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Chronic sinusitis

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Sinusitis is a very common chronic illness with a substantial health care impact. This review focuses on factors contributing to sinusitis pathogenesis and chronicity, including anatomic factors, disturbances in mucociliary clearance, microbial pathogens, and inflammatory factors. A distinction is made between “infectious” and “noninfectious” types of inflammation in chronic sinusitis. The inflammatory characteristics of noninfectious inflammation are reviewed primarily in the context of chronic hyperplastic sinusitis with nasal polyposis. Key features of this type of inflammation include the presence of chronic inflammatory cells, large numbers of eosinophils, and IL-5-producing T lymphocytes. Allergic fungal sinusitis is discussed as a special type of chronic sinusitis. Published studies on the outcomes of medical management are reviewed. Finally, algorithms for medical management of chronic sinusitis and allergic fungal sinusitis are presented. (J Allergy Clin Immunol 2000;106:213-27.)

Key words: Sinusitis, inflammation, nasal polyposis, eosinophil, fungal sinusitis

In a recent survey of practice patterns, sinusitis accounted for approximately 20% of office visits to specialists in allergy and immunology (AI). This makes sinusitis one of the most important diseases treated by AI subspecialists. Unfortunately, sinusitis is often very frustrating and difficult to treat, and medical “failures” often become surgical patients. Hence there is a strong need for greater understanding of the disease and for more effective treatments. Several recent consensus conferences have addressed this subject, summarized current definitions of acute and chronic sinusitis, and reviewed factors in sinusitis pathogenesis.¹ Rather than duplicating these efforts, the current review focuses on factors contributing to sinusitis pathogenesis and chronicity, microbial pathogens, the special case of “allergic fungal sinusitis,” and the outcomes of medical management. A suggested medical management strategy for chronic sinusitis is also presented.

Abbreviations used

ABPA:	Allergic bronchopulmonary aspergillosis
AEC:	Absolute blood eosinophil count
AFS:	Allergic fungal sinusitis
AI:	Allergy and immunology
CF:	Cystic fibrosis
CHS/NP:	Chronic hyperplastic sinusitis with nasal polyposis
CT:	Computed tomography
MRI:	Magnetic resonance imaging
mRNA:	Messenger RNA
OMU:	Ostiomeatal unit
T _H 1:	T helper type 1
T _H 2:	T helper type 2
VCAM-1:	Vascular cell adhesion molecule-1

THE IMPACT OF CHRONIC SINUSITIS

Sinusitis has a very substantial health care impact in the United States, as evidenced by an estimated \$5.8 billion expenditure in 1996.² Approximately 12% of Americans below the age of 45 years report symptoms of chronic sinusitis.³ Chronic sinusitis accounts for substantial health care expenditures in terms of office visits, antibiotic prescriptions filled, lost work days, and missed school days. Approximately 20% of patients with chronic sinusitis have nasal polyposis.⁴ There were approximately 200,000 sinus surgeries performed in the United States in 1994.¹ Chronic hyperplastic sinusitis with nasal polyposis (CHS/NP) 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.

FACTORS CONTRIBUTING TO SINUSITIS

Acute sinusitis may originate from or be perpetuated by local or systemic factors predisposing to sinus ostial obstruction and infection. These factors include anatomic or inflammatory factors leading to sinus ostial narrowing, disturbances in mucociliary transport, and immune deficiency (Fig 1). Sinus ostial narrowing may be caused by acute viral upper respiratory infection or chronic allergic inflammation. Review articles commonly list several anatomic variants that may predispose to ostiomeatal narrowing, including Haller's cells (infraorbital ethmoid cells), agger nasi cells (an anterior bulge in

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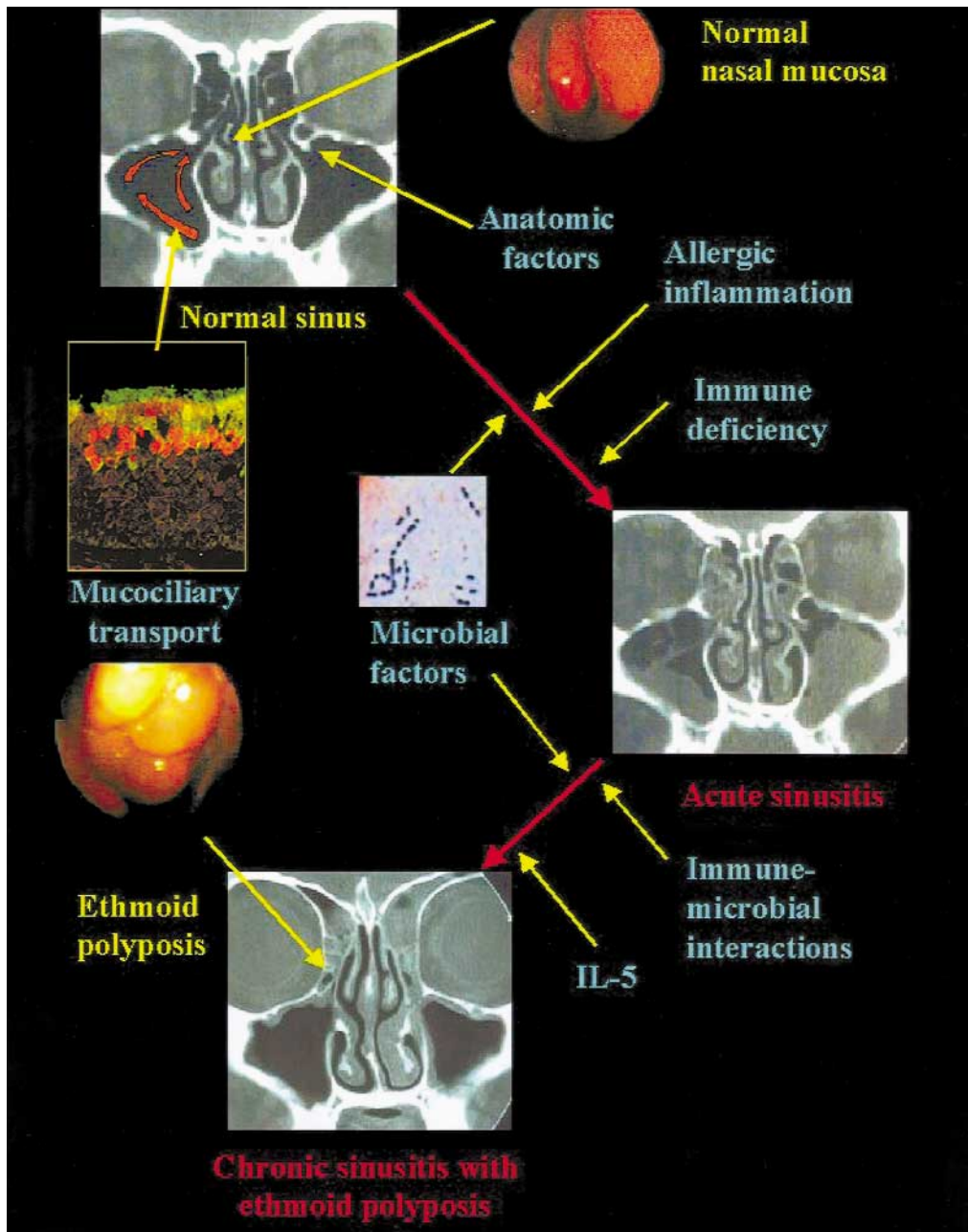


FIG 1. Acute sinusitis may originate from or be perpetuated by local or systemic factors predisposing to sinus ostial obstruction and infection. These include anatomic or inflammatory factors leading to sinus ostial narrowing, disturbances in mucociliary transport, and immune deficiency. Sinus ostial narrowing may be caused by acute viral upper respiratory infection or chronic allergic inflammation. A similar set of factors contributes to sinusitis chronicity, but in addition other aspects of the host immune-microbial interaction play a key role. The sinus mucosa normally has a pink healthy appearance (*upper inset*). In chronic sinusitis the mucosa may undergo marked inflammatory changes, sometimes leading to development of sinus or nasal polyposis (*lower inset*).

the most anterior superior insertion of the middle turbinate), paradoxical curvature of the middle turbinate, bulla ethmoidalis with apparent medial contact, deformities of the uncinate process, and concha bullosa deformity (pneumatization of the middle turbinate).⁵ However, several recent studies failed to confirm an increased incidence of sinusitis in association with most of these

anatomic deformities.⁶⁻⁹ Overall, about 40% of patients with chronic sinusitis and normal control subjects had ostiomeatal narrowing in one study.⁸ In another study anatomic variants were seen with equal prevalence in patients and control subjects, including concha bullosa deformity (54% vs 50%), paradoxical middle turbinate curvature (27% vs 22%), and Haller's cells (46% vs

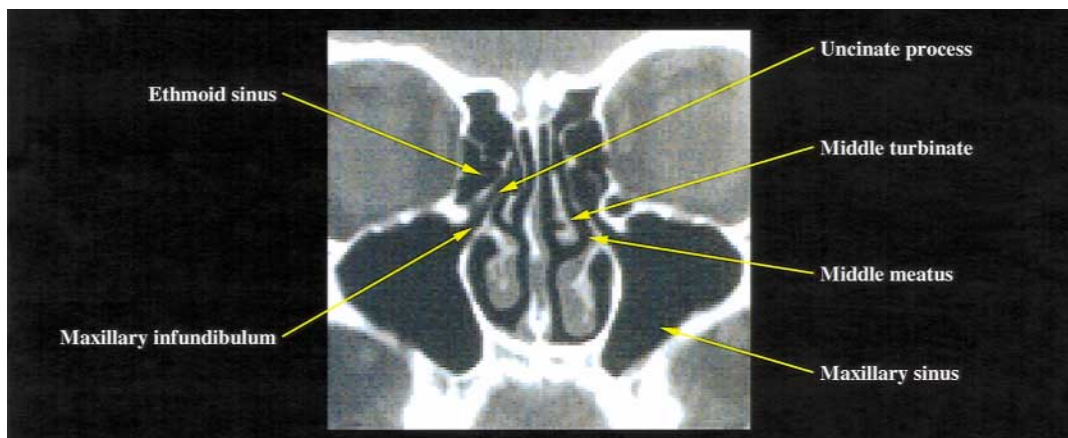


FIG 2. The normal anatomy of the OMU as seen on a limited sinus computed tomographic (CT) scan taken in the coronal projection.

42%).⁷ Disturbances in mucociliary clearance are a feature of cystic fibrosis and ciliary dyskinesia syndromes (immotile cilia syndrome). Patients with deficiencies in normal antibody production to bacterial pathogens are predisposed to sinus, ear, and respiratory tract infections, including sinusitis, otitis media, bronchitis, and pneumonia. The most common of these syndromes are selective IgA deficiency and abnormalities in production of IgG, including common variable hypogammaglobulinemia and, rarely, selective IgG subclass deficiencies. HIV-infected patients also have an increased incidence of acute sinusitis.¹⁰

FACTORS CONTRIBUTING TO SINUSITIS CHRONICITY

A similar set of factors contributes to sinusitis chronicity, but in addition other aspects of the host immune-microbial interaction play a key role.

Ostial blockage

The importance of sinus ostial patency was eloquently stated by Senior and Kennedy¹¹: "Sinus health in any patient depends on mucous secretion of normal viscosity, volume, and composition; normal mucociliary flow to prevent mucous stasis and subsequent infection; and open sinus ostia to allow adequate drainage and aeration. While defect of any of these elements can result in acute, recurrent acute, or chronic sinusitis, ostial blockage is key in the cycle for the vast majority of sinusitis in asthmatic and nonasthmatic patients alike."

The above statement applies to all sinuses, but the sinus ostia most commonly blocked are those that drain through the ostiomeatal unit (OMU). Hence the anterior ethmoid and maxillary sinuses are the most commonly affected sinus areas in both acute and chronic sinusitis. These structures are illustrated in Fig 2. Frontal sinusitis results from obstruction of the nasal frontal duct. Posterior ethmoid and sphenoid sinusitis results from obstruction of their respective ostia, which collectively drain through the sphenothmoidal recess. In chronic sinusitis inflammato-

ry mucosal thickening often persists despite treatment with antibiotics. This further impedes normal mucociliary clearance and may directly obstruct sinus ostia.

Delayed recovery of mucociliary function

Mucostasis, hypoxia, microbial products, and chronic inflammation probably all contribute to diminished mucociliary function in chronic sinusitis. Studies are conflicting on whether chronic sinusitis is associated with a significant reduction in ciliary beat frequency,¹² but a decrease in mucociliary clearance has been consistently demonstrated.¹³⁻¹⁷ Other contributing factors to slowing of clearance include changes in the viscoelastic properties of mucus, ciliary loss, and other ultrastructural signs of epithelial damage.^{13,14}

Studies performed on patients before and after surgical restoration of sinus ventilation have shown that mucociliary function improves gradually over 1 to 6 months postoperatively.^{15,16} Patients with hyperplastic sinus mucosa show a slower rate of recovery and incomplete restoration of mucociliary clearance after sinus surgery.^{13,15} These studies serve to illustrate the importance of careful medical management of patients after restoration of sinus patency by either surgical or medical treatment. The "recovery" period for mucociliary clearance clearly exceeds the period of antibiotic treatment in most cases. Hence, one reason for disease recurrence after medical or surgical treatment may be residual impairment in mucociliary clearance.

Mucus "recirculation" and osteitis

Other factors contributing to sinusitis chronicity include mucus "recirculation" and osteitis. Recirculation of sinus mucus from the maxillary sinus has been described in some patients with an accessory sinus ostium. Secretions exit the sinus through the natural sinus ostium and enter the middle meatus. Some of the secretions then re-enter the maxillary sinus through the accessory ostium, usually located inferior to the OMU on the lateral nasal wall.^{18,19} In my experience, accessory ostia to the maxillary sinus are quite common (approximately

20% of cases). Osteitis has been described by histologic analysis of ethmoid bone removed from patients with chronic sinusitis. It may occur as a direct result of infection or as a result of sinus surgery with lack of mucosal preservation.²⁰ The histologic findings include a marked acceleration in bone turnover with new bone formation, fibrosis, and the presence of inflammatory cells.²¹ It has been argued that these changes mimic osteomyelitis in the jaw and that osteitis may therefore represent a form of chronic osteomyelitis and a strong reason for disease recurrence despite surgery or antibiotic use.

Microbial factors in persistence

Most studies have pointed to differences between acute and chronic sinusitis in terms of microbial pathogens. In acute sinusitis, the predominant organisms are *Streptococcus pneumoniae*, *Hemophilus influenzae*, and (in children) *Moraxella catarrhalis*. In studies of chronic sinusitis the most common organisms identified were those described above plus *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, and anaerobic bacteria. The relative pathogenicity of the organisms in sinusitis is unknown, with the greatest uncertainty surrounding the role of coagulase-negative *Staphylococcus* and anaerobes. Relative to bacteria, much less is known about the role of viruses in chronic sinusitis pathogenesis.²²

Several factors confound microbiologic data reported in studies of chronic sinusitis. These include chronicity (duration) of the disease, prior or concurrent antibiotic use, presence or absence of prior sinus surgery, method of obtaining the sinus culture, and differences in the bacteriologic culturing techniques. These factors have impact on the divergent results that have been reported in various studies. Anaerobic bacteria are particularly difficult to culture, and special care must be taken to inoculate sinus aspirates or tissue specimens directly into anaerobic transport vessels and to culture in appropriate media to maximize the yield of anaerobic cultures.²³ It is likely that technical differences in handling of specimens account for the broad range of reported prevalence of anaerobes in chronic maxillary sinusitis aspirates that ranges from a high of 80% to 100% in some studies²⁴ and 0% to 25% in others.²⁵⁻²⁷

One study examined the microbiology of sinus aspirates taken sequentially during the transition from acute to chronic sinusitis.²⁸ Patients in this study had failed to respond to antibiotic treatment and had cultures performed sequentially over a period of 34 to 50 days after the initial infection. On the initial aspirate, *S pneumoniae*, *H influenzae*, non-type b and *M catarrhalis* were cultured. On the subsequent aspirates, a mixture of these organisms plus anaerobes, including *Fusobacterium*, *Prevotella*, *Porphyromonas*, and *Peptostreptococcus* were found. Interestingly, the aerobic organisms isolated were also found to become increasingly resistant to antibiotics. This study is interesting because it mimics the clinical scenario of patients who fail to clear from an episode of acute sinusitis. It also raises the possibility that anaerobic infection follows the initial insult of puru-

lent bacterial infection as a result of factors that favor the growth of anaerobic bacteria, namely, mucus stasis, sinus ostial obstruction, and hypoxia.

A major limitation in the treatment of chronic sinusitis is the difficulty in obtaining useful microbial cultures. Bacterial cultures are obtained in less than 5% of cases and usually only after failure of one or two courses of antibiotics. Cultures can be obtained from the maxillary sinus by direct puncture (antral or intranasal), simultaneous with endoscopic sinus surgery or directly from the middle meatus. Sinus puncture has a low likelihood of being contaminated by nasal organisms²⁹ but is an invasive procedure. One recent advance, the SinoJect (Atos Medical, Hörby, Sweden) offers the possibility of performing an antral puncture through the inferior meatus more easily and with less trauma. Cultures obtained at the time of endoscopic sinus surgery offer the advantage of direct visualization of the infected mucus or tissue. Cultures obtained in this manner have shown a high degree of concordance with specimens obtained endonasally from the middle meatus (see below).²³ Endoscopically guided aspiration cultures can be obtained directly from the middle meatus.^{30,31} The procedure requires decongestion of the nasal passage and anesthesia of the middle turbinate. In one study excellent agreement was reported between endoscopically guided aspiration cultures and those obtained by maxillary sinus puncture.³⁰

Insufficient attention has been given to the potential for emergence of antimicrobial resistance during antibiotic treatment for chronic sinusitis. As demonstrated in the study of Brook et al,³² β -lactamase-producing bacteria can emerge during antibiotic treatment during the transition from acute to chronic sinusitis. Another possibility is the emergence of intermediate- or high-level penicillin resistance during treatment. This type of resistance, resulting from alterations in penicillin-binding proteins, presently ranges from 28% to 44% for *S pneumoniae* isolates in various regions of the United States.³³ There are very limited data on the prevalence of these isolates in chronic sinusitis, but it appears that isolation of penicillin-resistant pneumococci is most commonly seen in patients with recent use of two or more antibiotics.³⁴ Many of these organisms also demonstrate multiple drug resistance.³³

Inflammatory factors in sinusitis

Inflammation plays a key role in chronic sinusitis pathogenesis. Infectious and noninfectious stimuli appear to contribute, but the precise role of each in chronic sinusitis remains unclear. Two types of inflammation occur in sinusitis, contributing variably to the clinical expression of disease (Fig 3). Infectious inflammation is most clearly associated with acute sinusitis resulting from either bacterial or viral infection. Noninfectious inflammation is so named due to the predominance of eosinophils and mixed mononuclear cells and the relative paucity of neutrophils commonly seen in chronic sinusitis.³⁵ Although its cause is unknown, it is associated with an increased presence of eosinophils and

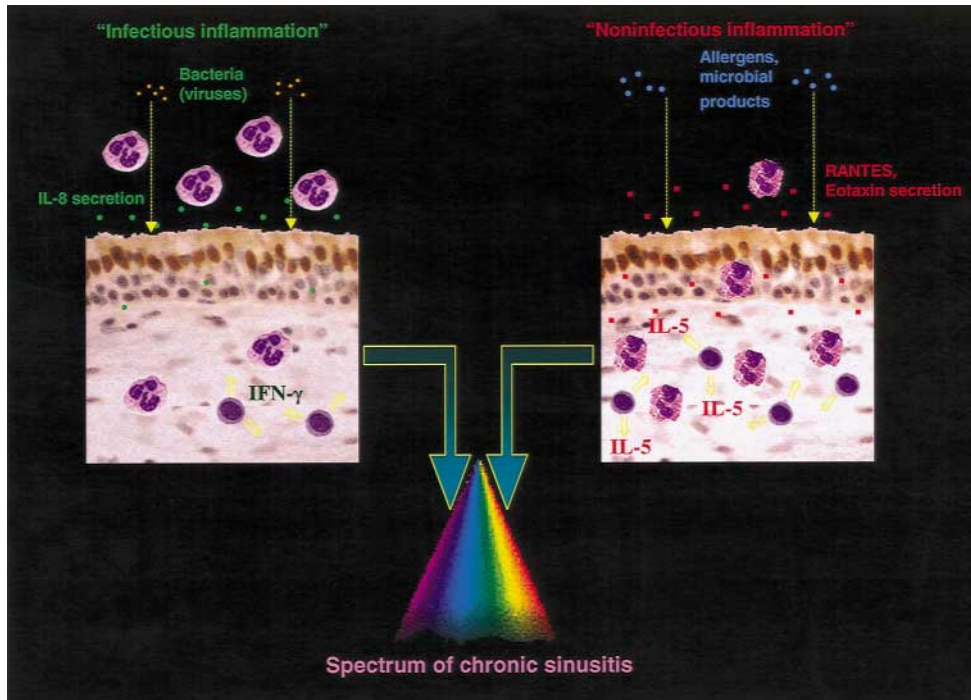


FIG 3. Two types of inflammation occur in sinusitis, contributing variably to the clinical expression of disease. Infectious inflammation is most clearly associated with acute sinusitis resulting from either bacterial or viral infection. Increased neutrophil influx into sinus secretions and IL-8 secretion has been implicated in this process. A T helper type 1 (T_H1) lymphocyte response is also likely to be involved. Noninfectious inflammation is so named because of the predominance of eosinophils and mixed mononuclear cells and the relative paucity of neutrophils commonly seen in chronic sinusitis. It is postulated that allergens and microbial products may drive this inflammatory response. It is associated with a T helper type 2 (T_H2) lymphocyte response, characterized by IL-5–producing T lymphocytes. RANTES and eotaxin secretion have also been implicated in this process. The clinical spectrum of chronic sinusitis is likely due to the variable overlap of “infectious” and “noninfectious” inflammatory components. (See text for discussion.)

IL-5–producing T lymphocytes. Noninfectious inflammation is most clearly seen in CHS/NP. The pathologic features seen in chronic sinusitis mucosa are likely the result of an overlap of infectious and noninfectious inflammatory stimuli (see Figs 1 and 3).

Understanding and differentiating infectious and noninfectious inflammatory stimuli are critical to understanding chronic sinusitis. This, however, remains enigmatic. Sinus mucosal thickening or opacification is seen throughout the clinical spectrum of chronic sinusitis, whereas nasal polyposis is more common in patients with marked hyperplastic sinus mucosa and little evidence of infection.

Infectious inflammation. Relatively little is known about the sinus mucosal response to bacterial or viral infection. The sinus mucosa is normally bathed by neutrophils even in the absence of infection. Hence passage of neutrophils into sinus secretions is probably a part of the normal mucosal response mechanism to maintain sterility of the sinus cavity. Lavage of the nasal cavity in healthy noninfected and nonallergic subjects has the following distribution of cells: epithelial cells (50%-60%), neutrophils (35%-40%), and lymphocytes, macrophages, and eosinophils (<5%).³⁶ Similar studies using puncture of the maxillary antrum followed by lavage of the maxil-

lary sinus in normal subjects have shown 63% epithelial cells, 28% neutrophils, 9% monocytes, and <1% eosinophils and mast cells.³⁷ Data from nasal and sinus lavage are in contrast to results from nasal and sinus mucosal biopsy specimens from healthy subjects because the latter show very few mucosal neutrophils.^{37,38} The cytokines or chemokines responsible for neutrophil passage into sinus secretions are unknown. However, there is evidence for a low level of IL-8 secretion.³⁹

In patients with chronic sinusitis, maxillary sinus lavage fluid contains increased numbers of neutrophils and dramatically increased IL-8 levels.³⁹ The highest levels of IL-8 and the highest percentages of lavage neutrophilia were seen in subjects classified as “nonallergic.” In contrast, patients with chronic sinusitis and associated allergic rhinitis had a modest increased percentage of neutrophils and an increase in IL-8 in the lavage fluid. In a related study Rhyoo et al⁴⁰ found increases in IL-8 by quantitative competitive PCR in sinus tissue obtained at the time of sinus surgery. A correlation was also found between the amount of IL-8 detected in the sinus tissue and the radiographic extent of disease on preoperative sinus CT scans.

Studies in patients with acute sinus infection have detected IL-1 β and IL-6 (and IL-8) in sinus tissues.⁴¹ Neutrophils were reported to be prominent in these tis-



FIG 4. An example of a case of severe chronic sinusitis treated with antibiotics but without systemic steroids for 4 weeks. The sinus CT scans, taken 5 weeks apart, show nearly complete clearing of disease in the maxillary sinuses. On the posttreatment film (right), it is apparent that the patient has had previous bilateral surgery in the OMU region. Although the patient improved symptomatically, the posttreatment CT showed marked polypoid anterior ethmoid mucosal thickening with opacification of several ethmoid cells. Failure to resolve mucosal inflammation with antibiotics alone is an argument for use of systemic steroids in the treatment of chronic sinusitis.

sues as well. In contrast, GM-CSF and IL-5 levels were not elevated. An increase in the local elaboration of IL-8, IL-1 β and IL-6 as well as TNF- α would be expected in association with bacterial infection owing to the capacity of airway epithelial cells to produce these cytokines in response to bacterial stimuli.⁴²⁻⁴⁴ Hence proinflammatory cytokines probably play an important role in acute mucosal thickening associated with sinusitis exacerbations. Dramatic reversal of mucosal thickening may also occur after antibiotic treatment for chronic sinusitis; however, some degree of mucosal thickening often persists, as shown in Fig 4.

Noninfectious inflammation. Most of the information available on "noninfectious" sinusitis comes from studies of nasal polyps, but a few studies have examined sinus mucosa and reported similar findings.^{38,45}

Chronic sinusitis inflammation can be associated with exuberant sinus mucosal thickening with little evidence for sinus pain or discomfort or other signs of infection (see Fig 6, B). For this reason, this type of inflammation has been regarded as "noninfectious." The predominant sinus symptoms may be nasal congestion, facial pressure or fullness, postnasal drainage and hyposmia, or anosmia. At the extreme of "noninfectious" chronic sinusitis, patients have extensive bilateral mucosal thickening associated with nasal polyposis and are labeled "chronic hyperplastic sinusitis with nasal polyposis" or CHS/NP. At least 50% of the patients have associated asthma, and roughly 30% to 40% of cases have associated aspirin sensitivity.^{4,46} Nasal polyposis also occurs in >20% of patients with cystic fibrosis (CF), but the pathogenesis of CF polyp formation is likely to be distinct from that of CHS/NP.⁴⁷

The cellular immunopathologic features of CHS/NP have been the focus of many studies. In comparison to normal control middle turbinate biopsy specimens, NP specimens contain a modestly increased number of inflammatory cells (CD45⁺), significantly increased numbers of eosinophils (MBP⁺ or EG2⁺), and mildly increased numbers of tryptase⁺ mast cells.^{38,48-50} The numbers of macrophages (CD68⁺), neutrophils (elastase⁺), and CD8⁺ T lymphocytes are not increased above those of controls. The numbers of CD4⁺ T lymphocytes are increased in CHS/NP subjects with positive allergy skin tests ("allergic CHS/NP") but not in subjects with negative skin tests ("nonallergic CHS/NP"). Altogether, between one half and two thirds of patients with CHS/NP are nonallergic on the basis of the results of allergy skin tests.^{38,46,51} The levels of tissue eosinophilia are equal in allergic and nonallergic CHS/NP. The cellular features of NP are similar to those described in asthma, with the exception that CD4⁺ T lymphocytes have been found to be increased in both allergic and nonallergic asthma.^{52,53}

Our group found that cytokines promoting the activation and survival of eosinophils, namely, GM-CSF, IL-3, and IL-5, were present in abundance in NP.^{38,48,50} The numbers of eosinophils in NP correlated with the density of GM-CSF and IL-3 mRNA⁺ cells in both allergic and nonallergic CHS/NP.³⁸ It is likely that much of the GM-CSF messenger RNA (mRNA) produced in NP represents autocrine production in eosinophils.⁵⁴ On the other hand, most of the IL-5 produced in NP appears to come from T cells. We found that T cells accounted for roughly 68% of the IL-5-positive cells in both allergic and nonallergic CHS/NP.⁵⁰ The remainder of the IL-5 was produced by eosinophils (18%) and mast cells (14%).

We described mechanisms leading to selective eosinophil accumulation in CHS/NP, namely, the expression of vascular cell adhesion molecule-1 (VCAM-1) and local production of C-C chemokines. VCAM-1 mediates selective eosinophil and lymphocyte transendothelial migration through interaction with its counterligand, very late activation antigen-4, which is expressed on eosinophils and lymphocytes but not neutrophils.⁵⁵⁻⁵⁷ With use of immunocytochemistry, we found that the mean intensity of VCAM-1 expression on vascular endothelium was significantly increased in CHS/NP compared with control middle turbinate biopsy specimens.⁴⁹ The density of endothelial VCAM-1 staining in CHS/NP correlated with the number of TNF- α mRNA⁺ cells present. We also found that the C-C chemokines RANTES and eotaxin were strongly expressed in CHS/NP, particularly in epithelial cells and in some submucosal inflammatory cells.^{49,58} These C-C chemokines facilitate the transendothelial migration of eosinophils and their movement into the epithelium. Increased mRNA expression of IL-8, a C-X-C chemokine, has also been reported in NP by others.⁵⁹

Different patterns of chronic sinusitis immunopathologic features have been found in allergic and nonallergic patients. In our studies of CHS/NP, patients were divided into "allergic" and "nonallergic" subgroups on the basis of the results of allergy skin testing. Allergic patients had one or more positive skin tests on a broad panel of prick and intradermal skin tests. These patients manifested increased expression of T_H2 cytokines IL-4, IL-5, and IL-13 mRNA and very little expression of IFN- γ mRNA.^{38,48,49} These findings are suggestive of chronic allergen exposure. In contrast, nonallergic patients showed no increase in expression of IL-4 or IL-5 mRNA, a modest increase in IL-5⁺ immunostaining T cells, and increased expression of IL-13 and IFN- γ . Hence the cytokine profile of nonallergic CHS/NP represents a mixture of T_H1 and T_H2 cytokines. Evidence of a T_H1 cytokine response in NP has also been reported by others.^{60,61} Increased production of IL-5 was a shared feature of allergic and nonallergic CHS/NP, and locally produced IL-5 was subsequently demonstrated to be the principal eosinophil survival-enhancing cytokine in NP.⁶² Interestingly, the intensity of tissue infiltration with eosinophils was similar in allergic and nonallergic CHS/NP.

In a study of chronic sinusitis without nasal polyps, Demoly et al^{37,39} subgrouped patients into "chronic sinusitis with allergic rhinitis" and "chronic sinusitis with nonallergic rhinitis." Allergic rhinitis was defined on the basis of a suggestive history of nasal allergic symptoms occurring some time of the year or every fall for several years in association with positive allergy skin prick tests or serum specific IgE to perennial allergens that correlated with the patient's pattern of symptoms. They found differences in the distribution of inflammatory cells in the maxillary sinuses of these two subgroups. Hence, in maxillary sinus lavage and mucosal biopsy specimens, allergic patients showed greater numbers of T cells. Nonallergic patients showed a greater percentage of neutrophils

and higher levels of IL-8 in maxillary sinus lavage.³⁹ In agreement with our studies of CHS/NP, allergic and nonallergic patients could not be distinguished in terms of the intensity of eosinophilic inflammation in sinus lavage or mucosal biopsy specimens.

Hence important features of chronic sinusitis inflammation are the presence of chronic inflammatory cells with a predominance of eosinophils, the presence of IL-5-producing T lymphocytes, the expression of C-C chemokines in the epithelial cells, and the expression of proinflammatory cytokines and the adhesion molecule VCAM-1. Furthermore, the allergic status of the patient appears to be an important determinant of the pattern of T_H1 and T_H2 cytokines produced in chronic sinusitis.

THE SPECIAL CASE OF ALLERGIC FUNGAL SINUSITIS

A distinct entity of allergic fungal sinusitis (AFS) was first proposed by Katzenstein et al⁶³ in 1982. It is caused by an intense allergic and eosinophilic inflammatory response to a fungal species and represents an upper airway equivalent to allergic bronchopulmonary aspergillosis (ABPA). The implicated fungi colonize stagnant mucus and are noninvasive. The disease appears to be more common in areas with hot, humid weather and high ambient mold spore counts. For instance, most AFS caused by *Bipolaris spicifera* has been reported in Texas, Louisiana, and Georgia. Other dematiaceous fungi implicated in AFS include *Curvularia* and *Alternaria*. Non-Dematiaceous fungi causing AFS include *Aspergillus* and *Fusarium*. The diagnostic criteria for AFS include the presence of chronic sinusitis usually with chronic mucosal thickening on sinus radiographs, the presence of "allergic mucin" and fungal hyphae within the allergic mucin.⁶⁴⁻⁶⁶ Nearly all patients with AFS have nasal polyps, and many have peripheral blood eosinophilia. Allergic mucin is defined as thick sinus secretions loaded with degranulating eosinophils. Sinus mucosal tissue characteristically shows intense chronic inflammation with large numbers of eosinophils. A positive fungal culture of the allergic mucin helps to confirm the diagnosis but is not required. Most patients with AFS have evidence of fungal allergy on the basis of prick or intradermal skin tests or fungal-specific IgE measurements.^{64,66} Fungal precipitins have been demonstrable in some but not all cases.

Certain radiographic features may alert the clinician to the possible presence of AFS. AFS may present as a persistently opacified sinus cavity despite prolonged antibiotic therapy. Most commonly, AFS causes unilateral sinus opacification, owing to obstruction of the sinus ostium by thick, inspissated mucus (Fig 5). Sinus CT images reveal the presence of a persistently opacified sinus cavity that may be expansile. Sinus CT images may also reveal high-intensity signaling within the opacified sinus. This signaling is felt to be caused by thick allergic mucin of high protein concentration.⁶⁷ The corresponding lesions have a characteristic "hypodense" appearance



FIG 5. An example of a case of AFS. The initial sinus CT scan (*left*) was taken after the patient's symptoms had failed to resolve despite 6 weeks of antibiotic treatment. The film shows complete opacification of the right anterior ethmoid sinus with bulging of the superior portion of the nasal septum from right to left, creating an "expansile mass." At sinus surgery allergic mucin was removed from the sinus cavity, and fungal cultures revealed the presence of *Aspergillus fumigatus*. The postsurgical sinus CT scan shows complete clearing of disease in the right anterior ethmoid sinus.

on T1- and T2-weighted images on sinus magnetic resonance imaging (MRI).⁶⁷ Such lesions are nearly pathognomic for AFS, but they are not always present.

The diagnosis of AFS is usually confirmed on the basis of surgical findings and examination (and possibly culture) of the allergic mucin. In rare cases the diagnosis may be made by performing Gomori's methenamine silver staining of pathologic specimens from a previous surgery.

Treatment of AFS requires surgical removal of the allergic mucin that obstructs sinus drainage.⁶⁶ However, systemic corticosteroids are also essential.⁶⁶ Guidelines for the use of prednisone for adults with AFS are patterned after treatment of ABPA. Treatment is initiated with prednisone 0.5 to 1.0 mg/kg daily for 2 weeks, and then the same dose given every other day for an additional 2 weeks before initiating a gradual tapering. In many cases it is necessary to continue a low daily or every-other-day dose of prednisone to maintain control of the disease. High-potency intranasal corticosteroids should also be used in AFS, preferably with the patient using the head-down-forward technique to maximize penetration of the drug into the OMU and ethmoidal area.^{68,69}

The total serum IgE level has been shown to be useful as a guide to steroid management of AFS.⁷⁰ Absolute blood eosinophil counts (AECs), drawn before prednisone is taken in the morning, may also be useful in this regard. AECs less than 400/ μ L are generally associated with control of the disease and suggest that the dose of prednisone may be tapered. The role of fungal-specific immunotherapy for AFS remains controversial, but a recent controlled study suggested that it may be an important adjunct to medical and surgical therapy of AFS.⁷¹

In a recent study Ponikau et al⁷² hypothesized that fungal colonization is an important inflammatory stimulus in most patients with chronic rhinosinusitis, especially those with nasal polyposis. The investigators cultured fungi from the nasal lavage fluid of 93% of patients meeting this description. Curiously, fungi were also cultured from 100% of a small group of "normal control subjects" studied. Unfortunately, the cultures of nasal lavage fluid did not differentiate the presence of viable fungal spores from colonization by fungal hyphae. The authors' contention that most chronic rhinosinusitis patients have underlying AFS is at odds with published surgical case series in which only about 7% of chronic sinusitis patients have been classified as having AFS.^{65,66} The difference may be due to the use of a less stringent definition of "allergic mucin" and more meticulous sampling techniques that allowed Ponikau et al to detect "allergic mucin" in the majority of cases of chronic rhinosinusitis. Clearly more information is needed before a firm conclusion can be made about the role of fungal allergens in chronic sinusitis pathogenesis.

RHINOSCOPIC APPEARANCE OF CHRONIC SINUSITIS

Examination of the nasal and sinus cavities with a flexible rhinoscope can provide important information about the presence or absence of purulent secretions, patency of sinus outflow tracts, nasal turbinate size, edema surrounding the eustachian tube orifices, hypertrophy of adenoidal tissue, and the appearance of the sinus mucosa. The latter may show changes of edema, pallor, polypoid degeneration, or frank polyposis. Fig 6 highlights some of



FIG 6. Rhinoscopic examination of the nose and sinuses. **A and B,** Normal appearance of right and left sphenoidal recesses. **C and D,** Normal appearance of right and left middle turbinate and middle meatus areas. Right middle meatus is not well seen. **E,** A large surgically created opening into right maxillary sinus. **F,** Extensive polyposis in the left anterior ethmoidal area. This area can be visualized because of prior surgery in this area. **G,** View inside right maxillary sinus (as in **E**) showing polypoid mucosal changes with a “cobblestone” appearance. **H,** A collection of tenacious green “allergic mucin” firmly attached to the mucosa within the left maxillary sinus of a patient with allergic fungal sinusitis. Culture of the mucus grew *Aspergillus flavus*.

the typical landmarks seen on rhinoscopic examination and some important pathologic findings. In patients who have not undergone sinus surgery, the normal rhinoscopic examination allows visualization of the sphenoidal recess, the inferior and middle turbinates, and the inferior and middle meatus. Rhinoscopy is also an excellent tool for postoperative evaluation of patients for signs of infection, edema, polypoid changes, or recurrence of disease. Depending on the surgery performed, the examination may allow visualization of the sphenoid sinus, the anterior and posterior ethmoid sinuses, the maxillary sinus, and the nasofrontal duct.

OUTCOMES OF MEDICAL MANAGEMENT

Despite the importance of chronic sinusitis, few if any controlled clinical trials of medical management have been performed. A series of 200 pediatric and adult patients was reported by McNally et al.⁷³ In their study, 55% of the patients also had a history of allergic rhinitis, which is consistent with the findings of other investigators.⁵⁰ The most common symptoms reported were nasal congestion (73%), postnasal drip (69%), purulent rhinorrhea (65%), headache (48%), cough (47%), facial pressure (42%), anosmia or hyposmia (39%), wheezing

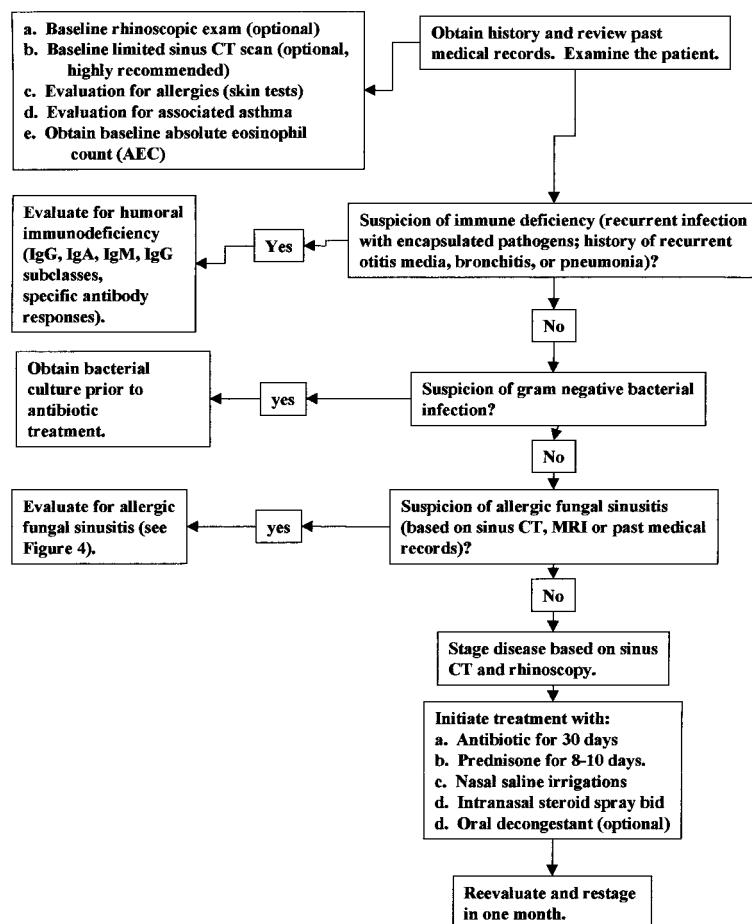


FIG 7. Approach to management of a patient with chronic sinusitis.

(34%), hyposmia (29%), and throat clearing (29%). The average duration of symptoms was 14 years. Medical treatment consisted of 4 weeks of oral antibiotics (mostly cefuroxime 500 mg twice daily or amoxicillin/clavulanate 500 mg three times a day), nasal lavage, nasal corticosteroids (given twice daily), and topical decongestants (for the first 2 weeks). Patients were assessed at 1 month and graded as improved if their symptoms or signs were reduced or resolved. No quantitative scoring was performed. All patients improved on treatment, and physical examination findings, including nasal crusting, nasal mucosal swelling, nasal polyps, and purulent secretions, improved in 50% to 84% of patients. Over a follow-up period of 1 to 27 months, only 6% of the patients required surgery.

We reported a retrospective series of medical treatment of 19 patients with chronic sinusitis.⁷⁴ A baseline limited sinus CT was obtained to confirm chronic sinusitis. A 10-day course of prednisone was given to reduce mucosal inflammation, and an antibiotic with mixed aerobic and anaerobic gram-positive coverage was administered for 4 to 6 weeks. Most patients were also advised to perform saline solution nasal irrigations and use an

intranasal steroid spray. A follow-up CT was obtained at the end of treatment. Baseline symptom scores ranged from 5 to 11 with a mean of 7.2 and radiographic extent of disease ranged from 8 to 32 with a mean of 21.3. Of the 19 patients, 17 had improvement in both symptom and CT scores. The mean symptom improvement was $-4.0 (\pm 2.2)$ and the mean radiographic improvement was $-10.3 (\pm 6.9)$. A weak but statistically significant correlation was found between the degree of symptomatic and radiographic improvement. Roughly equal improvement was seen in all sinus areas, but abnormalities in the ostiomeatal unit persisted in 8 out of 19 patients. In a follow-up study patients with a history of nasal polyposis or previous sinus surgery had a greater likelihood of symptomatic relapse within 8 weeks of completing treatment (Subramanian et al, in preparation).

These two studies demonstrate that medical management offers hope of improving symptoms and radiographic extent of disease and postpones the need for sinus surgery in some cases. However, the studies also attest to the refractoriness of symptoms and signs of disease in many patients and the need for more effective medical therapy.

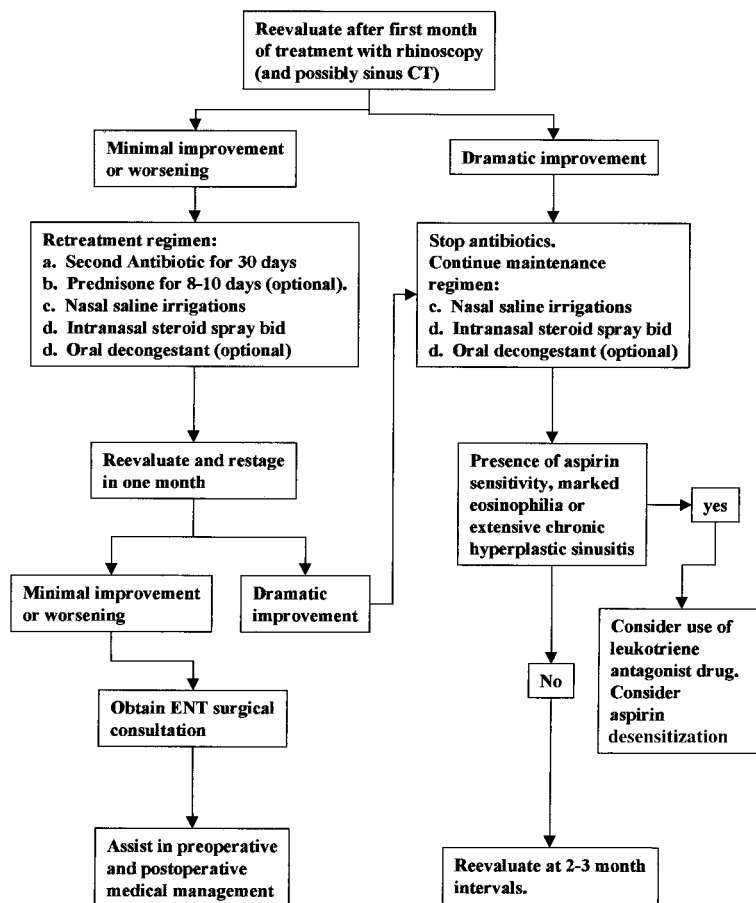


FIG 8. Reevaluation of the patient after initial treatment of chronic sinusitis.

MEDICAL MANAGEMENT STRATEGY

A suggested approach to managing the patient with chronic sinusitis is outlined below and summarized in Figs 7 and 8.

Evaluation of a patient with chronic sinusitis begins with a complete medical history, physical examination, and review of old medical records, including previous x-ray films and operative reports. In our clinic, the baseline evaluation includes a limited sinus CT scan and rhinoscopy. Many clinicians reserve the sinus CT scan for treatment failures or for patients referred for sinus surgery. The limited sinus CT scan offers the advantage of reduced cost and radiation exposure for the patient and is an excellent imaging study for chronic sinusitis.⁷⁵⁻⁷⁷ Contributing factors to sinusitis should be sought and treated as outlined in Fig 7. These include an evaluation for perennial allergic sensitivities and indoor allergenic exposures and, in selected cases, evaluation for hypogammaglobulinemia.

Certain conditions should raise suspicion for the presence of gram-negative sinus infection. These include a history of extensive antibiotic use or a history of gram-negative sinus infection. In such patients persistent severe symptoms and evidence of mucopurulent sinus

secretions warrant obtaining a sinus culture. If the baseline limited sinus CT scan shows evidence of high attenuation signaling or expansion of the sinus cavity, allergic fungal sinusitis should be considered.

As discussed previously, sinus mucosal thickening in chronic sinusitis is the result of both infectious or noninfectious inflammation. However, the contribution of each to the radiographic or rhinoscopic appearance of chronic sinusitis is difficult to judge. Even patients with advanced nasal polyposis may have superimposed infection and, conversely, patients with definite purulent infection may have prominent polypoid mucosal thickening. For these reasons, my initial approach to management of chronic sinusitis combines treatment with antibiotics and systemic steroids (prednisone). Adult patients receive antibiotics for 4 weeks and prednisone during the first 10 days of antibiotics (20 mg orally twice daily for 5 days followed by 20 mg daily for 5 additional days). Patients are also treated with nasal saline solution irrigations, intranasal steroids, and possibly oral decongestants. The use of systemic and topical corticosteroids for treatment of chronic sinusitis was recently reviewed.⁷⁸ The primary rationale for topical corticosteroids is their known efficacy for treatment of nasal polyp disease.⁷⁹ Use of topical corticosteroids has

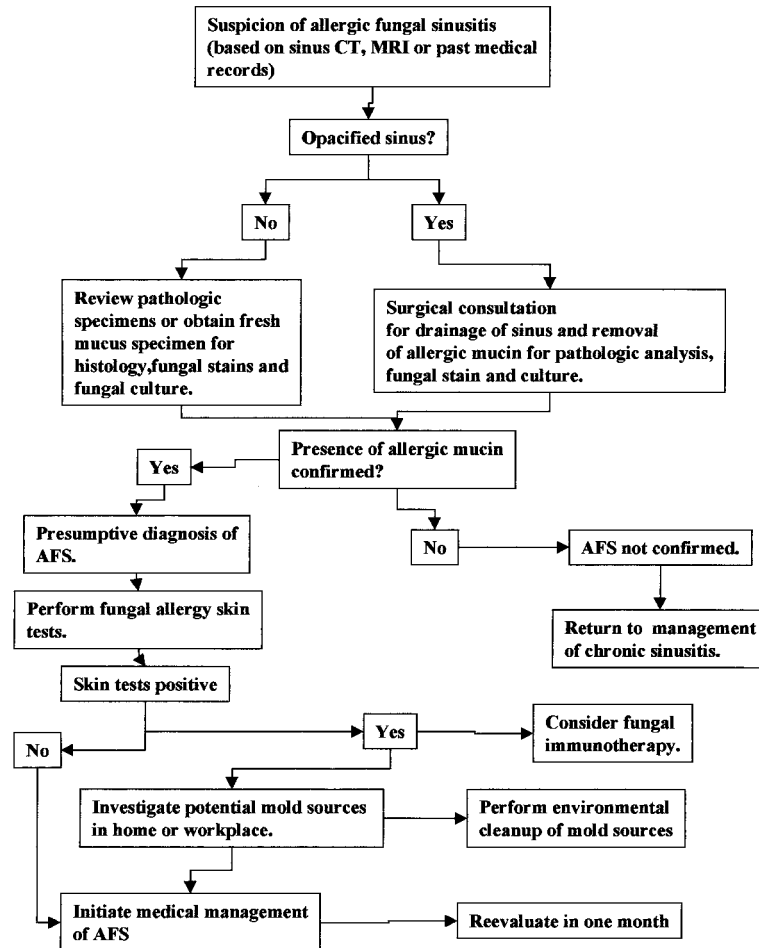


FIG 9. Evaluation and management of AFS.

also been advocated for treatment of chronic sinusitis as part of a "comprehensive" medical treatment program.⁷³ However, there are no controlled studies specifically addressing their value in chronic sinusitis.

Patients should be reevaluated after 1 month of treatment (Fig 8). This may include rhinoscopy and possibly a follow-up limited sinus CT scan. If dramatic improvement has occurred, antibiotics may be stopped, and nasal saline solution irrigations and intranasal steroids are continued. For patients demonstrating minimal improvement or worsening, a retreatment regimen is offered that includes a second antibiotic regimen and possibly another short course of prednisone. Again, the possibility of a gram-negative or an antibiotic-resistant gram-positive infection should be considered, which may justify obtaining a bacterial culture. The further empiric use of antibiotics at this point is clearly of unproved benefit. This is especially true for patients with advanced "noninfectious" chronic hyperplastic sinusitis with nasal polypoid. Nonetheless, in my experience, some patients improve during the second month of empiric antibiotic treatment and show regression of sinus mucosal thicken-

ing. Nasal saline solution irrigations, intranasal steroids, and oral decongestants are continued, and the patient is again reevaluated 1 month later. Patients who fail to improve after the second month of treatment are referred for consideration of sinus surgery. In my clinic only about 10% of cases fail to improve after 1 or 2 months of intensive medical treatment, but an additional 10% to 15% of cases relapse within a few weeks thereafter and ultimately are referred to a surgeon.

It is known that patients with extensive hyperplastic sinus mucosal thickening have a poorer outcome with sinus surgery,⁸⁰ and they may respond poorly to the medical treatment outlined above. Sinus tissues from these patients usually show large numbers of eosinophils. Patients may also have a persistently elevated AEC >500/ μ L. At least 50% of these patients have associated asthma. We have found that AECs >500/ μ L are associated with frequent exacerbations of chronic sinusitis leading to repeated use of antibiotics and progressive mucosal thickening. Patients in this category may require prednisone beyond the initial 10-day "burst," generally at a dose of 5 to 10 mg/d to maintain the AEC <500/ μ L.

For patients with a history of aspirin-induced asthma, the addition of a leukotriene antagonist should be strongly considered although there are no controlled studies of their effectiveness in treatment of sinusitis or nasal polyp disease. The use of leukotriene antagonists may help to reduce eosinophilic inflammation in the sinus tissues. Aspirin desensitization has also been advocated as a treatment for severe chronic hyperplastic sinusitis with nasal polyposis. However, most published experience with aspirin desensitization is in the form of small uncontrolled case series.⁸¹⁻⁸³

TREATMENT OF AFS

The treatment for AFS was discussed previously and is summarized in Fig 9. If the diagnosis of AFS is first suspected on the basis of a sinus CT or MRI scan, the patient should be referred to an ear, nose, and throat surgeon with a specific request to evaluate the patient for possible surgical drainage of AFS. It is worth making advance preparations for collection of mucin specimens for fungal stains, fungal cultures, and pathologic analysis. Improper handling of specimens probably contributes greatly to the low yield of fungal cultures and special fungal stains.⁷²

If the diagnosis of AFS is based on the findings at a recent surgery, an effort should be made to review the sinus pathologic specimens for histologic features and fungal stains. If possible, the allergic mucin should also be cultured for fungus. A presumptive diagnosis of AFS is usually made on the basis of the surgical and pathologic findings. This should be followed by an evaluation for fungal allergy with prick, and possibly intradermal, skin testing.

PREOPERATIVE AND POSTOPERATIVE MEDICAL MANAGEMENT

The role of the medical specialist in the preoperative management of patients with chronic sinusitis has been greatly underemphasized. Not uncommonly a patient is sent to surgery with minimal preoperative treatment. Patients may benefit significantly from medical treatment before surgery to minimize mucosal edema, polypoid thickening, and overriding infection. Such treatment may facilitate better anatomic visualization by the surgeon, minimize postoperative infection, and possibly promote faster postoperative recovery of mucociliary function. A coordinated effort between the ear, nose, and throat surgeon and the medical specialist is also highly desirable. In my experience, patients are routinely seen 2 weeks after surgery, at which time rhinoscopy is performed and the need for antibiotic and antiinflammatory treatment is reassessed.

SUMMARY

A better understanding of chronic sinusitis pathogenesis is sorely needed. No single hypothesis currently

explains the complex interplay of infectious and inflammatory stimuli that contribute to the disease. There is also a great need for improved therapies to combat this frustrating chronic illness. Specialists in AI have an opportunity to assume a leading role in this effort and a responsibility to their patients to strive for improved outcomes and a reduced need for sinus surgery.

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