symptoms, which are divided into major and minor symptoms (Table 1), and is classified as chronic (CRS) if symptoms have persisted for 12 consecutive weeks or longer. The typical presentation involves symptoms that, in most primary care situations, have been unresponsive to short courses of antimicrobial therapy. An underlying allergic condition may be present in up to 50% of patients with CRS who eventually undergo surgery.

Chronic rhinosinusitis with nasal polyposis presents the additional finding of one or more nasal polyps, frequently bilateral. Nasal polyposis may be missed on anterior rhinoscopy due to mucosal inflammation/edema, turbinate hypertrophy, deviated septum, or posterior location of the polyps (Table 2), and the diagnosis is more likely to be made after nasal decongestion and nasal endoscopy. Detection of small polyps, but no evidence of sinus disease, is relatively common, and reported as 32% in an endoscopic autopsy series. In this paper, we discuss only polyps that impair sinus ostial patency and, thus, cause sinus disease [2].

Hyposmia and nasal blockage are the predominant symptoms in CRSwNP, unlike routine CRS, in which facial pain and/or pressure are more common. If only unilateral polyps are present, other disease processes, such as mycetoma, nasal foreign body, inverted papilloma, antral choanal polyp, or encephalocele must be ruled-out with appropriate imaging and/or biopsy. Local IgE elevation without atopy is a frequent finding; allergic rhinitis is thought to be less of a factor for CRSwNP [3•] than for CRS. Up to 10% of polyp patients also have asthma and aspirin sensitivity, commonly referred to as Samter's triad [4]. A small percentage of patients with bilateral nasal polyposis have underlying disorders, such as cystic fibrosis, sarcoidosis, Wegener's granulomatosis, or Churg-Strauss syndrome. Allergic fungal rhinosinusitis (AFRS) is also associated with nasal polyposis, frequently unilateral, but it is a disorder in its own right apart from CRSwNP, and is beyond the scope of this review [1•].

Although CRS and CRSwNP can share similar symptoms and long duration, intranasal cytokine profiles suggest distinct processes. CR with NP usually demonstrates elevated levels of eosinophilic factors, such as vascular cell

Table 1. Factors associated with the diagnosis of rhinosinusitis

Major factors	Minor factors
Facial pain/pressure*	Headache
Nasal obstruction/blockage	Fever (all non-acute)
Nasal discharge/purulence/ discolored postnasal drainage	Halitosis
	Fatigue
Hyposmia/anosmia	Dental pain
Purulence in nasal cavity on examination	Cough
	Ear pain/pressure/fullness
Fever (acute rhinosinusitis only)†	

*Facial pain/pressure alone does not constitute a suggestive history for rhinosinusitis in the absence of another major nasal symptom or sign. †Fever in acute sinusitis alone does not constitute a strongly suggestive history for acute rhinosinusitis in the absence of another major nasal symptom or sign.

Table 2. Polyp grade according to clinical findings

Polyp grade	Clinical findings
0	No visible polyps
1	Polyps confined to the middle meatus
2	Polyps beyond the middle meatus, but not completely obstructing the nasal cavity
3	Polyps completely obstructing the nasal cavity

Adapted from Badia and Lund [43].

adhesion molecule (VCAM)-1, eosinophil cationic protein (ECP), interleukin (IL)-5, eotaxin, and local IgE [3•,5,6], whereas, in CRS, IL-1, IL-3, IL-6, IL-8, tumor necrosis factor (TNF)-α, and intercellular (I)CAM-1 tend to predominate [7–9]. Only 85% of nasal polyps are eosinophilic, with the remainder neutrophilic, as in bacterial infections of odontogenic origin, cystic fibrosis, ciliary dyskinesias such as Kartagener's syndrome, or in Young's syndrome [3•]. Indeed, a recently proposed histologic classification of CRS divides such into a more common type characterized by eosinophilia and polypoid changes, and another by glandular hyperplasia and neutrophilia [10•], the latter treated according to the underlying disorder and beyond the scope of this review.

Given the chronicity and inflammatory nature of both CRS and CRSwNP, medical therapy is the mainstay of treatment, and surgery is reserved for advanced-stage or refractory and symptomatic disease (Fig. 1). Pharmacologic therapy for CRS is largely focused on clearing the sinonasal cavity of pathogenic bacteria or fungi while reducing inflammatory sinus obstruction, to relieve symptoms and reduce the likelihood of recurrent infection. Pharmacologic therapy for CRSwNP seeks to involute polyps to re-establish a patent nasal airway and sinus ostia, restore a sense of smell, and prevent the recurrence of polyps after a successful pharmacotherapy-induced involution or surgical excision. In this review, we examine the drug classes most frequently used by the practitioner, and reveal that the pharmacologic strategies for treating CRS and CRSwNP are similar, yet distinct.

Antimicrobial Therapy

Antibiotics are among the most commonly prescribed drugs for CRS. Antibiotic selection is based largely on inference from studies of acute bacterial rhinosinusitis (ABRS), because there is a paucity of randomized, controlled trials of CRS. The inference is weakened by the observation that the microbiology of CRS differs from that of ABRS. Whereas *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are the predominant organisms in ABRS and in CRS in children, the principal pathologic organisms in CRS in adults are less clear. Coagulase-negative *Staphylococcus* (CNS) was the most common organism on nasal culture in five of seven prospective studies of CRS patients [11–17]. There is debate over the pathogenicity of CNS, because the organism is frequently cultured from normal subjects [18]. Gram-negative rods and anaerobes, and *Staphylococcus aureus*, Group A streptococcus, and *Streptococcus pneumoniae* organisms are also frequently cultured from patients with CRS; however, their prevalence varies widely between studies [19]. High-dose amoxicillin (2 g/d), amoxicillin/clavulanate, fluoroquinolones, later-generation cephalosporins, and, probably, the ketolides are first-line antibiotics of choice in adults with CRS, due to their broad-coverage and adequate bactericidal activity against staphylococci and anaerobic species [20], but endoscopically directed culture and antimicrobial sensitivity testing is prudent in patients not responding to therapy, or who have recently been treated for infection.

A search of *PubMed* limited to randomized, controlled trials from 1966 to the present, using the search terms chronic rhinosinusitis (and sinusitis) and antibiotics, found only three trials, involving a total of 628 patients with CRS [21–23]. These comparative trials of amoxicillin/clavulanate, ciprofloxacin, and third-generation cephalosporins given for 2 weeks or fewer demonstrate symptom resolution in 60% to 70% of patients. The roughly one third who remain symptomatic after a 2-week course received too little therapy, had resistant organisms, or had sinonasal inflammation due to noninfectious causes. Such resulted in the currently recommended 4-week course of a first-line antibiotic coupled with a nonspecific nasal anti-inflammatory medication (*eg*, steroid spray) to improve the clinical cure rate for CRS [24].

The cause and effect relationship between nasal polyposis and bacterial rhinosinusitis is a matter of debate. There is evidence that polyps form prior to infection from eosinophilic infiltration of the nasal mucosa in response to nonallergic inflammation or local mucosal trauma [25]. As the polyps enlarge, sinus ostia become blocked, leading to stasis of secretions and bacterial suprainfection.

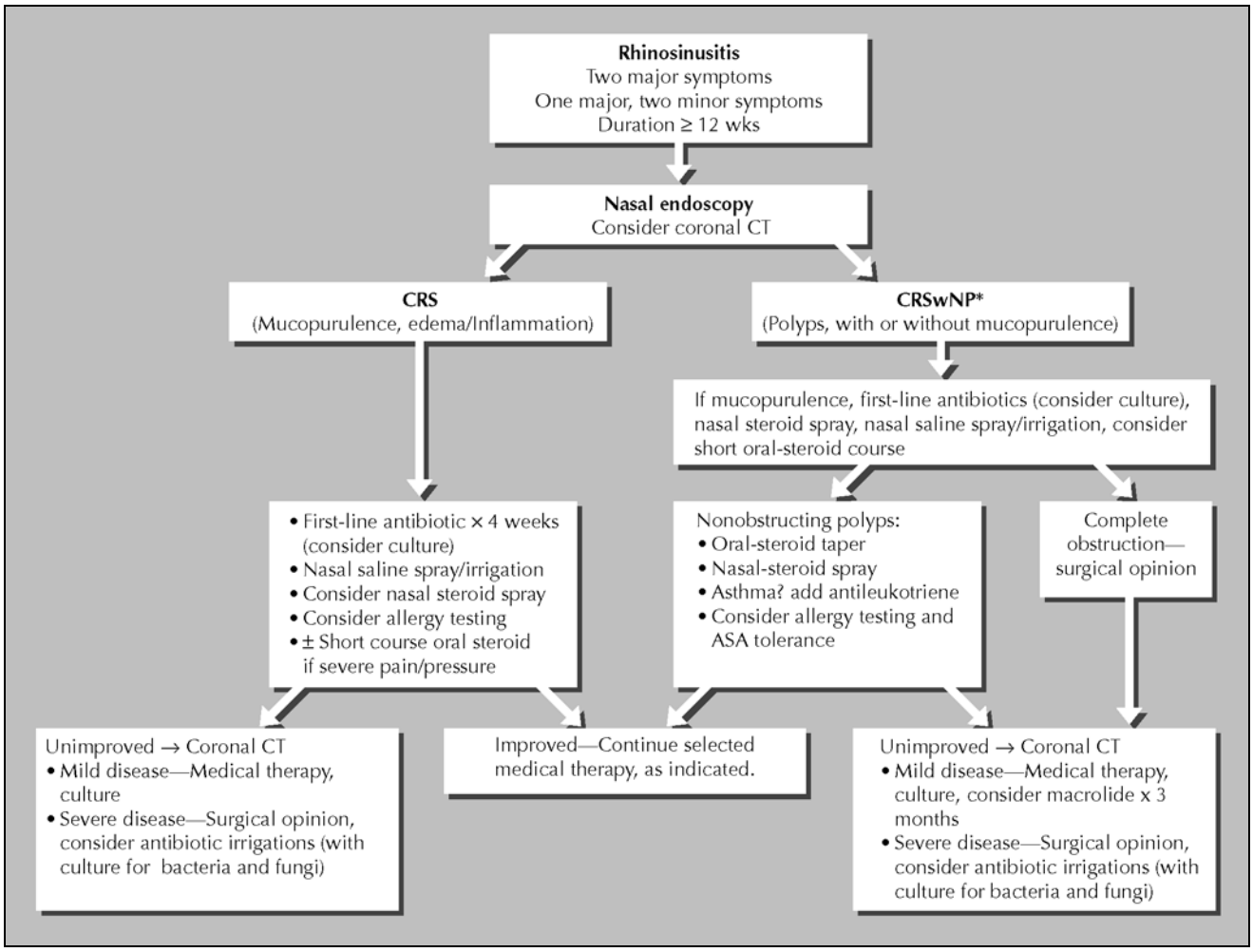

Figure 1. Algorithm for the management of chronic rhinosinusitis and chronic rhinosinusitis with nasal polyposis.[†]
CRS—chronic rhinosinusitis; CRSwNP—chronic rhinosinusitis with nasal polyps.
*Eosinophilic polyps, which are the predominant type, neutrophilic polyps, such as those associated with odontogenic infections, cystic fibrosis, ciliary dyskinesias, and the like are treated according to the underlying disease process.
[†]Assumes absence of indications of immune deficiency, mucociliary dysfunction, gastroesophageal reflux disease, cystic fibrosis, sarcoidosis, and the like, all of which must be considered in chronic rhinosinusitis that is refractory to aggressive medical therapy.

However, polyps have been shown to arise from bacterial infection in the maxillary sinus of dental origin. As a result, there are no currently accepted guidelines for the use of antibiotics as a primary therapy of CRSwNP. Like CRS, cases of CRSwNP presenting with facial pressure and nasal purulence usually respond well to a 4-week course of a first-line antibiotic. These symptoms, however, are relatively uncommon at the presentation of CRSwNP and, not infrequently, a prolonged course of an antibiotic provides minimal reduction in polyp size or relief of nasal obstruction and hyposmia.

Although clinical experience suggests that antibiotics have a limited role in reversing CRSwNP, recent research has disclosed the potential role of bacterial exotoxins in nasal polyp formation. Small series (<15 patients each) have found *Staphylococcus aureus* organisms in the nasal polyps in seven of 13 patients [26], or IgE-specific for *Staphylococcus aureus* exotoxins in 50% of polyp homogenates [27]. It is hypothesized that *Staphylococcus aureus* exotoxins on the major histocompatibility (MHC) II complex of antigen-presenting cells cross-link T lymphocytes, causing nonspecific upregulation. The exotoxins act as superantigens capable of nonspecifically activating up to 30% of T lymphocytes, in comparison with classic bacterial antigens, which activate less than 0.1% [28•].

Several studies have investigated the role of macrolides in reducing polyp formation in response to bacterial superantigens [29–31]. Reduction in size of approximately 50% has been observed after an 8- to 12-week course of daily treatment with either clarithromycin or roxithromycin in nonrandomized, unblinded studies [31], and anecdotal reports suggest that prolonged courses of low-dose macrolides may provide symptomatic relief to CRSwNP patients who have failed to respond to corticosteroids and surgery [31]. Although the mechanism of action of macrolides on nasal polyps is unknown, the clinical response is thought

to be attributable to immunoregulatory rather than antimicrobial effects [30]. Nasal polyp–cell culture studies suggest that macrolides are capable of suppressing fibroblast proliferation within the polyp, and inhibiting neutrophil and eosinophil degranulation [31]. Irrespective of their direct antibacterial effects, some macrolides prevent *Pseudomonas aeruginosa* biofilm formation in vitro [30]. Biofilms occur when bacteria attached to mucosal surfaces produce extracellular polysaccharides that impair both phagocytosis and antibiotic penetration. Biofilms have been demonstrated in animal models of otitis media [32] and may play a role in CRS and/or CRSwNP .

The role of macrolides in the management of CRSwNP requires further study, but current evidence appears to support empirical use in patients who have failed standard therapy.

Systemic Corticosteroids

Oral corticosteroids are principally used in the treatment of CRSwNP but may also be of use in severe cases of CRS. Although there are no placebo-controlled trials to document the efficacy, clinical practice confirms their effectiveness in providing rapid relief of facial pressure and nasal blockage by reducing mucosal edema and polyp bulk. A study that compared pre- and post-treatment MRI scans in patients with CRSwNP treated with a 12-day course of oral and intranasal steroids found polyp reduction of approximately 30% in 50% of the patients [33]. At the cellular level, corticosteroids enter the nasal epithelium, bind to a glucocorticoid receptor in the cytoplasm, and are transported to the nucleus, inhibiting the synthesis of inflammatory mediators, which, in turn, decreases vessel permeability and inflammatory cell influx [34]. This effect is especially profound in CRSwNP, because eosinophils require IL-1, IL-3, and IL-5 for survival and function [35].

The side effects of chronic systemic steroids are well known, so such are generally reserved for severe exacerbations of rhinosinusitis or to reduce tissue edema and polyp bulk immediately prior to surgery. Therapy in otherwise healthy adults typically starts at a mid-range dose (40–60 mg of prednisone equivalent per day) that is tapered over 5 to 14 days. Repeated courses are generally separated by 3-month intervals to reduce the risks of chronic steroid use. Patients who require more frequent systemic steroids while they are on maintenance therapy with topical corticosteroids should be considered for surgery.

Topical Corticosteroids

Topical intranasal steroid sprays are the mainstay of the long-term management of CRSwNP, and, in many, of CRS [36]. Like systemic steroids, topical steroid sprays reduce proinflammatory cytokine production, thereby decreasing mucosal edema and inflammatory cell influx. The therapeutic effects of intranasal steroids may be secondary to re-establishment of sinus ostia patency [3•]. The newer generation of sprays provides anti-inflammatory effects without the side effects of systemic steroid therapy. Several trials have failed to show significantly elevated serum cortisol levels, or significant growth retardation, in prepubescent children [37,38].

Although most placebo-controlled trials of intranasal steroids were designed for allergic rhinitis, one well-designed trial has examined the efficacy in CRS [39]. In such, 95 patients with an acute exacerbation of CRS were treated with a 21-day course of either two puffs of fluticasone propionate or placebo spray in each nostril along with xylometazoline (twice a day for 3 days) and cefuroxime axetil (250 mg, twice a day for 10 days). Patient report of cure was quicker in the nasal steroid group (median 6.0 days) compared with the placebo group (median 9.5 days). These findings and other studies involving ABRS suggest that topical steroid therapy at the least provides more rapid symptomatic relief during antibiotic therapy. Longitudinal studies are needed to determine whether continued maintenance prevents recurrence of acute exacerbations of CRS.

Multiple clinical trials of CRSwNP have confirmed that intranasal steroids are superior to placebo in reducing polyp size, decreasing nasal blockage and rhinorrhea, and increasing peak nasal airflow [40–42]. Treated nasal polyps demonstrate reductions in activated T cells, mast cells, and antigen-presenting cells [43]. Although topical steroids consistently reduce nasal obstruction, they have little effect in improving sense of smell [44,45].

The application of intranasal steroid requires a nasal airspace that is sufficiently open to allow drug distribution. Patients with massive polyposis secondary to allergic fungal rhinosinusitis, cystic fibrosis, Churg-Strauss, or fibrotic polyps that are unresponsive to systemic steroids may require surgical débridement before the initiation of topical nasal steroids. The combination of surgery and topical steroid therapy is synergistic, with each improving the success of the other in the long-term disease control. Several small trials (< 25 patients) demonstrated a trend toward reduced polyp regrowth after sinus surgery in patients treated with intranasal steroids compared with placebo controls [46,47]. Bross-Soriano *et al.* [48] reported a prospective study of 162 patients divided into three groups postpolypectomy, one receiving daily saline lavages, and the other two saline lavages followed by either fluticasone or beclomethasone. At 12 months, early polyp recurrence was evident in 44% of those on saline alone, 15% of those also receiving fluticasone, or 26% with beclomethasone. There was no tendency to recurrent bacterial rhinosinusitis in those on topical steroids versus saline, and no evidence of impaired postoperative healing.

Given their efficacy and tolerability, intranasal corticosteroids are a first-line therapy for CRSwNP. Daily therapy should be initiated, with follow-up in 8 to 12 weeks to

determine the effect on symptoms and polyp size. Nasal steroid sprays should be applied daily using proper technique that involves aiming the spray tip at the ipsilateral outer canthus or top of the auricle [49]. Six to 12 months of daily compliance may be required to attain the maximal beneficial effects [3•]. Patients who are unresponsive in the initial treatment period may require twice a day application that can be reduced after a steady state of relief is achieved. If twice-a-day therapy is necessary, preparations with low systemic bioavailability are preferred.

For grade 2 or 3 polyps, most use a short course of oral steroids when a longer term trial of topical steroids is initiated. Bonfils *et al.* [50•], in a study of 100 patients, used a regimen of decreasing doses of oral and topical steroids over a 3-year period, with a mean of 650 mg of prednisone (yearly total) and 2119 μg (daily total) of beclomethasone the first year, decreasing to 200 mg and 934 μg the third year; in only 15% was surgical intervention necessary.

Antileukotrienes

Leukotrienes are a class of inflammatory mediators produced by the cleavage of arachidonic acid in cell membranes, and released by a number of cell types, including eosinophils, mast cells, macrophages, and basophils [51•]. They increase vascular permeability, inflammatory cell chemotaxis, and smooth muscle constriction. Two classes of antileukotriene drugs are currently approved in the United States for the treatment of asthma. Leukotriene receptor blockers (montelukast and zafirlukast) work by competitively binding specific leukotriene receptors, whereas a 5-lipoxygenase inhibitor (zileuton) prevents an enzymatic step in the formation of leukotrienes. Antileukotriene therapy is generally well-tolerated, with the most common side effects being headache and dyspepsia.

The observation that leukotriene levels are increased in the nasal secretions of asthmatics with aspirin sensitivity and nasal polyposis raised the possibility that antileukotriene therapy could benefit patients with CRSwNP. An open-label, 3-month trial of montelukast in the treatment of 44 adults with asthma and nasal polyposis found a 64% reduction in nasal symptoms in aspirin-tolerant patients, and a 50% reduction in aspirin-sensitive patients [52]. Neither group demonstrated significant improvements in nasal inspiratory flow, no mention was made of changes in polyp size, and the effects were more impressive with respect to asthma than the polyps. A prospective, open-label study of 36 nasal-polyp patients treated with at least 1 month (mean 7.4 months) of antileukotriene therapy (zafirlukast or zileuton) found that 72% of patients had significant reductions in nasal symptoms, 50% had reduction in polyp size, and 60% of patients no longer required oral steroid therapy [53]. Another study demonstrated a significant reduction in polyp regrowth 3 months after sinus surgery in 18 subjects treated with combination montelukast and fluticasone compared with six controls treated with fluticasone alone [54]. An ongoing randomized, double-blind, placebo-controlled trial of montelukast after surgical polypectomy may provide greater insight [53]. There is no evidence at present to support the use of antileukotriene therapy in CRS without polyposis.

Although conclusive evidence awaits additional studies using placebo control and endoscopic examinations, current evidence suggests that antileukotriene therapy reduces symptoms in patients with CRSwNP and asthma, provides alternative therapy in polyposis patients intolerant of steroids, and reduces recurrence of polyp recurrence after surgery.

Other Medical Therapy

Antihistamines are among the most commonly prescribed medications for rhinosinusitis. Antihistamines significantly reduce symptoms of sneezing and nasal obstruction in allergic patients with acute rhinosinusitis [55], and reduce sneezing and rhinorrhea in patients with CRSwNP [56]. Although debate exists over the percentage of CRS patients with co-existing seasonal or perennial allergic rhinitis, most agree that underlying allergic rhinitis is an important predisposing factor for CRS. When paranasal CT is performed on patients with allergic rhinitis, 60% to 70% will have at least some changes consistent with rhinosinusitis [57,58], and in series of CRS patients evaluated by CT, history for allergic rhinitis and severity of sinus disease per radiography are frequently correlated [59]. Allergy is less of a factor in the etiology of CRSwNP, where the prevalence of allergy likely mirrors the 20% prevalence in the general population. Basically, allergy testing should be considered in all patients with CRS and CRPwNP, and those who test positive should be treated, as appropriate, with antihistamines, topical corticosteroids or cromolyn, and/or immunotherapy.

Nasal saline irrigation has long been advocated for CRS patients, to clear the nasal passages of inspissated mucus, bacteria, allergens, and/or environmental irritants. Such is supported by several randomized, controlled studies that demonstrate reduced sinus symptoms and improved sinus-related quality of life in saline users [60,61]. The intervention is well-tolerated and inexpensive. The addition of antimicrobials to nasal/sinus irrigations has been practiced for decades, as in the addition of tobramycin, gentamicin, or similar to daily (and self-administered) lavages of the nasal cavities in those with cystic fibrosis and a chronic *Pseudomonas* suprainfection [62]. Recently, the use of irrigations containing an anti-staphylococcal agent (*eg*, mucopiricin) in those with polyps deemed due to staphylococcal exotoxins functioning as superantigens, or amphotericin in those with fungal elements causing a similar enhanced local inflammatory response, have been advocated [26,63•,64]. The rationale in such instances has been that the staphylococcal or fungal organisms are

not invasive, but rather have colonized the nasal mucosa, and hence are relatively protected from serum-borne antimicrobial agents.

Surgical Management

Advances in pharmacotherapy may hold the key to consistently successful management of both CRS and CRSwNP. A plethora of agents are under investigation, and primarily involve targets in the inflammatory cascade, such as eosinophils with anti-IL-5, or the promotion of an immune deviation from T helper (Th)2 to Th0 or Th1 responses. Until such become available, current medical therapy (Fig. 1) fails in approximately 5% to 10% of cases of CRS and up to 30% of cases of CRSwNP [65]. Absolute indications for sinus surgery include orbital or intracranial spread of sinus infection, massive nasal polyps (grade 3), mucopyoceles, and invasive or allergic fungal infections [66]. Relative indications, and those for which the preponderance of sinus surgery is done in the United States, include symptoms that are refractory to aggressive pharmacotherapy (with immunotherapy as indicated) and with persistent signs of disease on nasal endoscopy and/or CT. Dursun *et al.* [67], with a 60-month median follow-up of 132 patients after endoscopic sinus surgery, observed a 94.8% surgical success rate in those with CRS alone, and a 73.6% rate in those with CRSwNP. In one innovative trial, 32 patients with CRSwNP received preoperative oral and topical steroid therapy followed by unilateral sinus surgery and bilateral nasal steroids for 12 months [68]. When compared with the unoperated sides, the sides that received both medical and surgical therapy demonstrated a significant decrease in nasal obstruction, nasal secretions, and polyp-size scores, but failed to achieve a significant improvement in smell.

Continued medical therapy is essential after sinus surgery, given the high rate of relapse in both CRS and CRSwNP; however, 60% to 80% of patients continue to have significantly reduced symptoms after a mean follow-up time of 5 years post-surgery [69]. Most prefer topical corticosteroid therapy for long-term maintenance after surgery [3•,36].

Conclusions

The primary therapy for CRS and CRSwNP is medical. Although CRS and CRSwNP present with similar symptoms of long duration, each condition is characterized by a distinct cytokine cascade and inflammatory process. These differences require appropriately tailored pharmacotherapy to obtain optimal disease control. Hopefully, further research will lead to novel strategies of medical intervention that will lessen the need for nonspecific therapies such as oral steroids and surgery.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.• Benninger M, Ferguson B, Hadley J, *et al.*: **Adult-chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology.** *Otolaryngol Head Neck Surg* 2003, **129(Suppl 3):**S1–S32.

Literature review and expert panel assessment of current knowledge about chronic rhinosinusitis is provided, with recommended tools for evaluating future clinical trials.

2. Larsen P, Tos M: **Origin of nasal polyps.** *Laryngoscope* 2004, **114:**710–719.

3.• Bachert C, Hormann K, Mosges R, *et al.*: **An update on the diagnosis and treatment of sinusitis and nasal polyposis.** *Allergy* 2003, **58:**176–191.

A broad overview of both acute and chronic rhinosinusitis, with or without polyposis, is provided, including the cytokine profiles, clinical diagnosis, and the efficacies of the various treatments from pharmacotherapy to surgery.

4. Kowalski ML: **Rhinosinusitis and nasal polyposis in aspirin-sensitive and aspirin-tolerant patients: Are they different?** *Thorax* 2000, **55(Suppl2):**S84–S86.

5. Jahnsen FL, Haraldsen G, Aanesen JP, *et al.*: **Eosinophil infiltration is related to increased expression of vascular cell adhesion molecule-1 in nasal polyps.** *Am J Respir Cell Mol Biol* 1995, **12:**624–632.

6. Simon HU, Youseti S, Schranz C, *et al.*: **Direct demonstration of delayed eosinophil apoptosis as a mechanism causing tissue eosinophilia.** *J Immunol* 1997, **158:**3902–3908.

7. Rhyoo C, Sanders SP, Leopold DA, Droud O: **Sinus mucosal IL-8 gene expression in chronic rhinosinusitis.** *J Allergy Clin Immunol* 1999, **103:**395–400.

8. Nonoyama T, Harada T, Shinogi J, *et al.*: **Immunohistochemical localization of cytokines and cell adhesion molecules in maxillary sinus mucosa in chronic sinusitis.** *Auris Nasus Larynx* 2000, **27:**51–58.

9. Bachert C, Wagenmann M, Rudock C, *et al.*: **The role of cytokines in infectious sinusitis and nasal polyposis.** *Allergy* 1998, **53:**2–13.

10.• Malekzadeh S, McGuire J: **The new histologic classification of chronic rhinosinusitis.** *Curr Allergy Asthma Rep* 2003, **3:**221–226.

Interesting and well-reasoned proposal for histologically classifying chronic rhinosinusitis, based on the inflammatory cell (and cytokine) profiles, into one type dominated by eosinophilia and polypoid changes, and another by glandular hyperplasia.

11. Doyle PW, Woodham JD: **Evaluation of the microbiology of chronic ethmoid sinusitis.** *J Clin Microbiol* 1991, **29:**2396–2400.

12. Hoyt WH: **Bacterial patterns found in surgery patients with chronic sinusitis.** *J Am Osteopath Assoc* 1992, **92:**209–212.

13. Hsu J, Lanza DC, Kennedy DW: **Antimicrobial resistance in bacterial chronic sinusitis.** *Am J Rhinol* 1998, **12:**243–248.

14. Biel MA, Brown CA, Levinson RM, *et al.*: **Evaluation of the microbiology of chronic maxillary sinusitis.** *Ann Otol Rhinol Laryngol* 1998, **107:**942–945.

15. Brook I, Frazier EH: **Correlation between microbiology and previous sinus surgery in patients with chronic maxillary sinusitis.** *Ann Otol Rhinol Laryngol* 2001, **110:**148–151.

16. Jiang RS, Lin JF, Hsu CY: **Correlation between bacteriology of the middle meatus and the ethmoid sinus in chronic sinusitis.** *J Laryngol Otol* 2002, **116:**443–446.

17. Finegold SM, Flynn MJ, Rose FV, *et al.*: **Bacteriologic findings associated with chronic bacterial maxillary sinusitis in adults.** *Clin Infect Dis* 2002, **35:**428–433.

18. Gordts F, Halewyck S, Pierard D, *et al.*: **Microbiology of the middle meatus: a comparison between normal adults and children.** *J Laryngol Otol* 2000, **114:**184–188.

19. Osguthorpe JD: **Adult rhinosinusits: diagnosis and management.** *Am Fam Physician* 2001, **63:**69–76.

20. Anon J, Jacobs M, Poole M, *et al.*: **Antimicrobial treatment guidelines for acute bacterial rhinosinusitis.** *Otolaryngol Head Neck Surg* 2004, **130(1 Suppl):**1–45.
21. Namyslowski G, Misiolek M, Czecior E, *et al.*: **Comparison of the efficacy and tolerability of amoxicillin/clavulanic acid 875 mg. b.i.d. with cefuroxime 500 mg b.i.d. in the treatment of chronic and acute exacerbation of chronic sinusitis in adults.** *J Chemother* 2002, **14:**508–517.
22. Legent F, Bordure P, Beauvillain C, Berche P: **A double-blind comparison of ciprofloxacin and amoxicillin/ clavulanic acid in the treatment of chronic sinusitis.** *Chemotherapy* 1994, **40(Suppl1):**8–15.
23. Dellamonica P, Choutet P, Lejeune JM, *et al.*: **Efficacy and tolerance of cefotiam hexetil in the super-infected chronic sinusitis. A randomized, double-blind study in comparison with cefixime.** *Ann Otolaryngol Chir Cervicofac* 1994, **111:**217–222.
24. Sinus & Allergy Health Partnership: **Antimicrobial treatment guidelines for acute bacterial rhinosinusitis.** *Otolaryngol Head Neck Surg* 2000, **123:**1–4.
25. Norlander T, Bronnegard M, Stierna P: **The relationship of nasal polyps, infection, and inflammation.** *Am J Rhinol* 1999, **13:**349–355.
26. Bernstein J, Ballow M, Schlievert P, *et al.*: **A superantigen hypothesis for the pathogenesis of chronic hyperplastic sinusitis with massive nasal polyposis.** *Am J Rhinol* 2003, **17:**321–326.
27. Bachert C, Gevaert P, van Cauwenberge P: **Staphylococcus aureus superantigens and airway disease.** *Curr Allergy Asthma Rep* 2002, **2:**252–258.
28.• Schubert MS: **A superantigen hypothesis for the pathogenesis of chronic hypertrophic rhinosinusitis, allergic fungal sinusitis, and related disorders.** *Ann Allergy Asthma Immunol* 2001, **87:**181–188.

Seminal paper detailing the potential for a "superantigen" origin to some types of chronic rhinosinusitis (See Bernstein *et al.* [26] and Bachert *et al.* [27].).

29. Iino Y, Sasaki Y, Kojima C, Miyazawa T: **Effect of macrolides on the expression of HLA-DR and costimulatory molecules on antigen-presenting cells in nasal polyps.** *Ann Otol Rhinol Laryngol* 2001, **110:**457–463.
30. Cervin A: **The anti-inflammatory effect of erythromycin and its derivatives, with special reference to nasal polyposis and chronic sinusitis.** *Acta Otolaryngol* 2001, **121:**83–92.
31. Garey KW, Alwani A, Danziger LH, Rubinstein I: **Tissue reparative effects of macrolide antibiotics in chronic inflammatory sinopulmonary diseases.** *Chest* 2003, **123:**261–265.
32. Post JC: **Direct evidence of bacterial biofilms in otitis media.** *Laryngoscope* 2001, **111:**2083–2094.
33. Damm M, Jungehulsing M, Eckel HE, *et al.*: **Effects of systemic steroid treatment in chronic polypoid rhinosinusitis evaluated with magnetic resonance imaging.** *Otolaryngol Head Neck Surg* 1999, **120:**517–523.
34. Schleimer R: **Glucocorticosteroids: their mechanisms of activation and use in allergic diseases.** In *Allergy: Principals and Practice,* edn 4. Edited by Middleton EJ, Reed CE, Ellis EF, et al. St. Louis: Mosby–Year Book; 1993:893–925.
35. Cox G, Ohtoshi T, Vancheri C, *et al.*: **Promotion of eosinophil survival by human bronchial epithelial cells and its modulation by steroids.** *Am J Respir Cell Mol Biol* 1991, **4:**525–531.
36. Senior B, Kennedy D, Tanabodee J, *et al.*: **Long-term results of functional endoscopic sinus surgery.** *Laryngoscope* 1998, **108:**151–157.
37. Allen DB, Meltzer EO, Lemanske RF, *et al.*: **No growth suppression in children treated with the maximum recommended dose of fluticasone propionate aqueous nasal spray for one year.** *Allergy Asthma Proc* 2002, **23:**407–413.
38. Skoner DP, Gentile D, Angelini B, *et al.*: **The effects of intranasal triamcinolone acetonide and intranasal fluticasone propionate on short-term bone growth and HPA axis in children with allergic rhinitis.** *Ann Allergy Asthma Immunol* 2003, **90:**56–62.
39. Dolor RJ, Witsell DL, Hellkamp AS, *et al.*: **Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis.** *JAMA* 2001, **286:**3097–3105.
40. Jankowski R, Schrewelius C, Bonfils P, *et al.*: **Efficacy and tolerability of budesonide aqueous nasal spray treatment in patients with nasal polyps.** *Arch Otolaryngol Head Neck Surg* 2001, **127:**447–452.
41. Filiaci F, Passali D, Puxeddu R, Schrewelius C: **A randomized, controlled trial showing efficacy of once daily intranasal budesonide in nasal polyposis.** *Rhinology* 2000, **38:**185–190.
42. Keith P, Nieminen J, Hollingworth K, Dolovich J: **Efficacy and tolerability of fluticasone propionate nasal drops 400 micrograms once daily compared with placebo for the treatment of bilateral polyposis in adults.** *Clin Exp Allergy* 2000, **30:**1460–1468.
43. Badia L, Lund V: **Topical corticosteroids in nasal polyposis.** *Drugs* 2001, **61:**573–578.
44. El Naggar M, Kale S, Aldren C, Martin F: **Effect of beconase nasal spray on olfactory function in post-nasal polypectomy patients: a prospective controlled trial.** *J Laryngol Otol* 1995, **109:**941–944.
45. Holmstrom M: **Clinical performance of fluticasone propionate nasal drops.** *Allergy* 1999, **54:**21–25.
46. Karlsson G, Rundcrantz H: **A randomized trial of intranasal beclomethasone dipropionate after polypectomy.** *Rhinology* 1982, **20:**144–148.
47. Drettner B, Ebbesen A, Nilsson M: **Prophylactic treatment with flunisolide after polypectomy.** *Rhinology* 1982, **20:**149–158.
48. Bross-Soriano D, Arrieta-Gomez J, Prado-Calleros H: **Infections after endoscopic polypectomy using nasal steroids.** *Otolaryngol Head Neck Surg* 2004, **130:**319–322.
49. Benninger M, Hadley J, Osguthorpe JD, *et al.*: **Techniques of intranasal steroid use.** *Otolaryngol Head Neck Surg* 2004, **130:**5–24.
50.• Bonfils P, Mores J, Halimi P, Avan P: **Corticosteroid treatment in nasal polyposis with a three-year follow-up period.** *Laryngoscope* 2003, **113:**683–687.

Presents a retrospective study of 100 patients with nasal polyposis treated with short-term oral steroids and long-term nasal steroid sprays over a 3-year period, and in which only 15% of patients required surgery.

51.• Parnes SM: **The role of leukotriene inhibitors in patients with paranasal sinus disease.** *Curr Opin Otolaryngol Head Neck Surg* 2003, **11:**184–191.

Provides a summary of literature regarding the role of anti-leukotrienes in the treatment of chronic rhinosinusitis, and of studies currently underway to further elucidate the efficacy of this class of medications.

52. Ragab S, Parikh A, Darby YC, Scadding GK: **An open audit of montelukast, a leukotriene receptor antagonist, in nasal polyposis associated with asthma.** *Clin Exp Allergy* 2001, **31:**1385–1391.
53. Parnes SM, Chuma AV: **Acute effects of antileukotrienes on sinusitis and sinonasal polyposis.** *Ear Nose Throat J* 1999, **79:**18–25.
54. Grundmann T, Töpfner M: **Leukotrienrezeptorantagonisten zur rezidivprophylaxe bei der ASS-assoczііerten polyposis-erste klinische ergebnisse zur wirkung auf entzundliche gewebeprozesse.** *Laryngol Rhinol Otol* 2001, **80:**576–582.
55. Braun JJ, Alabert JP, Michel FB, *et al.*: **Adjunct effect of loratidine in the treatment of acute sinusitis in patients with allergic rhinitis.** *Allergy* 1997, **52:**650–655.
56. Haye R, Aanesen JP, Burtin B, *et al.*: **The effect of cetirizine on symptoms and signs of nasal polyposis.** *J Laryngol Otol* 1998, **112:**1042–1046.
57. Berrettini S, Carabelli A, Sellari-Franceschini S, *et al.*: **Perennial allergic rhinitis and chronic sinusitis: correlation with rhinologic risk factors.** *Allergy* 1999, **54:**242–248.
58. Yariktas M, Doner F, Demirci M: **Rhinosinusitis among the patients with perennial or seasonal allergic rhinitis.** *Asian Pac J Allergy Immunol* 2003, **21:**75–78.

59. Ramadan HH, Fornelli R, Ortiz AO, Rodman S: **Correlation of allergy and severity of sinus disease.** *Am J Rhinol* 1999, **13:**345–347.
60. Bachmann G, Hommel G, Michel O: **Effect of irrigation of the nose with isotonic salt solution on adult patients with chronic paranasal sinus disease.** *Eur Arch Otolaryngol* 2000, **257:**537–541.
61. Rabago D, Zgierska A, Mundt M, *et al.*: **Efficacy of daily hypertonic saline irrigation among patients with sinusitis: a randomized controlled trial.** *J Fam Prac* 2002, **51:**1049–1055.
62. Davidson T, Murphy C, Mitchell M, *et al.*: **Management of chronic sinusitis in cystic fibrosis.** *Laryngoscope* 1995, **105:**354–358.
63.• Poinkau J, Sherris D, Kita H, Kern E: **Intranasal antifungal treatment in 51 patients with chronic rhinosinusitis.** *J Allergy Clin Immunol* 2003, **110:**862–866.
Presents a prospective study of amphotericin irrigations in the treatment of chronic rhinosinusitis, with 35% of patients becoming disease free. Further studies are necessary, but this paper provides the current literature regarding fungi and chronic rhinosinusitis.
64. Ricchetti A, Landis B, Maffioli A, *et al.*: **Effect of anti-fungal nasal lavage with amphotericin B on nasal polyposis.** *J Laryngol Otol* 2002, **116:**261–263.
65. Norès J-M, Avan P, Bonfils P: **Medical management of nasal polyposis: a study in a series of 152 consecutive patients.** *Rhinology* 2003, **41:**97–102.
66. Osguthorpe JD: **Surgical outcomes in rhinosinusitis: what we know.** *Otolaryngol Head Neck Surg* 1999, **120:**451–453.
67. Dursun E, Korkmaz H, Eryilmaz A, *et al.*: **Clinical predictors of long-term success after endoscopic sinus surgery.** *Otolaryngol Head Neck Surg* 2003, **129:**526–531.
68. Blomqvist EH, Lundblad L, Änggard A, *et al.*: **A randomized controlled study evaluating medical treatment versus surgical treatment in addition to medical treatment of nasal polyposis.** *J Allergy Clin Immunol* 2001, **107:**224–228.
69. Garrel R, Gardiner Q, Khudjadze M, *et al.*: **Endoscopic surgical treatment of sinonasal polyposis-medium term outcomes (mean follow-up of 5 years).** *Rhinology* 2003, **41:**91–96.