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Pathogenesis of chronic rhinosinusitis: role of airborne fungi and bacteria

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The cause and pathophysiology of chronic rhinosinusitis (CRS) have been the source of extensive controversy. Several competing hypotheses exist regarding the underlying cause and the mechanism of the persistence of pathology and the categorization of patients into subgroups.

There is broad agreement that a substantial number of patients continue to have active disease despite multiple courses of medical, and often surgical, therapy. There is a general consensus regarding patients with certain predisposing conditions, such as cystic fibrosis, common variable immunodeficiency, or primary ciliary dysfunction; however, these conditions are relatively rare compared with the prevalence of CRS.

This article addresses long-standing theories and newer proposed roles of pathogens in the development of CRS. Attention is given to the immune processes that occur in the development and persistence of the disease.

Traditional hypotheses

In the acute setting, an upper respiratory viral infection can contribute to secondary infection with aerobic bacteria. The inflammatory response to the viral infection leads to damage of the mucosa, disruption of the function of the mucociliary apparatus, and obstruction of the ostiomeatal complex. This environment is ideal for opportunistic bacteria to flourish. The subsequent bacterial infection and further inflammation lead to the continuation of this process and clinical manifestation of acute sinusitis.

If this acute bacterial infection does not resolve, several factors have been described as contributors to the development of CRS [1]. Ostial blockage by edema and inflammatory mucous, delayed recovery of mucociliary function, and mucous

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recirculation were described as mechanisms that directly lead to a transition from an acute to a chronic inflammatory process. Certain anatomic abnormalities may not be as much of a factor as previously believed.

Much of the literature in sinusitis reflects a belief that, like acute sinusitis, CRS is an inflammatory process that stems from a bacterial origin. In support of this thinking, cultures obtained using various aspiration techniques or obtained from surgical specimens have revealed differing, but overlapping, bacteriology in acute and chronic sinusitis. In children with acute sinusitis, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and nontypable *Haemophilus influenza* are cultured most frequently [2,3]. Adults have similar culture results, with the exception of *Moraxella* [4]. In CRS, cultures yielding *Staphylococcus aureus* and anaerobes are much more common [5–8].

The inflammatory infiltrates in acute sinusitis and CRS are notably different. In acute sinusitis, neutrophils predominate. In CRS, eosinophils and mixed mononuclear cells are found more frequently. These different infiltrates possibly indicate separate inciting processes.

Despite the frequent co-occurrence of bacteria with CRS, it is less certain that they have a vital role in the origin of the disease in all cases or are merely bystanders invading already inflamed tissue in some patients. This theory is relevant in guiding proper therapy, as many patients continue to have symptomatic disease despite repeated administration of antibacterial agents [9].

The potential role of airborne fungi

Molds are a subset of fungi that cover surfaces. They have been cultured from human sinuses with many different ramifications [10]. Their presence may be relatively benign, colonizing normal sinuses or forming saprophytic crusts. They also may cause a range of pathology, ranging from noninvasive fungus balls to invasive, debilitating disease. There is the increasing interest in the concept that the most common form of sinus disease induced by fungus may be caused by the inflammation stimulated by airborne fungal antigens.

Definitions of allergic fungal sinusitis and chronic rhinosinusitis

The term “allergic fungal sinusitis” (AFS) has been defined by several groups. Originally, Millar et al [11] in the United Kingdom and then Katzenstein et al [12] in the United States described this entity. Katzenstein et al reported on several patients and developed the following criteria for what was then known as allergic aspergillus sinusitis: (1) clumps or sheets of necrotic eosinophils, (2) Charcot-Leyden crystals, and (3) noninvasive fungal hyphae with morphology consistent with *Aspergillus* species. Further work led to efforts to refine the definition of the disease. Bent and Kuhn [13] proposed five criteria that included the demonstration of type I hypersensitivity to relevant fungi. Other investigators disputed the requirement for an IgE-mediated process in the pathogenesis of AFS. Because

only two thirds of the AFS cases reviewed revealed positive skin tests to mold, de Shazo and Swain [14] developed a definition of AFS that does not require demonstration of IgE involvement. This definition centered on the demonstration of eosinophilic mucous and evidence of fungal presence.

More recent work has suggested that AFS, as previously defined, may not represent a separate entity from the less dramatic presentations of CRS. In 1999, Ponikau et al [15] proposed that most patients with CRS exhibit eosinophilic infiltration and the presence of fungi by histology or culture. This assertion was based on finding positive fungal histology or culture in 202 of 210 (96%) patients with CRS who prospectively were evaluated in a cohort study. No increase in type I sensitivity was found in patients as compared with controls. The term “eosinophilic chronic rhinosinusitis” was proposed to replace previously used nomenclature. In Europe, Braun et al [16] used similar methods with equivalent results, supporting these conclusions.

Ferguson [17] proposed that CRS cases could be divided into two categories: AFS and eosinophilic mucin rhinosinusitis (EMRS). The former would be diagnosed by demonstration of hyphae on direct staining or the growth of fungus on traditional, less sensitive methods of culture than those used by Ponikau or Braun. Designation of EMRS requires the presence of allergic mucous, but not the identification of fungi. Ferguson reviewed existing literature that reported patients with AFS and evaluated a small number of additional patients not previously reported. A total of 431 patients fit the criteria for AFS, and 69 fit the criteria for EMRS. She concluded that these populations were significantly different, because the patients with EMRS, compared with those with AFS, were older (48 versus 30.7), had a higher rate of asthma (93% versus 41%), and a higher rate of aspirin sensitivity (54% versus 18%). Based on this review, she proposed that AFS represented a distinct entity involving type I hypersensitivity and that EMRS represented a more generalized dysregulation of immune control.

The body of literature that defines the clinical syndromes of CRS consists of case series and cohort studies [11–21]. Entry criteria, methods, endpoints, and the focus of different studies vary widely and are not directly comparable. It has been difficult to reach consensus regarding the definitions of disease entities and patient subpopulations because of these limitations. Current work is expanding this body of knowledge, particularly concerning the origin and mechanism of the inflammatory stimulus.

Identity of implicated fungi in chronic rhinosinusitis

A broad array of fungi has been identified in the sinus cavities of patients with sinusitis through varied staining and culture techniques. *Aspergillus* and the dematiaceous family of fungi frequently have been reported as the predominant isolates [21] using early histologic staining and culture techniques. Dematiaceous means “darkly pigmented,” and the appearance of the hyphae can resemble that of *Aspergillus*. Species in this family include *Alternaria*, *Curvularia*, *Cladosporium*, *Drechslera*, *Exserohilum*, and *Bipolaris*. Initial reports predominantly described

Aspergillus species, though this identification is complicated by the similar appearance of *Aspergillus* and other members of the dematiaceous family. As staining procedures have been better refined and the classification system of fungal genera has been revised, more precise identification is possible. Many limitations still remain.

Early studies involving sinus culture typically yielded growth of only one fungal species [14]. In more recent studies, a much broader range of species has been identified in culture using modified collection and culture techniques [15,16]. Increased attention to the collection and retention of mucous and the addition of mucolytic agents on processing have led to increased yields. Likely, more organisms were able to grow because of increased exposure to the growth media. Multiple organisms have been isolated from individual patients using these new techniques, averaging about three organisms per patient (range, 1–9). The most common species are listed in Table 1.

As with the isolation of bacteria in sinus cavities in these patients, the presence of fungi does not prove that these pathogens directly create or perpetuate disease.

Table 1

Most common fungal organisms found in patients with chronic rhinosinusitis

Organism	Braun et al (N = 92) [16] ^a	Ponikau et al (N = 210) [15] ^a	DeShazo and Swain (N = 105) [14] ^b	Bent and Kuhn (n = 16) [13]	Cody et al (N = 37) [18]
<i>Alternaria</i>	22.9%	44%	3.8%	6%	24.3%
<i>Ampelomyces humuli</i>	6.5%	—	—	—	—
<i>Aspergillus</i>	83.8%	29.5%	12.4%	19%	2.7%
<i>Aureobasidium pullularis</i>	12%	—	—	—	—
<i>Basidiomycota</i>	13%	—	—	—	—
<i>Bipolaris</i>	—	—	22.8%	19%	2.7%
<i>Candida</i>	8.7%	21.4%	—	—	—
<i>Cladosporium</i>	41.4%	39%	—	—	2.7%
<i>Curvularia</i>	—	—	23.8%	25%	8.1%
<i>Drechslera</i>	—	—	10.5%	—	5.4%
<i>Exserohilum</i>	—	—	3.8%	6%	—
<i>Fusarium</i>	—	16.2%	1%	—	—
<i>Helminthosporium</i>	—	—	1%	—	—
<i>Penicillium</i>	56.6%	43.3%	—	—	—
<i>Pithomyces</i>	—	6.7%	—	—	—
<i>Sclerotinia sclerotiorum</i>	10.9%	—	—	—	—
<i>Ustilago</i>	—	6.2%	—	—	—
Not identified	13.1%	3.8%	23.8%	25%	54.1%

^a These studies employed more sensitive culture techniques with much higher yields than previous studies. For simplicity of presentation, data presented are limited to genera comprising more than 5% of patients colonized.

^b Review of previously reported and original data.

The application of more sensitive culture methods to saline nasal washes obtained from normal individuals resulted in the isolation of molds in 100% and 91.3% of the specimens from normal individuals but no eosinophilic infiltration [15,16]. This finding initially was unexpected. Fungal isolates found in normal individuals represent a subset of those found in diseased sinus cavities and are listed in Table 2.

This universal presence of fungi in human sinuses and nasal cavities irrespective of disease status requires further explanation. One hypothesis suggested by Ponikau et al [15] indicates that patients with CRS may have an inherent hypersensitivity to fungal antigens that is absent in people without sinusitis. The underlying concept is similar to that of allergic rhinitis (ie, everyone is exposed to airborne allergens, but only those who are sensitized respond with expression of the disease).

Immunologic characterization of chronic rhinosinusitis

The specific immunologic mechanisms leading to chronic inflammation in sinusitis are unknown. Many reports document evidence of type I or type III hypersensitivity [13,22–30], but this finding is not universal in all patients.

Stewart et al [22] evaluated cohorts of patients with CRS, allergic rhinitis, or no disease. Participants in all cohorts exhibited specific IgG to one of the nine molds tested. Subjects with CRS were divided into groups based on the degree of evidence for AFS. The average number of positive fungal-specific IgG measurements per patient was increased in patients with CRS, particularly those with measurable characteristics of AFS. Specific IgE to molds was only present in patients with CRS who had evidence of allergic mucin with or without identification of fungal organisms. Increasing disease severity, which was measured by the extent of nasal polyposis, correlated with increased levels of specific IgE and specific IgG. Other investigators have found a much higher correlation with positive radioallergosorbent tests to mold [29] and other inhalants [30].

In 1995, deShazo and Swain [14] reviewed the current reports of AFS and noted that approximately two thirds of patients exhibited positive immediate hypersensitivity skin tests. In the same patients, 88% demonstrated serum precipitins, and 75% demonstrated elevated total IgE levels. This analysis was complicated by the

Table 2
Most common fungal organisms found in normal individuals

	Braun et al (N = 23)[16]	Ponikau et al (N = 14)[15]
<i>Alternaria</i>	17.3%	50.0%
<i>Aspergillus</i>	60.9%	42.9%
<i>Aureobasidium pullulans</i>	26.1%	—
<i>Cladosporium</i>	65.2%	57.1%
<i>Geotrichum</i>	—	28.6%
<i>Penicillium</i>	69.4%	21.4%

large number of case series reported that had small numbers of patients in each series, therefore resulting in a heterogeneous population.

The issue of specific fungal hypersensitivity was addressed prospectively in the study by Ponikau et al [15], which involved a population of sequential patients undergoing surgery for CRS. Almost all of the patients exhibited tissue eosinophilia and eosinophilic clusters in the mucin; however, skin tests to a broad range of fungi by prick or intradermal methods were positive in only 42% of patients. A modest elevation in total serum IgE levels was seen in 34% of patients, and specific IgE to molds was seen in 28%.

Attempts to detect immunologic markers within nasal polyp tissue have yielded variable results. At least one study indicates a high elevation in tissue eosinophilia, but scant tissue IgE [31]. Other studies have demonstrated high levels of IgE in nasal polyp tissues [32–34]. Bachert et al [35] described three groups of patients: (1) those with low total IgE levels and no specific IgE, (2) those with elevated total and specific IgE levels, and (3) those with elevated multiclonal IgE levels with specific IgE to *S aureus* enterotoxin A and *S aureus* enterotoxin B. These findings were unrelated to skin prick results. Skin test results did correlate with tissue IgE levels in patients without nasal polyps.

Non-IgE-mediated hypersensitivity

Work to further define the mechanism of the inflammatory response is ongoing at the authors' institution, though this work is in its early stages. They have been investigating the hypothesis that fungal antigens serve as stimuli that lead to a hypersensitivity response that does not seem to involve IgE.

Because only a subset of patients exhibit type I hypersensitivity with CRS, several options are possible. The patients with evidence of specific IgE to molds and other abnormalities may represent a subset of patients with CRS that is caused by a unique immune mechanism, possibly analogous to the mechanism that causes allergic bronchopulmonary aspergillosis (ABPA). Alternatively, CRS may develop with a similar pathogenesis in patients with and without specific IgE but who have a different disease expression. The authors have been investigating the possibility that fungi provide the antigenic stimulus for a hypersensitivity response that is not necessarily IgE-mediated in most patients with CRS.

Alternaria is a possible stimulus of the inflammatory response in CRS. Previous work in the authors' laboratory has indicated that co-culture of *Alternaria* extracts with peripheral blood mononuclear cells derived from patients with CRS leads to increased production of IL-5, IL-13, and interferon γ (IFN- γ), compared with that produced by mononuclear cells from healthy individuals [36]. This finding does not clearly fit the cytokine profile of a T helper cell type 1 (T_H1) or T helper cell type 2 (T_H2) response but is consistent with the cytokines expressed in the sinus tissue of patients with CRS [37–39]. Although one can speculate that these cytokines may initiate eosinophilic and other cellular immune responses to fungal organisms, further studies are necessary to better understand the implications of this abnormal cytokine generation in disease physiology.

Eosinophils seem to have a central role in the development of CRS. Several investigators have reported that the histologic hallmark of CRS, with or without nasal polyposis, is marked tissue eosinophilia [40,41]. A highly significant correlation was noted between the extent of disease, as examined by CT scan, and the peripheral blood eosinophil count [42]. Feger et al [43] reported higher levels of eosinophil cationic protein, a marker of eosinophil activation, in the mucin and blood of patients with AFS than in those with CRS who were not considered to have AFS. Wei et al [44] demonstrated that allergic mucin and tissue extracts in patients with CRS contain chemoattractants for eosinophils and that eosinophils from CRS patients are likely able to respond to those chemoattractants. More investigations are necessary to further characterize the involvement of eosinophils and to determine the stimuli needed for eosinophil activation and migration.

Correlation of allergic fungal sinusitis with allergic bronchopulmonary aspergillosis

ABPA and AFS have similar histopathologic findings—tenacious mucous, mucous plugging, and growth of fungi are present in both diseases. Reports of the coexistence of these diseases are rare, with only 17 patients reported to date [45–49]. Two of these studies noted the incidence of comorbidity in fairly sizable series of patients. DeShazo and Swain [14] studied 106 patients with AFS and found only four patients with ABPA. Review of 95 patients with ABPA revealed seven patients with AFS and 13 patients with documented sinusitis who refused further investigation. It is surprising that these two studies of similar respiratory diseases with pathologic similarity reveal such a low rate of coexistence in patients.

Implications of fungal involvement in the treatment of chronic rhinosinusitis

At this point, treatment of CRS consists of nonspecific suppression of the inflammatory response with corticosteroids, oral antibacterial agents, nasal washes, and surgery. No therapy has proved to be effective in randomized, controlled trials, and no therapy for CRS is approved by the Food and Drug Administration.

Corticosteroids seem to be effective, though systemic therapy often is required. Accompanying systemic corticosteroid therapy is the burden of a well-known side-effect profile. Antibiotic therapy can improve symptoms in the short term and is useful for the treatment of bacterial superinfection, but such drugs do not reliably eliminate the disease. Improved methods in surgical technique have led to greater benefit for patients, but multiple procedures often are required over time. Development of better treatment options is indicated for CRS.

Studies are ongoing to assess the efficacy of intranasal antifungal therapy. The hypothesis is that although the presence of fungi alone does not produce disease, reduction in antigen load by antifungal therapy may reduce the immune response and improve the clinical picture. In an uncontrolled pilot study, 51 patients were treated with antifungal nasal washes. Most patients experienced an improvement in

symptoms and endoscopic staging [50]. This study provided the foundation for randomized, placebo-controlled trials, and these trials are ongoing.

Some investigators have attempted allergen vaccine immunotherapy. Initial case reports indicated possible efficacy [51,52]. Use of immunotherapy after surgical reduction of antigen load in patients with AFS, demonstrating type I sensitivity to molds, showed some effect in a nonrandomized, controlled study. This intervention led to lower endoscopic staging scores, improved symptoms, and reduced corticosteroid use [53]. Further study in a small, uncontrolled case series also suggested that immunotherapy may have led to improved clinical outcomes [54].

The potential role of airborne pollens in chronic rhinosinusitis

Allergic rhinitis commonly is believed to lead to CRS. This idea is based on studies that categorized patients based on symptoms that can overlap considerably between the two diseases. Conversely, radiolabeled ragweed pollen was not demonstrated in the paranasal sinuses, despite the presence of high levels in the nasal cavity and nasopharynx [55]. Further study by CT, single photon emission computed tomography (SPECT), and PET scans revealed no inflammation on the paranasal sinuses in patients with ragweed sensitivity and allergic rhinitis [56]. There is no direct evidence of exposure to pollen-derived allergens leading to CRS, but epidemiologic studies suggest an association between allergic rhinitis and CRS.

The potential role of bacteria in chronic rhinosinusitis

Bacterial culture in chronic rhinosinusitis

In acute sinusitis, bacterial infection participates in the pathogenesis of the disease. The role of bacteria in CRS has been more difficult to document. Many studies have performed cultures of patients with sinusitis by antral puncture, aspiration through the middle meatus, or intraoperative collection of samples. Most of these studies are compromised by the fact that patients were treated with antibiotics or had undergone previous surgery. Control specimens from normal individuals have not always been examined. No firm evidence is available that the bacteria are pathogenic, rather than simply resident in the inflamed tissues.

In the middle meatus of normal healthy adults, coagulase negative staphylococci, *Corynebacterium*, and *S aureus* have been cultured most frequently. In contrast, *H influenzae*, *M catarrhalis*, and *S pneumoniae* predominate in the middle meatus of normal healthy children, mirroring the organisms frequently found in acute sinusitis (discussed earlier) [57]. In patients with CRS, some of the same organisms found in acute sinusitis can be found, but typically there is a shift. *S aureus*, coagulase negative staphylococci, anaerobes, and gram-negative organisms more frequently are cultured.

Superantigens

S aureus is known to produce several superantigens, many of which have been well defined. Superantigens activate the immune system by binding the T-cell receptor at a location that is separate from the antigen-specific region and major histocompatibility complex II on the B cell simultaneously. This step leads to the activation of as much as 30% of the T-cell population, whereas less than 0.01% of the T-cell population is activated in responses to specific antigens [58]. Superantigens have been implicated as a mechanism in the pathogenesis of atopic dermatitis [59,60] and other chronic inflammatory diseases, such as Kawasaki disease [61], psoriasis [62], and rheumatoid arthritis [63,64].

Schubert [65] has proposed that superantigens may have a role in CRS. He points out that the inflammatory infiltrate in CRS is not consistent with bacterial infection. Neutrophils are absent, and lymphocytes and eosinophils predominate. This report refers to two findings to support this assertion: (1) *S aureus* frequently is cultured in hyperplastic sinus disease, and (2) *S aureus* frequently has been cocultured with fungi in studies of AFS.

Defined abnormalities leading to sinus inflammation

Cystic fibrosis

Chronic sinusitis occurring in patients with cystic fibrosis likely stems from a unique pathogenesis. The cellular infiltrate differs from other types of disease, and neutrophils and macrophages predominate in these patients. T_H2 cytokines are absent, levels of IL-8 and IFN- γ are elevated [66]. These findings mirror the pathology in the lung in cystic fibrosis. Therapy with topical steroids typically is of little benefit in this setting, likely because the infiltrating cells are less susceptible to glucocorticoid effects than are eosinophils.

Patients with cystic fibrosis often have severe disease with frequent need for complicated surgery. *Pseudomonas aeruginosa*, particularly of the mucoid variety, is cultured more frequently than in other forms of sinusitis [67].

Cellular and humoral immune defects

In a tertiary care setting, Chee et al [68] reported a surprisingly high incidence of immune deficiency among patients with refractory sinusitis. Among 55 patients, 22 (40%) were anergic on delayed hypersensitivity skin testing. Fifty-four percent of patients had abnormal T-cell proliferation to recall antigens, and 26.3% exhibited a decreased response to T-cell mitogens. On measurement of immunoglobulins, 17.9% of patients exhibited IgG deficiency, and 16.7% had IgA deficiency. Almost 10% of patients were diagnosed with common variable immunodeficiency.

Patients with abnormally decreased levels of immunoglobulins are prone to bacterial infections of the respiratory tree. Chee et al [68] reported benefit from therapy with intravenous immunoglobulin in patients with documented hypogam-

maglobulinemia. In the authors' clinical experience, if involvement is isolated to the sinuses, immunoglobulin therapy is reserved for patients who are not responding to more conservative measures, including saline irrigation.

Diabetes mellitus

Patients with diabetes are rarely susceptible to invasive fungal sinusitis. Most commonly, an acute, fulminant form of fungal invasion occurs, but a more chronic disease can present after many months. The responsible pathogens belong to the Zygomycetes class, usually in the Mucorales order. These pathogens include the genera *Absidia*, *Mucor*, *Rhizopus*, *Rhizomucor*, *Cunninghamella*, *Mortirella*, *Saksengea*, and *Aphysomyces* [69]. Genera in the Entophthorales order, *Conidiobolus* and *Basidiobolus*, have been described as causing chronic invasive sinusitis. Infections with these genera have the unique presenting feature of nodular subcutaneous masses in the paranasal region or upper lip (*Conidiobolus*) or trunk and buttox (*Basidiobolus*) [70].

Though chronic invasive fungal sinusitis most frequently affects individuals with poorly controlled diabetes, it also can affect people with well-controlled disease or those who are presumably immunocompetent. Other predisposing factors include malignancy, malnutrition, dehydration, immunosuppression, and alcoholic cirrhosis.

Primary disorders of ciliary dysfunction

Although primary disorders of ciliary structure or function are rare, they should be considered in individuals with both CRS and pulmonary infections. The most frequent disorder of this type involves absence of dynein arms in the ciliary apparatus. Primary ciliary dyskinesia involves sinusitis, otitis media, bronchiectasis, and, in males, infertility. About 50% of patients also have situs inversus, which has the designation of Kartagener's syndrome. Primary ciliary dyskinesia and Kartagener's syndrome exhibit an autosomal recessive inheritance pattern. Approximately 1 in 15,000 white infants are born with this disease [71].

Other abnormalities may impair ciliary function, including abnormal orientation of the cilia or abnormal beat frequency. Primary disorders are distinguished from secondary causes of ciliary dysfunction (ie, viral infection), which typically involve only a subset of cilia in a patchy distribution.

Clinically, individuals with abnormal ciliary function present with chronic purulent nasal discharge that starts at birth. Newborns may experience mild respiratory distress requiring a short stay in the special care nursery. In contrast, individuals with hypogammaglobulinemia typically do not present until at least 3 months after birth because of the presence of maternal antibodies. Cultures of nasal discharge from patients with a primary ciliary disorder may reveal nontypable *H influenzae*, *S aureus*, and *Pseudomonas aeruginosa* of the nonmucoid variety [67].

Small vessel vasculitis

Wegener's granulomatosis can involve sinusitis as one its features. Microscopic polyangiitis and Churg-Strauss syndrome also may involve the upper respiratory tract [72]. Vasculitic diseases that involve the upper respiratory tract are associated with measurement of antineutrophil cytoplasmic antibodies, but it is unknown if these antibodies have a role in the pathogenesis. Patients with vasculitic diseases often complain of epistaxis and manifest mucosal ulceration, nasal-septal perforation, and nasal deformity. Definitive diagnosis of Wegener's granulomatosis involves a biopsy of affected tissue that reveals necrotizing granulomatous inflammation [73].

Aspirin sensitivity

The association of aspirin sensitivity, asthma, and sinusitis with nasal polyposis (triad asthma) has been well described [74]. There is considerable overlap with the clinical features of typical CRS than with the other patient-disease subsets discussed. Triad asthma may represent part of a spectrum of disease rather than a separate syndrome.

Interference with the function of cyclooxygenase 1 (COX-1) is associated strongly with aspirin sensitivity. Patients with triad asthma excrete 2 to 10 times the amount of leukotriene E₄ as compared with patients with asthma who tolerate aspirin and other COX-1 inhibitors [75].

The diagnosis of aspirin-sensitive disease generally requires provocation with oral aspirin or inhaled L-lysine. Skin tests to aspirin are negative, and researchers have not been able to demonstrate specific antibodies to aspirin [76].

The prevalence of aspirin sensitivity has been measured in questionnaire-based epidemiologic and practice-derived asthma populations to be between 8% and 11% [77,78]; however, McDonald et al [79] found a higher prevalence of 20% by aspirin challenge of asthmatics. It is possible that many patients with respiratory disease have undetected aspirin sensitivity.

Summary

The pathogenesis of CRS has not been defined clearly and remains controversial. Previously, persistent bacterial infection that is compounded by ostiomeatal obstruction, poor mucociliary clearance, and allergy to aeroallergens was believed to be the major contributor to the development of the disease. Some investigators have focused on hypersensitivity responses to fungi or overly activated responses to bacterial superantigens as potential instigators of the disease. Further study, with clarification of the true pathogenesis, is critical for developing effective therapy. Current knowledge includes the following:

It is known that eosinophils, T cells, and B cells infiltrate the tissue in patients with CRS, and this infiltrate is absent in normal controls.

There is a long history in the literature of implicating aerobic and anaerobic bacteria in CRS, but this theory has come into question.

Fungi are isolated from the sinus and nasal cavities in patients with CRS and from nasal cavities in normal controls.

One potential mechanism for the pathogenesis of sinusitis is hypersensitivity to ubiquitous fungal antigens.

Another proposed mechanism is that of bacterial superantigens initiating an inflammatory response.

There are some correlations between allergic fungal sinusitis and allergic bronchopulmonary aspergillosis.

Several known predisposing factors, such as cystic fibrosis, congenital abnormalities of the mucociliary clearance system, and diabetes mellitus, result in differing clinical presentations.

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