

Mechanisms of allergic diseases

Series editors: Joshua A. Boyce, MD, Fred Finkelman, MD, William T. Shearer, MD, PhD, and Donata Vercelli, MD

Genetics and phenotyping in chronic sinusitis

Spencer C. Payne, MD,^{a,b} Larry Borish, MD,^a and John W. Steinke, PhD^a Charlottesville, Va

Chronic sinusitis with nasal polyposis historically has been treated as a single monolithic clinical disorder. Just as asthma is now accepted as numerous heterogeneous diseases, chronic sinusitis should also be viewed as comprising several diseases with varying causes, with each one characterized by distinct histologic and gene and protein expression patterns. This includes recognition of the need to define these diseases based on the presence or absence of an eosinophilic infiltrate but also on additional distinctions based on unique agents that drive their development and perpetuation. As a collection of heterogeneous diseases, proper differential diagnosis is required to delineate appropriate therapeutic intervention. This review will focus on recognized distinct presentations of chronic sinus disease, including distinguishing the clinical presentations, cellular and molecular characteristics, genetic differences, and current treatment options for each. (*J Allergy Clin Immunol* 2011;■■■:■■■-■■■.)

Key words: *Fibrosis, chronic sinusitis, aspirin-exacerbated respiratory disease, eosinophils, nasal polyps*

Diseases within the sinuses produce one of the most common health care problems, affecting approximately 16% of the population and having a significant adverse effect on quality of life and daily functioning.¹ Historically, chronic sinusitis (CS) was considered a unimodal disease, and as such, all patients had the same treatment options. In recent years, this idea has been challenged, and it is now recognized that there exist multiple variants of CS, each requiring unique approaches to management. There has also been a move toward renaming this spectrum of diseases with the term *rhinosinusitis* in an attempt to emphasize the concept that patients present with symptoms attributable to not

Abbreviations used

AERD: Aspirin-exacerbated respiratory disease
AFS: Allergic fungal sinusitis
CCS: Corticosteroid
CF: Cystic fibrosis
CHES: Chronic hyperplastic eosinophilic sinusitis
CS: Chronic sinusitis
CT: Computed tomography
CysLT: Cysteinyl leukotriene
HIF: Hypoxia-inducible factor
LTC₄S: Leukotriene C₄ synthase
NES: Noneosinophilic sinusitis
NP: Nasal polyp
PAI-1: Plasminogen activator inhibitor 1
PG: Prostaglandin

only the sinuses but also to nasal inflammation that might often but not always be present. Our use of the term *sinusitis* throughout this review is to emphasize that we are focusing exclusively on the pathological component present in the sinuses to avoid confusion insofar as associated nasal diseases can comprise distinct pathological entities. Furthermore, this term can be misleading in suggesting that the natural progression of sinusitis is initially driven by inflammation in the nasal cavity. Although it might often be the case that sinus ostial obstruction and subsequent sinusitis can result from primary allergic or upper respiratory tract infectious inflammation in the nose, it remains unproved from prospective studies whether and how often this is the actual order of events.

This review will focus on the recognized subtypes of inflammatory diseases of the sinuses, including distinguishing clinical presentations, cellular and molecular characteristics, genetic differences, and treatment options for each, to better address these issues, while temporarily setting aside this controversy. Although CS with nasal polyps (NPs) is also a near-universal complication of cystic fibrosis (CF), this is already a well-recognized association and will not be a focus of this review.

STRUCTURE AND FUNCTION OF THE SINUSES

The paranasal sinuses and turbinates develop from primordial ridges that develop along the lateral nasal cavity wall during fetal development. With the exception of the inferior turbinate, the sinonasal structures all develop from these ethmoturbinates. Although there is a fairly consistent pattern to the formation of these structures, resulting in a series of oblique structures that attach to the lamina papyracea (uncinate process, ethmoid bulla, middle turbinate, superior turbinate, and sometimes a

From ^athe Asthma and Allergic Disease Center, Carter Immunology Center, Department of Medicine, and ^bthe Department of Otolaryngology–Head and Neck Surgery, University of Virginia Health System.

Disclosure of potential conflict of interest: S. C. Payne has received honoraria from Acclarent and has provided legal consultation or expert witness testimony in cases related to sinus surgery. L. Borish is a consultant for Hoffman LaRoche, Cephalon, Regeneron, and Pfizer; has received honoraria from Merck; has received research support from Genentech and Merck; and is a volunteer for the American Academy of Allergy, Asthma & Immunology and the Charlottesville Free Clinic. J. W. Steinke has received research support from the National Institutes of Health (NIH), the NIH Asthma and Allergic Disease Center, and Medtronic.

Received for publication April 4, 2011; revised May 6, 2011; accepted for publication May 10, 2011.

Reprint request: Larry Borish, MD, Asthma and Allergic Disease Center, Box 801355, Charlottesville, VA 22903. E-mail: lb4m@virginia.edu.

0091-6749/\$36.00

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doi:10.1016/j.jaci.2011.05.022

Terms in boldface and italics are defined in the glossary on page ■■■.

supreme turbinate), the extent and complexity of pneumatization can be variable. At birth, the maxillary, frontal, and sphenoid sinuses are fairly nascent, expanding out from these primary structures into their respective cranial bones during childhood and adolescence.²

Although the structure of the sinuses is well understood, the actual purpose of the paranasal sinuses remains unknown. Various ideas have been proposed over time, including lightening the weight burden of the head, enhancing vocal resonance, or providing a thermal insulating barrier. A recently proposed theory suggests that they serve as a “crumple zone” for the vital structures of the head (eyes and brain) to dissipate destructive forces resulting from trauma.³ Whether part of their original teleological function, they have now been found to also produce nitric oxide, an immune mediator capable of killing bacteria, viruses, fungi, and tumor cells that, through inhalation, can function as a bronchodilator. The sinuses thereby also contribute to the innate immune defense of the airway.

Proper functioning of the sinuses relies on adequate drainage of their produced mucus and normal ventilation. Even when against gravity, in the case of the maxillary sinus, this mucociliary clearance is a highly coordinated effort of millions of beating cilia that line the surface of the sinus epithelium, which have been preprogrammed to move any mucus or particles toward the natural, often slit-like opening (or ostium). This process can easily be compromised by swelling or inflammation of the nasal mucosa, which can result in both a decrease in ciliary beat frequency⁴ and ostial obstruction and poor drainage. This combination leads to stagnation of sinus secretions and a lack of oxygen in the sinus, further reducing mucociliary clearance and nitric oxide production.

CHRONIC SINUSITIS

By definition, CS is characterized by symptoms of nasal irritation, anterior and posterior rhinorrhea, and nasal blockage with the concomitant presence of pressure or pain in a “sinus” distribution that last more than 12 weeks.⁵⁻⁷ Corroboration with objective criteria on nasal endoscopy or computed tomographic (CT) imaging is essential because there can be significant overlap in these symptoms with severe nasal inflammation or self-diagnosed “sinus headaches,” which, although presenting with nasal congestion and rhinorrhea, are more likely to be of migraine or *midfacial pain syndrome* origin.^{8,9}

A summary statement has divided CS into 2 subsets exclusively defined by whether the chronic inflammatory sinus process is present with or without NPs.^{6,7} This distinction was driven in large part by research that indicated a significant association between nasal polyposis and the presence of tissue eosinophilia.¹⁰⁻¹³ Although the data are compelling that eosinophilia is more likely to be associated with the presence of NPs, both the presence and extent of eosinophilia in NPs can be quite variable, and a large subset of NPs observed in patients with idiopathic nasal polyposis do not demonstrate eosinophilia.^{12,14-19} These observations support the opposing expert view²⁰ that although certain forms of CS might be more likely to produce NPs, polyposis can develop as a complication of any form of CS and should not be used as the exclusive basis for diagnosis or treatment recommendations. The association of eosinophilia to NPs is driven, to a large extent, by recognition that certain, particularly proinflammatory, forms of CS, such as allergic fungal sinusitis (AFS)²¹ and aspirin-exacerbated respiratory disease (AERD),^{22,23} are characterized both by a strong predilection for NP growth and the presence of a robust eosinophilic infiltrate into the sinus cavity. The presence

GLOSSARY

B CELL-ACTIVATING FACTOR OF THE TNF SUPERFAMILY (BAFF), A PROLIFERATION-INDUCING LIGAND (APRIL): BAFF and APRIL are both ligands that bind to the TNF receptor family member transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) to activate B cells and induce class-switching. TACI mutations can cause common variable immunodeficiency.

BIOFILMS: Biofilms are comprised of bacteria embedded in a bacterial matrix of polysaccharide, proteins, and DNA and function as a resistance barrier to antibiotics and phagocytosis.

HYPOXIA-INDUCIBLE FACTOR (HIF): Hypoxia-inducible factor is a transcription factor that binds to hypoxia-responsive elements. It is activated during airway remodeling, is induced by vascular endothelial growth factor, and occurs in inducible (HIF-1 α) and constitutive (HIF-1 β) forms.

IL-4, SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION (STAT6): The STAT family of transcription factors become phosphorylated, dimerize, and bind to palindromic DNA elements in response to Janus-activated kinase pathways. STAT6 is important for IL-4 and IL-13 signals and activates *GATA3* gene expression.

IL-6: IL-6 is released by dendritic cells, primes for T_H2 effector cells, and inhibits the suppressive functions of CD4⁺CD25⁺ regulatory T cells.

IL-22: IL-22 is thought to be a key regulator of epithelial cell homeostasis and to be protective/regenerative rather than proinflammatory. It is made by T cells (T_H22 and T_H17) and natural killer (NK-22) cells, as well as by macrophages.

IL-33: IL-33 is an IL-1 family member that is produced by epithelial cells, smooth muscle cells, and fibroblasts that increase both IL-5 and IL-13 production.

MIDFACIAL PAIN SYNDROME: Also known as midfacial segmental pain syndrome. Midfacial pain syndrome is pain localized to the middle of the face and occurs because of migraine or sinus disease or after facial trauma.

OMALIZUMAB: Anti-IgE can be used for the treatment of severe asthma and has been used in clinical trials for the treatment of peanut allergy, immunotherapy, and eosinophilic gastroenteritis.

TGF- β : TGF- β is associated with both proinflammatory and anti-inflammatory states. High TGF- β production by gastrointestinal T_H3 cells is associated with tolerance to food antigens, and lack of TGF- β in mice is associated with autoimmunity. In patients with allergic inflammation, eosinophils and mast cells can make TGF- β , which contributes to airway and esophageal fibrosis and remodeling. TGF- β consists of a number of family members (TGF- β 1, 2, and 3) that reside on distinct chromosomes and have differential tissue expression patterns.

T_H17: T_H17 cells are defined by production of IL-17A, IL-17F, IL-6, IL-21, IL-22, and TNF- α and are involved in autoimmunity. Production of IL-17 is increased by IL-23, which uses the transcription factor STAT3 to maintain a T_H17 phenotype in CD4⁺ T cells.

VASCULAR ENDOTHELIAL GROWTH FACTOR, PLATELET-DERIVED GROWTH FACTOR: Vascular endothelial growth factor is a proangiogenic factor; is increased relative to antiangiogenic factors, such as endostatin, in asthmatic patients; can be produced by chymase-positive mast cells in the airway; and is associated with airway remodeling that can lead to airways dysfunction. Platelet-derived growth factor can switch the airway smooth muscle phenotype from contractile to proliferative.

The Editors wish to acknowledge Seema Aceves, MD, PhD, for preparing this glossary.

or absence of NPs can therefore be useful in clinical practice for defining patients who are more or less likely to have eosinophilic disease and, as such, are more or less likely to respond to eosinophil-targeted therapies. However, it is the overarching treatise of this review that the proper categorization of chronic sinus diseases should be based primarily on distinct pathological presentations and that this should form the basis for diagnostic and treatment considerations (Table I). However, it should be recognized that CS in reality presents as a spectrum of disorders in which the level of eosinophilia and predilection for polyposis exist on a continuum (Fig 1). Although we will emphasize the distinct features of the pathology of eosinophilic and noneosinophilic forms of these diseases, in reality patients can present with variable overlapping features.

CHRONIC INFECTIOUS SINUSITIS

All forms of CS are associated with the loss of barrier and innate immune functions that would normally prevent infection of healthy sinuses, and as such, these patients are highly predisposed to frequent and protracted bouts of acute sinusitis. Consequently, all forms of CS are also associated with the loss of sterility observed in healthy sinuses and, as such, are routinely associated with the presence of anaerobic bacteria, gram-negative organisms, *Staphylococcus aureus*, and other bacteria. However, chronic infection (ie, an episode of acute sinusitis that persists beyond 12 weeks despite antibacterial therapy) is less often the cause of CS and, when present, should raise suspicion for underlying immune deficiency, HIV, Kartagener syndrome, or CF. Additionally, current recommendations are that patients with CS should be evaluated for other factors that might have a causative or modifying role, such as allergic status or the presence of anatomic abnormalities. The exact role of either of these with respect to sinus inflammation is uncertain, but failure to address them might result in a decreased level of patient improvement.²⁴ Patients with chronic infectious sinusitis are identified pathologically by prominent neutrophilia and intense bacterial infiltration ($>10^5$ to 10^6 colony-forming units/mL) within their sinuses. However, these patients with primary infectious sinusitis should not be confused with most other patients with CS who have a noninfectious inflammatory disorder that can be complicated or exacerbated by overlying infection. In these latter patients, the presence of these bacteria reflects the loss of the usual mechanisms responsible for maintaining sterility in the healthy sinus cavity (eg, loss of mucociliary clearance and barrier function) and the resultant secondary bacterial colonization. These bacteria might be benign commensal organisms but, alternatively, likely promote or exacerbate each of the other presentations of CS through their ability to function as sources of antigens, immune adjuvants, and superantigens.

The role of *biofilms* as a major component of chronic infections has also been noted. Numerous studies have indicated the presence of biofilms in patients undergoing endoscopic sinus surgery.²⁵⁻²⁷ Additionally, the presence of these biofilms has prognosticated a poorer outcome after sinus surgery.²⁸⁻³⁰ It is not entirely clear what the role of biofilms is in the pathogenesis of CS in patients who have not had prior surgery. Furthermore, it remains uncertain whether refractory patients with biofilms have more severe disease as a direct result of the infection or as a function of the immune-modulating characteristics imparted by associated toxins or pathogen-associated molecular patterns. Biofilms are present

TABLE I. Presentations of CS

CF	
Infectious	Idiopathic
	With immune deficiency
Noneosinophilic	Idiopathic
	Caused by chronic rhinitis
	Caused by anatomic predisposition
Eosinophilic	CHES
	AERD
	AFS

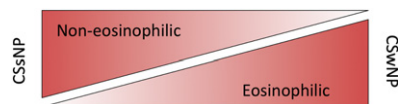


FIG 1. Eosinophilic and noneosinophilic forms of sinusitis present with distinct pathological features and require distinct clinical approaches. However, in individual patients CS presents along a spectrum in which the level of eosinophilia and predilection for polyposis exists on a continuum. CSsNP, Chronic sinusitis without nasal polyposis; CSwNP, chronic sinusitis with nasal polyposis.

and likely contribute to all forms of CS.³¹ Thus biofilms act as sources of bacteria that can emerge from this resting state and differentiate into their planktonic form, driving acute superinfections. Also, as in patients with chronic infectious disease, bacteria in biofilms can be sources of antigens, superantigens (eg, *Staphylococcus* species–derived superantigens), adjuvants, toxins, and other proinflammatory factors.³¹ This is particularly relevant, for example, to AERD in which *Staphylococcus* species–derived superantigens drive specific IgE production and promote the severity of inflammation.³² Regardless, the concept that all CS is primarily an infectious disorder, although mostly discredited, still leads to the inappropriate use of antibiotics and surgical drainage as primary modalities of treatment.

NONEOSINOPHILIC SINUSITIS

Idiopathic noneosinophilic sinusitis (NES) is thought to result from chronic or recurrent occlusion of the sinus ostia caused by viral rhinitis, allergic rhinitis, anatomic predisposition, or other causes. These processes lead to recurrent and protracted bacterial infections, possibly in association with barotrauma of the sinus cavities and damage to the respiratory epithelium, ciliary destruction, prominent mucous gland and goblet cell hyperplasia, bacterial colonization and biofilm formation, and chronic inflammatory changes.^{15,33} The inflammatory component of this form of sinusitis consists of a mononuclear cell infiltrate with few neutrophils.¹⁹ Neutrophils, when present, suggest recent infection, CF, or persistent infection. NES is associated with robust remodeling with dense deposition of collagen and other matrix proteins.

Many studies have addressed the role of lymphocytes in the various forms of CS. Although not a prominent feature of NES or, similarly, chronic hyperplastic eosinophilic sinusitis (CHES) or AERD, infiltrating CD4 and CD8 T lymphocytes are identified in all forms of CS.^{34,35} In contrast to these T-cell studies, what is particularly striking is the prominence of infiltrating B cells, often in the form of germinal center–like structures,^{15,36} and plasma cells, and this finding is particularly prominent in patients with NES. B-cell activation has been linked to the prominent expression of

B cell-activating factor of the TNF superfamily (BAFF) and a **proliferation-inducing ligand** (APRIL).³⁶ This B-cell activation is primarily associated with secretion of IgA antibodies.

The thick collagen remodeling seen in patients with NES is reflected by the high expression of growth factors involved in fibroblast and fibrocyte recruitment with secondary collagen production, including **TGF- β 2**, fibroblast growth factor, **platelet-derived growth factor**, and **vascular endothelial growth factor**.³³ However, other authors have had differing results when evaluating for TGF- β 1,^{37,38} showing a decrease in TGF- β 1 levels in polyps, which was accentuated in patients without asthma. Another characteristic of NES is the presence of large numbers of connective-tissue mast cells, which are less frequent in the eosinophilic forms of sinus disease.³³ These mast cells are also likely candidates as sources of the fibrotic factors demonstrated in these polyps. Increasing evidence points to the role of mast cells in many diseases characterized by chronic injury and repair and a resulting interplay between mast cells and fibroblasts.^{39,40}

Microarray analysis of NES-NP demonstrated increased expression of **hypoxia-inducible factor** (HIF) 1 α .⁴¹ This is consistent with the concept that occlusion of sinus ostia is a likely primary pathogenic mechanism in this form of CS and will lead to the development of relatively high levels of hypoxia within the sinuses.⁴² HIF-1 α is a transcription factor induced under hypoxic conditions (and in response to tissue injury) that is involved in the activation of inflammatory pathways.⁴³ NP-derived fibroblasts increase their production of HIF-1 α in response to hypoxia,⁴⁴ and a corresponding *in vivo* upregulation was also demonstrated⁴⁵ and is consistent with the hypoxic milieu observed in patients with CS.⁴⁶ Although the increased expression of HIF-1 α might simply be a stress response, the implication cannot be ignored that hypoxia might play a significant role in the pathogenesis of NES, promoting the production of inflammatory mediators and tissue fibrosis. This model is supported by the finding that hypoxia increased production of CXCL8 (IL-8) and several proangiogenic factors.^{44,47}

Genetics of NES

Little is known regarding the development of this disease, and as such, there are few studies that have directly assessed its genetic component. An early study by our group identified the plasminogen activator inhibitor 1 (*PAI-1*) gene as a possible candidate gene.⁴⁸ A role for PAI-1 is consistent, with recent observations regarding the expression of PAI-1 and thrombotic/fibrinolytic pathways in patients with CS.^{49,50} The 4G allele of this gene has been linked to the regulation of fibrosis in asthmatic patients and in particular to airway remodeling leading to irreversible obstruction.⁵¹ In our study the 4G allele was overrepresented in the NES group compared with the control group of subjects without sinus disease (0.53 vs 0.45).⁴⁸ In a recent study in which subjects were excluded if they had asthma, atopy, or aspirin intolerance (and thus were more likely to have NES), it was found that patients with CS had an increased prevalence of a GG genotype at position -174 of the **IL-6** promoter compared with a control group without sinus disease.⁵² This led to an odds ratio of 2.65 for having this genotype and having NES with NPs. Given the effect of IL-6 on the differentiation of naive CD4⁺ T cells toward a **T_H17** lineage, this correlates with other authors who have found an increased T_H17 signature in NE-NPs.^{37,38} IL-6 is also essential for plasma cell differentiation, and this linkage also fits

into the previously discussed role for humoral immunity in patients with NES.

Treatment

When caused by anatomic occlusion, chronic inflammatory sinusitis that has not resolved with conservative medical therapy is generally responsive to surgical interventions, specifically functional endoscopic sinus surgery.⁵³ The increased ventilation of the sinuses is likely able to contribute to the therapeutic benefit observed after surgery because of a secondary reduction of HIF-1 α and hypoxically induced inflammation and fibrosis. Furthermore, the increased ostial size allows for enhanced penetration of sinonasal irrigants.⁵⁴ When complicated by the presence of biofilms, patient improvement might be more limited, however. Additional topical therapies have been used to combat these limitations by augmenting the promotion of the mucus-clearing effect of nasal saline irrigation with surfactants^{55,56} and antimicrobial agents.⁵⁷

CHES

CHES is an inflammatory disease characterized by the prominent accumulation of eosinophils in the sinuses and, when also present, associated NP tissue.⁵⁸⁻⁶⁰ Although NPs frequently occur with CF, AFS, and AERD, in the absence of one of these conditions, the presence of nasal polyposis (especially in the concomitant presence of asthma) has been proposed as presumptive evidence for CHES.⁶¹ However, CHES can only be unambiguously diagnosed on histochemical staining of tissue for eosinophils or through quantification of eosinophil-derived mediators (eg, eosinophil cationic protein or major basic protein). In patients with CHES, the sinus tissue demonstrates a marked increase in cells that express cytokines (eg, IL-5 and GM-CSF), chemokines (eg, CCL5, CCL11, and CCL24), and proinflammatory lipid mediators (eg, cysteinyl leukotrienes [CysLTs]) that are responsible for the differentiation, survival, and activation of eosinophils.^{60,62-64} Because eosinophils are a prominent source of many of these cytokines and lipid mediators, this suggests that CHES is a disease of unrestrained inflammation and that once eosinophils are recruited, they provide the growth factors necessary for their further recruitment, proliferation, activation, and survival.^{58,62,63} Thus in contrast to NES, CHES behaves as a self-perpetuating syndrome and, as such, does not respond well to surgery alone.⁶⁵

The cause of CHES is poorly understood. Many, but not all, of these patients display allergic sensitization as determined by positive skin prick test or IgE immunoassay results. In general, aeroallergens do not access healthy sinus cavities, and this is likely to be even truer with the occlusion of the sinus ostia that occurs with this disease.^{66,67} However, these patients do display worsening of sinus inflammation after aeroallergen exposures, and nasal challenges exacerbate eosinophil influx into the sinuses.⁶¹ In the absence of direct access to the sinuses, these studies suggest systemic and/or local lymphatic recirculation of inflammatory cells (ie, eosinophils, eosinophil precursors,⁶⁸ dendritic cells, and T_H lymphocytes) between the nasal epithelium, nasal/sinus lymphatics, bone marrow, and sinus tissue that drive this disorder.⁶⁹⁻⁷² Alternatively, allergic (IgE) sensitization to commensal fungi and bacteria colonizing the sinuses (or residing in biofilms) might also be pathogenic.⁷³⁻⁷⁵ These patients often

have asthma, and this disease shares many histologic and immunologic features with asthma, suggesting that CHES and asthma might comprise the same idiopathic immune process, attacking the upper and lower airways, respectively.⁶⁹⁻⁷¹

Genetics of CHES

More than 30 studies have been performed addressing a possible genetic linkage to CHES and NP formation. Many of these are single studies that have not been replicated and have low numbers of subjects enrolled. As a result, only studies that have been replicated or contain sufficient numbers will be discussed here. Many of the genes associated with CHES fall into the category of inflammatory genes, possibly indicating a role for dysregulation of cytokine production in the induction and maintenance of CHES. An association of *IL-1α* with CS and NPs has been replicated in 3 separate studies with a G allele at position +4858 in exon 5 of the gene being associated with greater risk.⁷⁶⁻⁷⁸ Three studies have also described an association of CS and NPs with the -308 G-to-A polymorphism in the *TNF-α* gene^{77,79,80}; however, 2 other studies were unable to replicate this finding,^{78,81} making the true significance of this polymorphism unclear. In patients with asthma, we reported that a C-to-T polymorphism at position -590 of the *IL-4* promoter is associated with increased risk of asthma.^{82,83} The C allele has now also been associated with the development of NPs in 2 studies of Asian cohorts.^{84,85} Other inflammatory genes that have been reported include *IL-33*, *IL-22* receptor α1, *IL-1ra*, *IL-1* receptor-like 1, and matrix metalloproteinase 9. Another genetic region that has been linked with the development of CHES is the human major histocompatibility complex. Numerous genes within this region have been reported, suggesting a link to defects in antigen presentation as a cause for disease. The *HLA-DQA1*0201* allele has been found to confer a 2 to 5 times increased risk for disease.^{86,87} More than 12 other HLA alleles have been implicated in disease development, although many have not been replicated in subsequent studies.

Treatment

Because mucous inspissation and bacterial biofilms also contribute to CHES, nasal saline irrigation with or without surfactants is the mainstay of treatment for these disorders as well. As sources for antigens and superantigens, bacteria contribute to disease severity, and limited use of systemic (or possibly topical) antibiotics might be useful. The addition of mupirocin to the irrigations in patients with recalcitrant disease was shown to be effective in patients with polypoid mucosa.⁵⁷

Reflecting its pathological similarity to asthma, approaches that are effective in patients with asthma are often effective in patients with CHES, including corticosteroids (CCSs) and leukotriene modifiers. Topical CCSs, although shown to be effective in decreasing NP size and reducing recurrence after surgery, might have limited efficacy against the CHES component of this disease because of their limited capacity to access the sinus cavity.⁸⁸ Systemic CCSs can be extremely effective in the short term both in reducing polyp size and targeting the inflammatory component of CHES, and numerous studies have shown a reduction in IL-5, eotaxin, and eosinophil cationic protein levels with a decrease in polyp mass.⁸⁹ The combination of systemic CCSs followed by intranasal CCSs has also been shown to be an effective

long-term strategy.⁹⁰ This might reflect in part the use of the systemic CCS to help intranasal CCS sprays gain access to the sinus cavity. We found that budesonide nasal irrigations led to a decrease in the sinus CT score, a decrease in the reported sinus symptom score, and an increase in sense of smell after a minimum of 3 months' treatment,⁹¹ which we attribute to improved sinus access compared with nasal sprays. This effect is enhanced in the postsurgical patient, as we had noted previously. It is likely that providing the CCS in a large-volume liquid form (compared with an aerosol or droplet form in which direct contact is much more localized) is able to deliver the agent to areas otherwise unreached through more traditional applicators. The study also showed improvement in the severity of asthma in 75% of those whose symptoms had been poorly controlled.⁹¹

There are no well-performed controlled studies of leukotriene modifiers in patients with CHES, and most of the published studies with leukotriene modifiers were conducted as add-on therapy to intranasal CCSs, making them even more difficult to interpret. In one study 24 patients who were actively treated with intranasal steroids were followed for 3 months after starting montelukast. NP symptom scores improved in 17 of the subjects, and eosinophil polyp counts decreased when compared with pretreatment values.⁹² No studies have compared leukotriene receptor antagonists with 5-lipoxygenase inhibitors.

Surgery, as noted, is seldom effective by itself in providing long-term benefit but might be essential both to initially address aggressive hyperplastic disease before initiating optimal medical therapy and to provide access for topically acting agents (eg, nasal saline irrigants, surfactants, topical antibiotics, or intranasal CCSs, including especially those delivered by means of saline irrigation [budesonide inhalant suspension]).

Despite early enthusiasm, current studies do not support the use of topical antifungal agents.^{93,94} This might reflect the absence of a role for fungal colonization in patients with CHES; however, this might also reflect the use of an unstable compound (amphotericin B) that was not able to reduce fungal antigen load. The role of allergy-directed therapies (eg, immunotherapy or *omalizumab*) is reported but not established by compelling properly performed clinical trials. In a small unblinded study 4 subjects with atopic asthma received omalizumab after endoscopic sinus surgery and demonstrated improvement in NP scores, whereas a matched control group did not show improvements.⁹⁵ In a larger uncontrolled open-label study of 19 subjects with severe asthma and CS, treatment with omalizumab for 16 months led to a reduction in NP size, with no patients needing sinus surgery and a decrease in intranasal CCS use.⁹⁶ Antibodies that target IL-5 have also been shown to be effective in diminishing NPs,⁹⁷ specifically in the CS cohorts displaying high levels of this cytokine and eosinophilia. This observation emphasizes the utility of differentiating forms of CS based on their phenotype as opposed to merely the presence or absence of NPs.

AFS

Occasionally, mold present as a commensal in the sinuses can act as potent activators of pathogen-associated molecular pattern receptor-induced innate immune pathways and synergistically elicit robust T_H2 lymphocyte and eosinophilic inflammatory responses, thereby producing this distinct disorder. Originally, this disease was singularly ascribed to *Aspergillus* species; however, it is now recognized that many species of fungi, particularly

TABLE II. Features of AERD

Onset	Third or fourth decades of life, later than other forms of asthma
Eosinophilic sinusitis	Extensive pansinusitis, often with complete opacification of all sinuses
NPs	Robust, rapidly growing, and require frequent surgical removal
Anosmia	More frequently associated with complete anosmia than idiopathic eosinophilic sinusitis
Asthma	When present, tends to be severe and difficult to control Frequently associated with extensive remodeling and progressive irreversible decrease in lung function
Aspirin sensitivity	Sensitivity to aspirin and other nonselective COX inhibitors Patients generally tolerate selective COX-2 inhibitors
Eosinophilia	Robust eosinophilic infiltration of bronchial airways, as well as sinuses and NPs Also significant increases in circulating absolute eosinophil counts
CysLTs	Patients display constitutive overproduction and overresponsiveness to CysLTs. Aspirin (and other COX inhibitor)-induced reactions largely reflect surge in CysLT production.
Nonatopy	In contrast to other forms of asthma, patients are often nonatopic (do not display IgE sensitivity to aeroallergens or increased total IgE levels). When present, allergic rhinitis reflects coincidental presence of this common disorder.

dematiaceous varieties, are associated with AFS, including *Alternaria*, *Penicillium*, *Cladosporium*, *Curvularia*, and *Bipolaris* species.⁹⁸ This form of eosinophilic CS is characterized by specific IgE sensitization, as demonstrated by skin prick tests or serum immunoassays, along with increased total serum IgE concentrations.²¹ Development of AFS tends to occur in young, atopic, immunocompetent subjects, with a slight female preponderance.²¹ In contrast to other forms of eosinophilic sinusitis, this disease is often unilateral and limited to 1 or a few sinuses. The presence of intense eosinophilic infiltration and eosinophil-derived secretory products, fungal hyphae, and extensive goblet cell and mucus gland hyperplasia produces a thick dark brown to green exudate (“allergic mucin”) that has a distinct appearance both on CT examination and during surgical resection. The characteristic CT scan findings include heterogeneously dense material filling and expanding the sinuses while the mucus takes on a dense, highly viscous consistency comparable with that of paper cement.⁹⁹ The mucous and inflammatory responses often behave as a space-occupying lesion, with expansion into proximate tissue that obstructs the sinus ostia and might eventually cause bone absorption with resultant expansion into the orbits or cranium.^{100,101}

Genetics of AFS

Only 1 study has attempted to address a genetic linkage with AFS. In a modest study of 74 subjects, 44 with AFS, a weakly significant association of disease was observed with the MHC class II allele *HLA-DQB1*03*.¹⁰² The results should be interpreted with some caution because a high percentage of subjects in the control group had positive skin prick test responses to at least 1 fungal species.

Treatment

Treatment of AFS requires surgical removal with thorough debridement. Treatments to forestall recurrence are recommended, including immunotherapy^{103,104} and omalizumab, although these approaches have been poorly (if at all) studied. Most authors advocate for prolonged oral CCS use, but there have been no prospective randomized controlled trials. One article did indicate that the use of a modified CCS protocol similar to that used in allergic bronchopulmonary aspergillosis portended a better long-term

result. The role of topically administered CCSs in suspension (eg, budesonide suspension) has been advocated but not studied specifically.¹⁰⁵ Although the standard of care because of apparent efficacy in a few trials,¹⁰⁶ a role for immunotherapy in preventing AFS recurrence is difficult to understand given the absence of compelling evidence that immunotherapy is particularly beneficial when used for allergic rhinitis mediated by organisms associated with AFS, such as *Aspergillus*, *Curvularia*, or *Bipolaris* species. No role for topical or systemic antifungal agents has been clearly established.¹⁰⁷ Recent literature has indicated a potential role for itraconazole^{108,109} in some patients, but it remains uncertain whether this is secondary to its antifungal or anti-inflammatory properties.¹¹⁰ Unfortunately, the current absence of an established postsurgical medical approach has led to a poor prognosis with frequent recurrences and the need for further surgeries.

AERD

AERD is a distinct disorder, the features of which are summarized in Table II. AERD was originally defined by the triad of NPs, asthma, and aspirin sensitivity (Samter triad).¹¹¹ Aspirin intolerance occurs in as many as 20% of adult asthmatic patients and up to 30% of asthmatic patients with CS or nasal polyposis.^{112,113} Features of this disorder are its association with severe and extensive pansinusitis, often with complete opacification of all sinuses, and its tendency to develop *de novo* in adulthood. When present in patients who have avoided aspirin, extensive pansinusitis on CT scan examination is suggestive of aspirin sensitivity.²³ The nasal polyposis of AERD is aggressive, with multiple polyps and polypoid changes observed that are characterized by rapid growth and, in the absence of medical management, universal recurrence after surgery.^{112,114} Despite the extensive involvement of the sinuses with inflammatory tissue, this disease is surprisingly asymptomatic, and in contrast to acute sinusitis or NES, patients seldom complain about “sinus pressure” or headaches. The one consistent complaint is complete anosmia, a feature that produces perhaps the greatest morbidity.

In many patients asthma does not develop, and thus the current preference for the term AERD rather than aspirin-intolerant asthma or triad asthma. However, when present, AERD produces a particularly severe form of asthma that is often difficult to

control and is frequently associated with aggressive remodeling with a progressive irreversible decrease in lung function.^{23,115,116} The sinus and NP tissue display robust eosinophilia, which displays approximately 3-fold greater numbers of eosinophils than observed in patients with CHES³³ or that express approximately 5-fold greater numbers of eosinophils in the asthmatic airway.¹¹⁷ This can be a diagnostic feature of this disease. This eosinophilia extends into the circulation and, when present in patients with AERD who do not have asthma and have avoided aspirin, might result in many of these patients being erroneously classified as having a hypereosinophilic syndrome. Another feature that distinguishes this disease from other forms of asthma (or eosinophilic sinusitis) is the absence of a role for allergy.^{112,114} These patients often do not provide a history of allergic rhinitis and do not display IgE sensitization to aeroallergens, and total IgE concentrations tend to be modest. When present, allergic rhinitis is therefore likely the coincidental presence of this common disorder (although clearly this needs to be addressed as part of a comprehensive treatment plan). In contrast to the less common presence of IgE responses to inhaled aeroallergens, studies have indicated exaggerated local IgE responses to *S aureus* colonization and subsequent biofilm formation that frequently develops in the sinuses of patients with AERD. These responses take the form of both superantigen-mediated polyclonal IgE production and generation of IgE specific to the *S aureus* enterotoxins, both of which promote the severity of inflammation.³²

These patients have upper respiratory tract symptoms of nasal congestion, rhinorrhea, and paroxysmal sneezing, typically with severe exacerbations of their asthma after taking aspirin or other nonsteroidal anti-inflammatory drugs that inhibit COX. These are not allergic (ie, IgE-mediated) reactions to these medications, but instead, these reactions directly reflect their pharmacological mechanism. Ingestion of these agents leads to a decrease in production of the COX product prostaglandin (PG) E₂ and a surge in secretion of CysLTs. CysLTs are produced by activated eosinophils and mast cells. PGE₂ inhibits activation of mast cells and eosinophils, and when PGE₂ concentrations are reduced by COX inhibitors, they become activated.¹¹⁸ Several studies have addressed the expression of PGE₂ and the COX enzymes in patients with AERD and CHES and have consistently demonstrated diminished presence of both PGE₂ and COX-2.^{63,119} NP tissue obtained from patients with AERD also displays diminished expression of the anti-inflammatory PGE₂ receptor (EP2), exacerbating the harmful effects of its diminished production.¹²⁰ This baseline deficiency in PGE₂ renders patients with AERD increasingly susceptible to a massive inflammatory response because their eosinophils, basophils, and mast cells are dependent on the modest concentrations of PGE₂ that are available to prevent their activation. The ensuing further reduction in PGE₂ production after aspirin ingestion, along with the limiting number of EP2 receptors, releases these cells from the constraints provided by PGE₂ and leads to the explosive inflammatory response. Support for this concept is derived from the observation that exogenously administered PGE₂ prevents this response from developing.¹²¹ The PGE₂ that protects mast cells and eosinophils from activation appears to be derived from COX-1 because selective COX-2 inhibitors are generally well tolerated.¹²²⁻¹²⁴

AERD is also explained by the overproduction of and overresponsiveness to CysLTs.^{60,63} Patients with AERD display dramatic upregulation of 2 essential enzymes involved in CysLT synthesis: 5-lipoxygenase and leukotriene C₄ synthase (LTC₄S).^{63,117,125}

This overexpression drives both the constitutive overproduction of the CysLTs and the life-threatening surge in CysLTs that occurs with ingestion of aspirin and other nonselective COX inhibitors.¹²⁶ CysLTs have important proinflammatory and profibrotic effects that contribute to the extensive hyperplastic sinusitis and nasal polyposis that characterize this disorder. In addition to their overproduction, these patients display greatly enhanced sensitivity to the CysLTs, reflecting overexpression of the CysLT receptors,^{127,128} including both the 2 well-characterized receptors and newly described selective leukotriene E₄ receptors.¹²⁹⁻¹³¹ As with the overexpression of the synthesis enzymes, enhanced sensitivity to CysLTs is a diagnostic feature of this disease.

Genetics of AERD

As discussed, AERD is characterized by the overproduction of leukotrienes, and as a result, many studies have looked for association of genes involved with leukotriene synthesis or response. The rate-limiting enzyme in leukotriene synthesis is LTC₄S. An A-to-C base exchange at position -444 of the LTC₄S promoter has been described that, depending on cell type, increases expression of the gene.¹³² Several studies in different ethnic populations have found an association of this base change with AERD,^{48,133,134} whereas others have not found this association.^{135,136} The importance of this exchange is still unclear. The first committed enzyme in the synthesis of leukotrienes is 5-lipoxygenase. Within the promoter of the 5-lipoxygenase gene, there exist multiple variants of the tandem repeat GGGCGG that binds the transcription factor Sp1.¹³⁷ One study has found an increased odds ratio of 5.0 for the development of AERD in association with this gene,¹³⁶ and another study found a linkage of this polymorphism with increased severity of airway hyperresponsiveness in patients with AERD.¹³⁸ Other associations with the leukotriene pathway include the CysLT1 and CysLT2 receptors. As with CHES, a few studies have reported the histocompatibility locus as linking to the development of AERD; however, these have only been single studies awaiting replication.

Treatment

Approaches described for CHES should all be part of the AERD treatment regimen. Reflecting the important role of the CysLTs in patients with AERD, these patients are often therapeutically responsive to leukotriene modifiers. Although reported to improve asthma and upper airway symptoms and appropriate as first-line therapy, these patients seem less responsive to the leukotriene receptor antagonists (eg, montelukast and zafirlukast). In contrast, the leukotriene synthesis inhibitor zileuton has been shown in controlled clinical trials to improve asthma, reduce CCS requirements, reduce NPs, and restore anosmia.¹³⁹ The greater beneficial response to this agent is poorly understood but could reflect either a role for other leukotrienes (eg, leukotriene B₄) or for the CysLTs primarily acting through other CysLT receptors (eg, the putative leukotriene E₄ receptor or receptors).¹²⁹⁻¹³¹ These patients also uniquely benefit from aspirin desensitization and subsequent ingestion of high-dose daily aspirin (typically 1300 mg/d).^{140,141} Aspirin desensitization produces improved asthma control, fewer requirements for CCS "bursts," improved (or restored) sense of smell, reduced need for repeat polypectomies, and greatly reduced occurrence of bacterial superinfections of the sinuses.¹⁴² Although the basis for the benefit

TABLE III. Therapeutic implications and future directions for research

Disease	Therapeutic implications	Unanswered questions/potential therapies/ future directions for research
Chronic infectious sinusitis	Surgery Antibiotics As appropriate, therapies directed against underlying diseases (immune deficiency, CF)	Intranasal DNase
Noneosinophilic sinusitis	Surgery Limited role for systemic/topical antibiotics Nasal saline irrigation Surfactants	Role of hypertonic vs hypotonic irrigation Improved biofilm-targeting agents (xylitol, gold) B cell–targeting agents (belimumab; anti-BLyS [BAFF] antibodies)
Chronic hyperplastic eosinophilic sinusitis	Surgery Nasal saline irrigation Topical (intranasal) CCSs	Role of allergy/allergy-targeting therapies (anti-IgE, immunotherapy) Eosinophil-targeting modalities (anti-IL-5/anti-IL-5 receptor) Role of fungal antigens and antifungal therapies in certain subsets
AERD	Surgery Nasal saline irrigation Topical (intranasal) CCSs Aspirin desensitization Leukotriene modification, especially 5-lipoxygenase inhibitors	Specific leukotriene E ₄ antagonists Eosinophil-targeting modalities (anti-IL-5/anti-IL-5 receptor) IL-4/signal transducer and activator of transcription 6 antagonists Role of <i>Staphylococcus</i> species/staphylococcal superantigen–targeting approaches Systems biology approaches to identify molecular mechanism driving the AERD signature
AFS	Surgery Systemic CCSs Immunotherapy?	Improved targeted antifungal antibiotics, systemic or topical Better therapeutics for use in fungal immunotherapy Eosinophil-targeting modalities (anti-IL-5/anti-IL-5 receptor) Anti-IgE?

of aspirin is not known, it is noteworthy that this treatment is associated with both diminished production of the CysLTs and diminished expression of the CysLT receptors.^{127,143} Both *LTC₄S* and CysLT receptor 1 and 2 gene expression are stimulated by IL-4.¹⁴⁴ We have shown that aspirin interferes with **signal transducer and activator of transcription 6** signaling induced by IL-4 and prevents upregulation of these genes, providing a partial mechanistic explanation for the efficacy of aspirin desensitization.^{145,146} In the authors' clinical experience, this desensitization process is often more successful and safe when timed after surgery. This might reflect the dramatic reduction in local cytokines, a so-called IL-5-ectomy, that results from the removal of these inflammatory reservoirs, as suggested by the decrease in circulating absolute eosinophil counts that often accompanies AERD-related sinus surgery (personal observations). It is also likely that by removing much of the reservoir of eosinophils (and other cells), one can produce the CysLTs and the other mediators that drive these reactions; surgery thereby also improves the safety profile of the subsequent desensitization.

CONCLUSION

It is increasingly recognized that CS and nasal polyposis comprise several disease processes with varying causes characterized by distinct clinical presentations, distinct histologic gene and protein expression patterns, and distinct agents that drive their development and perpetuation. These diagnostic considerations include a primary need to characterize disease based on the presence or absence of an eosinophilic infiltrate. The presence of systemic eosinophilia, allergic sensitization, concomitant asthma, and a tendency to produce NPs support the diagnosis of one of the eosinophilic forms of this disease. Although predictive of an eosinophilic process, the presence of NPs alone is not an adequate

basis for making a proper diagnosis or predicting the response to treatment. Sinus or NP tissue sampling might ultimately be required to confirm classification. As a collection of heterogeneous diseases, proper diagnosis is required as the basis for recommending proper therapeutic interventions (summarized in Table III). Further work is needed both to delineate additional presentations of CS and to identify readily accessible diagnostic biomarkers for each subgroup that could be used in the clinical setting.

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