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Genetics and phenotyping in chronic sinusitis

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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List of Design Committee Members: Spencer C. Payne, MD, Larry Borish, MD, and John W. Steinke, PhD

Activity Objectives

1. To understand the differential diagnoses of chronic sinus disease.
2. To be able to appropriately treat various chronic sinus diseases.
3. To understand the need to define chronic sinusitis as a collection of heterogeneous diseases with varying causes.
4. To recognize distinct presentations of chronic sinus diseases, including distinguishing their clinical presentations, cellular and molecular characteristics, genetic differences, and current treatment options for each.
5. To understand the role that genetics plays in chronic hyperplastic eosinophilic sinusitis and nasal polyp formation.
6. To review the efficacy of various treatments in patients with chronic hyperplastic eosinophilic sinusitis and nasal polyposis.
7. To understand the recent literature regarding the genetics of noneosinophilic sinusitis.
8. To understand the different treatment options for chronic inflammatory sinusitis.
9. To become familiar with the diagnosis and treatment of chronic hyperplastic eosinophilic sinusitis, allergic fungal sinusitis, and aspirin-exacerbated respiratory disease.

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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;128:710-20.)

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

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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

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Terms in boldface and italics are defined in the glossary on page 711.

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
LTC_4S: Leukotriene C_4 synthase
NES: Noneosinophilic sinusitis
NP: Nasal polyp
PAI-1: Plasminogen activator inhibitor 1
PG: Prostaglandin

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 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 ethmoturbinals. 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 papyraceae (uncinate process, ethmoid bulla, middle turbinate, superior turbinate, and sometimes a 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

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-1α) and constitutive (HIF-1β) 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.

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