Clinical reviews in allergy and immunology

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Chronic rhinosinusitis: Epidemiology and medical management

Daniel L. Hamilos, MD *Boston, Mass*

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Activity Objectives

1. To know the statistics and epidemiology surrounding chronic rhinosinusitis (CRS) and its risk factors and implications for the patient.
2. To know the comprehensive management plan for CRS and nasal polyposis, including initial approach, diagnostics, and appropriate treatment.

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Chronic rhinosinusitis (CRS) affects 12.5% of the US population. On epidemiologic grounds, some association has been found between CRS prevalence and air pollution, active cigarette smoking, secondhand smoke exposure, perennial allergic rhinitis, and gastroesophageal reflux. The majority of pediatric and adult patients with CRS are immune competent. Data on genetic associations with CRS are still sparse. Current consensus definitions subclassify CRS into CRS without nasal polyposis (CRSsNP), CRS with nasal polyposis (CRSwNP), and allergic fungal rhinosinusitis (AFRS). Evaluation and medical management of CRS has been the subject of several recent consensus reports. The highest level of evidence for treatment for CRSsNP exists for saline lavage, intranasal steroids, and long-term macrolide antibiotics. The highest level of evidence for treatment of CRSwNP exists for intranasal steroids, systemic glucocorticoids, and topical steroid irrigations. Aspirin desensitization is beneficial for patients with aspirin-intolerant CRSwNP. Sinus surgery followed by use of systemic steroids is recommended for AFRS. Other modalities of treatment, such as antibiotics for patients with purulent infection and antifungal drugs for patients with AFRS, are potentially useful despite a lack of evidence from controlled treatment trials. The various modalities of medical treatment are reviewed in the context of recent consensus documents and the author's personal experience. (J Allergy Clin Immunol 2011;128:693-707.)

Key words: *Rhinosinusitis, sinusitis, nasal polyposis, epidemiology, medical management, treatment*

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Corresponding author: Daniel L. Hamilos, MD, Massachusetts General Hospital, Division of Rheumatology, Allergy & Immunology, 55 Fruit St, Bulfinch-422, Boston, MA 02114. E-mail: dhamilos@partners.org.

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According to the National Health Interview Survey of 1996, chronic sinusitis was the second most prevalent chronic health condition, affecting 12.5% of the US population or approximately 31 million patients each year.[1,2] According to an analysis of the 2008 National Health Interview Survey data, rhinosinusitis affected approximately 1 in 7 adults.[3] Because chronic rhinosinusitis (CRS) was classified solely on symptomatic criteria, CRS prevalence was likely overestimated in these surveys. A study by Stankiewicz and Chow[4] found a poor correlation of CRS symptoms with objective evidence of sinus disease either by means of nasal endoscopy or sinus computed tomographic (CT) scanning.[4] In 2003, a consensus panel redefined CRS (also known as chronic sinusitis) as an inflammatory disorder of the nose and paranasal sinuses of unknown cause defined on the basis of characteristic symptoms (≥2 of the following: nasal congestion, facial pain/pressure, anterior or posterior nasal drainage, and reduced or absent sense of smell), duration (>12 weeks), and objective evidence of sinus disease by means of direct visualization or imaging studies.[5]

Abbreviations used
AERD: Aspirin-exacerbated respiratory disease
AFRS: Allergic fungal rhinosinusitis
CF: Cystic fibrosis
CRS: Chronic rhinosinusitis
CRSsNP: Chronic rhinosinusitis without nasal polyposis
CRSwNP: Chronic rhinosinusitis with nasal polyposis
CT: Computed tomography
FESS: Functional endoscopic sinus surgery
LPR: Laryngopharyngeal reflux
NP: Nasal polyposis
OR: Odds ratio
SHS: Secondhand smoke
SNOT-20: Sinonasal Outcome Test 20
VAS: Visual analog scale

Regardless of its true prevalence, CRS accounts for substantial health care expenditures in terms of office visits, antibiotic prescriptions filled, lost work days, and missed school days. The number of workdays missed annually because of rhinosinusitis is similar to that reported for acute asthma (5.67 vs 5.79 days, respectively), and patients with rhinosinusitis are more likely to spend greater than $500 per year on health care than people with chronic bronchitis, ulcer disease, asthma, or hay fever.[6] Approximately 20% of patients with chronic sinusitis have nasal polyposis (NP).[7] There were approximately 200,000 sinus surgeries performed in the United States in 1994.[8] CRS with nasal polyposis (CRSwNP) is one of the most common indications for sinus surgery. Of patients participating in our nasal polyp research studies, 69% have had previous surgery, attesting to the high frequency of recurrent disease in these patients.

CRS

Anatomic abnormalities

Certain anatomic variants, such as septal deviation, Haller cells, paradoxical curvature of the middle turbinate, and agger nasi cells, have been suggested to predispose to obstruction of the ostiomeatal unit, development of CRS, or both. However, there is currently little evidence that these play a role in most cases of chronic sinusitis.[9-12] Furthermore, a recent study in a pediatric population found no correlation between anatomic abnormalities and the extent of CRS on sinus CT scanning.[13]

Air pollution

There have been relatively few studies examining the relationship between air pollutants and CRS incidence or prevalence. Bhattacharyya[6] performed a cross-sectional analysis to examine the relationship between the prevalence of "hay fever" and "sinusitis" and US-wide air quality measurements during the period 1997-2006. Using the National Health Interview Survey and pollutant level data from the US Environmental Protection Agency, a direct relationship was found between the prevalence of both hay fever and sinusitis and pollutant levels of carbon monoxide, nitrous dioxide, sulfur dioxide, and particulate matter. In contrast, the control condition kidney failure/weakening showed only a very weak relationship with these parameters. This study did not examine regional differences in hay fever, sinusitis, and pollutant levels, such as rural versus urban areas.

Heinrich et al[14] examined the relationship between decreasing ambient total suspended particles and sulfur dioxide levels in 3 study areas of East Germany after German reunification in 1990 and the prevalence of bronchitis, sinusitis, and colds in 7632 children aged 5 to 14 years of age. Data were collected in 3 phases: 1992-1993, 1995-1996, and 1998-1999. An association was found between total suspended particles and sulfur dioxide levels and for bronchitis (adjusted odds ratio [OR], 3.0; 95% CI, 1.7-5.3), sinusitis (adjusted OR. 2.6; 95% CI, 1.0-6.6), and frequent colds (adjusted OR, 1.9; 95% CI, 1.2-3.1). No relation was found between these conditions and nucleation-mode particles (10-30 nm), which increased after reunification (see www.newmediastudio.org/DataDiscovery/Aero_Ed_Center/Charact/A.what_are_aerosols.html for explanation of nucleation mode particles).

Specific components of air pollution

Irritants in air pollution, including sulfur dioxide,[15,16] ozone,[17] and formaldehyde (indoor pollutant),[18] but not diesel exhaust particles,[19] have been reported to adversely affect mucociliary clearance.

Indoor dampness and mold exposure

Although some studies of health effects associated with self-reported exposure to indoor dampness or mold have found an increase in sinusitis,[20] an Institute of Medicine report (Damp Indoor Spaces and Health, www.nap.edu/catalog/11011.html) concluded that there is little evidence associating sinusitis with either indoor dampness or moldy indoor spaces.

Active and secondhand cigarette smoking

Active cigarette smoking is associated with a decrease in mucociliary clearance measured based on saccharine transit time[21] and has been shown to have a negative effect on mucosal recovery after endoscopic sinus surgery in adults and children.[22-25]

In a study using the Third National Health and Nutrition Examination Survey (1988-1994) of 33,994 persons, Lieu and Feinstein[26] examined the relationship between chronic sinusitis, active cigarette smoking, and secondhand smoke (SHS) exposure. Active cigarette smoking was associated with an increased risk of sinus disease (relative risk, 1.22; 95% CI, 1.05-1.39); however, no increased risk was found in association with SHS exposure. A concern about this study is the fact that serum cotinine levels of less than 28.4 nmol/mL (<5 ng/mL) were regarded as indicative of nonsmokers without SHS exposure, and the prevalence of chronic sinusitis in this population served as the reference point for comparison with subjects with higher levels of SHS exposure. However, the mean serum cotinine level of nonsmokers at the time of the Third National Health and Nutrition Examination Survey study was only 0.20 ng/mL, and this level has been steadily decreasing to a level of 0.05 in 2001-2002 (www.cdc.gov/mmwr/preview/mmwrhtml/mm5541a7.htm), indicating that a significant degree of SHS exposure was present in the "unexposed" subjects in this study. With the high background SHS exposure of healthy unexposed adults in this study, it is possible that an effect of SHS on chronic sinusitis was missed.

Tammemagi et al[27] performed a matched case-controlled study to assess the association of SHS and CRS. In this study a questionnaire was used to quantify SHS exposure in the home, workplace,

public places, and private social functions outside the home in 306 nonsmoking patients with CRS and 306 age-matched, sex-matched, and race/ethnicity-matched nonsmoking control subjects over a 5-year period before the diagnosis of CRS. Using conditional logistic regression ORs, the authors reported higher levels of exposure to SHS in patients with CRS than control subjects in the home (9.1% vs 13.4%), work (6.9% vs 18.6%), public places (84.3% vs 90.2%), and private social functions (27.8% vs 51.3%). This study has potential for confounding because of recall bias and ascertainment bias on the part of CRS-affected patients.

Reh et al[28] performed a case-controlled study of 100 adult patients with CRS and 100 control subjects matched for age, sex, and smoking status by using a validated questionnaire to quantify both current and past SHS exposure. Using an OR computed based on comparison with those who reported no SHS exposure, they reported that current or childhood SHS exposure was associated with a higher risk of CRS (OR, 2.33; 95% CI, 1.02-5.34; $P = .05$). Although the method used for computing ORs in this study can be criticized, the authors also found that patients with CRS exposed to SHS had higher symptom scores for nasal obstruction/blockage, nasal discharge, headaches, and cough. SHS exposure was not quantified in this study.

Allergic rhinitis

The prevalence of IgE-mediated allergy to environmental allergens in patients with CRS (both with and without NP) is estimated at 60% compared with 30% to 40% for the general population.[29] Patients with CRS are typically sensitized to perennial rather than seasonal (ie, pollen) allergens.[30] Important perennial allergens include house dust mites, fungal spores from indoor and/or outdoor sources, animal danders, cockroaches, and sometimes feathers. Perennial allergens are generally present at higher levels for longer periods of time compared with pollen allergens. Fungal spores can germinate in sinus mucus, thereby increasing the allergenic stimulus.

Histopathologic studies of ethmoidal tissue and nasal polyp tissue have demonstrated that allergic patients with CRS have chronic allergic inflammation, with local T-cell infiltration and production of classic T_H2 cytokines, including IL-4, IL-5, and IL-13.[31,32] These cytokines promote local IgE production and eosinophil infiltration and prolong the survival of eosinophils in the tissues, leading to sustained allergic inflammation.

Despite these associations, the intensity of eosinophilic inflammation in patients with CRS without nasal polyposis (CRSsNP) and those with CRSwNP is independent of the presence of underlying systemic allergy.[33-35] Similarly, Robinson et al[36] found no relationship between the presence of atopy (defined as a positive *in vitro* IgE CAP RAST test result) and sinusitis disease severity or the rate of revision sinus surgery in a population of 193 patients with CRS.

Geographic and socioeconomic differences in allergic fungal rhinosinusitis prevalence

Allergic fungal rhinosinusitis (AFRS) is distinct among the CRS subtypes in having a significant geographic distribution of disease. Ferguson et al[37] surveyed 20 otolaryngologic practices in the United States and confirmed that areas such as Memphis, Tennessee, and other southern locations reported prevalences of AFRS relative to endoscopic sinus procedures of 10% to 23%, whereas other northern locations reported frequencies ranging from 0% to 4%.

In one of the areas of high AFRS prevalence (South Carolina), Wise et al[38] performed a retrospective review to examine socioeconomic and demographic factors that might differentiate AFRS from other forms of CRS, including CRSsNP and CRSwNP. They found that patients with AFRS were younger, more likely to be African American, more likely to be uninsured or Medicaid patients, and more likely to live in areas of high poverty or lower median income in comparison with patients with either CRSsNP or CRSwNP. The reason for these differences is not obvious. In contrast, the same authors did not find the same socioeconomic factor associations with bone erosion in patients with AFRS.[39]

Underlying genetic factors

Data on genetic associations with CRS are still sparse. However, Wang et al[40] found that the prevalence of CRS in an unselected group of obligate cystic fibrosis (CF) carriers was 36%, clearly much higher than the prevalence of chronic sinusitis (approximately 12.5% in the United States). Furthermore, the prevalence of CF carrier status in an unselected group of patients with CRS was found to be 7% or statistically higher than the 2% CF carrier status in the control population.[41] CF is a well-recognized cause of NP in children.

Primary ciliary dyskinesia is a rare recognized cause of CRS. It has been shown to be a risk factor for CRSsNP but not CRSwNP,[42] which distinguishes primary ciliary dyskinesia from CF.

Humoral or innate immune deficiency

Humoral or innate immune deficiency should be considered as an underlying factor in patients with CRS with a pattern of recurrent purulent infection. In a pediatric population Shapiro et al[43] found that 34 of 61 children with refractory sinusitis had abnormal results on immune studies, with decreased IgG_3 levels and poor response to pneumococcal antigen being the most common abnormalities found. In adult patients with CRS, a much lower prevalence of decreased humoral immunity has been found. Vanlerberghe et al[44] found that IgG_2, IgG_3, or a combined defect of major and/or minor IgG subclasses occurred in 22.8% of patients with refractory CRS. Hamilos[45] found a prevalence of any type of low immunoglobulin or poor response to vaccination of 12.7% in patients with CRSsNP and only 2.2% of patients with CRSwNP.

Innate immune deficiency is difficult to diagnose because of limited testing capabilities. Mannose-binding lectin deficiency is one of the most prevalent innate immune deficiencies, but there is little evidence for an increased prevalence of mannose-binding lectin deficiency in children or adults with CRS.[46]

Gastroesophageal reflux (laryngopharyngeal reflux)

Gastroesophageal reflux, specifically laryngopharyngeal reflux (LPR), has been proposed as a contributive factor to CRS. The mechanism for this is believed to be due to direct effects of refluxate on nasal/sinus mucosa, although no consistent effect of LPR on nasal mucociliary clearance has been demonstrated.[47] One study found that patients with LPR had higher scores on the Sinonasal Outcome Test (SNOT-20), even in the absence of

a diagnosis of CRS,[48] and another study showed that patients with LPR had higher scores for postnasal drainage.[49] Some of this association could be due to overlapping symptoms between LPR and CRS. However, a higher frequency of LPR determined by means of dual-channel 24-hour pH monitoring was found in a group of patients with CRS who had persistent CRS symptoms despite endoscopic sinus surgery[50] and a similarly higher frequency of LPR by pH monitoring and fluorometric pepsin assay of nasal secretions was found in a population of patients with CRS undergoing sinus surgery compared with a control group.[51] However, there are no controlled studies demonstrating improvement of CRS by means of antireflux therapy.

Biofilms

Biofilm formation is an important survival mechanism for microorganisms through attachment to surfaces.[52] Biofilm formation on sinonasal mucosal surfaces was first described in 2004[53] and has now been described in numerous other studies.[54,55] In one study the presence of bacterial biofilm was associated with more severe preoperative disease based on radiologic and nasal endoscopic scoring and worse sinus symptom and nasal endoscopy scores 16 months after surgery.[56]

The presence of bacterial biofilm was also strongly associated with persistent mucosal inflammation after endoscopic sinus surgery.[57]

CRS relation to asthma severity

Liou et al[58] examined causes and contributive factors to asthma severity in 149 asthmatic patients at an asthma specialty clinic and found that CRS was associated with more severe asthma (OR, 2.22; 95% CI, 1.08-4.60; $P = .032$). In a study in western Sweden, Lotvall et al[59] found an association between the presence of CRS and multisymptom (more severe) asthma by using the OLIN and GA2LEN respiratory- and allergy-focused questionnaires, whereas no association was found with allergic rhinitis. Aazami et al[60] examined a population of 90 asthmatic patients in Iran and found an association between the presence of CRS and more severe asthma judged by medication use and lower FEV_1. The link between asthma *per se* and CRS is strongest for polyp disease.[45,61,62]

MEDICAL TREATMENT OF CRS

Specific therapies

Nasal saline. Nasal saline irrigation and nasal spray are helpful in all types of CRS. A systematic review of 8 studies using various forms of irrigation and saline sprays (performed 1-4 times daily) found that nasal saline is an effective adjunctive treatment for CRS, although less effective as monotherapy than topical glucocorticoids.[63] Nasal saline irrigation is recommended in each of the recent rhinosinusitis consensus documents. Irrigation reduces postnasal drainage, removes secretions, rinses away allergens and irritants, and improves mucociliary clearance.[64]

Nasal lavage (with at least 200 mL of warmed saline per side) can be performed by using a variety of over-the-counter devices, including squeeze bottles, syringes, and pots.

Intranasal steroids (glucocorticoids). Topical aqueous steroid nasal sprays are helpful in all types of CRS and are the cornerstone of maintenance treatment.[65-69] Intranasal glucocorticoids include budesonide, ciclesonide, fluticasone furoate, fluticasone propionate, mometasone furoate, and triamcinolone acetonide. Efficacy in CRS is supported by a high level of evidence (grade A) from randomized trials, as reviewed in detail elsewhere.[67,69]

Systemic antibiotics. Consensus recommendations acknowledge that antibiotic treatment for CRS is controversial because of a lack of evidence from well-conducted clinical trials. Antibiotics are acknowledged as useful for acute exacerbations of CRS.[70-72] The most appropriate patients with CRS for antibiotic treatment are those with persistent purulent drainage and documented infection with pathogenic organisms, such as *Staphylococcus aureus*, methicillin-resistant *S aureus*, or gram-negative bacilli, such as *Pseudomonas aeruginosa*, *Klebsiella oxytoca*, *Stenotrophomonas maltophilia*, or other pathogens. These pathogens can be associated with either acute or chronic infection. In the author's experience managing more than 600 patients with CRS with the ability to obtain sinus cultures endoscopically,[73] evidence of purulent infection is present in less than 10% of patients, but eradication of infection has been associated with clinical improvement in some cases. Clinical trials that specifically attempt to eradicate pathogens are very limited. Eradication of infection also depends greatly on whether sinus aeration and adequate mucociliary clearance can be restored.

Systemic glucocorticoids. A brief course of oral glucocorticoids has been studied primarily as a treatment for NP (ie, a "medical polypectomy"). In most cases treatment results in significant clinical improvement and transient improvement in sense of smell. A systematic review of oral glucocorticoids for NP found only 1 randomized trial that met the inclusion criteria.[74,75] In this trial of adult patients with severe nasal polyps,[75] 60 were randomly assigned to oral prednisone (2-week taper starting at 30 mg daily for 4 days with 5 mg reduction every 2 days) followed by intranasal budesonide (400 μg twice daily) and had significant improvement in symptom scores and polyp size at 2 and 12 weeks compared with 18 patients who received placebo.[76] Since then, Hissaria et al[75] performed a randomized double-blind, placebo-controlled trial with 20 subjects per group. Prednisolone treatment (50 mg daily for 14 days) was associated with improvement in rhinosinusitis outcome measure scores, reduction in polyp size, and improvement in the extent of sinus disease on magnetic resonance imaging scanning. Other studies used different glucocorticoid doses but also tapered over a 2-week period.[77]

In the author's clinic a typical adult receives 20 mg of prednisone twice daily for 5 days, then 10 mg twice daily for 5 days, and then 10 mg daily for 5 days (ie, total of 15 days of treatment). Topical steroid are begun simultaneously. The British guidelines suggest prednisolone (0.5 mg/kg each morning for 5-10 days), accompanied by instillations of betamethasone nasal drops (not available in the United States).[65]

Systemic steroids are also advocated in the initial treatment of AFRS (see below).

Use of topical steroid irrigations. A 12-week, double-blind, placebo-controlled trial demonstrated the benefit of using topical corticosteroid nasal drops for the treatment of established nasal polyps.[78] In this study subjects were instructed to lie on their backs in a bed with their heads hanging down in an inverted vertical position over the edge of the bed while drops of 200 μg of fluticasone propionate were administrated per nostril once daily. They remained in this position for 2 minutes. The primary efficacy end point was based on a complicated scoring method that took into consideration patients' symptoms, sinus CT scores,

and the physician's impression of the patient's need for sinus surgery. Fluticasone nasal drops reduced the need for sinus surgery, improved hyposmia, and decreased nasal polyp volume.

Aqueous budesonide respules have been used off-label similar to the fluticasone nasal drops. The success of this treatment depends on delivery of the topical steroid to the polyp and polypoid tissue near the sinus ostia and in the sinus cavities. Usually, a 0.5-mg respule is mixed with 1 teaspoon of saline, and this mixture is instilled in the right nostril once daily with irrigation first in the head down forward position, then the right lateral supine position, and finally in the supine position, each for 1 to 2 minutes, after which the remaining nasal solution is expelled from the nose. The procedure is then repeated in the left nostril.[79] Although a controlled clinical trial has not been performed, many patients have benefitted from this treatment. Daily irrigation with budesonide respules, 0.25 mg per nostril, for 30 days was studied in 9 adults with chronic sinusitis. Significant improvement in sinusitis health status was reported with no suppression of the hypothalamic-pituitary axis.[80] Wight et al[81] demonstrated "no serious adverse effects" with using 800 μg/d budesonide intranasally during a 12-week cross-over study. However, longer-term use has not been studied and requires monitoring for systemic side effects, including monitoring of intraocular pressures.

Long-term macrolide treatment. The EP3OS document recommends long-term macrolide therapy based on a study by Ragab et al[66] graded as level Ib evidence. In this trial patients randomly assigned to medical treatment with erythromycin, alkaline nasal irrigation, and intranasal corticosteroids were found to have symptom scores and endoscopic findings at 6 and 12 months, which is not significantly different from scores seen in patients who underwent surgery. No sham surgery was performed on the medically treated subjects, making it impossible to rule out a placebo effect. Additionally, patients who underwent surgery also received medical therapy with erythromycin, intranasal corticosteroids, and alkaline nasal irrigation, and medical therapy late in the study could be tailored to each patient's symptoms, making it difficult to identify a true control group and assess the value of any one therapy. Another study cited as grade Ib evidence in EP3OS was a randomized, placebo-controlled investigation of 150 mg of roxithromycin versus placebo.[82] Patients in the roxithromycin group showed a statistically significant change from baseline in SNOT-20 score at 12 weeks not seen in the placebo group. By using a "change from baseline" analysis, the roxithromycin group also showed an improvement in saccharine transit time and nasal endoscopy not seen in the placebo group. However, the statistical analysis in this study was unconventional because it evaluated outcomes as the change from baseline in each study arm rather than comparing the outcomes directly at study's end.

Topical antibiotic treatment. A recent systematic review of topical antimicrobials for CRS concluded that there is some evidence for the use of antibiotic nasal irrigations or nebulizations.[83] The highest level of evidence exists for studies of postsurgical patients and culture-directed therapy. Both CRS and acute exacerbations of CRS might benefit. Most topical antibiotic studies have involved administration of nebulized antibiotic for 3 to 6 weeks in prospective observational studies only and not double blind or placebo controlled.[84,85] Excellent to good improvement was reported in 82% of cases.[84] Endoscopic improvement and an increase in infection-free interval after treatment were reported in another study.[85] Recent examples include the study of mupirocin irrigations for patients with refractory CRS with culture-proved *S aureus* infection.[86] Topical irrigation with 80 mg/L gentamicin or tobramycin can also be useful for this purpose.[87] Most studies reported a low rate of side effects. Twice-daily irrigation with gentamicin for 3 to 15 weeks caused low but measurable systemic absorption, with blood levels ranging from 0.3 to 0.7 μg/mL.[88] Sensorineural hearing loss was noted in 23% of patients with CF who had used frequent irrigations,[89] and for this reason, the author cautions against use of aminoglycosides for chronic administration, especially greater than once daily. Topical antibiotics can be administered with or without a nebulizer. Delivery of antibiotic to the sphenoethmoidal region is challenging and contraindicated with aminoglycosides because of potential ototoxicity.

Antifungal treatment. A double-blind, placebo-controlled trial of topical amphotericin B involving 24 patients treated for 6 months produced a small but statistically significant improvement in sinus mucosal thickening.[90] However, a subsequent double-blind, placebo-controlled trial in Europe involving 116 patients treated for 3 months failed to show efficacy over placebo.[91] Suboptimal delivery of a topical antifungal medication to affected sinus areas is a potential explanation for failure of antifungal treatment. However, a study of oral terbinafine given at a dose of 625 mg daily versus placebo also failed to show efficacy in terms of symptomatic or radiographic improvement for the treatment of CRS in a 12-week randomized controlled clinical trial of 56 patients.[92] Therefore the published clinical trials of antifungal treatment fall short of providing compelling proof for the "fungal hypothesis" of CRS pathogenesis. A major limitation of these trials, however, is the lack of demonstration that antifungal treatment actually reduces the burden of colonizing fungi.

Antileukotriene treatment. Antileukotriene agents can be used as an adjunct to topical glucocorticoids in the treatment of CRSwNP.[93-95] Small randomized trials demonstrated modest benefit after 1 to 3 months of montelukast, either as monotherapy[93] or as adjunctive therapy to oral prednisolone and budesonide nasal spray.[95] Antileukotrienes might not benefit all patients with nasal polyps equally; they might be more effective in those with concomitant asthma and aspirin intolerance (ie, the syndrome of aspirin-exacerbated respiratory disease [AERD]).[96] It is unclear whether the 5-lipoxygenase inhibitor zileuton is any more effective than cysteinyl leukotriene D_4 receptor blockers (eg, montelukast or zafirlukast). Patients with AERD are recommended to receive some form of long-term antileukotriene therapy.

Aspirin desensitization and therapy. Patients with the combination of CRSwNP, asthma, and aspirin intolerance (AERD) might be candidates for aspirin desensitization, followed by daily aspirin therapy. A beneficial effect of aspirin desensitization on NP had been noted by several groups.[97-100] Aspirin desensitization requires close monitoring for bronchospasm and is usually conducted by a specialist in drug desensitization.

Long-term aspirin therapy has been shown in retrospective studies to reduce upper and lower airway inflammation in some patients, although it is rarely sufficient as monotherapy. Gastrointestinal side effects from daily oral aspirin therapy preclude long-term treatment in some patients. The initial maintenance dose of aspirin has traditionally been 650 mg twice daily, but recent studies recommend attempting to lower the dose to 325 mg twice daily for long-term maintenance.[101]

Treatment of underlying allergic rhinitis. Patients with underlying allergic rhinitis might additionally benefit from a daily, nonsedating second-generation antihistamine, particularly

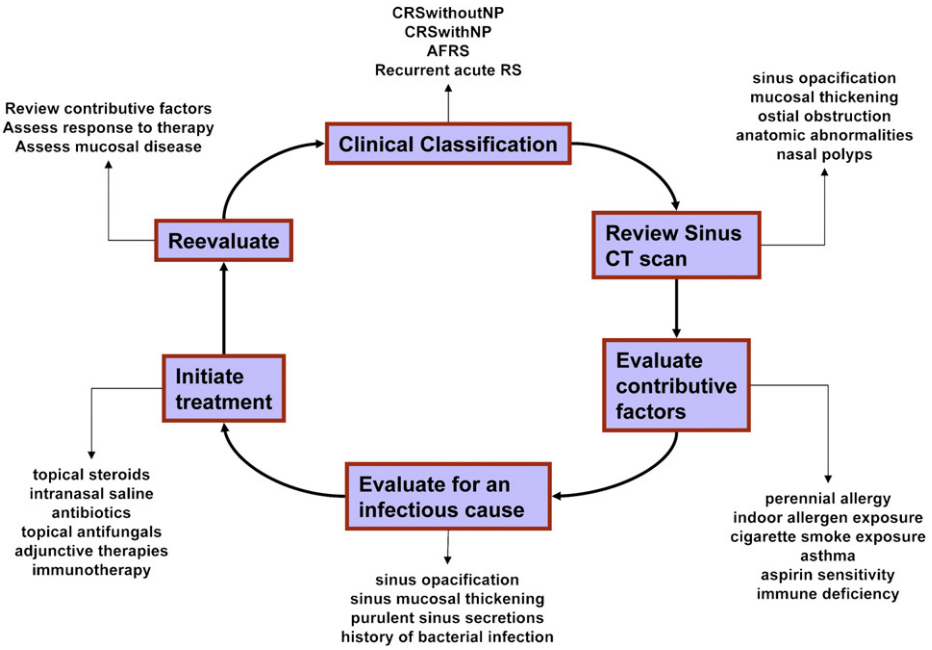

FIG 1. Stepwise evaluation of the patient with CRS. *RS,* Rhinosinusitis.

if sneezing and rhinorrhea are present.[102] Allergen remediation measures in the home or workplace and specific allergen immunotherapy to reduce sensitivity to specific allergens can help reduce mucosal edema over time.

Adjunctive therapies. Chronic use of oral decongestants is generally not recommended for maintenance treatment because of concerns about increasing blood pressure and lack of supportive clinical evidence. There is little evidence supporting use of mucolytics; however, a recent study found that S-carboxymethylcysteine in combination with clarithromycin was more effective than clarithromycin alone.[103] Furthermore, a pilot cross-over study reported that nebulized dornase alfa improved SNOT-20 scores in 5 patients with CF, whereas physiologic (0.9%) saline did not.[104]

Evaluation of the patient with CRS

Evaluation of the patient with CRS has been reviewed in detail elsewhere[79,105] and is summarized in Fig 1. Treatment guidelines assume that each patient with CRS has first undergone a comprehensive evaluation, including assessment of the extent of sinus disease either by means of imaging studies or nasal endoscopy. The role of fiberoptic nasal endoscopy in the evaluation and management of CRS was recently reviewed.[73]

CRS TREATMENT*

Overview

Several recent consensus documents have been published addressing CRS.[65,70,106-108] Each acknowledges the lack of controlled treatment trials for CRS. As a result, treatment recommendations are based heavily on expert opinion rather than high-grade clinical evidence. Presently, there are no US Food and Drug Administration–approved treatments for CRS, and intranasal mometasone furoate is the only US Food and Drug Administration–approved therapy for treatment of NP.

The most comprehensive treatment recommendations for CRS are put forth in the EP3OS guidance document.[106] Recommendations are given for CRS subtypes and stratified further according to disease severity, as summarized below. The other guidance documents do not distinguish CRS subtypes, provide less information regarding treatment, or both.

Treatment guidelines based on CRS subsets and disease severity (EP3OS guidelines)

CRSsNP. In the EP3OS guidelines[106] for mild symptoms (visual analog scale [VAS] score, 0-3), the initial management consists of intranasal corticosteroids along with nasal saline lavage. If these fail to improve the condition after 3 months, culture should be performed and long-term macrolide therapy instituted; CT scanning might be useful at this stage. Lack of response to this strategy after another 3 months should prompt further evaluation with CT scanning and consideration of sinus surgery. In patients who respond, continued use of intranasal corticosteroids and nasal saline lavage is recommended with or without long-term macrolide therapy. For moderate/severe symptoms (VAS score, >3-10), initial management includes intranasal corticosteroids, nasal saline lavage, culture, and long-term macrolides. Failure to respond after 3 months warrants further evaluation with CT scanning and surgical workup.

CRSwNP. EP3OS guidelines for managing CRSwNP are generally similar to those for CRSsNP, with the notable exception that antibiotics are not recommended for CRSwNP. For symptoms of mild severity (VAS score, 0-3), treatment with an intranasal corticosteroid is recommended. For patients whose symptoms do not improve within 3 months, a short course of oral steroids for 1 month is recommended. If this is unsuccessful, CT scanning is recommended, and the patient should be evaluated as a potential surgical candidate.

*Adapted from a recent publication: Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. Mayo Clin Proc 2011;86:427-3.

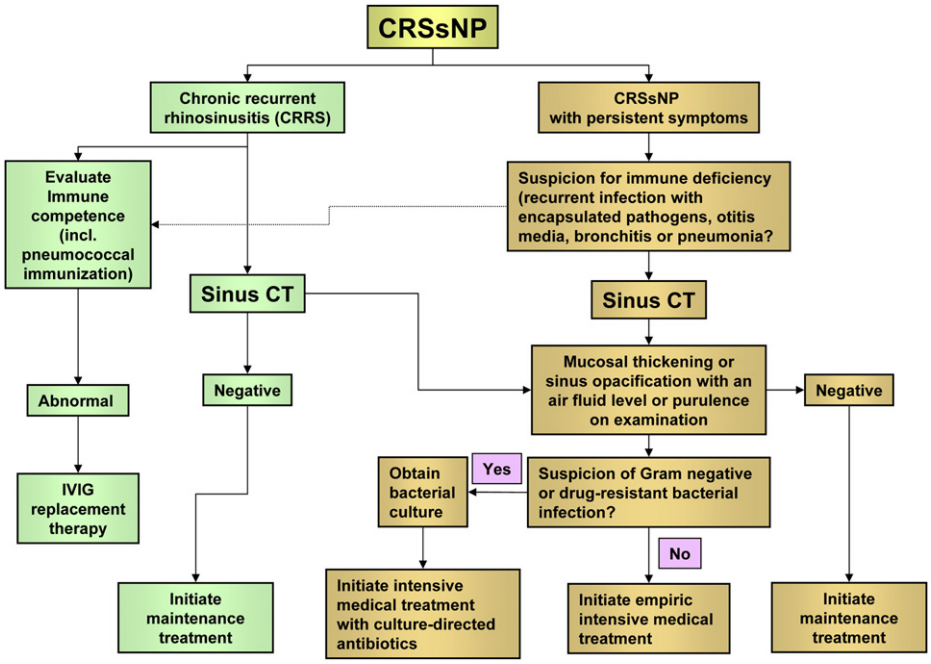

FIG 2. Evaluation and management of the patient with CRSsNP. *IVIG*, Intravenous immunoglobulin. Reproduced with permission from Mafee.[118]

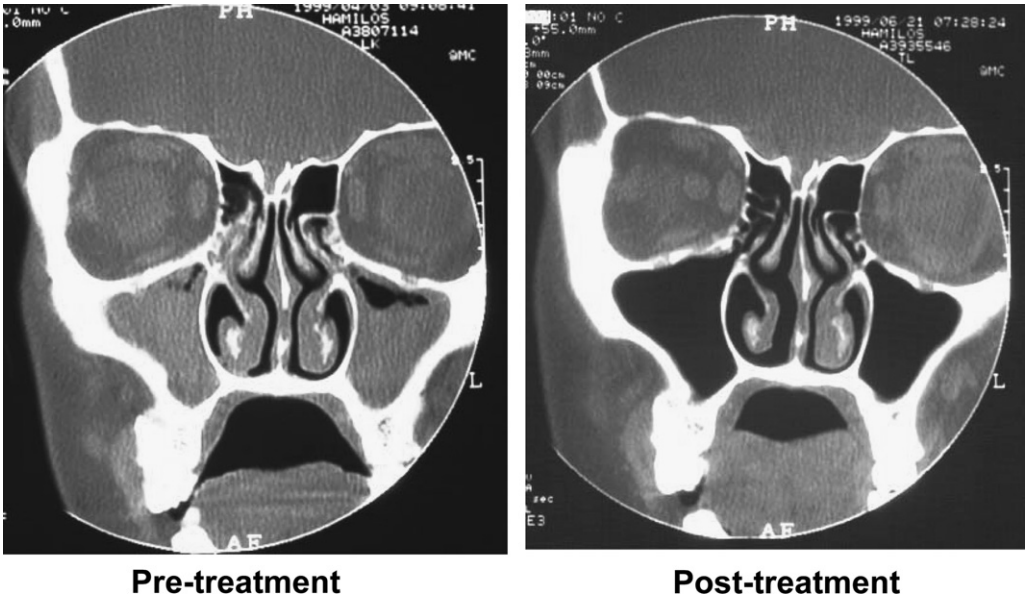

FIG 3. Example of a patient with CRSsNP who received "intensive medical treatment" with antibiotics plus oral steroids. The *left* and *right panels* show the pretreatment and posttreatment sinus CT scans. Reproduced with permission from Subramanian et al.[109]

For symptoms of moderate severity (VAS score, >3-7), topical corticosteroid drops are recommended initially for 3 months. If there is no improvement after the initial 3 months, a short course of oral corticosteroids can be added for 1 month. If this strategy fails, CT scanning is recommended, and the patient should be evaluated as a potential surgical candidate. If improvement is noted after the 1-month oral corticosteroid course, the patient can be switched back to topical corticosteroid drops.

Severe cases of CRSwNP (VAS score, >7-10) should initially be managed with a short course (1 month) of oral corticosteroids in combination with topical corticosteroids. Patients who show improvement on this regimen might be switched to topical corticosteroids alone. Patients who do not initially improve should be evaluated by means of CT scanning and considered for surgical intervention. After polypectomy, maintenance treatment with intranasal corticosteroids is generally recommended.

AFRS. EP3OS guidelines do not provide a detailed treatment algorithm for AFRS. Surgery is indicated as first-line treatment, along with topical or systemic antifungal drugs.[106]

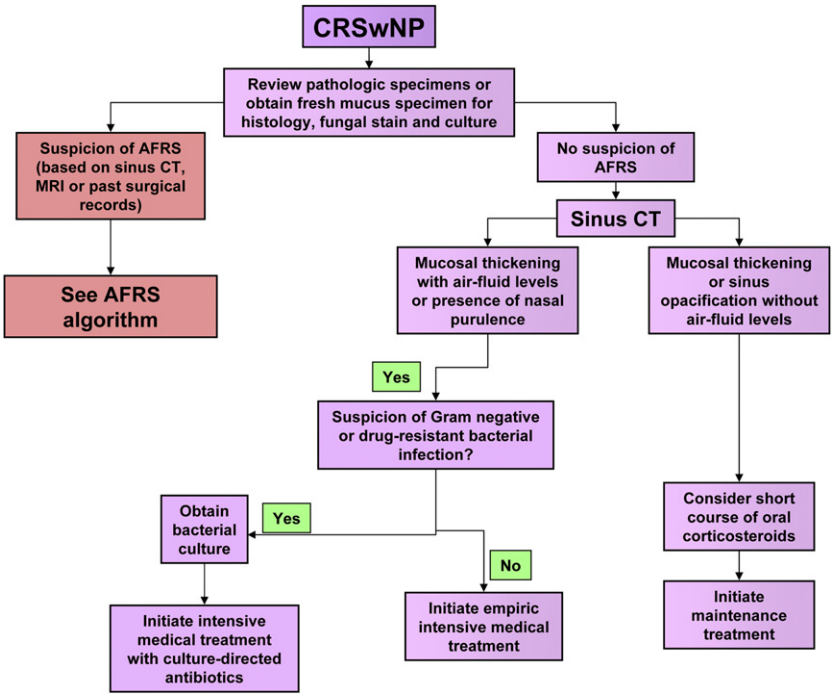

FIG 4. Evaluation and management of the patient with CRSwNP. *MRI,* Magnetic resonance imaging. Reproduced with permission from Mafee.[118]

Treatment guidelines based on CRS subtypes and author's experience

Evaluation and management of CRSsNP, CRSwNP and AFRS is summarized below and schematized in Figs 2 to 4.

The patient with CRSsNP. The characteristic presentation of CRSsNP is that of persistent symptoms with periodic exacerbations characterized by increased facial pain/pressure, increased anterior or posterior drainage, or both. Fatigue is a frequent accompanying symptom. Fever is usually absent or low grade. A subset of patients has recurrent acute rhinosinusitis symptoms, which respond well to antibiotic treatment. Such patients might be completely symptom-free between episodes or have persistent symptoms characteristic of CRSsNP (Fig 2).

The diagnostic modality of choice is the sinus CT scan.[107] Although some consensus reports reserve the sinus CT scan for patients in whom an initial attempt at medical therapy does not succeed, it is acknowledged that the predictive value of CRS symptoms for objective evidence of CRS by nasal endoscopy or sinus CT scanning is low.[4] Therefore a CT scan is often helpful in establishing the diagnosis of CRS or excluding it and avoiding unnecessary antibiotic treatment.

Intensive medical treatment

For patients with symptoms and objective CT findings of CRSsNP who have not received treatment in the immediate past, initial "intensive medical treatment" is recommended consisting of a brief course of systemic glucocorticoids combined with a prolonged course of oral antibiotics and 1 or more adjunctive therapies. This approach is based on a retrospective analysis of outcomes after intensive medical treatment in which it was found that the majority of patients with CRSsNP improved symptomatically and radiographically (Fig 3).[109] In a retrospective series of children with CRS, oral glucocorticoids alone, but not antibiotics alone, led to significant radiologic improvement.[110]

The typical regimen includes oral prednisone (in adults), 20 mg twice daily for 5 days, followed by 20 mg daily for 5 days (ie, total of 10 days of treatment) plus 3 to 4 weeks of oral antibiotics (see below). This can be extended for up to 6 weeks (or for 7 days after symptoms have cleared) in patients with colored secretions that are improving gradually but have not cleared.[111] In addition, topical intranasal steroids and saline lavage are recommended as in EP3OS.

When possible, the choice of antibiotic treatment should be guided by cultures of purulent mucus obtained from the middle meatus or another accessible sinus ostium. This is especially important where there is a suspicion for infection with a gram-negative or drug-resistant organism. In the unoperated patient the choice of antimicrobial agent is usually made empirically. The antibiotic should be effective against the most likely bacterial causes, including both aerobic (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*) and anaerobic (*Fusobacterium nucleatum*, pigmented *Prevotella* species, *Porphyromonas* species, and *Peptostreptococcus* species) pathogens. If there are risk factors for methicillin-resistant *S aureus* (eg, frequent antibiotic use, especially in children),[112] a sinus culture should be strongly considered before initiation of antibiotic treatment.

Amoxicillin-clavulanate is an excellent choice for most patients. For patients with penicillin allergy in whom methicillin-resistant *S aureus* is not suspected, monotherapy with clindamycin or moxifloxacin could be considered. The following regimens cover aerobic and anaerobic organisms with a single preparation:

- amoxicillin-clavulanate (in children, 45 mg/kg per day divided every 12 hours; in adults, 500 mg 3 times daily or 875 mg twice daily or 1000-mg extended-release tablets twice daily);

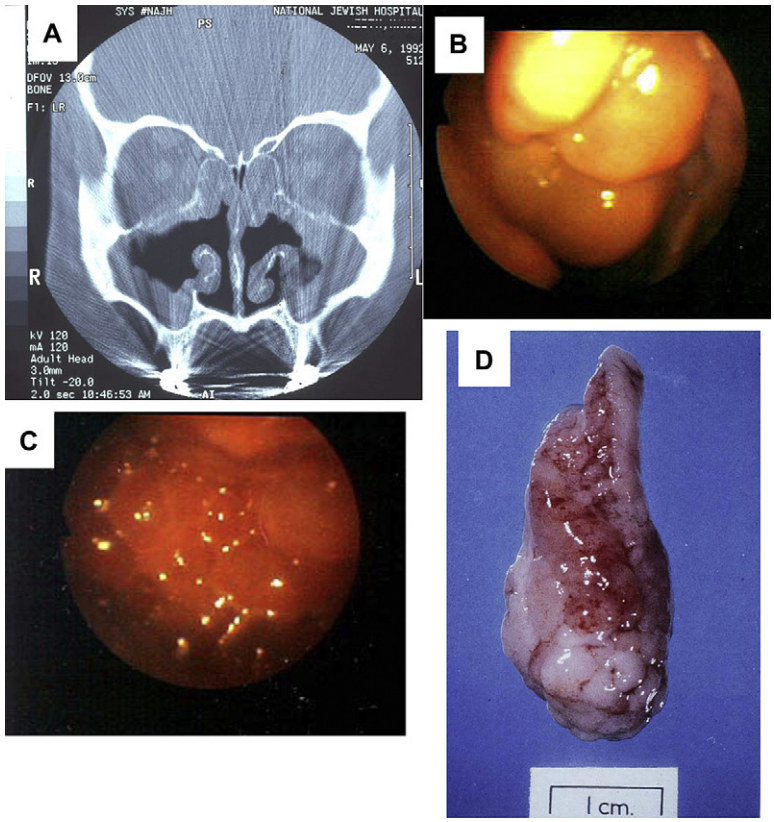

FIG 5. Typical features of CRSwNP. **A,** Coronal sinus CT scan showing extensive polypoid mucosal thickening in the anterior ethmoid and maxillary sinuses bilaterally. The patient had previous FESS. **B,** Regrowth of polypoid tissue (ie, polyps) in the anterior ethmoid sinus viewed endoscopically. **C,** Polypoid tissue in the maxillary antrum viewed endoscopically. **D,** Gross appearance of nasal polyp removed from 1 nasal cavity.

- clindamycin (in children, 20-40 mg/kg per day orally divided every 6 to 8 hours; in adults, 300 mg 4 times daily or 450 mg 3 times daily); and
- moxifloxacin (400 mg once daily) generally in adults only.

Alternatively, metronidazole (for coverage of anaerobes) can be combined with cefuroxime axetil, cefdinir, cefpodoxime proxetil, levofloxacin (recommended for adults only), azithromycin, clarithromycin, or trimethoprim-sulfamethoxazole.

Empiric antibiotic treatment is not recommended if the patient has recently experienced failure of antibiotic treatment with a similar regimen; the patient has a history of infection with gram-negative or methicillin-resistant *Staphylococcus* species or another highly drug-resistant bacteria; there is clinical suspicion that the patient has AFRS; the patient is immunosuppressed and considered at risk for invasive fungal rhinosinusitis; or the patient has signs of extrasinus involvement or appears toxic.

In patients with a partial or unsustained response to intensive medical treatment, a second course of empiric treatment might be considered, but the likelihood of success after such treatment is less than that with the initial course. Sinus surgery should be considered for patients whose condition does not stabilize despite intensive medical treatment.

Maintenance treatment

The EP3OS guidelines are recommended with the exception that the author considers long-term macrolide treatment optional because of the limited data supporting its efficacy. The efficacy of glucocorticoid nasal sprays was evaluated in a trial of 167 patients with CRS and persistent symptoms despite 2 weeks of oral antibiotics in which subjects were randomized to budesonide nasal spray (128 μg twice daily) or placebo for 20 weeks.[69] The active therapy significantly reduced both morning (−1.40; 95% CI, −2.18 to −0.62) and evening (−1.37; 95% CI, −2.15 to −0.58) symptom scores from baseline compared with placebo, with the greatest effect in patients with underlying allergic rhinosinusitis. For patients who have persistent symptoms despite consistent use of glucocorticoid nasal sprays, switching to nasal glucocorticoid instillations could be considered.

The patient with CRSwNP. The usual patient with CRSwNP is bothered mostly by nasal congestion, vague facial or sinus fullness, postnasal drainage, and anosmia/hyposmia and lacks features of acute or chronic infection (Fig 4). Nasal polyps should be evident on sinus CT or endoscopically (Fig 5). If previous surgical specimens show evidence for fungi or the sinus CT shows hyperdensities, AFRS should be ruled out (see below). Assuming the patient does not have facial pain/pressure or purulent drainage, bacterial infection is unlikely, and initial treatment focuses on establishing a regimen that reduces mucosal inflammation and regresses nasal polyps. However, if the patient with CRSwNP has nasal purulence (best detected by nasal endoscopy), intensive medical treatment, including both oral steroids and oral antibiotics, is recommended (as in CRSsNP above).

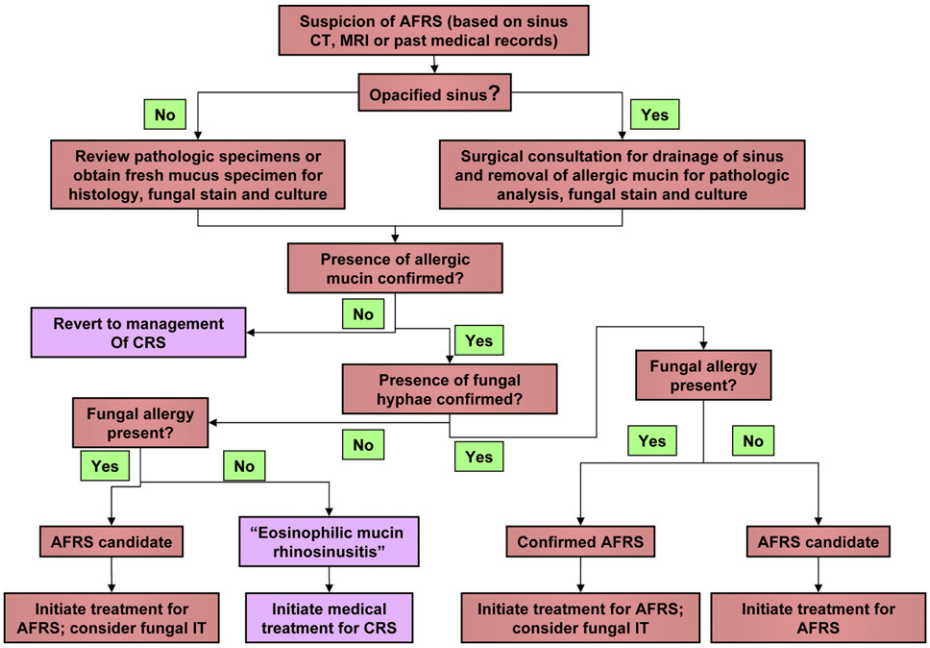

FIG 6. Evaluation and management of the patient with AFRS. *IT,* Immunotherapy; *MRI,* magnetic resonance imaging. Reproduced with permission from Mafee.[118]

Initial treatment. Initial treatment is intended to reduce the size and extent of nasal polyps and control mucosal inflammation. Assuming the patient does not have facial pain/pressure or purulent drainage, bacterial infection is unlikely, and initial treatment consists of a brief course of oral glucocorticoids (see the "Medical treatment of CRS" section). Topical steroids are begun simultaneously.

Maintenance treatment. The mainstay of maintenance treatment is topical glucocorticoids.[65,113] Randomized trials have demonstrated that these agents are effective when delivered either by means of intranasal spray[77,114] or intranasal instillation.[78] Topical glucocorticoids are also helpful in preventing the regrowth of nasal polyps after sinus surgery.[115]

Mucosal colonization with *S aureus* has been found in 64% of patients with CRSwNP compared with roughly 30% of healthy subjects or patients with CRSsNP. In addition, IgE antibodies directed against staphylococcal superantigens have been found in the tissues of a high percentage of colonized polyposis patients. On the basis of these observations, a randomized, double-blind, placebo-controlled trial was conducted to assess whether doxycycline could reduce nasal polyp size and provide anti-inflammatory effects.[116] Doxycycline (200 mg on the first day followed by 100 mg once daily for 20 days) caused a small but statistically significant reduction in polyp size beginning at week 2 and persisting for 12 weeks. A significant reduction in nasal secretion of eosinophil cationic protein was also found after 20 days of doxycycline treatment. However, doxycycline caused no statistically significant improvement in nasal peak inspiratory flow rate.

Use of antileukotrienes and aspirin desensitization was discussed previously (see the section on specific treatments). Sinus surgery should be considered for the patient with CRSwNP whose condition does not stabilize despite intensive medical treatment.

The patient with AFRS. AFRS (Fig 6) should be suspected when an immunocompetent patient has the following objective findings[117]:

1. One or more opacified sinus cavities despite extensive medical therapy, including use of both antibiotics and oral glucocorticoids: This is the least specific finding for AFRS.
2. Characteristic CT hyperdensities within the opacified sinuses, which suggest accumulated allergic mucin (Fig 7): Hyperdensities on CT are not entirely specific for AFRS and are not required to make the diagnosis. Furthermore, the presence of allergic mucin alone is neither highly sensitive nor specific for AFRS and can be seen in other subtypes of CRS.[118]
3. Evidence of IgE-mediated allergy to fungus by means of skin testing or *in vitro* immunoassays: Both epicutaneous (ie, prick/puncture), and intradermal test results are relevant.[119] Most patients with AFRS show allergy to more than 1 fungus, although sensitization to multiple fungi is not required for the diagnosis.

Patients should fulfill all 3 of the criteria above to receive a diagnosis of AFRS. In addition, uncontrolled diabetes mellitus or other immunodeficiency states should be excluded, and there should be no evidence of invasive fungal disease. AFRS usually presents subtly, with symptoms similar to CRSwNP. Patients might describe semisolid nasal crusts that are similar in appearance to allergic mucin.[107] Fever is uncommon. Occasionally, AFRS presents dramatically with complete nasal obstruction, gross facial asymmetry, and/or visual changes.

Because none of these findings is specific for AFRS, establishing the diagnosis almost always requires surgery to confirm the presence of allergic mucin (which typically is thick, inspissated, and light tan to brown to dark green in color). This mucus should be examined pathologically for degranulating

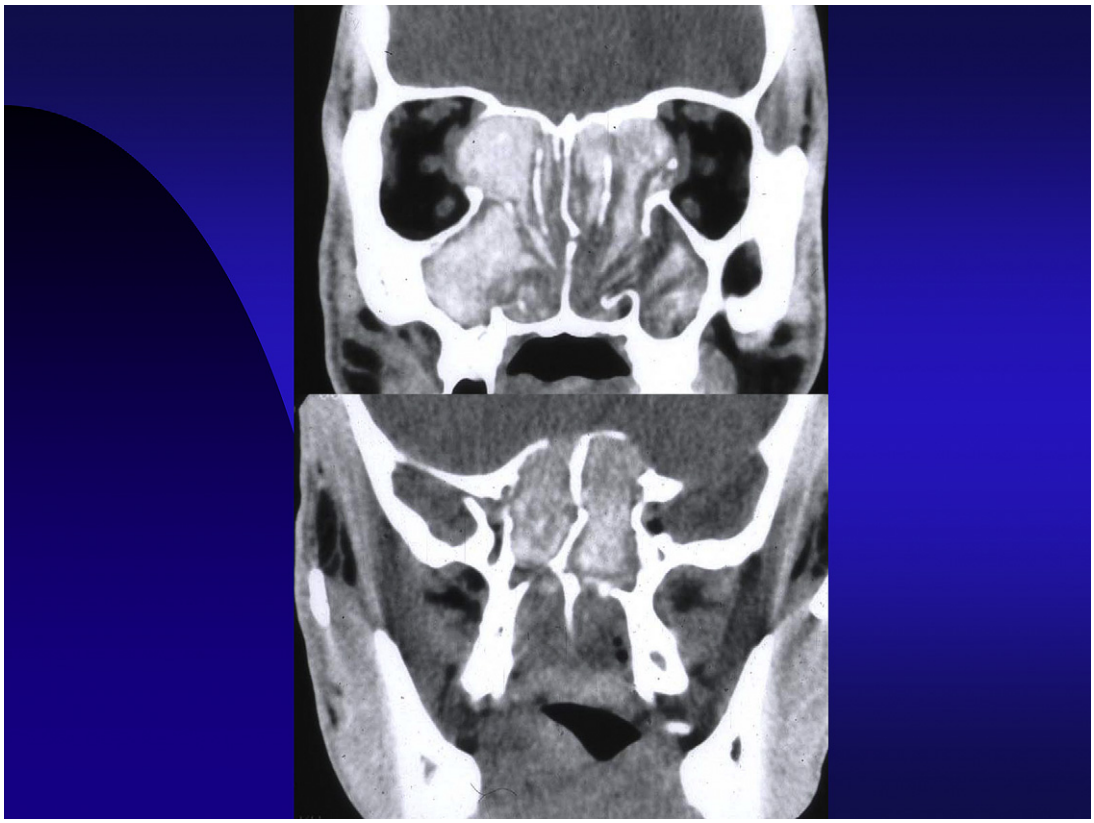

FIG 7. AFRS. Coronal CT scans showing opacified nasal cavities and paranasal sinuses. Note the "hyperdensities" within the opacified sinuses, as well as local and linear areas of increased density within the nasal cavities. Note also expansion of the right ethmoid caused by mucocele formation. Reproduced with permission from Mafee.[118]

eosinophils. The presence of fungi in the mucin should be demonstrated by staining or culture,[120] but the pathology of sinus tissue should not show fungal invasion. Biopsy of mucosal tissue characteristically shows features of CRSwNP, including an infiltration with mixed mononuclear cells and abundant eosinophils. Another laboratory feature of patients with AFRS is an increase in total serum IgE levels. In one study of 99 patients with either AFRS or CRS, total IgE levels in patients with AFRS were significantly higher than in those with CRS (mean levels, 1146 vs 247 kU/L, respectively).[121]

Some cases of CRS have allergic mucin but lack the other features of AFRS. These have been labeled "eosinophilic mucin rhinosinusitis" by some authors.[122] When the patient has allergic mucin and evidence of fungal allergy but no fungi by staining or culture, the patient can be considered to be an "AFRS candidate."[117]

Initial treatment. Patients with AFRS usually require surgery to remove inspissated mucus and maximize sinus ventilation and drainage. The removed material should be cultured for fungus. If a specific fungal species is detected, evidence of fungal-specific IgE against this organism should be sought with skin testing or fungus-specific IgE RAST testing.

Systemic steroids are also advocated in the initial treatment of AFRS (usually associated with presence of nasal/sinus polyposis). The study by Landsberg et al[123] showed that treatment with 1 mg/kg prednisone for 10 days before sinus surgery caused a significant improvement in magnetic resonance imaging scan Lund-MacKay scoring and "normalization" of sinus mucosal appearance in patients with AFRS.

Patients should receive oral glucocorticoids after surgery.[124] In a retrospective series of 67 postsurgical patients, protracted courses of oral prednisone delayed the need for repeat surgery.[125] Prednisone is usually started at 0.5 mg/kg daily and tapered over a few weeks to approximately 10 mg daily. Thereafter, the dose is slowly reduced by 1 to 2.5 mg/wk to the lowest possible dose necessary to maintain control of sinus symptoms.

Maintenance treatment. As soon as the sinus mucosa has healed after sinus surgery, topical glucocorticoid instillations with budesonide are begun (see the section on specific treatments). Although there are no controlled studies using this approach, it has been highly effective in the author's experience.

The consensus guidelines do not advocate use of oral or topical antifungal agents because there are no trials demonstrating benefit. However, in the author's experience some patients respond to this treatment. The rationale for systemic antifungal treatment is to facilitate stabilization of marked sinus inflammation and reduce long-term use of systemic glucocorticoids. The author has administered 200 mg twice-daily oral itraconazole to adults for 3 to 6 months with monitoring of aspartate aminotransferase and alanine aminotransferase levels monthly during treatment. Once stabilized, an attempt should be made to wean the patient from oral antifungal agents and maintain with topical glucocortocoid irrigations.

Surprisingly, there are no published studies of topical antifungal treatment for AFRS; however, there is rationale for their use. In the author's experience topical amphotericin B or itraconazole should be considered optional unproved treatments for AFRS.

Immunotherapy for fungal allergy. Fungal immunotherapy with a mixture of fungal allergens based on the results of skin testing or *in vitro* testing has been shown to be safe, with evidence for reduced rates of disease recurrence in treated patients.[126] However, the magnitude of effect relative to glucocorticoids is unclear.

Indications for sinus surgery. CRS is an inflammatory disorder of the sinonasal mucosa, and surgery should not be the first intervention in most cases, with the possible exception of AFRS. Functional endoscopic sinus surgery (FESS) is so named because it is intended to restore physiologic sinus ventilation and drainage. Absolute indications for FESS in children include the following[106]:

1. complete nasal obstruction in CF caused by massive polyposis or caused by medialization of the lateral nasal wall;
2. orbital abscess;
3. intracranial complications;
4. antrochoanal polyp;
5. mucocoeles or mucopyocoeles; and
6. fungal rhinosinusitis.

Possible indications include CRS with frequent exacerbations persisting despite optimal medical management and after exclusion of any systemic disease. FESS should be followed by medical management to control mucosal inflammation, or symptoms will invariably return.[127] This is particularly true for surgical polypectomy; polyps usually reaccumulate within a few years without medical maintenance therapy.[127,128] FESS is indicated in cases of AFRS to (1) restore sinus ostial patency and ventilation, (2) establish the diagnosis, and (3) remove inspissated allergic mucin. Bony erosion would be another indication for surgery, given that it signifies extension of disease beyond the sinus cavities.

Outcomes of sinus surgery. The outcomes of FESS have been evaluated in several studies.[129,130] One of the most comprehensive studies summarized the outcomes of 120 consecutive patients with a mean follow-up of 18 months.[129] Nearly all patients (98%) reported improvement in their CRS symptoms at the time of final follow-up visit (85%, 13%, and 2% were markedly, mildly, and not improved, respectively). However, 45% of the sinus cavities undergoing operations were endoscopically abnormal at the end of the study. The phenotype of CRS appeared to influence surgical outcome because patients with advanced polypoid changes preoperatively had a much higher rate of recurrence of disease and relapse after surgery. In a subsequent survey of 72 patients from the original cohort with an average follow-up of 7.8 years postoperatively, 98% of the patients reported sustained subjective improvement.[130]

There is some evidence that medical management results in improved long-term outcomes comparable with those derived from FESS.[66] There is also evidence that the combination of FESS, careful postoperative care, and medical management result in improvement in favorable long-term effects on both CRS and asthma.[131]

What do we know?

- **Chronic sinusitis is the second most prevalent chronic health condition, affecting 12.5% of the US population or approximately 31 million patients each year.**
- **On epidemiologic grounds, some association has been found between CRS prevalence and air pollution, active cigarette smoking, SHS exposure, perennial allergic rhinitis, and gastroesophageal reflux.**
- **A direct relationship was found between the prevalence of sinusitis and pollutant levels of carbon monoxide, nitrous dioxide, sulfur dioxide, and particulate matter.**
- **The prevalence of IgE-mediated allergy to environmental allergens in patients with CRS (both with and without NP) is estimated at 60% compared with 30% to 40% for the general population.**
- **AFRS is distinct among the CRS subtypes in having a significant geographic distribution of disease.**
- **Current consensus definitions subclassify CRS into CRSsNP, CRSwNP, and AFRS.**
- **The highest level of evidence for treatment for CRSsNP exists for saline lavage, intranasal steroids, and long-term macrolide antibiotics.**
- **The highest level of evidence for treatment of CRSwNP exists for intranasal steroids, systemic glucocorticoids, and topical steroid irrigations.**
- **Aspirin desensitization is also beneficial for patients with aspirin-intolerant CRSwNP.**
- **Sinus surgery followed by use of systemic steroids is recommended for AFRS.**

What is still unknown?

- **The underlying genetic associations with CRS are largely unknown.**
- **There is little known about the role of local innate immune deficiency as a possible cause of CRS.**
- **There is still a paucity of data on clinical treatment trials of CRSsNP, CRSwNP, and AFRS.**
- **A role for systemic or topical antifungal drugs as a treatment for CRS remains unproved.**

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