

When Surgery, Antibiotics, and Steroids Fail to Resolve Chronic Rhinosinusitis

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KEYWORDS

- Omalizumab • Zileuton • Immunodeficiency • Adenoiditis
- Aspirin • Desensitization • Montelukast • Odontogenic
- Sinusitis

Chronic rhinosinusitis (CRS) is a clinical syndrome encompassing a heterogeneous group of diseases characterized by sinonasal mucosal inflammation for at least 12 consecutive weeks.¹ Culture-directed antibiotic therapy and systemic and intranasal corticosteroid (INCS) therapy are considered the mainstay therapies for CRS. Consensus documents from the Rhinosinusitis Task Force and European Position Paper on Rhinosinusitis and Nasal Polyps codify diagnostic criteria and treatment strategies to guide and streamline CRS management.¹ This article discusses recalcitrant CRS after standard medical therapy and primary endoscopic sinus surgery (ESS). Optimal management is centered on a rational approach designed to identify and treat underlying etiologic and exacerbating factors, to maximize antiinflammatory therapy, and to ensure that confounding causes of sinus symptoms are addressed.

CONFOUNDING LOCAL AND REGIONAL FACTORS THAT MIMIC PURULENT CRS

Endoscopy and sinus computed tomography (CT) scan are essential to the diagnosis of CRS, and both techniques are useful in evaluating local and regional processes that mimic purulent CRS (**Box 1**). With endoscopy, the presence of a foreign body or tumor should be readily apparent.

Adenoiditis is less obvious although recognized as the primary source of nasal purulence in children. In adults, persistent mucopurulent postnasal drainage may be secondary to an infected Thornwaldt diverticulum or bursa. A Thornwaldt bursa represents the embryonic remnant of adhesion of the pharyngeal ectoderm to the cranial end of the notochord. If this becomes closed at the orifice, a cyst develops. Remnants

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Box 1
Differential diagnosis of chronic rhinosinusitis in patients with mucopurulence
Sinonasal
Rhinitis (acute, chronic)
Foreign body
Neoplasia
Locoregional
Adenoiditis
Thornwaldt cyst
Dental abscess
Neoplasia

that fail to close, and instead form a diverticulum, may be a source of repeated episodes of purulent postnasal drainage in the absence of sinus pathology. Treatment is endoscopic marsupialization or removal.

Underlying dental pathology should be considered in any patient with recalcitrant purulent CRS, particularly those with unilateral disease. Identification of dental disease not only helps with appropriate antibiotic selection but also facilitates improved long-term outcomes.^{2,3} Sinus CT is helpful in assessing periodontal disease or periapical abscess as a cause of sinusitis and is more sensitive than plain dental films or a panorex.⁴ A recent study showed that more than 80% of CT scans with maxillary sinus fluid levels greater than two-thirds the height of the sinus and with mucosal thickening had dental pathology compared with 10% incidence of dental pathology in normal maxillary sinuses.⁴ Not all patients have specific dental symptoms or signs. However, once the diagnosis is established, appropriate treatment of the offending tooth by dental surgeons frequently obviates the need for sinus procedures. Directed endoscopic sinus surgery is reserved for situations in which persistent edema prevents maxillary sinus drainage.

LOCOREGIONAL AND SYSTEMIC FACTORS ASSOCIATED WITH PERSISTENT DISEASE

In persistent CRS (after medical therapy and primary ESS), locoregional and systemic factors known to be predictive of failed ESS include smoking, allergies,⁵ and asthma and aspirin intolerance.^{6,7} Additional factors that can play a role in actual or simulated persistent sinus symptoms include gastroesophageal reflux disease (GERD) and allergies.

Gastroesophageal Reflux Disease

GERD is associated with CRS in several studies; however, there is no direct evidence of causality.⁸ In a prospective trial using pH probe monitoring, acid reflux into the nasopharynx was significantly greater in patients with refractory CRS after surgery than in patients in whom ESS successfully relieved symptoms. DelGaudio⁹ suggested that there was an association between GERD and recalcitrant CRS. An alternative explanation for failure could be that CRS was not causing the patient's symptoms; rather the inadequately treated GERD caused the symptoms, as the sensation of post-nasal discharge can be simulated by pharyngeal and glottic irritation from GERD. Proton pump inhibitors can reduce the frequency of postnasal drainage symptoms in patients with extraesophageal manifestations of GERD.¹⁰ An open-label study

showed decreased sinonasal symptom scores in patients treated with omeprazole twice daily for 3 months.¹¹ No prospective, randomized controlled trials show the effectiveness of antireflux regimens in treating CRS.

Allergy

The association of allergic rhinitis (AR) and CRS is conflicting.^{12,13} Patients with the most extensive disease on sinus CT are less likely to be allergic or to respond to allergy management than patients with lesser sinus disease. Houser and Keen⁵ implicated AR as a predictive factor for decreased quality of life and poorer surgical outcomes in CRS. Although there is no evidence linking the pathogenesis of AR with CRS, the mucosal changes due to AR can alter mucociliary clearance, which can negatively affect CRS. In addition, AR symptoms such as drainage and nasal congestion mimic CRS symptoms. Management of concomitant AR is important in the comprehensive management of CRS; many symptoms are common to both conditions.

ALLERGY MANAGEMENT

The senior author (BJF) prefers to prescribe a treatment algorithm that includes progressive addition or replacement of various medications described in this section, including INCS, to arrive at a treatment regimen that is optimal for the individual. The cornerstone of this “rational patient experiment” is that the patient introduces 1 medication at a time for a sufficient duration to determine its efficacy in managing symptoms. The algorithm is provided to the patient in written form for reference until the next visit (**Table 1**). Immunotherapy is generally reserved for those with inadequate relief with environmental controls and medical therapy or for those with symptoms for at least 6 months of the year, so that the potential for cure is worth the time and small risks of immunotherapy. A detailed discussion of immunotherapy is beyond the scope of this article; however, it should be noted that immunotherapy is currently the only allergy treatment that offers a chance for a cure of AR symptoms.

Antihistamines

Histamine released from mast cells is responsible for most early phase symptoms of AR (sneezing, itching, and edema) by interaction with the H1 receptor. First-generation antihistamines (diphenhydramine, hydroxyzine, chlorpheniramine, and brompheniramine) can be sedating, can impair performance, and can exacerbate dryness, urinary retention, and narrow-angle glaucoma because of anticholinergic effects. Newer second-generation antihistamines are generally nonsedating, or have a lower sedating profile, and lack anticholinergic effects. Oral antihistamines are poor nasal decongestants; however, topical antihistamines are similar to INCS in terms of their symptom-relieving effect but with a more rapid onset of action. Side effects of topical antihistamines (azelastine HCl and olopatadine) include sedation (2%) and perverse taste. Concomitant usage with INCS may increase the control of symptoms.¹⁴

Decongestants

Decongestants are used for acute events and have little role in CRS. Common oral decongestants include pseudoephedrine and phenylephrine. Topical decongestants, including oxymetazoline and phenylephrine, also receive widespread use for nasal congestion because of the rapid onset of action; however, chronic use causes rebound congestion and tachyphylaxis.

Table 1
The rational patient experiment

Try Each Medicine in the Order Indicated	Medication	Dose	Number of Times a Day	Symptoms Which Should Improve and How Long it Should Take to Work	Check if Sample Given
	Nasal steroid spray Generic fluticasone propionate (Flonase) Triamcinolone (Nasacort) Mometasone furoate monohydrate (Nasonex) Budesonide (Rhinocort AQ) Fluticasone furoate (Veramyst) Ciclesonide (Omnaris) If any of the above are effective, let us know which ones on your formulary	1–2 puffs each nostril. Direct spray using right hand to spray left nose, and vice versa to maximize delivery laterally	1–2 times, use lowest dose that relieves symptoms	Nasal congestion, drainage, allergy symptoms—may take a week to work Slow to act	
	Antihistamine nasal spray Azelastine (Astelin) Azelastine (Astepro) Olopatadine (Patanase)	As above. Lean forward and do not sniff × 1 minute to minimize bad taste	2 times, take first dose before bedtime to see if it makes you sleepy	Nasal congestion, drainage, itch May work in less than half an hour Fast	
	Montelukast (Singulair)	10-mg pill	1 time	As above plus cough, fast	
	Antihistamines Loratadine (over the counter), Fexofenadine (Allegra) Levocetirizine (Xyzal), Cetirizine (Zyrtec)		1 time	Itch, sneeze Fast	

Guaifenesin (Mucinex)	600 mg	2 pills 2 times	Over the counter, less expensive generic on the Internet
Proton pump inhibitor			Take 0.5–1 h before a meal
Antibiotic			Eat yogurt, kefir, or take probiotics or acidophilus tablets (over the counter, health food store) while on an antibiotic to replenish good bacteria in your system
Saline nasal rinse Neil Med; Simply Saline (Blairx Laboratories, Inc., Columbus, Indiana), etc.			Use saline rinses before applying prescription nasal sprays
Queen Helene cocoa butter cream	Apply to front of nose	As needed	Available at Rite Aid, Wal-Mart, and on the Internet

Try each checked medicine *one at a time*.

If the medicine does *not* make you feel better in 3 to 4 days, then *stop* the medicine and try the next medicine listed.

If the medicine makes you feel *partially* better but not completely symptom free, then *add* the next medicine listed to the medicine that was partially helping you.

If the medicine *relieves* your symptoms, then *continue* it for at least several days or weeks. If you are feeling back to normal, then stop the medicine, but restart it if your symptoms start to return.

Anticholinergic Sprays

Ipratropium bromide, a topical anticholinergic nasal spray, blocks parasympathetic input to mucus glands and reduces rhinorrhea. Although decreased mucus production is desirable in some settings, it may lead to increased thickness of secretions and paradoxically worsen perceived postnasal drainage. It is formulated as a 0.03% solution for the treatment of AR rhinorrhea and a 0.06% solution for the treatment of rhinorrhea from the common cold.

Leukotriene Receptor Antagonists

Leukotrienes are produced about 1.5 hours into the allergic response, and their synthesis begins with oxidation of arachidonic acid from membrane phospholipids. Leukotriene effects include bronchoconstriction, increased vascular permeability, and leukocyte recruitment.

Montelukast blocks the cysteinyl-leukotriene receptor and is approved for asthma and seasonal and perennial AR. Montelukast added to INCS can improve symptom scores in CRS patients. As with all medications, some patients respond, others do not. The safety profile is excellent; however, in June 2009, the Food and Drug Administration (FDA) required that a warning of increased risk of neuropsychiatric events, including suicide and depression, be included in the label of all cysteinyl-leukotriene receptor antagonists. It is the authors' practice to give the patient a 1-week trial of therapy, and if no improvement in AR or CRS symptoms is noted, the patient is told not to fill the prescription.

Zileuton inhibits the 5-lipoxygenase enzyme and can inhibit leukotriene effects more potently than montelukast. In a randomized controlled study, a significant improvement in olfaction was noted in patients with CRS and concomitant aspirin sensitive asthma treated with zileuton.¹⁵ Zileuton is only approved for asthma, and the dosage is zileuton CR 600 mg twice a day. Liver function (alanine transaminase [ALT] level) should be monitored monthly for 3 months. Up to 2% of patients on zileuton will experience an elevation in ALT, which normalizes on cessation of the medication.

Mast Cell Stabilizers

Mast cell stabilizers prevent histamine release from mast cells, most likely by calcium channel modulation. These medications do not affect the downstream effects of histamine, and therefore are only effective as prophylaxis. Cromolyn sodium nasal spray should be taken 4 times daily, which often compromises compliance. There are no serious side effects reported with this medication, and it can be used during pregnancy.

SYSTEMIC DISEASES AND ASSOCIATED MEDICAL CONDITIONS

Immune Deficiency

Immunodeficiency is estimated to occur in 8% to 20% of patients with persistent or recurrent acute sinusitis. Before effective antiretroviral therapy for human immunodeficiency virus (HIV), sinusitis was a common finding in the acquired immune deficiency syndrome. CRS associated with immunodeficiency may be responsive to antibiotic therapy but recurs when antibiotics are withdrawn.¹⁶ The most common primary immunodeficiency in adults, the common variable immune deficiency (CVID), is reported to occur in up to 10% of patients with refractory CRS, whereas general immunoglobulin deficiencies are as high as 22% in the same population.^{17,18} Because CVID is associated with additional risks, such as autoimmunity and malignancy, an accurate diagnosis has ramifications beyond CRS. CVID is treated with

replacement immunoglobulin G; however, other identified immunodeficiencies may not be treatable. Identification is important because it alerts the physician and patient that the likelihood of an infection in this patient is greater and culture-directed antibiotics should be administered more promptly than in patients with normal immunity. IgA deficiency is less common in the CRS population than in the population at large.¹⁹

A general workup of immunity by the senior author (BJF) is displayed in **Box 2**. Costs of such a workup are less than the cost of a sinus CT scan. In addition, any patient suffering from recurrent acute infections should be offered a pneumococcal vaccine, which will theoretically immunize him or her to most, but not all, streptococcal pneumonia serotypes. Specific polysaccharide antibody deficiency syndrome is diagnosed by deficient responses to pneumococcal vaccine comparing the levels before 6 weeks after vaccination, in the context of normal systemic immunoglobulin levels.²⁰

Asthma and Sensitivity to Aspirin and Analgesics

The triad of sinusitis, bronchial asthma, and aspirin intolerance is known as Widal syndrome, Samter triad, and aspirin exacerbated respiratory disease (AERD). Patients with CRS with nasal polyps (NPs) are more likely to have aspirin hypersensitivity or asthma than the general population. NPs are reported in up to 70% of aspirin-intolerant patients with asthma. Aspirin or analgesic intolerance is not always associated with the full clinical picture of NPs and asthma but may be restricted to just the upper airway. In sensitive individuals, even a very small single dose of aspirin or other cyclooxygenase-1 (COX-1) inhibitor can cause rhinorrhea, bronchospasm, and shock. This mechanism is not caused by an IgE-mediated allergy; rather the reaction occurs because these individuals produce increased amounts of leukotrienes. Prostaglandin E₂ (PGE₂), produced by the cyclooxygenase pathway, is an inhibitor of 5-lipoxygenase and leukotriene production. A COX-1 inhibitor, such as aspirin, inhibits production of PGE₂, causing a release of inhibition of the 5-lipoxygenase enzyme and an increase in leukotriene production. The gold standard for the diagnosis of AERD is an oral provocation test under close supervision. AERD patients may tolerate COX-2 inhibitors, and occasionally patients report improvement in symptoms on a COX-2 inhibitor, although the mechanism is unknown.²¹

Aspirin desensitization may be beneficial and must be performed under supervised conditions. Various aspirin doses (100–1300 mg) and routes of administration (oral, intranasal) are reported. Once desensitized, the patient must take aspirin daily. Failure to take aspirin for several days renders the patient hypersensitive to its effects once more. Up to 30% of patients cannot tolerate the side effects from daily aspirin therapy. Even though other COX-1 inhibitors such as ibuprofen can trigger bronchospasm in these individuals, to date, it has not been possible to desensitize a patient with any

Box 2

Immunodeficiency evaluation

Complete blood count with differential

Quantitative immunoglobulins: IgA, IgE, IgG, IgM

Immunoglobulin subclasses: secretory IgA, IgG1, IgG2, IgG3, IgG4

T-cell subpopulations: CD4, CD8

Pneumococcal antibody titers: before and 6 weeks after pneumococcal vaccination

agent except aspirin. Desensitization can improve asthma control and prevent continued growth of NPs, but it does not usually cause NP regression.²²

Vasculitides and Granulomatous Disorders

Wegener's granulomatosis (WG) is a rare granulomatous vasculitic disorder, occurring in approximately 3 per 100,000 people, affecting primarily whites (97%) aged between 50 and 60 years.^{23–25} Sinonasal manifestations occur in up to 89% of patients.²³ Common symptoms include nasal obstruction, rhinorrhea (frequently bloody), epiphora, and crusting. Patients may present with recalcitrant CRS, septal perforation, mucocoele, orbital pseudotumor, or saddle-nose deformity. In patients with clinical features consistent with WG, positive cytoplasmic antineutrophil cytoplasmic antibodies and an elevated erythrocyte sedimentation rate suggest the diagnosis. However, definitive diagnosis depends on histopathologic analysis of affected mucosa.²⁶ Treatment of WG should be given in consultation with a rheumatologist.

Churg-Strauss syndrome (CSS) is characterized by multisystem granulomatous eosinophilic tissue infiltration. Nasal involvement can occur in up to 75% of patients. Clinical presentation is similar to WG, with the exception of a more profound and systemic neuropathy. Diagnosis is based on clinical findings, positive perinuclear antineutrophil cytoplasmic antibodies, and biopsy.

Sarcoidosis, an inflammatory multisystem disorder of uncertain etiology, is characterized by noncaseating granulomas. Although the lower respiratory tract is frequently involved, the sinonasal cavity is affected in only 0.7% to 6% of cases.²⁷ Common examination findings include mucosal hypertrophy, purple mucosa with nodules (granulomas), and lupus pernio.^{26,27} Diagnosis is based on clinical findings, chest radiography, elevated angiotensin-converting enzyme levels, and findings of mucosal biopsy from affected mucosa.²⁶ Treatment of CSS and sarcoidosis often requires oral steroids and immunosuppressants, and surgery is reserved for extreme or complicated cases.

OPTIMIZING MEDICAL THERAPY FOR PERSISTENT CRS

An assessment of compliance and an evaluation of treatments that have worked or have not worked for the patient should be undertaken at every visit to facilitate step-wise introduction and testing of efficacy of various therapeutic interventions. In addition to allergy medications, including leukotriene modulators that are discussed in the allergy section, this section completes the discussion of available medical therapies, beyond steroids and antibiotics (**Box 3**).

Antifungals

In double-blind randomized controlled trials, the topical antifungal amphotericin is no more effective in reducing CT scan scores than saline (level 1 evidence).^{28,29} In another double-blind, placebo-controlled study, oral terbinafine failed to improve symptoms or radiographic appearance of CRS.³⁰ In a retrospective review of 23 patients from Australia with refractory allergic fungal sinusitis (AFS) and nonallergic fungal sinusitis, use of the antifungal oral agent itraconazole 100 mg twice daily for 6 months led to improvement of refractory disease in 19 patients, with 11 patients disease-free at 6 months.³¹

Three patients had to stop the itraconazole because of elevated liver enzymes. Earlier randomized controlled studies on topical antifungals did not specifically enroll patients with evidence of eosinophilic fungal disease, which could explain the differences in findings in these studies. A randomized controlled study of patients with

Box 3**Medical treatment options for chronic rhinosinusitis: beyond steroids, antibiotics, and surgery**

Treatment strategies

Antifungals

Topical and systemic

Allergy management

Antihistamines

Topical sprays, oral

Allergen avoidance

Fix water leaks, avoid dust mites, use BreathePure (Breathepure Healthcare, LLC, Santa Barbara, California) nasal filters

Immunotherapy

Subcutaneous, sublingual

Food allergy

Elimination challenge diet

Topical saline irrigation

Hypotonic, hypertonic, isotonic

Mucus modifiers

Guaifenesin

Anticholinergics

Leukotriene modulators

Leukotriene receptor antagonist (montelukast)

5-Lipoxygenase inhibitor (zileuton)

Decongestants

Topical

Systemic

Diet modification

Omega 3, vitamins, probiotics

Lifestyle modification

Stop smoking, get adequate sleep, exercise regularly, avoid pollution

eosinophilic fungal disease is required to assess the efficacy of antifungal therapies in this subset of CRS patients.

Mucolytics

Mucolytics, including guaifenesin or acetylcysteine, decrease the viscosity of secretions in the upper airway, theoretically improving mucociliary transport. Guaifenesin has been approved for use by the FDA since 1952 and is a common component of over-the-counter cough and cold formulations. In a randomized placebo-controlled study in HIV-positive patients before effective antiretrovirals were available, guaifenesin at a dose of 1200 mg twice daily led to reduced congestion and postnasal drainage.³² Because of the limited data related to CRS management,

recommendations for or against mucolytic use cannot be clearly argued. However, with an excellent safety profile, use of mucolytics should not be discouraged in patients who perceive a benefit.

Topical Nasal Saline

Nasal saline is widely used in the treatment of CRS and is applied by various methods, including spray, nebulization, and irrigation. Nasal saline irrigations improve symptom scores and improve symptom control in CRS with persistent disease. Nasal saline irrigation can be used to deliver baby shampoo, sodium hypochlorite, xylitol, Dead Sea salt, and povidone-iodine (Betadine). None of these additions have been studied with a randomized controlled trial. In unoperated sinuses, the effect of saline irrigations is limited to the nasal cavity.

In cystic fibrosis (CF), hypertonic nasal saline may be more effective than isotonic saline. This is inferred from a double-blind randomized controlled study that showed hypertonic saline to be more effective than isotonic saline in pulmonary nebulization in patients with CF.³³ Up to 8% of CRS patients are heterozygotes for CF.³⁴ Potentially, CRS CF carriers may also benefit from hypertonic saline irrigations; other CRS patients would benefit from isotonic irrigations.

Anti-IgE

Omalizumab (Xolair) is a monoclonal antibody that selectively binds to human IgE and is currently approved for use in patients older than 12 years with moderate to severe persistent asthma with a positive skin test or in vitro reactivity to perennial aeroallergens and whose symptoms are inadequately controlled with inhaled corticosteroids. Other inflammatory conditions such as AR and CRS with NP have been reported to improve with omalizumab. Omalizumab has been reported to resolve allergic bronchopulmonary aspergillosis. The senior author (BJF) treated a patient with AFS who improved dramatically after starting omalizumab treatment. However, anti-IgE therapy is costly (\$10,000–12,000 per year), somewhat inconvenient (requiring a shot once or twice a month), and carries potential risk (rare anaphylaxis has been reported), and a possible increased risk of cardiovascular and cerebrovascular adverse events.

Mepolizumab is an anti-interleukin-5 monoclonal antibody that binds to interleukin-5, the cytokine most potent in stimulating eosinophil production, activation, and maturation. Treatment with mepolizumab causes a sustained reduction in the number of circulating eosinophils because of its long terminal half-life.³⁵ Mepolizumab currently has an orphan drug status, and its use remains investigational in the treatment of hypereosinophilic syndrome. Its role in the treatment of AR and CRS has yet to be determined.

Food Allergy

Food allergy by prick testing is present in more than 70% of CRS patients with NP compared with only 34% of controls. The incidence of inhalant allergy by prick testing in patients with NP is only 35%.³⁶ Making this diagnosis is challenging, often because of an inability to clearly define the inciting foods and because skin prick tests and in vitro tests can miss this diagnosis, as many food hypersensitivities may not be IgE-mediated. The gold standard for diagnosis of food allergy is a double-blind, placebo-controlled, oral challenge; however, this is often impractical. Patients can perform similar elimination challenge procedures at home. Although not blinded or controlled, this allows for a convenient inexpensive self-diagnosis. Most common “masked” food allergens in adults in the United States are those foods commonly eaten and include wheat, dairy, soy, corn, and, occasionally, eggs. To perform an

elimination food challenge, the targeted food is eliminated from the diet for 5 to 7 days and then reintroduced into the diet during this hyperresponsive period of 5 to 10 days following elimination. If the food causes symptoms, then the patient will generally be aware of either nasal or nonnasal symptoms (fatigue, bloating, and abdominal cramping) within 15 minutes to 6 hours after the food challenge. Patients are advised to test for the 5 foods listed in succession. Those who note symptoms on reintroduction of the food are instructed to eliminate the food from their diet for approximately 3 months, after which time the food may be reintroduced into their diet, although the food should not be eaten on a daily basis.³⁷

Lifestyle and Dietary Modifications

These factors are addressed to promote a healthier lifestyle that influences sinonasal health. Patients are encouraged to maintain adequate hydration with noncaffeinated drinks for optimal mucus quality. A study in patients with CF showed that dehydration was associated with increased biofilms, ineffective defense,³⁸ and decreased mucociliary clearance.³⁹ Other advice includes adequate exercise, cessation of smoking, and use of nasal air filters or masks to reduce exposure to inhaled allergens and pollution.

ALTERNATIVE THERAPIES

Alternative therapies include acupuncture and several herbal remedies. There is little objective evidence of efficacy for these measures. A study on acupuncture showed no significant difference in health-related quality of life compared with conventional medical therapy, which consisted of 2 to 4 weeks of antibiotics, corticosteroids, 0.9% sodium chloride solution, and local decongestants.⁴⁰ The conventional treatment group had better symptom scores and physical scores than the acupuncture group.

Phototherapy using a combination of ultraviolet (UV) A and UV B and laser therapy can reduce mucosal inflammation by inducing apoptosis and functional alteration of lymphocytes, antigen-presenting cells and eosinophils, and by altering cytokine levels and other chemical mediators, including histamine. Phototherapy has been used to treat AR, and its use may extend to a select group of patients with CRS.⁴¹ Preliminary studies show no adverse effect on the regenerative capacity of nasal epithelium.⁴² The other immune modulatory and suppressive agents that have potential to either provide immunostimulation and protection or to reduce mucosal inflammation include microbial and T-cell vaccines, bacterial-derived stimulants (ribomunyl), and T-cell suppressants (pimecrolimus).

SUMMARY

Management of CRS can be complex, and definitive evidence-based protocols cannot be currently defined because of disease heterogeneity, incomplete understanding of refractory cases, and differences in individual responses to various interventions. An accurate diagnosis of CRS and treatment of associated conditions facilitates effective management. Included in the differential for purulent CRS mimics are adenoiditis, Thornwaldt cyst, and dental infection. Control of AR and GERD can provide symptom relief, if not necessarily improve sinusitis. Immunodeficiency, systemic granulomatous diseases, and vasculitides are systemic disorders that may predispose patients to recalcitrant CRS. Successful management is generally dependent on resolution or optimization of the underlying systemic disorder. Finally,

in refractory patients, antifungals (in patients with positive fungal cultures and eosinophilic mucin), leukotriene modulators (montelukast /zileuton), aspirin desensitization (if aspirin-sensitive), and omalizumab (anti-IgE, for those with elevated IgE) may be beneficial. To determine empirically if the intervention is helpful, patients should introduce only 1 therapeutic variable at a time and monitor symptom response.

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