



Review

Chronic rhinosinusitis phenotypes

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ABSTRACT

Objective: To review the current knowledge surrounding different chronic rhinosinusitis (CRS) presentations and the relative roles of nasal polyps, eosinophilia, and allergies in discerning phenotypes.**Data Sources:** PubMed literature review.**Study Selections:** Articles discussing the various phenotypes of CRS with emphasis on pathologic and immune mechanistic studies that distinguish disease.**Results:** Current guidelines primarily separate CRS based on the presence or absence of nasal polyps. This is largely driven by the tendency of eosinophilic disease to present with nasal polyps (NPs) in contrast to noneosinophilic presentations, which less often lead to the development NPs. Further separations have been proposed based on expression of aeroallergen sensitization.**Conclusion:** The presence of NPs may only poorly predict the presence of an underlying eosinophilic process and as such may have poor utility in forming the basis for recommending eosinophil-target therapies. Similarly, there is little evidence to support a significant role for aeroallergen exposure in contributing to the presence, severity, or natural history of CRS. Appropriate separation of CRS into specific phenotypes will allow therapeutic approaches to be individualized to each distinct presentation.

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Introduction

Chronic rhinosinusitis (CRS) is an increasingly important medical problem with significant adverse effects on patient quality of life and well-being and for which current therapies often prove inadequate. For the purposes of evaluating and treating these patients, current recommendations divide CRS into 2 subsets defined by the presence or absence of nasal polyps (NPs): CRS with NPs (CRSwNPs) and CRS without NPs (CRSSNPs).¹ Factors that drive this distinction are the significant association between NPs and the presence of tissue eosinophilia.^{2,3} It is this presence of eosinophilia that defines a distinct pathogenic disease process (phenotype) that predicts both clinical responses and prognosis. Although eosinophilia is often associated with NPs, the presence and extent of eosinophilia in NP can be variable such that a substantial subset of cases of CRSwNPs do not have eosinophilic infiltration. Conversely, eosinophilic inflammation may be present in the hyperplastic tissue of patients who do not (yet) have NPs.^{3–7} These observations support an alternative viewpoint that the presence or absence of NPs should not be used as the primary criterion for diagnosis or

treatment recommendations. However, for this review, CRS is classified using the distinct eosinophil-based pathologic presentations that better serve as a basis for defining immune pathogenic mechanisms and driving treatment considerations (Table 1).

This PubMed literature review examines the current knowledge surrounding different CRS presentations and the relative roles of NPs, eosinophilia, and allergies in discerning phenotypes. Articles on the various phenotypes of CRS with emphasis on pathologic and immune mechanistic studies that distinguish disease were selected for review.

Bacterial Colonization and Acute Infection in CRS

Healthy sinuses remain infection free in large part through the presence of an intact epithelial layer with tight junctions that prevent bacterial access to the submucosa and efficient mucociliary clearance of pathogens that access the sinus cavity. This sinus mucus is also enriched for antimicrobial proteins. All presentations of CRS are associated with variable degrees of epithelial cell disruption, ranging from loss of tight junctions to complete denudation. Even when epithelial remnants remain, the loss of functioning cilia results in deficient mucociliary clearance. In lieu of epithelial cells, what remains are epithelial cells that have been metaplastically transformed into mucous-producing goblet cells. Along with submucosal glandular hypertrophy, this leads to the excessive mucus that fills the sinuses but also provides growth media for the bacterial biome. Consequently, all forms of CRS are

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Table 1
Phenotypes of CRS

Type of CRS	Phenotype
Noneosinophilic	Chronic infectious sinusitis Idiopathic noneosinophilic CRS
Eosinophilic	Idiopathic eosinophilic CRS Aspirin-exacerbated respiratory disease Allergic fungal rhinosinusitis
Mixed or variable	Cystic fibrosis

Abbreviation: CRS, chronic rhinosinusitis.

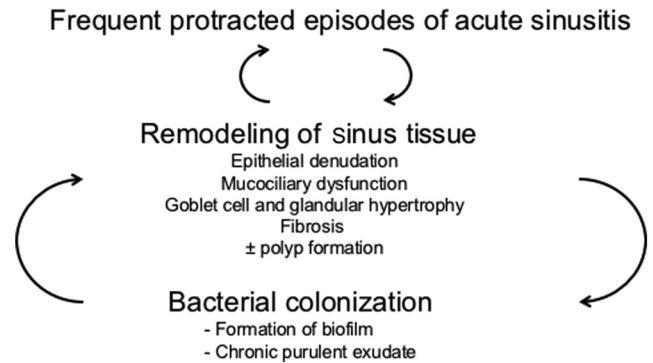
associated with extensive colonization with anaerobic bacteria, gram-negative organisms, *Staphylococcus aureus*, and other pathogenic bacteria.^{8–10} These bacteria reside in a relatively indolent state in biofilms that are almost universally present in the sinuses of patients with CRS.^{11,12} However, either through emergence of bacteria from their biofilms or as a consequence of de novo exposure, there is a loss of barrier and innate immune functions that predisposes these patients to frequent and protracted bouts of acute rhinosinusitis (ARS).

Infectious CRS

In contrast to the universal presence of bacterial colonization in CRS and the recurrent acute sinusitis that affects these patients, CRS as a chronic infection (ie, bacterial sinusitis persisting >12 weeks) is an unusual cause of chronic sinusitis. When present, infectious CRS should raise suspicion for underlying immune deficiency, human immunodeficiency virus infection, Kartagener syndrome, cystic fibrosis (CF), or anatomical cause (eg, after trauma or odontogenic sinusitis). Patients with infectious CRS are identified pathologically by prominent tissue neutrophilia accompanied by intense bacterial expression in their sinuses. However, as mentioned, this is a rare disorder and should not be confused with other patients with CRS who, although having sinuses highly enriched with bacteria, have what is primarily a noninfectious inflammatory disorder. Although rare, this condition requires early recognition and likely surgical referral because untreated it can progress to potentially life-threatening invasive bacterial infections of the orbit and central nervous system.

Noneosinophilic CRS

Noneosinophilic CRS is thought to present as a consequence of the chronic inflammation and remodeling that occurs with frequent and protracted episodes of ARS. Historically, this was thought to reflect occlusion of the sinus ostia secondary to allergic rhinitis (AR), anatomical predisposition, or other causes. However, this concept is no longer accepted because noneosinophilic CRS routinely develops in patients without anatomical occlusions and individuals with anatomical variants thought to be predisposing seldom develop CRS.¹³ Through whatever mechanism, noneosinophilic CRS once initiated, as with other forms of CRS, predisposes patients to recurrent and protracted bacterial infections, further damage to the epithelium, ciliary destruction, goblet cell metaplasia, prominent mucous gland and goblet cell hyperplasia, bacterial colonization, and biofilm formation, ultimately leading to a inexorably worsening chronic inflammatory state.^{5,6} By helping break this cycle of recurrent infections that exacerbate tissue remodeling and create a microenvironment conducive to bacterial colonization and growth (Fig 1), surgical intervention can often provide long-term cures for these patients.^{14–16} The inflammatory component of this form of sinusitis consists of a mononuclear cell infiltrate with few neutrophils.⁷ Although previously thought to reflect a type 1 cytokine-associated disease (high interferon

**Figure 1.** Model of interaction of frequent protracted acute bacterial sinusitis in the pathogenesis of noneosinophilic chronic rhinosinusitis. See text for details.

[IFN]– γ), most current studies find little evidence of T-effector lymphocyte infiltration or any particular cytokine milieu.^{17,18}

Noneosinophilic CRS is associated with robust remodeling with dense deposition of collagen and other matrix proteins.^{6,19} The collagen remodeling in noneosinophilic CRS is a response to the expression of growth factors involved in fibroblast activation. These growth factors include transforming growth factor β 2, fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor.⁶ Another characteristic of noneosinophilic CRS is large numbers of connective tissue type mast cells.⁶ Mast cell recruitment and activation are frequently observed features of tissue repair but also characterize virtually all fibrotic diseases,¹⁷ and they serve as important sources of these fibrotic growth factors.²⁰

Eosinophilic CRS

Idiopathic eosinophilic CRS is characterized by the prominent accumulation of eosinophils in the sinuses and, when they are also present, associated NP tissue.^{2,21} Usually, NPs occur with CF, allergic fungal rhinosinusitis (AFRS), and aspirin-exacerbated respiratory disease (AERD). In the absence of 1 of these conditions and without access to tissue samples for pathologic examination, the presence of nasal polyposis has been used as presumptive evidence for eosinophilic CRS.²² The presence of concomitant asthma and elevated circulating eosinophil numbers may also suggest an eosinophilic process. However, eosinophilic CRS can only be unambiguously diagnosed on histochemical staining of tissue for eosinophils or eosinophil-derived mediators (eg, eosinophil cationic protein or major basic protein). In eosinophilic CRS, the sinus tissue demonstrates a marked increase in cells that express cytokines (interleukin [IL] 5, granulocyte-macrophage colony-stimulating factor), chemokines (CCL5, CCL11, CCL24, and others), and lipid mediators (cysteinyl leukotrienes and prostaglandin D₂) that are responsible for the differentiation, recruitment, survival, and activation of eosinophils.^{2,18,23} Eosinophils are a prominent source of many of these mediators. Thus, once eosinophilic inflammation is established, they provide the means necessary for their further recruitment, proliferation, activation, and survival.^{18,21} Thus, in contrast to noneosinophilic CRS, eosinophilic CRS behaves as a self-perpetuating syndrome, and, as such, in contrast to noneosinophilic CRS, it is unlikely to be cured by surgery alone.^{14–16}

The origin of eosinophilic CRS is poorly understood. These patients often have asthma, and eosinophilic CRS shares many histologic and immunologic features with asthma (Fig 2), suggesting that eosinophilic CRS and asthma may comprise the same immune process involving the upper and lower airways, respectively.^{24,25} Similar to eosinophilic asthma, eosinophilic CRS is characterized by a high type 2 cytokine milieu, that is, a milieu enriched for IL-4,

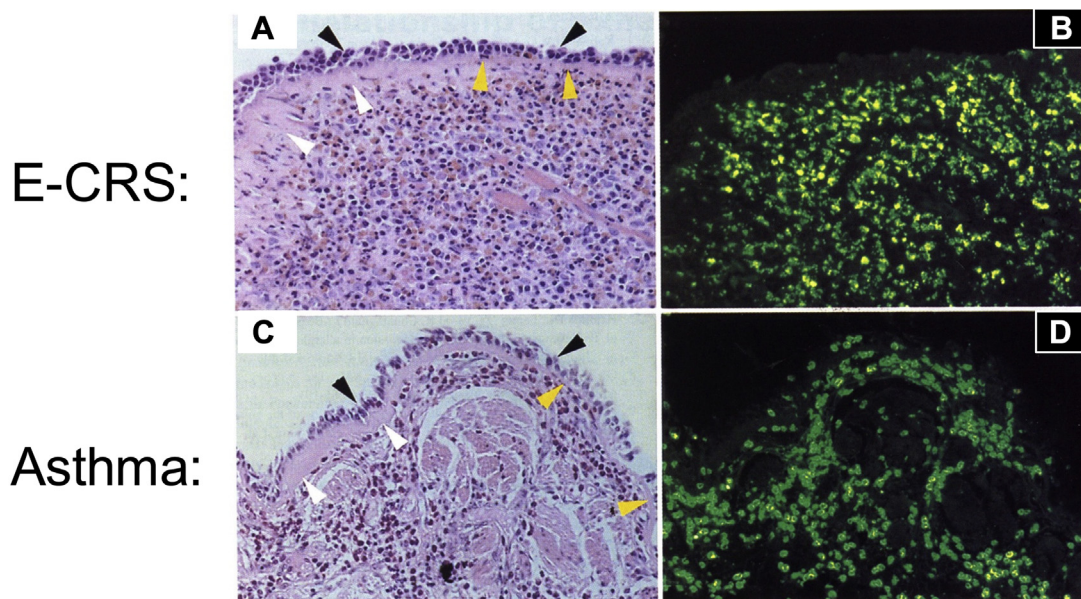


Figure 2. Pathologic similarity of eosinophilic chronic rhinosinusitis (CRS) nasal polyps (A and B) to asthma (C and D). Hematoxylin-eosin–stained sections (A and C) show epithelial denudation (black arrows) and both early (yellow arrows) and advanced (white arrows) basement membrane thickening. Major basic protein immunofluorescence staining (B and D) show intensity of eosinophilic infiltration. Reprinted from *J Allergy Clin Immunol*, Vol 112, Ponikau JU, Sherris DA, Kephart GM, et al, Features of airway remodeling eosinophilic inflammation in chronic rhinosinusitis: is the histopathology similar to asthma, Pages 877–882, Copyright 2003, with permission from Elsevier.²⁵

IL-5, and IL-13 (Fig 3).^{17,18,21} Although not particularly enriched for T-effector (T_H2) lymphocytes, numerous cell types drive this type 2 cytokine milieu, including mast cells, eosinophils, basophils, $CD34^+$ hematopoietic progenitor cells, and the recently described type 2 innate lymphoid cell.^{26,27} It is this enrichment with IL-5 that underlies the current desire to better identify and define this phenotype because only these patients will be responsive to biotherapeutics that target IL-5.²⁸ Similarly, the high IL-4/IL-13 nature of eosinophilic CRS underlies the apparent efficacy of

biotherapeutics targeting these cytokines for individuals with this phenotype.²⁹

Allergic Fungal Rhinosinusitis

AFRS is a unique disorder that develops when mold present as commensals in the sinuses simultaneously activates pathogen-associated molecular pattern receptor–induced innate immune pathways and elicits robust type 2 cytokine responses. Originally, this disease was ascribed to *Aspergillus*; however, it is now recognized that many species of fungi are associated with AFRS, including *Alternaria*, *Penicillium*, *Cladosporium*, *Curvularia*, and *Bipolaris*.³⁰ This form of eosinophilic CRS is characterized by specific IgE sensitization along with elevated total serum IgE concentrations. In contrast to other forms of eosinophilic sinusitis, this disease is often unilateral and limited to 1 or a few sinus cavities. The presence of intense eosinophilic infiltration with extensive goblet cell and mucous gland hyperplasia produces a thick dark brown exudate (allergic mucin) that has a distinct appearance. Allergic mucin is hyperdense on computed tomographic examination, reflecting primarily the low water content of this highly viscous material.³¹ The mucous and inflammatory responses often behave as a space-occupying lesion that may cause bone absorption with resultant expansion into the orbits or cranium.³² AFRS can often be diagnosed by its characteristic computed tomographic findings that include the presence of this heterogeneously dense material filling that is present in only 1 or a few sinuses and through its expansion into adjacent tissue. Surgical intervention is essential for these patients, but current postsurgical medical therapies often prove inadequate, leading to high recurrence rates. Phenotype-specific biotherapeutics have yet to be evaluated.

Aspirin-Exacerbated Respiratory Disease

AERD was originally defined by the triad of NPs, asthma, and aspirin sensitivity (Samter triad).³³ AERD tends to develop in adulthood and is recognized in as many as 30% of asthmatic patients with CRSwNPs.³⁴ Features of this disorder are its association with severe pansinusitis, often with complete opacification of all

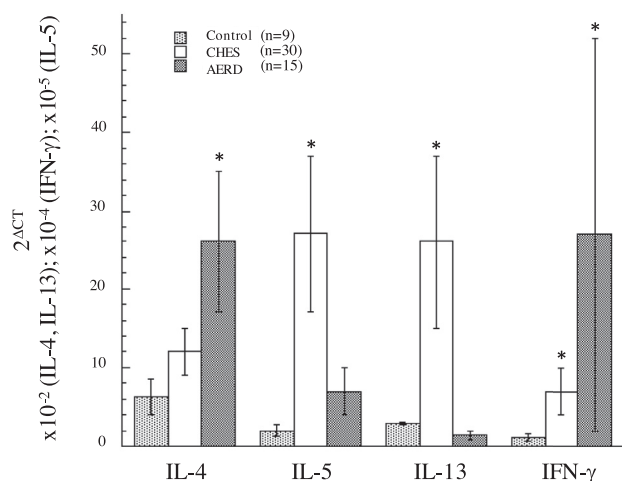


Figure 3. Cytokine signature in eosinophilic chronic rhinosinusitis (CRS) and aspirin-exacerbated respiratory disease (AERD). Tissue samples were homogenized after surgical removal and RNA isolated. Quantitative polymerase chain reactions were performed for interleukin (IL) 4, IL-5, IL-13, and interferon (IFN)– γ . Data reflect relative expression of each gene in comparison to β -actin ($2^{\Delta CT}$). Control samples ($n = 9$) are depicted in black bars, eosinophilic CRS ($n = 30$) in gray bars, and AERD ($n = 15$) in white bars. Error bars indicate SEMs. Reprinted from *J Allergy Clin Immunol*, Vol 132, Steinke JW, Liu L, Huyett P, Negri J, Payne SC, Borish L, Pages 856–865.e853, Copyright 2013, with permission from Elsevier.¹⁷

sinuses. When present in patients who have avoided aspirin, pansinusitis on computed tomographic examination is suggestive of AERD.³⁵ NPs in patients with AERD are aggressive, with multiple polyps that are characterized by rapid growth and, in the absence of medical management, universal recurrence after surgery.³³ These patients develop upper respiratory tract symptoms of nasal congestion, rhinorrhea, flushing, and paroxysmal sneezing, typically with exacerbations of their asthma after taking aspirin or other nonsteroidal anti-inflammatory drugs. These are not allergic reactions to these medications, but instead these reactions directly reflect their pharmacologic mechanism of action.³³ In many patients, asthma does not develop; thus, the term *AERD* rather than *aspirin-intolerant asthma* is preferred. However, when present, AERD produces a particularly severe form of asthma that is often difficult to control and is frequently associated with an irreversible decline in lung function.^{35–37} Another feature that distinguishes this disease is the absence of allergic sensitization.³³ When present, AR is a coincidental presence of this common disorder.

The sinus and NP tissue display robust eosinophilia, with approximately 3-fold greater numbers of eosinophils than is observed in eosinophilic CRS.⁶ As would be predicted, these patients have a robust type 2 cytokine environment,¹⁸ but our studies found this T_H2 -driven condition to be exacerbated by the additional presence of IFN- γ (Fig 3).¹⁷ This disease is characterized by robust constitutive overexpression of cysteinyl leukotrienes, and these patients are uniquely responsive to interventions that target their production, including leukotriene modifiers and aspirin desensitization.³⁸

Cystic Fibrosis

CRS with NPs is virtually universal in CF, and NPs are often the presenting concern.³⁹ Historically, the CRS that complicates the CF was assumed to be an infectious disorder. More recent studies have argued that chronic infection is an unusual phenotype of sinusitis in CF, which, instead, can have features of eosinophilic or non-eosinophilic disease. Noneosinophilic CRS in CF reflects the sequelae of the excessive inspissated mucus produced in this disorder, followed secondarily by colonization of the sinuses with bacteria and biofilm formation.³⁹ However, other patients have typical features of eosinophilic CRS, suggesting that eosinophilic inflammation may be a stereotypic immune response of the inflamed sinus.⁴⁰ A striking feature of both presentations of CF is the frequent concomitant presence of neutrophilia, something virtually never observed in other forms of CRS, suggesting the high prevalence of acute superinfections in these patients or a phenotype that indeed does have a chronic infection superimposed on their underlying noneosinophilic or eosinophilic CRS.

Proposed Pathogenic Mechanisms of Eosinophilic CRS

Many theories have been put forward to define pathogenic mechanisms and additional phenotypes in CRS. Some of these are listed in Table 2, but few survive close scrutiny.

Allergies in CRS

Traditionally, CRS has been routinely subclassified as diseases with and without an allergic component.⁴¹ Part of the argument for the existence of a separate allergic phenotype is the high prevalence of AR or allergic sensitization to aeroallergens (atopy) in these conditions. One study reported the presence of AR in 56% of patients with CRS, increasing to 78% in those with severe disease. Similarly, in children with recalcitrant sinusitis, atopy was reported in 50% of patients.⁴² There is a problem in properly interpreting these results because atopy and AR are common conditions. Sensitization to at least 1 aeroallergen via prick skin testing is present in as many as 54% of American adults⁴³ and in 40% of

Table 2
Possible Mechanisms of Eosinophilic CRS

Mechanism	Argument: Pro and Con
Allergic	Aeroallergens cannot access the sinuses Allergic sensitization is not required for eosinophilic CRS to develop Allergen avoidance has never been studied, and there is no benefit of worsening of CRS with seasonal exposures Immunotherapy has never been shown to benefit the sinus (as opposed to nasal) symptoms or objective findings
IgE	High IgE level in eosinophilic CRS better reflects a high IL-4/IL-13 milieu and can occur in the absence of allergic sensitization Beneficial effects of omalizumab were equally frequently reported in the nonallergic cohort
Sinus ostia occlusion	Sinus ostia occlusion is no longer considered an important component of eosinophilic CRS pathogenesis
Fungi	Evidence for <i>Alternaria</i> and other fungal colonization of the sinuses with a high IL-5 T-effector response limited to those with eosinophilic CRS
<i>Staphylococcus aureus</i>	No benefit observed with antifungal antibiotics Eosinophilic CRS frequently associated with <i>Staphylococcus</i> colonization and associated expression of <i>Staphylococcus</i> -derived superantigens
Autoimmunity	High frequency of specific IgE to <i>Staphylococcus</i> B-cell follicles observed in CRS in association with cytokines that drive B-cell maturation B cells extracted from CRS tissue demonstrate autoantibody production

Abbreviations: CRS, chronic rhinosinusitis; IL, interleukin.

children.⁴⁴ However, only approximately half of atopic individuals have symptoms on natural exposure to aeroallergens and are given the diagnosis of AR, so sensitization alone is not indicative of the presence of allergic disorder.^{43,44} However, it may prove difficult or, indeed, impossible to properly diagnose concomitant AR in individuals with coexisting CRS given the large overlap of symptoms. With the further arguments given below, it may be reasonable to conclude that the prevalence of allergic sensitization is not particularly enriched in CRS compared with the general population, and this frequency of sensitization in CRS may merely reflect the coincidental coexpression of a common condition without supporting causality.

IgE

In addition to a seemingly high prevalence of aeroallergen sensitization in CRS, what is also often seen in these individuals are high concentrations of total IgE. Some of this IgE can be ascribed to specific aeroallergen-targeted molecules, but, in the case of non-atopic individuals, specific IgE obviously cannot explain any of the total. For example, in a recent AERD study, 6 individuals had IgE concentrations ranging from 110 to as high as 1,760 IU/mL, none of whom were atopic.⁴⁵ An explanation for the high concentrations of IgE observed in CRS is that this is a reflection of the type 2 cytokine milieu characterizing these disorders.^{17,18} Studies on eosinophilic CRS consistently find high concentrations of IL-4 and IL-13, cytokines central to driving the IgE isotype switch.¹⁸ CRS tissue is replete with maturing B cells and germinal centers.^{5,46} Any B-cell maturing in this high IL-4 and IL-13 milieu will have the tendency to switch to IgE, regardless of what the antigen is to which the B cell is responding. That is, this nascent IgE could be directed against bacterial, viral, or other pathogen-derived proteins. Thus, the presence of high total IgE in CRS only argues for the presence of a

robust type 2 cytokine milieu and by itself does not argue for the presence of an allergic process.

Sinus Ostial Occlusion in Eosinophilic CRS

A previously proposed role for AR in CRS was the concept that AR-associated nasal disease promotes occlusion of the sinus ostia, which leads to the development of CRS. A role of ostial occlusion in noneosinophilic CRS remains controversial but is supported by some studies and could explain the beneficial results obtained from sinus surgery. However, what is no longer controversial is the recognition that there is no role for primary ostial occlusion in the pathogenesis of eosinophilic CRS.¹³ Eosinophilic CRSwNPs and CRSsNPs readily develop even with widely patent sinus openings. In addition, in this condition, sinus surgery to create a sinus window by itself is seldom, if ever, curative.

Aeroallergen Accessibility to the Sinuses

Another argument against a primary role for allergic sensitization in CRS is derived from the question of whether aeroallergens can even access the sinuses. In one study that used radiolabeled allergen, the conclusion was that aeroallergens do not access the sinus.⁴⁷ Another study, which also used radiolabeled particles, similarly concluded that aeroallergens cannot access the sinuses during normal breathing, sneezing, or coughing, although some ingress was observed with nose blowing.⁴⁸ Aeroallergens may more freely access the sinuses after sinus surgery, although, if important, that mechanism could still not support a mechanism of primary importance to CRS pathogenesis.

Absence of Evidence of Aeroallergen Exacerbation of CRS

If allergies were making an important contribution to the presence of CRS, presumably exacerbations would be observed with seasonal or other exposures. Early pilot studies reported that increased metabolic activity could be detected in the sinuses during relevant seasonal allergy exposures. However, when these studies were stringently followed up using multiple methods to demonstrate seasonally associated increased inflammation in the sinuses (using single-photon emission computed tomography, indium¹¹¹-labeled leukocyte uptake, and positron emission tomography), the results were categorically negative.⁴⁹ One well-performed study identified seasonal exacerbations of CRS (Fig 4); however, in this study, the season during which worsening

occurred was winter, and the worsening could only be ascribed to viral respiratory infections without any contribution observed during actual allergy seasons.⁵⁰

Absence of Benefit for Allergy-Directed Therapies in Eosinophilic CRS

An alternative argument for an allergic CRS phenotype could theoretically be derived from studies with allergy-directed therapies. There has never been a study of aeroallergen avoidance as a therapeutic modality in CRS; however, immunotherapy is well studied. The overarching problem with these investigations is the challenge of distinguishing nasal from sinus symptoms and properly ascribing any benefit of the immunotherapy to objective evidence supporting improvement in the CRS component. In studies in which improvements in CRS have been reported,⁵¹ sinonasal symptoms that were evaluated and scored included sneezing, itching, nasal congestion, eye itching, and epiphora (excessive tearing), parameters certain to be improved with immunotherapy in patients with AR, whereas no objective data were presented regarding improvement in sinus disease. Thus, in a recent retrospective analysis of 6 randomized studies in which immunotherapy was evaluated, the authors report consistent improvements in allergy-specific outcomes without any evidence of improvement in any of the sinus-specific outcomes.⁵²

Omalizumab

An alternative argument for therapeutic intervention supporting an allergic origin of CRS is derived from the reported beneficial effects seen with omalizumab. In a controlled trial, omalizumab was associated with reduced NP size, improved sense of smell, reduced computed tomographic opacification, and improvements in symptom and quality of life.⁵³ The problem is that even if confirmed in more definitive studies, it is not necessary to ascribe any beneficial effects of omalizumab to its targeting of inhalant allergies. Omalizumab is effective in nonatopic asthma,⁵⁴ including in nonallergic patients with AERD.⁵⁵ In addition, most problematic in ascribing omalizumab's benefit in CRS to an allergic basis is that in the previously mentioned study,⁵³ improvements were equally likely to occur whether or not the patient was atopic.

Endogenous Allergy in Eosinophilic CRS

Fungi

A distinct mechanism for an allergy contribution to CRS would be if the hypersensitivity response were to an endogenous allergen. These allergens include fungi, bacteria, or perhaps other pathogens that colonize the airway. A central mechanism for colonizing fungi in driving CRS is unambiguous in AFRS. What has been controversial is whether there is a role for endogenous fungi in eosinophilic CRS. Support for this concept is based on the observation that fungi are universally present in the sinus cavity,⁵⁶ with the suggestion that eosinophilic CRS could develop in individuals in whom the usual state of immune nonresponsiveness breaks down, allowing a T_H2 response to develop. These investigators intriguingly found that patients with eosinophilic CRS (and not the healthy controls) had circulating T-effector lymphocytes that secreted IL-5 in response to *Alternaria*.⁵⁶ Subsequently, this line of research has been dismissed because of the overwhelming evidence that sinus irrigation with antifungal antibiotics fails to produce clinical benefit.^{57,58} However, this argument seems unfair against this as a mechanism because antifungals are consistently ineffective in AFRS despite universal acceptance that it is a fungally mediated disease. These failures presumably reflect the impossibility of eradicating fungi from the CRS environment.

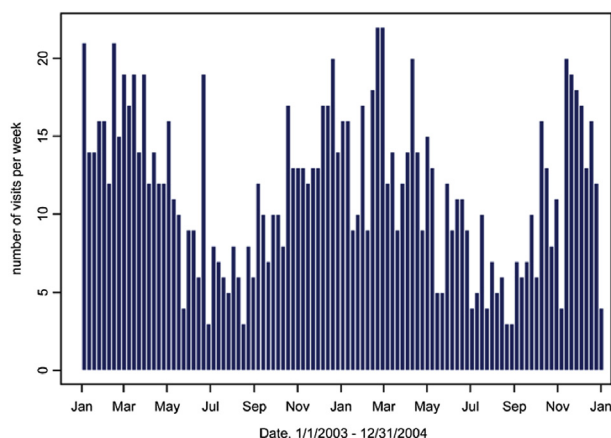


Figure 4. Seasonal patterns of chronic rhinosinusitis exacerbation visits (n = 1217). Each bar represents 1 week. Reprinted from *J Allergy Clin Immunol*, Vol 126, Rank MA, Wollan P, Kita H, Yawn BP, Acute exacerbations of chronic rhinosinusitis occur in a distinct seasonal pattern, Pages 168–169, Copyright 2010, with permission from Elsevier.

Staphylococcus aureus

As in other atopic diseases (especially atopic dermatitis), *Staphylococcus* colonization is common in eosinophilic CRS, reflecting, in addition to loss of barrier function and mucociliary clearance, the recognition that type 2 inflammation inhibits production of antimicrobial proteins, such as β -defensin, that are required to restrict this bacteria.⁵⁹ Thus, the incidence of *Staphylococcus* colonization in eosinophilic CRS is as high as 60% to 80%.^{8,60} These *Staphylococcus* produce T-cell–activating superantigens that further exacerbate the high T_H2 state.⁶¹ As discussed previously, in the presence of an elicited *Staphylococcus*-directed humoral immune response, this high IL-4/IL-13 milieu results in generation of *Staphylococcus* specific IgE.^{8,60} Although not suggesting a typical allergic disease, a role for *Staphylococcus* specific IgE may underlie some of the benefit observed with omalizumab.

Autoimmunity in CRS

Finally, a recent study reported the production of autoantibodies by CRS-derived B cells, including antibodies directed against double-stranded DNA, BP180, IgG, and IgA.⁶² As such, autoimmunity could explain the development and persistence of this severe progressive inflammatory disease of the sinuses.

Conclusion

In summary, current CRS guidelines fail to take into account the multiple disease processes that drive sinus inflammation and therefore are not adequate in directing individualized treatment. Rather than the simple division of CRS into those with and without NPs, phenotypes that separate and accurately describe the disease process will ultimately prove much more valuable. Currently, it is at least possible to characterize the inflammatory infiltrate, which has proven useful in identifying CRS phenotypes. Specifically, a useful designation involves the identification of eosinophilic and non-eosinophilic CRS and, within the eosinophilic group, subtypes that include AERD, AFRS, and idiopathic eosinophilic CRS. Less typical noneosinophilic subtypes include CF (usually) and infectious CRS. With the likely pending availability of biotherapeutics to treat CRS, proper phenotyping, as with asthma, will prove essential. Already, efficacy of IL-5 antagonists in CRS is limited, not surprisingly, to the high IL-5 cohort.²⁸ In addition, although comprising a plurality of CRSwNPs (at least in North America and Europe), this is not true of all patients with NPs, and many patients with CRSwNPs can have an eosinophilic disease and likely will respond to these agents. Similarly, many agents being developed for asthma, such as IL-4, IL-13, and thymic stromal lymphopoietin antagonists, are likely to only be effective in the high T_H2 /eosinophilic cohorts, regardless of their polyp status.

The pathogenic mechanism driving the development of CRS is currently unknown. Currently, there is little compelling evidence to support a role for IgE against aeroallergens in driving the pathogenesis or severity of CRS. There is no compelling evidence that allergy-directed therapies, such as immunotherapy, provide clinical benefit in this disorder, and even the studies demonstrating benefit with omalizumab seem adequately ascribed to mechanisms that do not target inhalant allergen specific IgE. However, it must be appreciated that there exists a subset of patients with CRS who do have AR, although this can be difficult to discern given their shared symptoms. In addition, where AR and CRS coexist logically, they synergize to promote patient misery. As such, both conditions need to be addressed as part of an appropriate treatment plan.

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