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Rhinosinusitis: Establishing definitions for clinical research and patient care

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Background: There is a need for more research on all forms of rhinosinusitis. Progress in this area has been hampered by a lack of consensus definitions and the limited number of published clinical trials.

Objectives: To develop consensus definitions for rhinosinusitis and outline strategies useful in clinical trials.

Methods: Five national societies, The American Academy of Allergy, Asthma and Immunology; The American Academy of Otolaryngic Allergy; The American Academy of Otolaryngology Head and Neck Surgery; The American College of Allergy, Asthma and Immunology; and the American Rhinologic Society formed an expert panel from multiple disciplines. Over two days, the panel developed definitions for rhinosinusitis and outlined strategies for design of clinical trials.

Results: Committee members agreed to adopt the term "rhinosinusitis" and reached consensus on definitions and strategies for clinical research on acute presumed bacterial rhinosinusitis, chronic rhinosinusitis without polyposis, chronic rhinosinusitis with polyposis, and classic allergic fungal rhinosinusitis. Symptom and objective criteria, measures for monitoring research progress, and use of symptom scoring tools, quality-of-life instruments, radiologic studies, and rhinoscopic assessment were outlined for each condition.

Conclusion: The recommendations from this conference should improve accuracy of clinical diagnosis and serve as a starting point for design of rhinosinusitis clinical trials. (J Allergy Clin Immunol 2004;114:155-212.)

Key words: Rhinosinusitis, sinusitis, nasal polyposis, quality of life, clinical trials

I. PREFACE

Recognizing a need for evidence-based rhinosinusitis guidelines, 5 national societies, The American Academy of Allergy, Asthma and Immunology (AAAAI); The American Academy of Otolaryngic Allergy (AOAA); The American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS); The American College of Allergy, Asthma and Immunology (ACAAI); and the American Rhinologic Society (ARS), convened a group of 30 physicians from a wide range of disciplines: allergy-immunology, otolaryngology, infectious disease, and radiology. Over 2 days, this panel worked together to develop definitions of rhinosinusitis for clinical research and to suggest clinical trial designs for studies that would allow for more appropriate use of pharmacologic, immunologic, and surgical interventions. Using an anonymous electronic audience response system, the committee was
able to reach consensus (≥80% of committee members) on definitions and clinical research strategies for acute (bacterial) rhinosinusitis, chronic rhinosinusitis (CRS) without polyps, CRS with polyps, and allergic fungal rhinosinusitis (AFRS). Diversity of opinion was expressed on whether rhinosinusitis would best be characterized as rhinosinusitis (AFRS). Diversity of opinion was expressed without polyps, CRS with polyps, and allergic fungal rhinosinusitis, chronic rhinosinusitis on definitions and clinical research strategies for acute disease and eosinophils predominating in most chronic disease. Additionally, there has been an evolution of thought moving away from the notion that all of CRS can be explained on the basis of sinus ostial obstruction and persistent bacterial infection to an appreciation that CRS has a significant inflammatory component that might be caused simultaneously or independently by various factors. Evidence for the varying potential sources of this condition is discussed. These include but are not restricted to the possible roles of:

1. persistent infection as a factor in CRS, including biofilms and osteitis1-4;
2. allergy and other disorders of immunity;
3. intrinsic factors of the upper airway;
4. superantigens from Staphylococcus aureus in CRS with nasal polyps5,6;
5. colonizing fungi that induce and sustain eosinophilic inflammation7-9; and
6. metabolic perturbations, such as aspirin sensitivity.

It was emphasized that several mechanisms might be acting simultaneously or independently in a given patient. Thus, this document reviews various causative factors in rhinosinusitis and highlights areas in which their roles in rhinosinusitis are controversial and in which new information is emerging. Various physicians authored individual sections to serve as background information on the controversies and definitions presented later in this article. The document also presents a classification scheme for CRS on the basis of current knowledge and consensus opinion and, furthermore, discusses the subjective and objective measures used in the diagnosis and evaluation of rhinosinusitis. Important factors in the design of clinical trials are discussed. Ultimately, consensus definitions for rhinosinusitis are put forth for:

1. acute presumed bacterial rhinosinusitis;
2. CRS without polyps;
3. CRS with polyps; and
4. classic AFRS.

Initial proposals are made for clinical trial designs, including an outline of suggested subjective and objective assessments applicable to these studies.

This group concluded that (1) promoting more research on both acute rhinosinusitis and CRS is essential, (2) a better understanding of the pathophysiology of these diseases is needed, and (3) study designs for the evaluation of potential therapeutic modalities for rhinosinusitis, as well as appropriate outcome studies, must be carefully considered.

These consensus recommendations are based on the clinical expertise of the participants, which is, in turn, based on a review and understanding of the clinical literature. They do not represent the position of any regulatory agency or pharmaceutical company. Much work needs to be done before definitive study designs for rhinosinusitis can be recommended, although this document represents an essential beginning to that process. The development of recommendations for study designs in the study of therapeutic modalities for the treatment of rhinosinusitis will be the responsibility of this collaborative group in the future.

The group decided by consensus to use the term rhinosinusitis instead of sinusitis throughout this document. This decision was based on the fact that sinusitis is almost always accompanied by concurrent nasal airway inflammation, and, in many cases, sinusitis is preceded by rhinitis symptoms. Therefore, it was believed that the use of the term rhinosinusitis more accurately describes the spectrum of infectious and inflammatory conditions previously grouped under the term sinusitis. The group endorsed and adopted the previously developed definition of the Sinus and Allergy Health Partnership Task Force for Rhinosinusitis: “Rhinosinusitis is a group of disorders characterized by inflammation of the mucosa of the nose and the paranasal sinuses.”

For acute rhinosinusitis, CRS without nasal polyposis, CRS with nasal polyposis, and classic AFRS, diagnostic criteria are outlined, including the pattern of symptoms that defines each one, the typical symptoms necessary to diagnose the disease, and the objective criteria required. Measurements for monitoring progress to determine clinical efficacy are also suggested. It is hoped that the establishment of a consensus of these definitions and recommendations by recognized experts in the diagnosis and assessment of rhinosinusitis will provide clinicians and researchers with the tools necessary for developing and implementing appropriate clinical studies and serve as a catalyst for further research of rhinosinusitis.

II. EXECUTIVE SUMMARY

Rhinosinusitis is increasing in prevalence and incidence and has been estimated to affect approximately 31 million patients in the United States each year.10 It causes significant physical symptoms, negatively affects quality of life (QOL), and can substantially impair daily functioning. Advancing existing definitions that describe all manifestations of rhinosinusitis, discussed elsewhere as sinusitis, has proved to be difficult. This is due, in part, to the numerous causes of the condition, including viral, bacterial, fungal, and allergic causes; in addition, many
patients have seemingly idiopathic disease. Rhinosinusitis is commonly divided into acute and chronic forms because these are 2 major categories that are listed in the International Classification of Diseases–Ninth Revision, Sixth Edition, although other classes (ie, subacute, recurrent acute, acute exacerbation of chronic, community acquired bacterial, and nosocomial) are described elsewhere in the medical literature.

Acute rhinosinusitis is usually infectious in nature, whereas chronic disease might result from a wide range of processes. Related to the complexities of this health care problem and because of practical constraints, the primary focus of this article is to establish clear definitions of acute rhinosinusitis and CRS for research and to advance existing definitions for clinical care. These goals are achieved on the basis of evidence in the literature and consensus of opinions (>80% of committee members) for these proposed definitions.

There is a clear need for more research on all forms of rhinosinusitis. Not enough is understood about the pathophysiology of these conditions, and without better understanding, safer and more effective treatment options cannot be developed. To date, most clinical research, including drug trials, have focused on acute rhinosinusitis. Reasons for the limited number of therapeutic trials for CRS have included the lack of widespread acceptance of existing definitions for the disorder and the acknowledged difficulty in establishing the causes for this condition. As a result, clinicians have been left to use empiric guidelines or their best judgment in choosing interventions for the treatment of CRS. Likewise, there is a lack of evidence-based guidelines to aid in developing successful rhinosinusitis clinical trials. Notwithstanding the need for additional research, there is widely held agreement that careful consideration of parameters for trial designs and outcomes studies is required as a starting point.

Various causative factors play a role in rhinosinusitis, including microorganisms, allergic and nonallergic immunologic inflammation, and noninfectious, nonimmunologic causes. Infection is defined as the invasion and multiplication of microorganisms within sterile host tissues. Inflammation is a series of cellular and molecular responses designed to eliminate foreign agents and promote repair of damaged tissues. Histologic patterns of inflammation are a function of at least 3 factors: nature of the inciting agent, time of the observation, and immune status of the host.

The common cold involves both the nasal passages and the paranasal sinuses. During a cold, nasal fluid containing viruses, bacteria, and inflammatory mediators are blown into the sinuses where they produce inflammation, infection, or both. This results in mucosal edema, cellular infiltration, and mucus thickened by means of exocytosis of mucin from the numerous goblet cells in the sinus epithelium.

A sinus infection can be caused by one or more bacteria in high density (at least 1000 colony forming units [cfu]/mL); commonly isolated bacteria in patients with rhinosinusitis include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Bacterial rhinosinusitis can be classified as acute, subacute, or chronic, depending on the duration of the symptoms. The role of bacterial infection in children and adults with CRS is controversial. Bacterial superantigens, biofilms, and osteitis might play an important role in CRS and warrant further study.

AFRS is a distinct clinical subset of CRS in which patients will have positive evidence of allergy to the fungus colonizing their “allergic mucin” in the majority of cases. Patients with AFRS typically demonstrate 5 characteristics: gross production of eosinophilic mucin containing noninvasive fungal hyphae, nasal polyposis, specific radiographic findings, immunocompetence, and allergy to cultured fungi. The presentation of AFRS might be dramatic, giving rise to acute visual loss, gross facial dysmorphia, or complete nasal obstruction, but more often, the presentation is subtle. Recent studies suggest that fungi might play an alternate role in the development of CRS, whereby patients mount innate immune responses to colonizing fungi through non–IgE-mediated mechanisms. These responses are hypothesized to lead to local eosinophilic infiltration, inflammation, and tissue injury. This concept of “eosinophilic fungal rhinosinusitis” encompasses most patients with CRS.

There are documented allergic and immunologic factors associated with the development of rhinosinusitis. Clinically, perennial allergic rhinitis is a predisposing condition for acute bacterial rhinosinusitis. Histologically, CRS without nasal polyps (CRSsNP) is characterized by a predominantly neutrophilic inflammation with a lesser contribution of eosinophils, whereas CRS with nasal polyps (CRSwNP) is characterized by eosinophilic inflammation. IL-5 and eotaxin could play a role in the latter process. Neither total IgE concentrations nor eosinophilic cationic protein (ECP), IL-4, or IL-5 concentrations in nasal polyps are different in atopic versus nonatopic subjects, suggesting a discordance between systemic allergic phenotype and local inflammatory mechanisms leading to eosinophilic inflammation in nasal polyps (NPs). A role has been proposed for IgE specific for staphylococcal-derived superantigens in the pathogenesis of CRS associated with nasal polyps.

Not all rhinosinusitis is inflammatory. Overactivity or underactivity of autonomic nerve pathways, abnormalities in leukotriene production or responsiveness, nociceptive dysfunction, or local irritation caused by gastroesophageal reflux are demonstrable in select subsets of patients with rhinosinusitis and could predispose to the pathogenesis of CRS. Defects in mucociliary clearance and antibody deficiency syndromes predispose to rhinosinusitis. Aspirin-associated respiratory disease also predisposes to rhinosinusitis.

Examining the histology of middle turbinate tissues from subjects with polypoid versus nonpolypoid disease might allow for distinction between these 2 entities. Samples from patients with CRSsNP versus CRSwNP generally show different patterns in cellular content and gross histologic changes within the tissue, especially with regard to fibrosis and edema. The mucosal lining in
CRSwNP is characterized by basement membrane thickening, goblet cell hyperplasia, limited subepithelial edema, prominent fibrosis and mononuclear cell infiltration. Histomorphologic characterization of CRSwNP reveals frequent epithelial damage, a thickened basement membrane, and mostly edematous to sometimes fibrotic stromal tissue, with a reduced number of vessels and glands but virtually no neuronal structures.

Characteristic symptoms and signs of CRSwNP include nasal congestion, facial pain-pressure-fullness, postnasal drainage, hyposmia-anosmia, and the presence of bilateral NPs. Histologically, NPs typically show an inflammatory infiltrate with increased numbers of eosinophils. At least 4 processes might contribute to variable degrees to the inflammatory process of CRSwNP: (1) late-phase allergic inflammation in response to airborne allergens; (2) T-cell activation with production of IL-5, IL-13, and IFN-γ in response to fungal antigens (hyphae) in sinus mucus; (3) T-cell activation, cytokine production, and local IgE production in response to bacterial superantigens; and (4) dysregulation of sinus epithelium with overproduction of chemokines, such as RANTES.

Numerous subjective and objective assessment measures can be used in the diagnosis and evaluation of rhinosinusitis, including symptoms, QOL scores, rhinoscopic examination, imaging, and nasal-sinus challenges. All relevant rhinosinusitis symptoms, their severity, and their time course should be documented. Characteristic symptoms and signs of rhinosinusitis include nasal congestion, facial pain-pressure-fullness, anterior and postnasal drainage, and hyposmia-anosmia. The symptom list is not necessarily different between patients with acute versus chronic disease, and some symptoms are present in patients with rhinitis who do not have evidence of sinusitis. A 7-point analog scale can be used to report individual symptom severity scores, a total rhinosinusitis severity score, a global severity score, an overall QOL score, and the effect of current and past treatments.

For a complete and thorough assessment of the morbidity associated with rhinosinusitis and the evaluation of treatment, it is imperative that the physical, social, emotional, and functional problems associated with this condition be measured in a valid way. Investigators should strive to report quality-of-life (QOL) data in a fashion that is most clinically meaningful. There are several validated rhinosinusitis outcome measures, and the instrument that seems best suited for the particular research question should be selected.

Anterior rhinoscopy is the basic tool of the physical examination that relates to determining the existence of pathology in the sinonasal passages. It is best to evaluate the patient after decongestion with topical decongestants. However, even with this method, examination of the nasal passages beyond the anterior portion can be limited. Nasal endoscopy helps identify erythema, edema, polyps or polypoid swelling, crusting, eosinophilic mucin, and mucopurulent or frank pus deep in the nasal cavity. Cultures obtained endoscopically are less invasive and associated with less morbidity; however, this technique was not found to be equivalent to antral puncture in children with sinus infections.

Although rhinosinusitis can be diagnosed in the majority of patients by using only the history and physical examination (including endoscopy), patients with persistent sinus disease often require imaging studies. These studies are an absolute requirement in patients undergoing functional endoscopic sinus surgery. Computed tomography (CT) has 2 major roles in the management of rhinosinusitis: (1) to define the anatomy of the sinuses before surgery and (2) to aid in the diagnosis and management of recurrent rhinosinusitis or CRS. Although magnetic resonance imaging (MRI) does not display the bony anatomy as does CT, it does provide an excellent display of the mucosa, and it is better than CT in distinguishing between bacterial-viral inflammatory disease and fungal concretions.

Nasal-sinus challenge is useful in defining the pathophysiology of rhinosinusitis and the interactions between the nose and the sinuses, as well as the lower airway. Nasal challenge has also been used to confirm the presence of allergy, to assess nasal threshold responses, and to study the mediators, inflammatory cells, and cytokines associated with rhinosinusitis.

The integrated airway syndrome, also called chronic inflammatory respiratory syndrome, has a wide spectrum of severity: at the low end, its manifestations are clinically evident in the form of rhinitis, and at the high end, manifestations can include asthma and possibly rhinosinusitis. There is a very strong link between the upper and lower airways: both allergic rhinitis and nonallergic rhinitis are risk factors for asthma; allergic rhinitis is almost ubiquitous in asthma; even in the absence of nasal symptoms, the nasal mucosa of patients with asthma shows evidence of inflammation; and the rhinitis of asthmatic patients tends to be more severe than the rhinitis of nonasthmatic patients. Moreover, allergic reactions and their inflammatory consequences appear to propagate systemically; therefore, the link between the nose, the sinuses, and the lower airways might be considered a systemic process.

Agreement on definitions, histopathology, and diagnostic criteria is an important prelude to the selection of an appropriate design for clinical studies of rhinosinusitis. The efficacy of a treatment modality for rhinosinusitis must be demonstrated through adequate and well-controlled studies showing that the intervention will have the effect that is claimed. Factors to consider in developing a protocol for such a study include (1) primary and secondary study objectives, (2) overall study design, (3) the basis for dose selection and route of administration, (4) the study population, (5) inclusion-exclusion criteria, (6) control subjects, (7) safety and efficacy outcome variables, and (8) statistical considerations, such as powering the study. For example, the prospective choice of end points is an important decision in designing clinical studies. Efficacy end points for studies that will form the basis of approval for such a treatment modality should be clinically relevant and validated.
III. INTRODUCTION

Rhinosinusitis is increasing in prevalence and incidence, and has been estimated to affect approximately 31 million patients in the United States each year. It causes significant physical symptoms, negatively affects QOL, and can substantially impair daily functioning. Advancing existing definitions that describe all manifestations of rhinosinusitis, discussed elsewhere as sinusitis, has proved to be difficult. This is due, in part, to the numerous causes of the condition, including viral, bacterial, fungal, and allergic causes; in addition, many patients have seemingly idiopathic disease. Rhinosinusitis is commonly divided into acute and chronic forms because these are 2 major categories that are listed in the International Classification of Diseases–Ninth Revision, Sixth Edition, although other classes (ie, subacute, recurrent acute, acute exacerbation of chronic, community acquired bacterial, and nosocomial) are described elsewhere in the medical literature.

Acute rhinosinusitis is usually infectious in nature, whereas chronic disease might result from a wide range of processes. Related to the complexities of this health care problem and for practical constraints, the primary focus of this article is to establish clear definitions of acute rhinosinusitis and CRS for research and to advance existing definitions for clinical care. These goals are achieved on the basis of evidence in the literature and consensus of opinions of international leaders for these proposed definitions.

There is a clear need for more research on all forms of rhinosinusitis. Not enough is understood about the pathophysiology of these conditions, and without better understanding, safer and more effective treatment options cannot be developed. To date, most clinical research, including drug trials, have focused on acute rhinosinusitis. Reasons for the limited number of therapeutic trials for CRS have included the lack of widespread acceptance of existing definitions for the disorder and the acknowledged difficulty in establishing the causes for this condition. As a result, clinicians have been left to use empiric guidelines or their best judgment in choosing interventions for the treatment of CRS. Likewise, there is a lack of evidence-based guidelines to aid in developing successful rhinosinusitis clinical trials. Notwithstanding the need for additional research, there is widely held agreement that careful consideration of parameters for trial designs and outcomes studies is required as a starting point.

IV. CAUSATIVE FACTORS IN RHINOSINUSITIS

As a preface to this section, the terms infection and inflammation are discussed and defined. Infection typically induces an inflammatory response and has been defined in various ways. Although it is important to note that some choose to define infection as a microbial phenomenon characterized by an inflammatory response to the presence of microorganisms, others believe that true infection is defined as the invasion and multiplication of microorganisms in tissue. Additionally, they hold that infection is distinct from colonization by the immune response and development of disease in the host (J. Gwaltney, personal communication, 2004).

Inflammation is a series of cellular and molecular responses that are designed to eliminate foreign agents and promote repair of damaged tissues. It begins with a reaction of blood vessels, leading to the accumulation of fluid and leukocytes in extravascular tissues. There is increasing evidence that in addition to infection, immunologic inflammatory responses play major roles in the cause and pathophysiology of CRS.

In this article infection is distinguished from inflammation along the more traditional concepts of tissue invasion. It is acknowledged, however, that the histopathologic evidence of this distinction in all forms of rhinosinusitis is not carefully studied. Additionally, the 2 most hotly debated hypotheses to explain CRS relate to colonization of the sinonasal mucosa with microorganisms and the host response to their presence (eg, superantigens-producing S. aureus and colonizing fungi). A substantial concern is that identifying rhinosinusitis as an infection alone might promote continued widespread use of antimicrobial agents. Current evidence to support their use, particularly in chronic disease, is limited, and there is an obvious concern that this will contribute to the increasing rates of antimicrobial resistance.

Histologic patterns of inflammation are a function of at least 3 factors: nature of the inciting agent, time of the observation, and immune status of the host. Timing is traditionally defined on the basis of clinical onset and duration of the response. Specifically, inflammation has been referred to as acute when signs or symptoms appear over minutes to hours, subacute when it spans days to weeks, and chronic when it occurs over weeks to months. The main pathologic characteristic of acute inflammation is the exudation of fluid and plasma proteins (edema) and the emigration of leukocytes, predominantly neutrophils. Chronic inflammation is histologically associated with the presence of lymphocytes, macrophages, and occasionally eosinophils and basophils and the proliferation of blood vessels, fibrosis, and tissue necrosis. A clear distinction between acute and chronic inflammation is somewhat artificial because of numerous overlapping patterns of inflammation. Despite the evolutionary benefits to inflammation and repair, alterations in the balance between proinflammatory and anti-inflammatory mediators can lead to harmful effects.

A. Microorganisms and rhinosinusitis

1. Viral infection.

Summary Statements:
- In the nonimmune individual, the nasal passages are unable to clear or inactivate an infecting virus.
- The common cold involves both the nasal passages and the paranasal sinuses.
Evidence supports the concept that during a cold, nasal fluid containing viruses, bacteria, and inflammatory mediators might be blown into the sinuses, where they produce inflammation, infection, or both. Mucosal edema, cellular infiltration, and mucus thickened by exocytosis of mucin from the numerous goblet cells in the sinus epithelium are the result.

Although symptoms of the common cold have been recognized since antiquity, the first cold virus, rhinovirus, was not discovered until 1956. Within 30 years of its discovery, the replication strategy and atomic structure of the virus was determined. The rhinovirus enters the body through the nose by means of either contaminated fingers or large airborne particles. The virus is then transported in the mucus stream to the adenoid region of the nasopharynx, reaching an area where there are specialized lymphoepithelial cells (M cells) overlying lymphoid follicles. These lymphoepithelial cells are rich in the rhinovirus receptor intercellular adhesion molecule 1 (ICAM-1).

This series of events is very efficient. One of the central features in the pathogenesis of infections caused by rhinovirus is that in the nonimmune individual the nasal passages are unable to clear or inactivate the virus. For example, when 343 nonimmune healthy young adults were challenged by dropping rhinovirus in their nose, 321 (95%) of these individuals became infected. However, only three quarters of those who became infected had symptoms of illness, reflecting an apparent infection rate similar to that observed under natural conditions. Initiation of rhinovirus infection is not only an efficient mechanism, but also occurs quite rapidly. After intranasal rhinovirus challenge of susceptible volunteers, newly produced virus was recovered in nasal secretions within 8 to 10 hours. This is the same amount of time required for rhinovirus replication in cell culture. Also, in this study symptoms were observed to appear after a relatively short time. Sore throat, nasal obstruction, and rhinorrhea were symptoms that appeared to occur after a relatively short time. Sore throat, nasal obstruction, and rhinorrhea were symptoms that appeared to occur after a relatively short time. Sore throat, nasal obstruction, and rhinorrhea were symptoms that appeared to occur after a relatively short time.

It is now recognized that the common cold not only involves the nasal passages but also the paranasal sinuses (Fig 1). Sinus CT scans obtained in 31 young adults with early common colds revealed frequent abnormalities in the sinus cavity. These abnormalities were observed in the maxillary sinus in 87% of the patients, the ethmoid sinus in 65%, the frontal in 32%, and the sphenoid in 39%. A subset of these patients underwent repeat CT scans 2 weeks later; most of the original changes resolved spontaneously after resolution of the corresponding upper respiratory tract infection. The findings of sinus abnormalities during colds have been confirmed in adults and children. The nature of these findings has been debated, but one explanation is the development of thick exudates adhering to the sinus wall with such tenacity that the material is not moved by ciliary action. The epithelium of the sinus cavity contains a high concentration of goblet cells, and exocytosis of large amounts of mucin might occur when these cells are stimulated. It is important to determine the nature of the abnormality because this has implications for understanding the pathogenesis of the process and the appropriate approach to its treatment. Whatever its nature, this self-limited process represents a viral rhinosinusitis that is occurring as part of the common cold.

An unusual finding on CT scanning of the sinus of a patient with a fresh common cold was closely evaluated to explore possible causes of sinus abnormalities during a common cold. The scan showed the maxillary sinus to be filled with what were unquestionable air bubbles, giving a frothy appearance to the material (Fig 2). A sinus CT scan taken 3 days later showed typical findings associated with viral sinusitis “exudates” containing a few “air bubbles.” This led to the hypothesis that in this patient nasal fluid had been blown into the infundibulum and into the sinus, producing multiple air bubbles as the fluid exited the narrow lumen of the infundibulum under pressure and entered the relatively large sinus cavity. Later, the material was believed to have been thickened by means of exocytosis of mucin and coalesced to form an exudate.

Intranasal pressures were measured in volunteers during quiet respiration, nose blowing, sneezing, and coughing to determine how nasal fluid might be propelled into the sinus cavity. The mean ± SD maximal intranasal pressure was 66 ± 14 mm Hg during 35 nose blows, 4.6 ± 3.8 mm Hg during 13 sneezes, and 6.6 ± 3.8 mm Hg during 18 coughing bouts (Fig 3). Sneezing and coughing did not increase intranasal pressures to greater than those observed during quiet respirations. Contrast medium was placed in the pharynx of volunteers who then blew their nose, sneezed, or coughed to further investigate the pressure effects in the nasal passages of nose blowing, after which CT scans of the sinuses were obtained. Contrast medium appeared in one or more sinuses in 4 of the 4 subjects after a nose blow but not after sneezing or coughing (Fig 4).
Calculations revealed that when the middle meatus is filled with viscous fluid, a single nose blow can propel up to 1 mL of this material into the maxillary sinus. These findings might explain the origin of the sinus cavity abnormalities in colds and also might explain why abnormalities are usually irregular in occurrence among various sinuses. One sinus might have considerable involvement, and another might be perfectly normal.

In summary, these findings support the hypothesis that during a cold, nasal fluid containing viruses, bacteria, and inflammatory mediators might be blown into the sinuses, where it produces inflammation, infection, or both and is thickened by means of exocytosis of mucin from the numerous goblet cells in the sinus epithelium. Thus the CT abnormalities observed in viral rhinosinusitis could be the result of inflammation alone or of viral infection of the cells in the sinus epithelium. In sinus puncture studies in patients with acute community-acquired rhinosinusitis, 15% of the sinus aspirates have yielded rhinovirus, 5% have yielded influenza virus, 3% have yielded para-influenza virus, and 2% have yielded adenovirus. It is not known whether this actually represents viral replication in the sinus cavity. Some sinus aspirates have yielded both viruses and bacteria.

Criteria to define a case of viral rhinosinusitis are lacking. However, attention has been given to trying to define situations in which viral agents are not the sole cause; that is, the 0.5% to 2% of cases of viral rhinosinusitis that are estimated to be complicated by secondary bacterial infections. However, it should be recognized that no studies have ever been conducted in which the sensitivity and specificity of various clinical findings have been evaluated and the comparison standard is a positive viral or bacterial sinus aspirate culture. The current clinical diagnostic criteria for a large proportion of the cases of acute community-acquired bacterial rhinosinusitis and for the use of antimicrobial treatment that is the most widely accepted today include a cold that is no better or worse after 10 to 14 days. Conversely, the current clinical diagnostic criteria for viral rhinosinusitis include a cold that is beginning to resolve after a few days and is better by a week to 10 days after onset. For purposes of research, the criteria standards for diagnosis of viral rhinosinusitis are a positive virus culture or detection of viral nucleic acid in cells of the sinus epithelium, indicating active viral replication.

2. Bacterial infection.

Summary Statements:

- The most common cause of rhinosinusitis is a community-acquired viral infection that leads to a self-limited period of upper respiratory symptoms (nasal symptoms [ie, discharge], congestion, and cough). On occasion, there might be a secondary bacterial infection of the paranasal sinuses that requires specific antimicrobial therapy. These infections are characterized by the presence of one or more bacteria in high density (at least 1000 cfu/mL). Commonly isolated bacteria in patients with rhinosinusitis include *S pneumoniae*, *H influenzae*, and *M catarrhalis*. Rhinosinusitis syndromes can be classified as acute, subacute, or chronic according to the duration of symptoms.
- The role of bacterial infection in children and adults with CRS is controversial. Bacterial superantigens, biofilms, and osteitis might play a role in CRS and warrant further study.

Although the paranasal sinuses are believed to be sterile under normal circumstances, the upper respiratory tract, specifically the nose and nasopharynx, are heavily colonized with normal flora. Normal nasal flora in adults and children include coagulase-negative staphylococci (CNS), *Corynebacterium* species, and *S aureus*. In children the organisms frequently cultured from the nasal cavity are the most common cause of rhinosinusitis.
include *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae*. Normal nasal-sinus flora in patients with CRS and the role of bacterial pathogens in CRS are poorly defined. In CRS the mucosal response to bacterial colonization or bacterial infection in an otherwise normal host is likely to be different than that in acute rhinosinusitis. Given this possibility, different criteria to define colonization and infection are probably needed but have not been established.

*a. Microbiology of acute rhinosinusitis in children.* The microbiology of paranasal sinus infection can be anticipated according to the age of the patient, clinical presentation, and immunocompetence of the host. Despite the substantial prevalence and clinical importance of rhinosinusitis in childhood, studies of the microbiology of acute and subacute rhinosinusitis in pediatric patients have been relatively limited. By using a study design similar to one described by investigators at the University of Virginia, an investigation of the microbiology of acute sinusitis in pediatric patients was conducted at the Children’s Hospital of Pittsburgh in 1979. Patients were eligible for this study if they were between 2 and 16 years of age and presented with one of 2 clinical pictures: onset with either persistent or severe respiratory symptoms.

Sinus radiographs were performed on eligible children with either of these 2 presentations. When a maxillary sinus aspirate (by using a transnasal approach) was performed on children presenting with either persistent or severe symptoms and significantly abnormal sinus radiographs, bacteria in high density were recovered from 70%. The bacterial isolates in their relative order of prevalence are shown in Table I. *S. pneumoniae* was most common, followed closely by *M. catarrhalis* and *H. influenzae*. Both *H. influenzae* and *M. catarrhalis* might be β-lactamase producing and thereby amoxicillin resistant. Approximately a third of *S. pneumoniae* also exhibit intermediate or high resistance to penicillin. The *H. influenzae* found in sinus aspirates, like those found in infected middle ear cavities, are almost always the non-typeable organisms, reflecting their frequent colonization of the nasopharynx, in contrast to *H. influenzae* type b. Only a single anaerobic bacterial species, a peptostreptococcus, was isolated. No staphylococci were recovered. Mixed infection with heavy growth of 2 bacterial species was occasionally found. In 25% of patients with bilateral maxillary sinusitis, there were discordant bacterial culture results. In some patients one sinus aspirate was positive, whereas the other was negative. In the remaining patients different bacterial species were recovered from each.

*b. Microbiology of subacute rhinosinusitis in children.*

The signs and symptoms of children with subacute rhinosinusitis were described in 1989. These youngsters were evaluated in the context of several different comparative trials of antimicrobial therapy. All children had persistent respiratory symptoms (ie, nasal discharge, cough, or both lasting between 30 and 120 days). These children were generally in good health, with minimal constitutional complaints, except for their respiratory symptoms. Intermittent fever was a complaint in 25% of patients but was rarely documented at the time of presentation. Some of these children had previously received one or more courses of antimicrobial agents. In each case they either failed to respond to the antimicrobial agent or improved only slightly and experienced recurrence of symptoms after cessation of antibiotics.

Table II shows the bacterial species cultured from 40 children. Again, the 3 predominant organisms were *S. pneumoniae, H. influenzae*, and *M. catarrhalis*. The signs and symptoms of children with subacute rhinosinusitis were described in 1989. These youngsters were evaluated in the context of several different comparative trials of antimicrobial therapy. All children had persistent respiratory symptoms (ie, nasal discharge, cough, or both lasting between 30 and 120 days). These children were generally in good health, with minimal constitutional complaints, except for their respiratory symptoms. Intermittent fever was a complaint in 25% of patients but was rarely documented at the time of presentation. Some of these children had previously received one or more courses of antimicrobial agents. In each case they either failed to respond to the antimicrobial agent or improved only slightly and experienced recurrence of symptoms after cessation of antibiotics.

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*FIG 3. Intranasal pressure time histories for a representative nose blow, coughing bout, and sneeze shown on the same scale for comparison (dashed line, nose blow; solid line, coughing bout; dotted line, sneeze). Reprinted with permission from Gwaltney JM, Jr, Hendley JO, Phillips CD, et al. Nose blowing propels nasal fluid into the paranasal sinuses. Clin Infect Dis 2000;30(2):387-92. Published by The University of Chicago Press. © 2000 by the Infectious Diseases Society of America.*
In patients with acute exacerbations of CRS characterized by persistent or intermittent episodes of purulent nasal discharge, the usual microorganisms associated with acute sinusitis are causative. However, in patients with chronic persistent rhinosinusitis (nasal congestion or nonspecific rhinorhea or cough, alone or in combination), the role of bacterial agents is less clear. Most organisms have been recovered in low density, and frequently, these were recovered at a time when the patient was receiving antibiotics to which the organisms were susceptible. The lack of quantitation of organisms also complicates interpretation because the middle meatus in children is known to be colonized with the usual sinus pathogens. The persistence of symptoms despite multiple courses of appropriate antimicrobial agents in many children is counter to the notion that bacterial infection is a significant component of CRS. All of these observations support the hypothesis that bacterial infection has a minor role in many children with CRS.

### TABLE I. Bacterial species cultured from 79 sinus aspirates in 50 children with acute rhinosinusitis

| Species                        | Single isolates | Multiple isolates | Total |
|--------------------------------|----------------|------------------|-------|
| Streptococcus pneumoniae       | 14             | 8                | 22    |
| Moraxella catarrhalis          | 13             | 2                | 15    |
| Haemophilus influenzae         | 10             | 5                | 15    |
| Eikenella corrordens           | 1              | 0                | 1     |
| Group A streptococcus          | 1              | 0                | 1     |
| Group C streptococcus          | 0              | 1                | 1     |
| α-Streptococcus                | 1              | 1                | 2     |
| Peptostreptococcus             | 0              | 1                | 1     |
| Moraxella species              | 1              | 0                | 1     |

### TABLE II. Bacterial species cultured from 52 sinus aspirates in children with subacute rhinosinusitis

| Species                        | Single isolates | Multiple isolates | Total |
|--------------------------------|----------------|------------------|-------|
| Streptococcus pneumoniae       | 9              | 3                | 12    |
| Haemophilus influenzae         | 9              | 2                | 11    |
| Moraxella catarrhalis          | 6              | 2                | 8     |
| Streptococcus pyogenes         | 2              | 0                | 2     |
| Streptococcus viridans         | 0              | 1                | 1     |
| Moraxella species              | 0              | 1                | 1     |

FIG 4. Sinus CT scan of an adult after instillation of contrast medium into the nasopharynx, followed by nose blowing. A, Contrast in an anterior ethmoid sinus cell (short arrow) and in the floor of the nasal cavities (long arrow). B, Contrast in the infundibulum bilaterally (short arrows) and in the maxillary sinus outlining a bubble (arrow). C, Contrast in the posterior ethmoid sinus (arrow). D, Contrast in the sphenoid sinus outlining a bubble (arrow). Reprinted with permission from Gwaltney JM, Jr, Hendley JO, Phillips CD, et al. Nose blowing propels nasal fluid into the paranasal sinuses. *Clin Infect Dia* 2000;30(2):387-92. Published by The University of Chicago Press. © 2000 by the Infectious Diseases Society of America.
d. **Microbiology of acute community-acquired rhinosinusitis in adults.** In adults bacteriologic information is derived mainly from cultures of mucus obtained by means of aspiration from the maxillary sinus, the most accessible of the paranasal sinuses. Although there is no certainty that cultures from the maxillary sinus can be extrapolated to all the other paranasal sinuses, the findings of sinus puncture studies performed in the United States and abroad have provided fairly similar results. In general, a sinus infection is caused by a single bacterial isolate in high density. In 25% of cases, 2 bacterial species, each in high density, were recovered. The 2 most important causes of acute community-acquired rhinosinusitis in adults are *S. pneumoniae* and nontypeable *H. influenzae* (Table IV). These 2 species account for more than 75% of the bacterial isolates. One remarkable change observed by Gwaltney and colleagues between 1975 and 1991 was the increase in the prevalence of β-lactamase–producing *H. influenzae*. In the first decade, β-lactamase–mediated resistance was rare; however, from 1986 through 1991, more than half of 29 strains of *H. influenzae* were β-lactamase producing. There has been no increase in β-lactamase–positive *H. influenzae* over the last 10 years, and this mechanism of resistance appears to have stabilized at less than 40% of isolates. Next in frequency were streptococci other than *pneumococci*, such as *streptococcal α and β strains*, and anaerobic bacterial species. The role of anaerobes in acute community-acquired disease is variable. Although anaerobic bacteria have a more remarkable role in chronic sinus disease, they are not as established in acute sinus disease and account for only 2% to 6% of acute cases, some of which arise from primary dental pathology.

*S. aureus* and *Streptococcus pyogenes* are uncommon causes of acute rhinosinusitis in children and adults. The actual role of *S. aureus* might occasionally be exaggerated when surrogate nasal cultures are substituted for sinus aspirates. Although uncommon, *S. aureus* and *S. pyogenes* may cause serious intracranial suppuration or, rarely, subperiosteal or orbital abscess as complications of acute rhinosinusitis.

e. **Microbiology of nosocomial rhinosinusitis.** Patients with nosocomial rhinosinusitis are usually those who require extended periods of intensive care (postoperative patients, burn victims, and patients with severe trauma) involving prolonged endotracheal or nasogastric intubation. Nasotracheal intubation provides a substantially higher risk for nosocomial sinusitis than orotracheal intubation.

Nasotracheal intubation may cause serious intracranial suppuration or, rarely, subperiosteal or orbital abscess as complications of acute rhinosinusitis.

### TABLE III. Chronic rhinosinusitis in children

| Author            | Criteria | No. | Age (y) | Sterilization | Quantitation | Off antibiotics | Microbiology |
|-------------------|----------|-----|---------|---------------|--------------|----------------|--------------|
| Brook, 1981<sup>19</sup> | ≥21 d    | 40  | 6-16    | Yes           | No           | Yes            | . 37/40 = +cx |
|                   |          |     |         |               |              |                | . Anaerobes in all |
|                   |          |     |         |               |              |                | . (GPC, GPR, GNR) |
|                   |          |     |         |               |              |                | . Aerobes in 38% (GPC) |
| Otten and Grote, 1988<sup>81</sup> | ≥90 (purulent d/c) | 141  | 3-10    | NA            | NA           | NA             | . 70% +cx; Usual acute flora |
| Tinkleman and Silk, 1989<sup>46</sup> | ≥30 d    | 35  | 0.9-16  | Yes           | Yes          | No             | . 63% +cx; Usual acute flora |
| Muntz and Lusk, 1991<sup>45</sup> | NA       | 105 | 0.7-17  | NA            | No (mucosa)  | No             | . Contaminants: majority |
|                   |          |     |         |               |              |                | . Acute agents ~ minority |
|                   |          |     |         |               |              |                | . Bs of ethmoid cultured |
| Oroello et al, 1991<sup>43</sup> | ≥42 d (or recurrent) | 39  | 1.2-19  | Yes           | Semi (irrigation) | No   | . Contaminants: majority |
|                   |          |     |         |               |              |                | . Usual acute flora: very light density |
| Otten, 1994<sup>42</sup> | ≥90 d (purulent d/c) | 79  | 2-12    | NA            | No           | Yes            | . Usual pathogens |
| Brook et al, 2000<sup>40</sup> | ≥90 d (purulent) | 32  | 4-11    | Yes           | No (irrigation) | Yes  | . Usual pathogens and anaerobes |
| Slack et al, 2000<sup>47</sup> | ≥56 d    | 119 | 0.8-14.5| No            | No (irrigation) | No   | . Usual pathogens |
| Don et al, 2001<sup>44</sup> | ≥90 d    | 70  | 0.9-15  | Yes           | No (irrigation) | No   | . Usual pathogens (60%) |
|                   |          |     |         |               |              |                | . Contaminants |

Contaminants: CNS, α-strep, and coagulase-positive staphylococci.

<sup>+cx</sup>, Positive culture; <sup>GPC</sup>, gram-positive cocci; <sup>GPR</sup>, gram-positive rods; <sup>GNR</sup>, gram-negative rods; <sup>d/c</sup>, discharge; <sup>NA</sup>, not available; <sup>Bx</sup>, biopsy.

*Prospective.
f. Microbiology of CRS in adults. In contrast to the agreement among investigators with regard to the microbiology of acute rhinosinusitis, there is disagreement with regard to the microbiology of CRS. The many factors that contribute to the difficulty in summarizing the literature include various methods used to sample the sinus cavity (ie, aspiration, irrigation, Calginate swab or biopsy), failure to sterilize the area through which the trocar or endoscope is passed, different sinuses or areas that are sampled (ie, ethmoid bulla or maxillary antrum or middle meatus), lack of assessment of the inflammatory response, lack of quantitation of bacteria, previous or current use of antibiotics, and variable patient selection (ie, age, duration, extent of disease, surgical or non surgical subjects, presence of nasal polyps, time of culture transport and method of culture).

Seven studies of patients with CRS performed since 1991 are shown in Table V.57-63 Three studies were prospective. The importance of a prospective investigation is that there is more assurance that patients are identified and cultures are processed in a standard fashion. CNS was the most common aerobic isolate in 5 of the 7 studies, often accompanied by S. aureus and viridians streptococci. The absence of quantitation or performance of Gram stains in almost all studies prohibits an assessment of both the density of organisms and the accomplishment of an inflammatory response. Although CNS is traditionally discounted as a pathogen in both acute rhinosinusitis and CRS, its role as a pathogen in other body sites has been well documented and reviewed by Hsu et al.146 Neutropenic sepsis, infections of indwelling catheters, and in burn patients. Frequent bacterial recovery from swabs obtained from the middle meatus of healthy subjects suggests that these bacteria are commensals and likely contaminants.164 Nadel et al165 suggested that the difference might be of a quantitative nature. In the unusual situation in which a large number of white blood cells and organisms were present on Gram stains and there was heavy growth of CNS, the possibility of a true infection should be entertained.

The surprising isolates in 5 of the 7 studies were gram-negative enteric rods, including P. aeruginosa, K. pneumoniae, P. mirabilis, Enterobacter species, and Escherichia coli. Because these are rarely found in cultures of the middle meatus obtained from healthy individuals, their isolation from these symptomatic patients suggests 2 possibilities: (1) these organisms are causative, or (2) gram-negative organisms might colonize or secondarily infect because of underlying defects in host defense, such as impaired mucociliary clearance, nasal polyps in patients with CRS, or cystic fibrosis with the corresponding transport defect. Furthermore, the frequent use of antibiotics in these patients might promote the emergence of gram-negative bacterial colonization or infection.

An excellent illustration of the complexities of dealing with the microbiology of CRS is assessing the role of anaerobes in this condition. The isolation of anaerobes is critically dependent on culture techniques, and most studies have not used optimal techniques to isolate them. The frequency with which these organisms are recovered from patients who have been studied varies between zero and 100% and every number in between. In reviewing a series of studies, anaerobes were found primarily in the investigations of Finegold et al63 and Brook and Frazier.61 The reconciliation of these studies with all others and the significance of the recovery of these anaerobes is unclear.

In support of a role for anaerobic bacteria in chronic maxillary sinusitis, Finegold et al63 found recurrence of signs and symptoms twice as frequent when cultures showed anaerobic bacterial counts of greater than 10^4 cfu/mL. A role was further supported by the detection of antibodies (IgG) to 2 anaerobic organisms commonly recovered from sinus aspirates (Fusobacterium nucleatum and Prevotella intermedia). Antibody levels to these organisms decreased in the patients who responded to therapy and were cured but did not decrease in those in whom therapy failed.

Anaerobes have been identified in chronic sinusitis primarily when special techniques for their cultivation were used. The predominant isolates identified were pigmented Prevotella, Fusobacterium, and Peptostreptococcus species; the predominant aerobic bacteria were S. aureus, M. catarrhalis, and Haemophilus species. In several studies aerobic and anaerobic β-lactamase-producing bacteria were isolated from more than one third of patients studied.39-66 69 The β-lactamase–producing bacteria identified were S. aureus, Haemophilus species, Prevotella species, and Fusobacterium species. Since 1974, a total of 1758 patients with CRS were evaluated in 18 studies using methods adequate for the recovery of anaerobic bacteria.63,70,71 Anaerobes were recovered in 12% to 93% of patients. The variability in recovery might result from differences in the methodologies used for transportation and cultivation, patient population, geography, and previous antimicrobial therapy.

Some investigators have argued that CRS represents a repeatedly damaged mucosal lining that has lost its normal state of sterility.43,72,73 These authors do not ascribe a major role for bacteria in the pathology of CRS unless there is an acute exacerbation characterized by purulent nasal discharge. Obviously, more work is needed to resolve these discrepant data. A suggested strategy would be to conduct a prospective investigation in which (1) patients are carefully identified and characterized, (2) cultures and Gram stains are obtained by using aseptic techniques with rigorous and standardized handling of specimens, (3) at least semiquantitative culture methods are used so that the density of bacteria can be assessed, and

| **TABLE IV.** Community-acquired acute rhinosinusitis in adults |
|-----------------|--------|
| **Streptococcus pneumoniae** | 41% |
| **Haemophilus influenzae** | 35% |
| Anaerobes | 7% |
| **Streptococcus species** | 7% |
| **Moraxella catarrhalis** | 4% |
| **Staphylococcus aureus** | 3% |
| Other | 4% |
TABLE V. CRS in adults 17 to 79 years of age

| Author          | Year | No. of patients | Sterilization | Quantitation | Aspiration | Biopsy | Endoscopic | Antibiotic | WBC | Microorganism |
|-----------------|------|-----------------|---------------|--------------|------------|--------|------------|------------|-----|--------------|
| Doyle and Woodham | 1991 | 59              | Yes           | (semi)       | –          | +      | –          | +          | +   | CNS; SA; GNR  |
| Hoyt            | 1992 | 197             | NA            | NA           | +          | +      | –          | NA         | –   | CNS; SA; GNR  |
| Hsu et al       | 1998 | 34              | No            | –            | –          | –      | +          | NA         | NA  | CNS; SA; GNR  |
| Biel et al      | 1998 | 174             | No            | –            | –          | –      | +          | NA         | NA  | SA           |
| Jiang et al     | 2000 | 186             | Yes           | –            | –          | –      | +          | NA         | NA  | CNS; GNR; SA  |
| Finegold et al  | 2002 | 150             | NA            | –            | +          | –      | –          | NA         | NA  | GNR; ACS; anaerobes; + + |

WBC, White blood cell; CNS, coagulase-negative staphylococcus; SA, Staphylococcus aureus; GNR, gram-negative enteric rods; NA, not available; VS, viridans streptococci; ACS, acute community-acquired pathogens; + +, peptostreptococcus, prevotella, fusobacterium.

*Prospective.

(4) the inflammatory infiltrate is characterized as neutrophilic or eosinophilic (which mark different pathogenic mechanisms).

g. New insights into the role of bacteria in CRS.

1) BACTERIAL SUPERANTIGENS. A number of bacteria, viruses, and fungi can produce exotoxins (sometimes referred to as enterotoxins) that are able to activate T lymphocytes by cross-linking the MHC II molecule on antigen-presenting cells with the variable beta (V8) region of the T-cell receptor. These exotoxins are termed superantigens because they activate subpopulations representing up to 30% of T lymphocytes in contrast to classical antigens, which activate less than 0.01% of T lymphocytes. In addition, superantigens can also act as classical antigens, leading to concomitant generation of anti-superantigen antibodies. These includes antibodies of the IgE isotypes.5,6

A potential role for superantigens from S aureus in the pathogenesis of nasal polyposis has been suggested and is discussed in the section “Factors involved in nasal polyposis.”

2) BIOFILMS. A biofilm is a communicating organization of microorganisms surrounded by a glycocalyx that frequently forms on an artificial or damaged biologic surface. Organisms living in a biofilm are relatively impervious to host defenses and antimicrobial agents. Bacterial biofilms have been elegantly demonstrated in an animal model of otitis media by using scanning electron microscopy and confocal microscopy.1 The possibility that a bacterial biofilm could be contributing to CRS has not been formally studied. This possibility is theoretically attractive and might help to explain the clinical situation in which patients frequently have negative cultures, improve symptomatically while receiving antibiotics, and relapse when antibiotics are withdrawn. In a biofilm, planktonic bacteria leave the biofilm, cause symptoms, and are susceptible to host defenses and antibiotics. However, the biofilm itself is relatively impervious to antimicrobial agents and is never eradicated. Mechanical debridement appears to be the only mechanism that resolves a biofilm. In some refractory patients this might explain improvement with surgery and irrigation.

3) OSTEITIS: THE ROLE OF BONE. To date, bacterial organisms have not been identified in the bone in either human subjects or animal models of CRS. However, in chronic osteomyelitis it is known that organisms can be scarce and difficult to identify. Whether bacteria induce bony remodeling because of associated inflammation or whether they truly infect bone is unknown.2 Areas of increased bone density and bony thickening are frequently seen on CT scans in areas of chronic inflammation and might be a marker of the chronic inflammatory process. However, during the initial phases of severe CRS, the effect frequently appears as rarefaction of the bony ethmoid partitions.

In one study bone specimens from 34 patients with CRS and 9 healthy control subjects were labeled with tetracycline by means of oral ingestion and then 2 weeks later with demeclocycline.3 The bone then underwent biopsy 3 to 7 days after completion of the second antibiotic course. In the patients with CRS, there was a significantly greater remodeling activity than in the control group, as demonstrated by significant separation of the 2 lines of fluorescence resulting from the tetracyclines. The bone was also evaluated for bone turnover semiquantitatively and qualitatively by applying techniques of histomorphometry. Indices evaluated included bone volume, osteoid surface, eroded surface, fibrosis, osteoblastic surface, and tetracycline labeling. Statistically significant differences were again obtained, and the bone turnover seen in the CRS group was similar to that seen in patients with osteomyelitis and trauma.

In rabbit studies of experimentally induced Pseudomonas maxillary sinusitis, Perloff et al5 demonstrated that not
only does the bone become involved adjacent to the involved maxillary sinus but also that the inflammation typically spreads through the Haversian canals and might result in bone changes consistent with some degree of chronic osteomyelitis at a distance from the primary infection. A study by Khalid et al. using both *Pseudomonas* species and *S. aureus* in a rabbit study demonstrated similar results. Bone involvement was noted in 92% of the animals on the ipsilateral side to the infection, and in some specimens clear osteonecrosis was identified. Inflammatory bone changes were also noted on the contralateral side in 52% of the animals. The inflammation caused well-defined changes in the bone in rabbits, both adjacent to the infection and at a distance from the primary site of inflammation, which were compatible with a histologic diagnosis of chronic osteomyelitis. The inflammatory spread within the bone appears to occur as a result of well-defined changes in the Haversian canals, leading first to widening of the canals and increased vascularity, then to an inflammatory cellular collection within the canals, and later to fibrosis in the involved area. It is certainly possible that these changes, if further confirmed in patients, might, at least in part, explain why CRS is relatively resistant to medical therapy.

3. Fungal colonization-sensitization.

Summary Statements:

- AFRS is a distinct clinical subset of CRS in which patients will have positive evidence of fungal allergy to the fungus colonizing their allergic mucin in the majority of cases.
- Those patients with AFRS typically demonstrate 5 characteristics: gross production of eosinophilic mucin containing noninvasive fungal hyphae, nasal polyposis, characteristic radiographic findings, immunocompetence, and allergy to cultured fungi.
- The presentation of AFRS might be dramatic, giving rise to acute visual loss, gross facial dysmorphia, or complete nasal obstruction, but more often, the presentation is subtle.
- Recent studies suggest that fungi can play an alternate role in the development of CRS, whereby patients become sensitized by colonizing fungi through a non-IgE-mediated mechanism. This sensitization is hypothesized to lead to local eosinophilic chemotaxis, inflammation, and tissue injury. This concept of eosinophilic fungal rhinosinusitis encompasses most patients with CRS.

The spectrum of fungal involvement in CRS runs from benign colonization to potentially life-threatening invasive disease. Fungal colonization of the nose and paranasal sinuses appears to be a common finding in both normal and diseased states, although there is considerable debate over the prevalence of colonization. Invasive fungal colonization is presumed to be due to the ubiquitous nature of fungal spores in ambient air and the propensity of these spores to germinate in nasal and sinus mucus. In rare circumstances this leads to macroscopic fungal proliferation in the form of fungus balls (formerly referred to as mycetomas) or saprophytic growth of fungus. In these cases fungal mycelia accumulate and occupy available spaces within the nose and paranasal sinuses in the absence of significant mucosal inflammation. Treatment is simply directed toward extirpation of the offending fungal growth. Occurring more commonly than in the case of fungus balls, microscopic quantities of fungal hyphae in sinus mucus elicit an intense local immune response. In AFRS this gives rise to the pathognomonic feature of the disease, namely the presence of allergic mucin (described below). It is important to realize that AFRS and fungal balls represent noninvasive forms of fungal rhinosinusitis, which must be distinguished from invasive forms.

Invasive fungal rhinosinusitis is often an acute fulminating disease that carries a high mortality rate. Acute fulminant invasive fungal rhinosinusitis is usually caused by fungi such as *Absidia* species, *Aspergillus* species, *Basidiobolus* species, *Mucor* species, and *Rhizopus* species. However, in patients whose immunologic deficiency is mild or unapparent, invasive fungal rhinosinusitis might run a more indolent chronic course. The diagnosis is made on the basis of histologic evidence of invasive fungi in the nose and paranasal sinuses that is present for more than 12 weeks. Management requires repeated surgical debridements, correction of any immunologic deficiency, and long-term systemic and topical antifungal therapy. Despite close medical attention, all invasive cases of fungal rhinosinusitis can progress to a fatal outcome or become a recurrent problem. Chronic invasive fungal rhinosinusitis has been divided into granulomatous and nongranulomatous subtypes on the basis of histopathology; however, the clinical distinction in terms of prognosis and management between these 2 subtypes is not clear. Chronic invasive fungal rhinosinusitis has been specifically associated with *Aspergillus* species, *Mucor* species, *Alternaria* species, *Curvularia* species, *Bipolaris* species, *Candida* species, *Sporothrix schenckii*, and *Pseudallescheria boydii*.

Traditional classification of fungal rhinosinusitis emphasizes differentiating these diseases on the basis of the presence or absence of tissue invasion. Little emphasis has been placed on differentiation of fungal inflammation induced by colonization versus infection. There is little question that the invasive forms of fungal rhinosinusitis constitute infection, but the issue of whether the noninvasive forms represent infection versus inflammation in response to colonizing fungi offers more confusion. At present, current data suggest that the mucosal inflammatory process with noninvasive fungal colonization represents a noninfectious process.

a. Allergy to fungi. Unlike invasive forms of fungal rhinosinusitis, it is the potential for colonizing fungi to elicit allergic mucosal inflammation in the absence of invasion that characterizes AFRS. The ability of fungi or, more specifically, protein components of fungi to elicit IgE-mediated allergic mucosal inflammation is well documented.

Moreover, when those sensitized individuals are placed in environments of high fungal exposure,
symptoms of airway hyperresponsiveness increase significantly over those of nonsensitized individuals in similar situations.80 Virtually all studies of the pathophysiology of AFRS have been based on the premise that IgE-mediated allergy to one or more fungi underlie the disease, with the predominant finding of eosinophil-predominant tissue infiltration akin to late-phase allergic inflammation. In this way AFRS has features quite similar to those of allergic bronchopulmonary aspergillosis.80

b. Classic AFRS. Over the course of the past 25 years, AFRS has emerged as a clinically distinct subset of CRS. AFRS possesses characteristic clinical, radiographic, pathologic, and immunologic features.

1) History and Physical. Occasionally, the presentation of AFRS might be dramatic, giving rise to acute visual loss, gross facial dysmorphia (described below), or complete nasal obstruction.80-82 but more often, the presentation of AFRS is subtle. Patients typically complain of gradual nasal airway obstruction and production of semi-solid nasal crusts that, on inquiry, match the gross description of allergic fungal mucin. The development of nasal airway obstruction might have been so gradual that the patient is unaware of its presence. Pain is uncommon among patients with AFRS and suggests the concomitant presence of a bacterial rhinosinusitis.83,84 In contrast to the often subtle symptoms of AFRS, physical findings are often more remarkable. The range of physical findings on examination is typically broad, ranging from nasal airway obstruction resulting from intranasal inflammation and polyposis to gross facial disfigurement and orbital or ocular abnormalities.81

2) Radiologic Findings. The slow accumulation of allergic fungal mucin provides unique and rather predictable characteristics to the disease. Allergic fungal mucin is sequestered within involved paranasal sinus cavities, and its accumulation eventually leads to the increasingly well-recognized radiographic findings characteristic of AFRS (Table VI). A recent study of sinus CT scans from 45 patients with AFRS objectively supports several previous clinical observations.86 AFRS, although bilateral in 51% of the cases reviewed, caused asymmetric involvement of the paranasal sinuses in 78% of the cases. Bone erosion and extension of disease into adjacent anatomic areas was encountered in 20% of the patients and was more likely to occur in the presence of bilateral advanced disease. Expansion, remodeling, or thinning of involved sinus walls was common (and was thought to be due to the expansile nature of the accumulating mucin). These findings were corroborated by Nussenbaum, et al,86 who reviewed CT scans of 142 patients treated for AFRS at a single institution and also found demineralization of bone in approximately 20% of the subjects.

Heterogeneous areas of signal intensity within paranasal sinuses filled with allergic fungal mucin are frequently identified on CT scans (Fig 5). Although these findings are not specific for AFRS, they remain relatively characteristic of the disease and might provide preoperative information supportive of a diagnosis of AFRS.85 Current evidence points to the presence of accumulations of heavy metals (eg, iron and manganese) and calcium salt precipitation within inspissated allergic fungal mucin as the most likely cause of these radiographic findings.85,87 Desiccation of sinus contents might also contribute to the hyperdense areas seen on CT scans.

MRI can also provide information useful in the preoperative identification of allergic fungal mucin. This effect is more pronounced on T2-weighted images as a result of prolonged magnetic field relaxation times. The high protein and low water concentration of allergic fungal mucin, coupled with the high water content within surrounding edematous paranasal sinus mucosa, gives rise to rather specific magnetic resonance characteristics. The combined CT and MRI findings provide a radiographic appearance that is highly suggestive of AFRS.88,89

3) Immunologic Testing. A study by Manning and Holman84 prospectively compared 8 patients with culture-positive *Bipolaris* species AFRS with 10 control subjects with CRS. Both groups were evaluated with (1) RAST and ELISA inhibition to *Bipolaris* species-specific IgE and IgG antibodies and (2) skin testing with *Bipolaris* species antigen. All 8 patients with AFRS had positive skin test reactions to *Bipolaris* species antigen, as well as positive RAST and ELISA inhibition results to *Bipolaris* species-specific IgE and IgG. In comparison, 8 of the 10 control subjects had negative results on both skin and serologic testing.

Several other studies have also demonstrated a positive correlation between skin test and *in vitro* (RAST) responses for both to fungal and nonfungal antigens in patients with AFRS.84,89 Moreover, patients with AFRS appear to demonstrate a broad sensitivity to a number of fungal and nonfungal antigens.90 On the basis of these and other studies, it is generally agreed that patients with AFRS will have positive evidence of fungal allergy to the fungus colonizing their allergic mucin in the majority of cases. In those cases not showing such a correlation, it might be that technical problems in fungal culture or a lack of skin testing reagents might explain the discrepancy. Sensitivity to numerous fungi has been indicated by means of both *in vitro* (RAST) and *in vivo* (skin testing) methods, although generally only a single fungus is isolated by means of culture of corresponding allergic fungal mucin. This has been previously thought to be the result of either a common fungal epitope or a genetic predisposition toward fungal allergy in AFRS. Recent work by Chrzanowski et al91 identified the presence of an 18-kd protein in allergic mucin obtained from patients with AFRS, which might represent a fungal panantigen.

Total IgE values are also generally increased in patients with AFRS, often to more than 1000 IU/mL, and have been proposed as a clinically useful indicator of AFRS disease activity.90,92 In some cases fungus-specific IgG precipitins have also been detected analogous to those described in allergic bronchopulmonary aspergillosis.

4) Histologic Characteristics of Allergic Mucin. It is the production of allergic mucin that is considered pathognomonic of AFRS. Grossly, allergic mucin is thick, tenacious, and highly viscous in consis-
tency; its color can vary from light tan to brown or dark green.\textsuperscript{93,94} It is the mucin, rather than paranasal sinus mucosa, that provides the histologic information necessary to make the diagnosis of AFRS.\textsuperscript{95,96} Examination of mucosa and polyps obtained from involved paranasal sinuses reveal findings of chronic inflammation, usually with an abundance of eosinophils. Pathologic examination of these tissues should be done to establish that fungal invasion is not present.\textsuperscript{96}

The histologic appearance of allergic mucin reveals the characteristic findings of branching noninvasive fungal hyphae within sheets of eosinophils and Charcot–Leyden crystals.\textsuperscript{97-99} Hematoxylin and eosin staining accentuates the mucin and cellular components of allergic fungal mucin but fails to stain the fungal hyphae. Fungi are recognized for a unique ability to absorb silver. This is the basis for various silver stains, such as Grocott’s or Gomori’s methamine silver stain, which stain fungi black or dark brown. Unfortunately, silver-based stains have high specificity but low sensitivity. A more sensitive method for identification of fungi has been recently developed that makes use of a fluorescein-labeled chitin-specific binding protein. In a study that compared mucus retrieved from 54 patients with CRS, use of this technique allowed for identification of fungal elements in 100% of specimens, whereas fungi were only detected in 41 (76%) of the 54 specimens by using a Grocott stain.\textsuperscript{100} Using this technique, Taylor et al\textsuperscript{100} identified fungal hyphae in the vast majority of sinus mucus samples obtained from patients with CRS, even though most of these patients lacked the other classic features of AFRS. This has become one of the major tenets of the hypothesis associated with the concept of eosinophilic fungal rhinosinusitis (see below).

5) CULTURE OF FUNGI. Fungal cultures of allergic fungal mucin might provide supportive evidence for the diagnosis and subsequent treatment of AFRS but must be interpreted with caution. It is important to realize that the diagnosis of AFRS is neither established nor eliminated on the basis of the results of these cultures. The variable yield of fungal cultures (64% to 100%) renders AFRS in the presence of a negative fungal culture quite possible.\textsuperscript{84} Conversely, a positive fungal culture fails to confirm the diagnosis of AFRS because it might merely represent the

| TABLE VI. Characteristic radiographic findings for AFRS |
|-----------------------------------------------|
| **CT findings** | **MRI findings** |
| Diagnosis requires | 1. At least one opacified paranasal sinus | General: |
| Other strongly supportive radiographic findings | 1. Expansion of the involved sinus | 1. involvement of at least one paranasal sinus |
| | 2. Attenuation-erosion of bone bordering involved sinus (best demonstrated with bone algorithm) | 2. Expansion of involved paranasal sinus |
| | 3. Signal heterogeneity within involved sinus (best demonstrated with soft tissue algorithm) | 3. Displacement of adjacent anatomic compartments |
| | 4. Unilateral or asymmetric distribution of disease | 4. Lack of signal enhancement involving adjacent anatomic compartments |
| | 5. Displacement of adjacent anatomic compartments | |

*Optional but should not be used in the absence of CT.
presence of saprophytic fungal growth. For this reason, the histologic appearance of allergic mucin remains the most reliable indicator of AFRS.

6) Diagnostic criteria. The constellation of clinical, radiographic, and immunologic features help to define the disease and have been the focus of a number of diagnostic criteria. Those patients with AFRS uniformly demonstrated 5 characteristics: gross production of eosinophilic mucin containing noninvasive fungal hyphae, nasal polypsis, characteristic radiographic findings, immunocompetence, and allergy to fungi. Taking into account the current literature, the diagnosis of AFRS is minimally dependent on identifying the combination of histologic evidence of fungal hyphae within eosinophilic mucin and host allergy to that fungus. The diagnosis might be suspected on the basis of physical examination or radiographic findings; however, in most cases the diagnosis is not established until sinus tissue and mucus obtained during sinus surgery have been reviewed. At the time of surgery, the patient might have a persistently opacified sinus cavity, and eosinophilic mucus plus polypoid tissue might be found to account for this opacification. Patients nearly always have type I allergic sensitivity to fungal antigens. Because of these distinctive features plus the distinctive complications of this disease, including bony erosion and facial dysmorphia, AFRS represents a distinct subset from the much broader group of patients with CRS.

c. Non–IgE-mediated eosinophilic fungal inflammation (eosinophilic fungal rhinosinusitis). In 1999, a hypothesis of CRS was proposed by Ponikau et al that suggested colonizing fungi in sinus mucus play a much broader role in the pathogenesis of CRS. By using an ultrason sensitive culture technique, 93% of 101 consecutive patients with CRS demonstrated positive fungal cultures from nasal lavage. Examination of surgically obtained specimens from these patients also revealed eosinophils and fungal hyphae in the sinus mucus of nearly all patients. It was also observed that 100% of a group of healthy control subjects had positive fungal cultures from nasal lavage. Conventional IgE-mediated allergy to fungi was not consistently observed in the patients with CRS. It was proposed that virtually all cases of CRS were associated with sensitization to colonizing fungi. It was further suggested that the term allergic fungal rhinosinusitis be replaced with eosinophilic fungal rhinosinusitis.

An intriguing issue raised by this study is the possibility that certain fungi could elicit eosinophilic inflammation in the absence of conventional IgE in subjects with CRS. This concept was supported by in vitro studies in which PBMCs from patients with CRS were found to produce large quantities of IL-5 and IL-13 after exposure to certain fungal antigens. In contrast, PBMCs obtained from healthy control subjects failed to produce the same response. Thus patients with CRS show evidence of sensitization and immune activation in response to colonizing fungi in the nasal and sinus mucus, and this process might be responsible for the production of cytokines that recruit and activate eosinophils in CRS. For further discussion of this issue, see the section “Controversy 3: Should CRS be classified on the basis of the proposed definition of eosinophilic fungal rhinosinusitis.”

B. Allergic and immunologic factors of rhinosinusitis

Summary Statements:

- Perennial allergic rhinitis appears to be a predisposing factor for acute bacterial rhinosinusitis.
- CRS without nasal polyps is characterized by a predominantly neutrophilic inflammation with a lesser contribution of eosinophils; in contrast, nasal polyps are characterized by eosinophilic inflammation, and IL-5 and eotaxin have been shown to play a role in this process.
- Neither total IgE concentrations nor ECP, IL-4, or IL-5 concentrations in nasal polyps are different in atopic versus nonatopic subjects, indicating a discordance between systemic allergic phenotype and local inflammatory mechanisms leading to eosinophilic inflammation in NP.
- A role has been proposed for IgE specific staphylococcal-derived superantigens in the pathogenesis of CRS associated with nasal polyps.

1. Allergic inflammation. The contribution of allergic responses in CRS has long been controversial. Nonetheless, there is now evidence that at least perennial allergic rhinitis could be a facilitating factor for acute bacterial rhinosinusitis, as demonstrated in a prospective sinus CT scan study. Although seasonal allergic rhinitis has been shown to be a risk factor for orbital complications of acute rhinosinusitis in children, similar evidence is not available for acute rhinosinusitis in adults. In a mouse model allergic inflammation induced by means of sensitization to ovalbumin has also been demonstrated to augment the inflammatory response to acute bacterial infection. Furthermore, allergic reactivity is a poor prognostic factor after surgery in some, but not all, studies.

Most studies of allergic factors in CRS involved studies of NPs. The results of these studies are unclear. Slightly less than half of the patients with CRS and NPs have associated allergies. Furthermore, seasonal allergen exposure does not increase symptoms or mediators in the nasal lavage of patients with NPs and ragweed sensitivity. However, there is a substantial discordance between skin prick tests and evidence of local IgE antibody levels in polyp homogenates. As early as 1982, Drake-Lee and McLaughlin reported their finding of IgE antibody in NPs and no difference in local IgE levels in allergic and nonallergic subjects. Recent studies have found IgE in NPs specific for enterotoxins from S. aureus, which act as superantigens resulting in a multyclonal stimulation of T and B lymphocytes. Another study reported skewing of the Vβ phenotype of T lymphocytes in NPs toward those responsive to staphylococcal exotoxins detected in the tissues. It has been repeatedly demonstrated, at least qualitatively speaking,
that neither IgE levels nor ECP, IL-4, or IL-5 concentrations in NPs differentiate atopic versus nonatopic subjects, indicating that the phenotype of systemic allergy defined as skin prick test positivity does not correlate with the local features of allergic inflammation in NPs. The full explanation for these findings remains elusive, but the implication is that local inflammatory mechanisms might be important in NP pathogenesis. Furthermore, a positive skin test response in a patient with CRS should not be interpreted as an allergic case of CRS. One exception to this rule is AFRS, in which a systemic allergic response to fungi colonizing the sinus mucus is demonstrated in the vast majority of cases (see section “Controversy 3: Should CRS be classified on the basis of the proposed definition of eosinophilic fungal rhinosinusitis?”).

A significant body of work has been done to characterize the T-cell cytokine profile in NPs (reviewed below). Some of these studies subclassified NPs into allergic and nonallergic subtypes on the basis of results of allergy skin testing and the profile of T-cell cytokines found in NP tissue, but it is not clear that this distinction is important in the underlying disease pathogenesis because both allergic and nonallergic patients with NPs manifest prominent eosinophilic tissue infiltration (see section “Factors involved in nasal polyposis”).

Studies of patients with CRS without polyposis are limited but have also shown differences between subjects with and without allergic sensitivities. The principal differences involve a greater degree of neutrophilic inflammation and a lesser degree of eosinophilic inflammation in nonallergic patients; however, eosinophil infiltration is seen to some degree in both allergic and nonallergic patients analogous to the findings in NPs. Also similar to results in patients with NPs, the T-cell cytokine profiles of allergic and nonallergic subjects with CRS show differences precisely as described in subjects with NPs, namely that the full cadre of Th1 cytokines is found in allergic subjects, and a mixed Th1/Th2 profile is found in nonallergic subjects. However, once again, the degree of tissue infiltration with eosinophils is not substantially different in allergic and nonallergic subjects, raising the question of the relevance of systemic allergic phenotype to the underlying pathogenesis.

2. Other inflammatory features. In CRS (without NPs) a range of mediators and cytokines has been shown to be increased in comparison with levels seen in control tissue, mostly inferior turbinate. These include IL-1, IL-6, IL-8, TNF-α, IL-3, GM-CSF, ICAM-1, myeloperoxidase, and ECP. CRS is characterized by a predominantly neutrophilic inflammation, with a lesser contribution of eosinophils. Interestingly, vascular cell adhesion molecule 1 (VCAM-1), an adhesion molecule involved in selective eosinophil recruitment, and IL-5, a key cytokine for eosinophil survival and activity, have been shown not to be increased. This cytokine and mediator profile resembles very much the profile found in acute viral rhinosinusitis, with the exception of a small, although significant, increase of ECP. These findings therefore suggest that the underlying pathologic process might involve unresolved inflammation after infection or a response to chronic infection. This profile is distinct from the pattern in NP.

By comparison, many more studies have been done to describe the inflammation in NPs (see section “Factors involved in nasal polyposis”). A hallmark inflammatory feature is the presence of abundant eosinophils. A variety of mechanisms have been proposed to account for the presence of eosinophils in NPs, as discussed below.

As previously mentioned, a characteristic feature of NPs is the local production of IgE, with a more than 10-fold increase of IgE-producing plasma cells compared with that seen in control subjects. Analysis of specific IgE revealed a multiclonal IgE response in NP tissue and IgE antibodies to S. aureus enterotoxins (SAEs) in about 60% of the patients and in about 80% of subjects with NPs and asthma. Total and specific IgE levels in polyp homogenates are only partially reflected in the serum of these patients.

The classical SAEs, especially toxic shock syndrome toxin 1 and staphylococcal protein A, are excellent candidates to induce multiclonal IgE synthesis by increasing the release of IL-4, as well as the expression of CD40 ligand on T cells and B7.2 on B cells. Staphylococcus protein A further interacts with the VH3 family of immunoglobulin heavy chain variable gene products and thus preferentially activates plasma cells presenting such immunoglobulins on their surface, which leads to a VH3 bias. In fact, follicle-like aggregates can be found in nasal polyps expressing CD20+ B cells, CD3+ T cells, and IgE plasma cells but largely lacking CD1a+ dendritic antigen-presenting cells, supporting the concept of superantigen stimulation. SAEs further stimulate T cells by binding to the variable β chain of the T-cell receptor, which induces cytokine production of IL-4 and IL-5, directly activate eosinophils and prolong their survival, and also might directly activate epithelial cells to release chemokines. SAEs further activate antigen-presenting cells to increase antigen uptake. In fact, when comparing SAE-IgE+ NPs with SAE-IgE- NPs, the number of IgE+ cells and eosinophils is significantly increased. The more severe inflammation is also reflected by significantly increased levels of IL-5, ECP, and total IgE in the NPs. In conclusion, SAEs are able to induce a more severe eosinophilic inflammation, as well as the synthesis of a multiclonal IgE response with high total IgE concentrations in the tissue, which would suggest that SAEs are at least modifiers of disease in NP. Interestingly, similar findings have recently been reported in asthma, which is known to occur concurrently with nasal polyposis.

IgE antibody formation to SAE is rarely seen in CRS in the absence of NPs.

C. Noninfectious and nonimmunologic factors of rhinosinusitis

Summary Statements:

- Overactivity or underactivity of autonomic nerve pathways, abnormalities in leukotriene production or respon-
siveness, nociceptive dysfunction, or local irritation caused by gastroesophageal reflux are demonstrable in select subsets of patients with rhinosinusitis and likely predispose to the pathogenesis of CRS.

- Defects in mucociliary clearance and antibody deficiency syndromes might predispose to rhinosinusitis.
- Aspirin-associated respiratory disease predisposes to rhinosinusitis.

Rhinosinusitis can be classified as resulting from either inflammatory or noninflammatory causes (Table VII). Within these classifications, each cause can be further divided. The following sections will review the various causal factors for rhinosinusitis, with emphasis on noninfectious and nonimmunologic causes.

1. Presence of inflammatory changes.
   a. Eosinophilic rhinosinusitis. Conditions associated with eosinophilic tissue infiltration are summarized in Controversy 2.
   b. Neutrophilic rhinitis. The neutrophilic group includes acute bacterial sinusitis, cystic fibrosis, and chronic bacterial infections complicating immunodeficiencies and foreign bodies. Nasal polyps with neutrophilia in children are highly suggestive of cystic fibrosis.
   c. Mixed inflammatory patterns. Complex mixed or as yet poorly defined nasal mucosal cell populations are present in viral infection, autoimmune diseases, and idiopathic diseases. The leukocytes attracted to the nasal and sinus mucosa vary with the chronology and specific virus causing acute common cold syndromes (rhinovirus, parainfluenza virus, adenovirus, coronavirus, and others), influenza (might cause epithelial destruction), potentially sterile (nonbacterial) rhinosinusitis, or adenoiditis.
   d. Epithelial dysplasia. Epithelial changes occur as CRS progresses from mild to severe. The epithelium shows an inexorable trend from normal ciliated to goblet cells predominant, microvillous cell predominant, and ultimately squamous epithelium with breaches in the basement membrane and surface erythrocytes, indicating bleeding. This epithelial progression roughly parallels CT scan severity. Exposures to organic toxins, fine particulate material, oxidizing minerals (eg, iron), and other materials can lead to epithelial differentiation from ciliated to squamous metaplasia without leukocytosis. The olfactory mucosa might be particularly susceptible. An example of this type of response is the exposure to complex particulates. Some toxins cause an early and transient neutrophilic inflammation that clears rapidly once the exposure has ended. These types of changes have been examined in rodent and screening toxicologic studies, but there are much fewer data in human exposure situations.

2. Noninflammatory changes.
   a. Trigeminal dysfunction. Many of these disorders involve afferent trigeminal and efferent autonomic nerves. They are often dismissed as a functional disorder of nasal complaints without physical findings and lumped together as vasomotor rhinitis (idiopathic rhinitis). This is a misnomer that does no justice to the patient or his or her complaints. Perennial noninfectious, nonallergic rhinitis is an alternative term. There are no clear vascular, motor, or inflammatory cellular patterns. Inquiries about key historical issues can classify and direct therapy to these symptomatic and frustrated patients. These individuals appear to have increased afferent trigeminal nerve sensitivity to inhaled irritants, disordered axon response mechanisms, and potentially altered dorsal horn processing of nociceptive input that contribute to increased perception of these mucosal or visceral stimuli and hence greater complaints of symptoms. An alternative term, irritant rhinitis, describes the syndrome more accurately.
   b. Cholinergic rhinitis. The afferent stimuli can recruit overactive parasympathetic cholinergic reflexes that mediate cholinergic (muscarnic receptor M3-mediated) glandular secretion. This mucus hypersecretion might confound observations of mucopurulent discharge and therefore suggest that rhinosinusitis is present. The effectiveness of anticholinergic agents suggests that parasympathetic cholinergic outflow is the major factor contributing to chronic or long-lasting irritant-induced (eg, cold dry air in skiers) nasal discharge in nonallergic rhinitis. Acute stimulation of nociceptive nerves (eg, by eating capsaicin-laden foods that stimulate vanilloid receptor 1 bearing type C trigeminal neurons) also recruits overwhelming lacrimal, nasal, and salivary glandular discharge. When excessive, this is termed cholinergic rhinitis. Again, anticholinergic agents are effective at
blocking this CNS trigeminal-facial (Vidian parasympathetic) nerve-mediated reflex.

c. Sympathetic dysfunction. Impaired sympathetic outflow can lead to default dilatation of venous sinusoids. This thickens the mucosa and reduces the cross-sectional area for airflow and therefore leads to obstructed nasal airflow. Horner syndrome is an example.

d. Other. Hormonal, structural, and neoplastic disorders also lead to symptoms, including referred pain suggestive of rhinosinusitis. The hormones of pregnancy are notorious for causing nasal obstruction symptoms that can be very problematic to patients. This congestion clears with delivery of the placenta. Hypothyroidism leads to sympathetic dysfunction with ineffective noradrenergic effects and the absence of venous sinusoid vasoconstriction that results in default blood pooling and thickening of the nasal mucosa. Drugs that block this vasoconstrictor function (central and peripheral acting antihypertensive agents) will also lead to mucosal thickening and nasal obstruction to airflow.

3. Nociceptive dysfunction in rhinosinusitis.

The importance of nociceptive neural mechanisms and hyperalgesia in rhinosinusitis is demonstrated by studying the tenderness of the sinus regions. Although pain is the patient’s subjective complaint, tenderness to palpation is a function of spinal cord pain processing (hyperalgesia). Subjects with acute rhinosinusitis and CRS have significantly lower pain thresholds over their sinus regions compared with healthy control subjects (Fig 6). These studies validate the sign of sinus tenderness in the diagnosis of rhinosinusitis. Differences in sensitivity to usually nonpainful stimuli (allodynia) have not been studied in rhinosinusitis.

Patients with allergic rhinitis had intermediate tenderness thresholds that were not significantly different from those of control subjects. Nerve growth factor or potentially other neurotrophins released by mast cells, lymphocytes, or other activated cells in allergic rhinitis might induce these hyperalgesic sensory changes.

### TABLE VII. Mechanistic classification of the differential diagnosis for rhinosinusitis

| Eosinophilia | Neutrophilia | Mixed or poorly defined | Epithelial dysplasia | Neural involvement | Trigeminal nociceptive dysfunction of “visceral sensations” |
|--------------|--------------|-------------------------|----------------------|--------------------|----------------------------------------------------------|
| Allergic, IgE/mast cell–mediated rhinitis | Acute bacterial rhinosinusitis | Viral infections | Atrophic rhinitis | A6 first pain–VRL-1/50°C |
| Nonallergic rhinitis with eosinophilia syndrome (NARES) | Bacterial exacerbations of chronic sinusitis | Vasculitis–Wegener granulomatosis/midline granuloma | Oxena | A6 Cold (L)-menthol receptor: regulation of airflow (dyspnea, work of breathing) |
| Chronic eosinophilia sinus syndrome (CESS) | Ciliary dysfunction–Kartagener syndrome | Basophilic nonallergic rhinitis | Sjogren syndrome | Type C-second pain (parasthesia)/VR1+/neuropeptides |
| Nasal polyposis and polypoid rhinosinusitis | Immune dysfunction–IgA deficiency/common variable hypogammaglobulinemia | Glandular hyperplastic chronic rhinosinusitis | Acute oxidant–particulate exposure (eg, smoke, occupational agents) | Type C-second pain (parasthesia)/VR1+/isolectin B(4) lectin+ |
| Aspirin-NSAID sensitivity | Dentogenic sinusitis | | Transient epithelial denudations with neutrophilia and appropriate repair | Type C itch–histamine/H-1 receptors/flare (axon response release of CGRP vasodilator) |
| Eosinophilic granuloma | Foreign body | Epithelial metaplasia leading to permanent keratinization | | Mechanical stretch (assess degree of sinusoidal swelling?/mucosal contact?) |
| Allergic fungal rhinosinusitis and other syndromes of eosinophilic-fungal disease | | | | Irritant rhinitis of chronic fatigue syndrome (CFS), multiple chemical sensitivity and chronic multisymptom illness (CMI) |

**NSAID**, Nonsteroidal anti-inflammatory drug; **VRL**, vanilloid receptor-like; **VR1**, vanilloid receptor subtype 1, recently renamed transient receptor potential vanillloid receptor 1 (TRPV1); **ACE**, angiotensin-converting enzyme.
However, it has been a challenge to demonstrate these alterations in allergic rhinitis because severely symptomatic, untreated patients with allergic rhinitis must be challenged with highly painful doses of capsaicin to identify these responses. CRS might represent a better model to investigate neurogenic changes because of the larger magnitude of the hyperalgesia. Studies in patients with rhinosinusitis are just beginning.

An important finding of this study was that subjects with chronic fatigue syndrome, particularly those who complain of CRS, had significantly lower sinus pain thresholds than the control group, as well as the acute rhinosinusitis and CRS groups. This is of importance because many of these subjects have normal sinus CT scans and carry the diagnosis of nonallergic irritant rhinitis. Their inclusion in rhinosinusitis studies might confound study outcomes because they might not respond to any rhinosinusitis therapies. They can be identified by means of questionnaires and their systemic tenderness.

4. Aspirin-exacerbated respiratory disease.

Aspirin-exacerbated respiratory disease is an adult-onset disorder defined as a triad of asthma, NPs, and rhinosinusitis. The disease progresses irrespective of whether the individual ingests cyclooxygenase 1 inhibitors (aspirin or nonsteroidal anti-inflammatory drugs), but ingestion triggers a severe upper and lower respiratory tract reaction. The disorder can be diagnosed by means of oral aspirin challenge or (outside the United States) by means of inhalation of lysine-aspirin (but this would not be useful in identifying pure nasal reactors). Nasal inhalation of lysine-aspirin has also been studied, and although highly sensitive, it can be difficult for some patients to endure (20% withdraw), and it is not as specific as the oral challenge (86%).

Antihistamines and high doses of oral steroids should be avoided before the challenge because these can prevent nasocular reactions to aspirin. However, nasal steroids and leukotriene modifiers (zileuton and montelu-
kast) can be continued because they do not appear capable of inhibiting nasocular reactions.144,145 Leukotriene modifiers do not block the upper airway response in aspirin-sensitive patients because zileuton only inhibits the 5-lipoxygenase enzyme by about 40%, and the dose of montelukast appears to be a significant factor.

5. Gastroesophageal reflux disease.

Gastroesophageal reflux disease (GERD) is typically produced by the reflux of stomach acid into the lower esophagus, especially when supine.146,147 Acid can also reflux into the oropharynx, nose, and sinuses, producing upper airway symptoms, including rhinosinusitis.148 Symptoms include hoarseness, cough, postnasal drip, nasal congestion, and drainage; this condition is also referred to as supraesophageal reflux disease (SERD). Although rhinosinusitis symptoms can and do occur in patients with typical GERD,149 studies have shown that 57% to 94% of patients with ear, nose, and throat symptoms do not have typical GERD.150

The pathophysiology of this condition is believed to be direct contact of the upper airway with gastric contents, including acid and pepsin; duodenal contents, including bile acids and pancreatic enzymes like trypsin; or both. Vagal-mediated reflexes have also been implicated. Additional possible mechanisms include defective upper esophageal sphincter pressure, esophageal dysmotility, and poor acid clearance.151

The diagnosis of supraesophageal reflux is somewhat difficult. The tests commonly used to diagnose GERD are less effective in SERD.152,153 Acid suppression in treating CRS.155,156 Both studies were open treatment protocols in children with difficult-to-manage CRS. Dual pH probe monitoring was performed, but not all enrolled subjects in one of the trials had SERD.155 In any case patients were noted to improve in both studies.

6. Other contributive factors to rhinosinusitis (defects in mucociliary clearance and antibody deficiency syndromes).

A great deal has been written regarding the role of defects in mucociliary clearance and humoral immune deficiency as contributive factors to rhinosinusitis. These have been extensively reviewed in recent articles.12,157,163 and were therefore not discussed at length in the conference.

D. Histologic factors of CRS

Summary Statements:

- Examining the histology of middle turbinate tissues from subjects with CRS suggests a distinction between cases of CRSsNP and cases of CRS with NPs
(CRSwNP; ie, different patterns in cellular content and gross histologic changes within the tissue, especially with regard to fibrosis and edema).

- The mucosal lining in CRSsNP is characterized by basement membrane thickening, goblet cell hyperplasia, limited subepithelial edema, prominent fibrosis, and mononuclear cell infiltration.
- In contrast, CRSwNP reveals frequent epithelial damage, a thickened basement membrane, and mostly edematous to sometimes fibrotic stromal tissue, with a reduced number of vessels and glands but virtually no neuronal structures.

1. Polypoid versus nonpolypoid CRS.

CRS is known to manifest as polypoid and nonpolypoid forms. Recent studies examining the histology of middle turbinate tissues from subjects with polypoid versus nonpolypoid disease support the distinction between them. In the study by Malekzadeh et al., preoperative sinus CT scans and histologic specimens of middle turbinate samples obtained during sinus surgery were examined retrospectively in 34 patients and compared with those of 7 control patients undergoing simple and sphenopalatine surgery. CT scan severity was classified according to the May classification. Tissue sections were stained for mucus cells in glands with Alcian Blue. Goblet cells were often not present because of epithelial metaplasia. The area of tissue sections below the epithelial basement membrane were assessed by means of digitized image analysis, and the percentage area stained blue was determined (Fig 7). Normal (May class 0) and mild (May class I) sinusitis showed approximately 6% mucous cells in nasal airway mucosa. A similar percentage was found in class II. However, these subjects could be divided into those with relatively normal histology and those who showed cobblestoned mucosa or small polyps during surgery. This was accompanied by suggestions of increased mucosal edema. As shown by Biedlingmaier and Trifillis, these subjects have goblet cell metaplasia with a decrease in ciliated cells. A major difference in mucosal histology was seen in class III. One population of subjects showed thickened mucosa on visual inspection and had glandular mucous cell hyperplasia, with 22% of the mucosa stained with Alcian Blue. This indicates that some mechanism was active to cause glandular hyperplasia. Potential mechanisms could be similar to those suggested for chronic bronchitis and murine models showing IL-13–induced goblet cell hyperplasia. The other population of patients had visual evidence of polyposis. The histology from the patients with polyps showed a decrease in percentage Alcian Blue area as disease severity worsened from class II to class IV (pansinusitis). Ultimately, the polypoid degeneration totally obliterated normal mucosal histology in the region of the poly root. Patients with polyposis were also more likely to manifest changes of pansinusitis on sinus CT. These results strongly suggest that distinct molecular mechanisms underlie the polypoid and glandular hypertrophy subsets of CRS.

These distinct histologic patterns have been independently supported by several studies. A similar dichotomy was seen in clinical, radiologic, and treatment responses by Eichel. Patients with polyposis detected by means of observation or CT scanning were more resistant to medical therapy and often needed a combination of surgical and long-term medical interventions. The polypoid disease was generally recurrent, despite the medical follow-up treatment. The nonpolypoid sinusitis group generally responded more favorably to medical therapy and in some cases had total resolution of symptoms.

As previously stated, the histology of the epithelium has also been noted to change with radiographic disease severity, as assessed with the May classification. Normal nasal epithelium is ciliated and pseudostratified. In class I and II these cells are replaced by goblet cells. In class III epithelial cells are the predominant population. Squamous metaplasia is present in class IV. Erythrocytes and patches of denuded epithelium are also seen. This
suggests a mechanism for invasion of microbes through the usually protective lining. In essence, the nasal and sinus mucosa differentiates into a skin-like squamous epithelium. These epithelial changes offer novel ecologic niches for microbial colonization and invasion. This might explain the differences in bacterial organisms cultured from acute rhinosinusitis (presumably ciliated epithelium) versus CRS (microvillous to squamous epithelium) groups. These epithelial changes are amenable to treatment and might improve with intensive therapy after surgery.169

Polypoid and nonpolypoid CRS (CRSwNP vs CRSsNP) also generally show different patterns in cellular content and gross histologic changes within the tissue, especially edema and fibrosis formation. In the sinus fluid of patients with CRSsNP undergoing surgery, inflammatory cells are predominantly neutrophils, as is observed in acute sinusitis, but a low percentage of eosinophils, mast cells and basophils might also be found.170,171 In a recent study evaluating the percentage of eosinophils (of 1000 inflammatory cells counted per vision field), 31 patients with untreated chronic sinusitis without NPs all had less than 10% eosinophils (overall mean, 2%), whereas in specimens from 123 untreated patients with NPs, 108 samples showed more than 10% eosinophils (overall mean 50%).172 Among the inflammatory cells, EG2⁺ (activated) eosinophils are a prominent and characteristic feature in about 80% of patients with CRSwNP.173 Eosinophils are localized around the vessels and glands and directly beneath the mucosal epithelium.174

The mucosal lining in patients with CRSsNP is characterized by basement membrane thickening, goblet cell hyperplasia, limited subepithelial edema, prominent fibrosis, and mononuclear cell infiltration. Histomorphologic characterization of NP tissue (CRSwNP) reveals frequent epithelial damage, a thickened basement membrane, and mostly edematous to sometimes fibrotic stromal tissue, with a reduced number of vessels and glands but virtually no neuronal structures.174-176 The stroma of mature polyps is mainly characterized by its edematous nature and consists of supporting fibroblasts and infiltrating inflammatory cells localized around empty pseudocyst formations. In small polyps, not larger than 5 mm, growing on normal-looking mucosa of the middle turbinates in patients with bilateral polyposis, early processes of polyp growth have been studied.177 Numerous subepithelial EG2⁺ eosinophils were present in the luminal compartment of the early-stage polyp, forming a cap over the central pseudocyst area. Fibronectin deposition was noticed around the eosinophils in the luminal compartment of the early-stage polyp and formed a network-like structure in the polyp center and within the pseudocysts. The presence of myofibroblasts was limited to the central pseudocyst area. Interestingly, albumin and probably other plasma proteins were deposited within the pseudocysts adjacent to the eosinophil infiltration. These observations suggest a central deposition of plasma proteins, regulated by the subepithelial eosinophilic inflammation, as a pathogenic principle of polyp formation and growth. The extravasated plasma, for reasons of distance, binding force, or extracellular matrix damage or abnormality, might not find its way to the airway surface.178

For additional discussion of the significance of polypoid versus nonpolypoid CRS, see the section below on controversy 1 (p. S181).

2. Infectious versus noninfectious-inflammatory CRS.

Can we distinguish infectious and noninfectious-inflammatory subtypes of CRS on histologic grounds? Unfortunately, although other evidence presented in this conference would suggest that there might be infectious and noninfectious-inflammatory subtypes of CRS, there is a general lack of information to support or refute this on histologic grounds. This is an important area in need of further study.

E. Factors involved in nasal polyposis

Summary Statements:

- Characteristic symptoms and signs of CRSwNP include nasal congestion, facial pain-pressure-fullness, postnasal drainage, hyposmia-anosmia, and the presence of bilateral NPs.
- Histologically, NPs typically show a chronic inflammatory infiltrate with increased numbers of eosinophils.
- At least 4 processes might contribute to variable degrees to the inflammatory process of CRSwNP: (1) late-phase allergic inflammation in response to airborne allergens; (2) T-cell activation with production of IL-5, IL-13, and IFN-γ in response to fungal antigens (hyphae) in sinus mucus; (3) T-cell activation, cytokine production, and local IgE production in response to bacterial superantigens; and (4) dysregulation of sinus epithelium with overproduction of chemokines, such as RANTES.

Most of what we know about the pathology of NPs comes from studies of inflammatory NPs; that is, those that would best fit the description of edematous, eosinophilic type NPs but might include some NPs with neutrophilic or mixed inflammation cells. Initial studies found heterogeneity in the appearance of NPs, despite the fact that all subjects had symptoms of CRS for a minimum of 12 weeks in association with a history of bilateral NPs and mucosal thickening on sinus CT scans.179 Likewise, other studies have reported heterogeneity in the histologic appearance of NPs.174,175 The pathologic significance of this heterogeneity is unclear but should be kept in mind when interpreting data from NP studies.

The characteristic symptoms of CRSwNP include nasal congestion, facial pain-pressure-fullness, postnasal drainage, and hyposmia-anosmia. Facial pain and fever are uncommon. The most characteristic clinical appearance is that of bilateral NPs. In fact, the presence of unilateral NPs should prompt consideration of other conditions, such as AFRS, inverting papilloma, an antral choanal nasal polyp, other unusual polypoid lesions, or nasal tumors. On radiographic or sinus CT scanning, sinus mucosal thickening is usually present in multiple sinus areas bilaterally,
along with bilateral NPs. When assessed by means of prick and intradermal skin testing, approximately 50% of patients are nonallergic. Overall, about 50% of patients have asthma, and 40% of patients have aspirin intolerance.\textsuperscript{180}

1. Noninfectious CRS.

In the majority of cases of CRS in which prominent polypoid tissue is present, the results of bacterial culture are negative. Even more sensitive PCR techniques have failed to demonstrate bacterial infection in most cases.\textsuperscript{181} This is consistent with a study in which antral punctures of the maxillary sinus were performed in 12 subjects with CRSwNP. A positive culture was found in only 3 patients.\textsuperscript{179} Because of the lack of evidence for bacterial infection, the lack of sinus pain-pressure and fever experienced by patients, and the typical appearance of NP tissue showing a pattern of chronic inflammation with a predominance of eosinophils and a relative paucity of neutrophils, CRSwNP has been referred to as noninfectious CRS.\textsuperscript{181,182}

2. What are early features of NPs?

Only one study has attempted to describe the early features of edematous, eosinophilic-type NPs. In this study the subjects had evidence for a developing polypoid lesion on the middle turbinate before ever having had polyps.\textsuperscript{177} An early feature in these lesions was the presence of eosinophils forming a subepithelial cap over a pseudocyst area filled with albumin. A later feature was a large pseudocyst area containing albumin surrounded by subepithelial eosinophils.

3. Hallmark inflammatory features of CRSwNP.

Histologically, NPs show a chronic inflammatory infiltrate with increased numbers of eosinophils. There is an influx of CD34\textsuperscript{+} eosinophil-basophil bone marrow progenitor cells. Special stains typically reveal a mild increase in the number of mast cells and evidence of mast cell degranulation. Plasma cells are increased in comparison with the normal nasal mucosa.\textsuperscript{183} By means of immunohistochemical staining, the numbers of macrophages, neutrophils, and CD8\textsuperscript{+} T lymphocytes are normal. However, in one study of cells isolated from digested nasal polyp tissue, CD8\textsuperscript{+} T lymphocytes predominated over CD4\textsuperscript{+} T lymphocytes.\textsuperscript{184} Most studies have reported normal or mildly increased numbers of CD4\textsuperscript{+} T lymphocytes. However, there is an increase in activated T cells (CD45RO\textsuperscript{+}),\textsuperscript{184} and dual immunostaining reveals an increase in the number of IL-5–producing T lymphocytes in both allergic and nonallergic patients.\textsuperscript{185} There is also increased expression of ICAM-1, VCAM-1, E-selectin, and P-selectin on NP endothelium\textsuperscript{186,187} and increased local production of chemokines (eg, RANTES, and eotaxin), especially in the epithelium,\textsuperscript{185,188} but also in the submucosal fibroblasts.\textsuperscript{189}

Numerous cytokines and chemokines are overexpressed in NPs. With respect to T lymphocytes, the profile is a mixed T\textsubscript{H}1/T\textsubscript{H}2 cytokine profile. An increase in GM-CSF, IL-3, and IL-13 levels is also present, and their levels are relatively similar in allergic and nonallergic subjects. There is also increased expression of proinflammatory cytokines.\textsuperscript{186}

In addition to cytokines and chemokines, other mediators, such as histamine, are also markedly increased in nasal polyps, exceeding levels of 4000 ng/mL.\textsuperscript{111} Increased levels of tryptase, histamine, and ECP have been reported in polyv tissue and in nasal lavage fluid from patients with NP compared with that seen in those without NP.\textsuperscript{111,190} In addition, increased levels of IgA, IgE, IgG, and IgM in polyv fluid and tissue have been reported.

There is also evidence for remodeling in NPs, including an increase in glanular proliferation, increased numbers of blood vessels, an increase in $\alpha$-SMA\textsuperscript{+} myofibroblasts, and deposition of collagen types I, III, and V.\textsuperscript{191,192} Several profibrotic cytokines have been found to be increased in NP, including GM-CSF, TGF-$\beta$, platelet-derived growth factor, fibroblast growth factor and vascular endothelial growth factor, epidermal growth factor, insulin-like growth factor, and IL-11.\textsuperscript{186,193-196} A significant amount of constitutive matrix metalloproteinase (MMP) 1 mRNA has been reported in NP fibroblasts, and this expression was found to be upregulated by cytokines.\textsuperscript{197}

4. Role of mast cells in NPs.

Mast cells are known to play a key role in IgE-mediated diseases but are also involved in non-IgE-mediated inflammatory diseases. Mast cells can be detected in both the epithelium and the stroma of NPs, as also seen in the nasal mucosa of patients with allergic rhinitis. By contrast to that in the allergic nasal mucosa, the majority of degranulated mast cells are localized to the deep stroma, suggesting that mast cells in NPs are not likely to be activated by inhalant allergens. These mast cells express a variety of cytokines, such as IL-4, IL-5, IL-6, IL-13, GM-CSF, TNF-$\beta$, and IL-8, and mast cell mediators, such as histamine and tryptase. IL-4 and IL-13 are capable of upregulating the release of RANTES, GM-CSF, stem cell factor, and thymus and activation-regulated chemokine from NP epithelial cells, fibroblasts, or both, indicating a vicious cycle perpetuating the eosinophilic inflammation. In fact, it was recently observed that there are increased levels of tryptase and ECP in recurrent NPs compared with levels found in fresh untreated NPs.\textsuperscript{190} Also, a good correlation was detected between the levels of ECP and tryptase. These findings are further supported by the observations of Di Lorenzo et al\textsuperscript{98} that the levels of tryptase and ECP in nasal lavage samples of patients with NPs correlated with symptom scores. Furthermore, histamine from mast cells can upregulate the production of fibronectin and chymase, and tryptase can upregulate the production of MMP-9.\textsuperscript{190} Because mast cells can be stimulated in a variety of ways other than conventional allergy, (eg, bacteria, virus, fungi, complement, or autoantibodies), mast cells might contribute to the induction of eosinophilic inflammation through the release of various inflammatory mediators and indirectly through the activation of structural cells, thus contributing to the formation and progression of NPs.
5. Mechanisms of eosinophil accumulation in CRSwNP.

Several pathologic processes act in concert to promote the accumulation of eosinophils in NPs. These include infiltration of the NP by CD34^+ eosinophil-basophil progenitor cells,^195; increase in the local survival of eosinophils in NP tissue (which is dependent on local IL-5),^206; evidence for local production of GM-CSF and IL-3,^179; upregulation of endothelial VCAM-1 and P-selectin,^186,187,201; production of C-C chemokines in epithelium and NP fibroblasts,^185,188,189,202; and local production of IL-13, which might contribute to adhesion molecule expression and enhance the action of IL-5 and eotaxin in airway tissue.^120,186

There is an increase in the local production of IL-5 in both allergic and nonallergic subjects with CRSwNP. The majority of IL-5-producing cells in NPs are T lymphocytes (68%), with the remainder being primarily eosinophils (18%) and mast cells (14%).^185 This at least suggests that an immune specific activation process might be involved in the disease process. IL-5 is the principal survival-promoting cytokine in NPs. Locally produced IL-5 might also serve as a systemic stimulus for bone marrow eosinophilopoiesis in these patients.

GM-CSF and IL-3 are abundantly produced in CRSwNP and correlate with the numbers of eosinophils present. These contribute to the sustained activation and survival of eosinophils in the NPs. Much of the local production of GM-CSF in NPs probably results from the autoactivation of eosinophils.

Proinflammatory cytokines, such as TNF-α and IL-1β, are also highly overexpressed. They promote NP inflammation through induction of endothelial adhesion molecules, including ICAM-1, VCAM-1, and P-selectin. Several investigators have found increased expression of these molecules in NPs.^186,187

Several chemokines are overproduced in NPs, including the C-X-C chemokine IL-8 and the C-C chemokines RANTES and eotaxin. It might be imprecise to state that IL-8 is dysregulated in CRS. Rather, production of IL-8 by epithelial cells might well be a part of the innate immune response to sinus infection. However, there is evidence for dysregulation of epithelial C-C chemokine production, including RANTES and eotaxin, in NP epithelium, and these chemokines might be important in promoting the local chemotaxis of eosinophils. ^177,185,188,189,202,204

IL-13 is increased in NPs from both allergic and nonallergic subjects.^186 The functions of IL-13 are mediated through the IL-4 receptor chain but are distinct from those produced by IL-4. Given the lack of evidence for overexpression of IL-4 in nonallergic patients, IL-13 might play an important role in disease pathogenesis.

According to the current understanding, IL-5 and eotaxin are the major factors in this eosinophilic inflammation, and IL-5 correlates significantly with ECP.^13,120 Very recently, the regulation of the IL-5 receptor, which exists in the soluble and transmembrane isoform, has been investigated.^205 In NPs the probably antagonistic soluble isoform is upregulated, and the signal-transducing transmembrane isoform is downregulated, especially if associated with asthma.

6. T-cell phenotype in CRSwNP.

Several groups have investigated the cytokine profile of T lymphocytes in NPs. Most have found a mixed phenotype of TH2 and TH1 cytokines, with evidence for local production of IL-5, IL-13, and IFN-γ. The cytokine profile is somewhat different in allergic and nonallergic subjects. A more characteristic TH2 cytokine profile is seen in subjects with CRSwNP and associated allergies, whereas the mixed TH1/TH2 cytokine profile is characteristic of the nonallergic subjects. However, both allergic and nonallergic subjects have increased IL-5 and IL-13 production,^166,208 and the extent of tissue eosinophil infiltration is indistinguishable in these 2 groups. Similar differences in the pattern of cytokines expressed has been found in allergic versus nonallergic subjects with CRSsNP. The local production of IL-5 by T lymphocytes is likely to be of great importance in promoting the survival of tissue eosinophils in NPs. The cytokine profile is somewhat different in allergic and nonallergic subjects with CRSwNP and associated allergies, whereas the mixed TH1/TH2 cytokine profile is characteristic of the nonallergic subjects. However, both allergic and nonallergic subjects have increased IL-5 and IL-13 production,^166,208 and the extent of tissue eosinophil infiltration is indistinguishable in these 2 groups. Similar differences in the pattern of cytokines expressed has been found in allergic versus nonallergic subjects with CRSsNP. The local production of IL-5 by T lymphocytes is likely to be of great importance in promoting the survival of tissue eosinophils in NPs. The cytokine profile is somewhat different in allergic and nonallergic subjects with CRSwNP and associated allergies, whereas the mixed TH1/TH2 cytokine profile is characteristic of the nonallergic subjects. However, both allergic and nonallergic subjects have increased IL-5 and IL-13 production,^166,208 and the extent of tissue eosinophil infiltration is indistinguishable in these 2 groups. Similar differences in the pattern of cytokines expressed has been found in allergic versus nonallergic subjects with CRSsNP. The local production of IL-5 by T lymphocytes is likely to be of great importance in promoting the survival of tissue eosinophils in NPs. The cytokine profile is somewhat different in allergic and nonallergic subjects with CRSwNP and associated allergies, whereas the mixed TH1/TH2 cytokine profile is characteristic of the nonallergic subjects. However, both allergic and nonallergic subjects have increased IL-5 and IL-13 production,^166,208 and the extent of tissue eosinophil infiltration is indistinguishable in these 2 groups. Similar differences in the pattern of cytokines expressed has been found in allergic versus nonallergic subjects with CRSsNP. The local production of IL-5 by T lymphocytes is likely to be of great importance in promoting the survival of tissue eosinophils in NPs.

7. Potential mechanisms of inflammation in NPs.

On the basis of the pathologic features of CRSwNP and a limited number of investigations, it is possible to consider 4 processes that might contribute to the inflammatory process: (A) late-phase allergic inflammation in response to airborne allergens (in allergic subjects with CRSwNP); (B) T-cell activation with production of IL-5, IL-13, and IFN-γ in response to fungal antigens (hyphae) in sinus mucus; (C) T-cell activation, cytokine production, and local IgE production in response to bacterial superantigens; and (D) dysregulation of sinus epithelium with overproduction of chemokines, such as RANTES.

A. In allergic subjects with CRSwNP, the presence of the complete TH2 profile of cytokines suggests that late-phase allergic inflammation might contribute to the disease. However, on the basis of studies of Adkins et al,^209 it is doubtful that airborne allergens penetrate into sinus cavities. This leaves open the question as to how the late-phase inflammatory process is driven in the sinuses. The answer might lie in systemic cross-talk of allergic inflammation (ie, the ability of allergen-induced inflammation at one site to induce a similar response at a remote site). This type of interaction has been demonstrated between the nose and the lungs,^210-212 and preliminary studies suggest that a similar interaction might occur between the nose and the sinuses. Increased levels of IgE receptor (FeCRI) expression were detected in NPs from atopic subjects, and the functional relevance of this could be to cause an increase in IgE-dependent histamine release from NP mast cells. In these patients the levels of specific IgE have been found to be higher in the NP tissue compared with that found in the serum of the same patients, indicating local IgE synthesis.
B. Controversy 1: Should CRS be subclassified as without NPs versus with NPs?

Many published studies of CRS have made a distinction between CRS and CRS with concomitant NPs. Most of these studies have regarded patients with bilateral NPs as forming a distinct subset of the patients with CRS. At the conference, a discussion centered on whether CRS should be formally subclassified as CRSsNP and CRSwNP for the purposes of advancing our knowledge of the underlying pathologic processes involved in each and as a means of sharpening the focus of therapeutic trials. The consensus opinion was in favor of such a subclassification.

Evidence discussed previously in the sections “Histologic factors of CRS” and “Allergic and immunologic factors of rhinosinusitis” support the concept that different pathogenic processes are involved in CRSsNP and CRSwNP. In addition to differences in the inflammatory cellular infiltrate, cytokine and mediator profiles, and the immune response to SAEs, differences have also been described in remodeling processes in CRSsNP versus CRSwNP. The expression of TGF-β1 at the protein and RNA level is significantly higher in CRSsNP versus CRSwNP and linked to a fibrotic cross-anatomy. In contrast, edema and pseudocyst formation characterize CRSwNP, with only few areas of fibrosis. Furthermore, an imbalance of MMPs with an upregulation of MMP-7 and MMP-9 in CRSwNP has been found, whereas in CRSsNP MMP-9 and TIMP-1, a natural antagonist, are increased. This results in the enhancement of MMP-9 in CRSwNP, whereas in CRSsNP MMP-9 activity is inhibited. Differences in TGF-β1 and metalloproteinase levels might account for edema formation with albumin retention in CRSwNP versus fibrosis in CRSsNP.

Most published studies have required that patients have bilateral NPs visible in the middle meatus to satisfy the criteria for NPs. On the basis of histologic assessment, the presence of eosinophils and the general nature of the inflammatory response are similar in NPs and maxillary polypoid mucosa. In patients with previous surgeries, all evidence of polyposis might have been removed, but it is reasonable to classify such a patient postoperatively in the CRSwNP category, at least for a period of time. This might be the case, for instance, in a drug study in which the putative action of the drug might be to prevent the recurrence of NPs. In the earliest stage of polyposis, it is likely that CRSwNP could not be distinguished from CRSsNP. Focal polypoid mucosal changes on the middle turbinate have been suggested as an early feature of CRSwNP; however, prospective studies testing this hypothesis have not been done. Other manifestations of polypoid tissue on the nasal turbinates or in the sinus cavities have unclear significance and do not satisfy the criteria for NPs. Thus for the purposes of classification of
a patient with CRS, the presence of NPs in the middle meatus, either in the past or at present, defines the subset of patients with CRSwNP.

Although there are a paucity of studies directly comparing the clinical features of patients with CRSsNP and CRSwNP, the clinical differences between these subgroups can only be described in terms of general tendencies. The symptom of facial pain-pressure-fullness is generally less common and reduced sense of smell (hyposmia or anosmia) is generally more common in CRSwNP. However, there is a large overlap in the symptoms of each form of CRS, and for this reason, the same general symptom criteria were proposed to define CRS in each case (see section “Rhinosinusitis consensus definitions and clinical trial guidelines”). Patients with NPs are more likely to manifest blood eosinophilia, asthma, and aspirin sensitivity. Patients with CRSsNP appear more likely to manifest signs of bacterial infection and have been reported to have a better response to medical treatment. The development of CRSsNP has long been viewed as a result of abnormal ventilation and drainage of the sinuses to the nasal cavity. However, there is an increasing appreciation of the complexity of this disorder and acknowledgement that persistent inflammation is usually present in CRSsNP, frequently including some degree of tissue eosinophil infiltration. Glandular dysfunction might also play an important role in the pathogenesis of CRSsNP, as suggested by Malekzadeh et al.

The phenotype of CRS also appears to affect prognosis after surgical or medical intervention. Using a rhinoscopic grading system, Kennedy et al found that patients with advanced mucosal polyloid changes preoperatively had a much higher rate of recurrence of disease and relapse after endoscopic surgery. Similarly, Subramanian et al found that patients with a past history or current evidence of NPs had a higher rate of relapse after intensive medical treatment. There is a high rate of recurrence of NPs despite surgical or medical treatment.

The extremely strong association between the development of classic AFRS and the presence of underlying NPs also deserves mention as a distinguishing feature between CRSsNP and CRSwNP. The reason for this close association is unknown, but the marked skewing of AFRS cases into the CRSwNP category was considered another argument for classifying CRSwNP as distinct from CRSsNP. Also, the clinical features of classic AFRS were considered distinctive enough to further subclassify the CRSwNP subgroup into 2 groups, with one represented by patients with classic AFRS and the other group represented by all other patients.

Another question highlights the diversity of opinion on this subject: Does polyoid swelling always evolve into a polyp? As such, are patients with polyoid swelling considered to be different from those with polyps? We acknowledge that there is an earlier intermediate stage of NP formation that is not addressed with the current classification scheme; however, this stage remains undefined and in need of further study.

C. Controversy 2: Should CRS be classified as eosinophilic versus noneosinophilic?

A suggestion was made to classify CRS in terms of the presence or absence of mucosal infiltration with eosinophils or conversely on the basis of the presence of degranulating eosinophils in sinus mucus (eosinophilic mucin rhinosinusitis). The term chronic eosinophilic sinusitis syndromes or chronic eosinophilic sinusitis syndrome has also been suggested to emphasize the role of eosinophilic diseases in rhinosinusitis. Within the category of eosinophilic CRS would fall classic AFRS; eosinophilic inflammation without fungal hyphae (also described as eosinophilic mucin rhinosinusitis by Ferguson); aspirin-exacerbated respiratory disease consisting of NPs–CRS, asthma, and aspirin sensitivity; and eosinophilic granuloma. In terms of the classification scheme in Fig 8, nearly all cases of CRSwNP and a subset of cases of CRSsNP would fall into the category of eosinophilic inflammation. Eosinophilic diseases limited predominantly to the nasal cavity are worth mentioning because of their strong association and potential overlap with rhinosinusitis. These include allergic rhinitis, nonallergic rhinitis with eosinophilia syndrome, and blood eosinophilia with nonallergic rhinitis with eosinophilia syndrome. Obviously, the finding of nasal and sinus eosinophilia is the common element that groups these very diverse and distinct pathologic syndromes into a single classification that can then be further delineated by other findings, such as the presence of atopy, mucosal edema (polyposis), and fungal hyphae.

The noneosinophilic category would include all other cases and could be broken down further into distinct subsets. For instance, one subset would include those with a predominance of neutrophilic inflammation, as well as most of those associated with vasomotor rhinitis, GERD, and sarcoidosis.

The rationale for this subclassification is that eosinophilic inflammation is an important feature of the pathogenesis of CRS, even though multiple causative factors, both allergic and nonallergic, might contribute to it. Another important observation is the strong clinical and pathologic association of the eosinophilic category with asthma. In contrast, the pathologic processes believed to be most likely in CRS without eosinophilic inflammation are those that impair local or systemic immunity (innate or acquired), mucociliary clearance, or sinus ventilation.

This proposed subclassification incorporates many of the concepts discussed at the consensus conference; however, it was not formally adopted. The level of tissue eosinophils needed to define CRS with eosinophilic inflammation has not been established. Furthermore, because histologic findings (including a quantification of eosinophils) are not readily available in patients who have not undergone sinus surgery, this classification scheme could not be applied clinically without obtaining sinus tissue.
D. Controversy 3: Should CRS be classified on the basis of the proposed definition of eosinophilic fungal rhinosinusitis?

The recent hypothesis of Ponikau et al. to describe CRS as eosinophilic fungal rhinosinusitis or eosinophilic fungal rhinosinusitis was discussed. This hypothesis was based on the finding of fungal hyphae in association with degranulating eosinophils in the sinus mucus of 93% of patients with CRS, regardless of the presence or absence of allergy, NPs, or other classic features of AFRS. The authors proposed that eosinophilic fungal rhinosinusitis accounts for the vast majority of cases of CRS. Their proposal has stimulated a great deal of controversy. One contentious issue pertains to the prevalence of finding fungal hyphae in sinus mucus and what level of hyphae would be considered abnormal. Using greatly refined mucus collection and staining methods, Ponikau et al. found fungal hyphae in the mucus of nearly all patients with CRS. Confirmatory results were recently published from Graz, Austria, by using similar methods of mucus handling and histologic staining for fungal hyphae.

The apparent differences between the findings of Ponikau et al. and those of earlier reports might be due to the different techniques used for mucus handling and fungal staining, but because this has been a controversial issue, it will be helpful to have additional studies to confirm Ponikau et al.’s observations. Part of the controversy seems to stem from the fact that an inflammatory process stimulated by fungal hyphae had previously been implicated in only a small subset of cases defined as AFRS. The Ponikau et al. proposal to redefine CRS as AFRS seems to dismiss the importance of defining a small subset of cases as AFRS. However, the consensus opinion expressed at the conference was that the term classic AFRS should be retained as the name for the condition classically described as having distinct immunologic, allergic, clinical, and histologic features (see previous discussion of these features). If the Ponikau hypothesis is ultimately widely accepted, the subgroup of patients with classic AFRS are still likely to represent a distinct clinical subset based on these distinctive features.

Given the emerging data from the Ponikau group, it is clear that the role of fungi in CRS pathogenesis could assume much greater importance than was previously ascribed to it on the basis of studies of classic AFRS.

E. Consensus classification scheme for CRS

A classification scheme for CRS, intended for both clinical use and clinical research, is presented in Fig 8. The distinction between factors that are directly evident in the disease versus factors that underlie the disease is somewhat arbitrary but was viewed as the most practical means for classifying CRS. Important distinguishing features in the scheme are (1) the presence or absence of NPs; (2) the presence or absence of eosinophilic or other inflammatory features; and (3) the presence or absence of fungal hyphae in sinus mucus. The role of bacterial infection as a causative factor in CRS remains
controversial, but bacterial infection is regarded as a potentially important factor in both CRSsNP and CRSwNP. Similarly, other underlying or predisposing factors to the disease, such as mucus recirculation, humoral immune deficiency, abnormal mucociliary function, and allergic rhinitis, are extremely important and are listed. Anatomic abnormalities have anecdotally been listed as a predisposing factor for rhinosinusitis, but existing studies do not support this role. An important question arising from the classification scheme is how strongly are certain factors, such as bacterial infection, associated with either CRSsNP or CRSwNP. At present, it is not possible to provide definitive answers to this question. Precise classification of a patient in terms of inflammatory features, namely as having eosinophilic or other inflammatory features, requires evaluation of sinus tissue and sinus mucus. In cases in which this information is unavailable, the minimal clinical classification will be either CRSsNP or CRSwNP. However, for research purposes, the committee believes this information is essential to classify patients.

VI. DIAGNOSIS AND ASSESSMENT OF RHINOSINUSITIS

A. Symptoms assessments

Summary Statements:

- All relevant rhinosinusitis symptoms, their severity, and time course should be documented.
- The symptom list is not necessarily different in patients with acute and chronic disease, and some symptoms are present in patients with only rhinitis.
- A 7-point analog scale could be used to report individual symptom severity scores, a total rhinosinusitis severity score, a global severity score, an overall QOL score, and the effect of current and past treatments.

The history of patients who present with a possible diagnosis of rhinosinusitis should document all relevant symptoms, their severity, and their time course. Sinusitis is often preceded by and rarely occurs without rhinitis. Therefore for the purposes of accuracy and definition, the term rhinosinusitis is preferred, and all appropriate symptoms should be noted. Several classifications of relevant symptoms have been proposed. The first, developed at a meeting sponsored by the AAAAI, lists symptoms associated with “acute bacterial rhinosinusitis” (Table VIII). Another classification was developed through the Task Force on Rhinosinusitis, sponsored by the AAO-HNS. This one is less specific for the etiology of the rhinosinusitis (Table IX). Like the earlier list, symptoms are divided into major and minor groups. However, it is not clear whether these categories were based on the prevalence rates, the severity degree, or the specificity of the symptoms. Additional lists have been generated. These do not necessarily divide symptoms into major and minor categories. Some suggest symptoms such as facial erythema and maxillary toothache have high specificity but low sensitivity in the diagnosis of acute community-acquired bacterial rhinosinusitis. Others state the same symptoms are seen with both acute rhinosinusitis and CRS, although they might be more vague in patients whose symptoms have persisted for a longer time. Although a single symptom or sign might have only fair sensitivity-specificity, the combination of symptoms has very good predictive value.

1. Relevant symptoms.

The most recent relevant symptom survey was a modification of the clinical diagnostic criteria suggested by the AAO-HNS for CRS. In it, anterior and posterior purulent drainage were compressed into the single symptom of nasal discharge, and fever was omitted as a major symptom because this was not a study of acute rhinosinusitis but rather a study of patients with a disease duration of 12 weeks or longer. This survey was given to 322 patients (mean age, 42 years), and the percentage of patients with each symptom was tabulated (Table X). Symptoms could be aggregated further into nasal symptoms (nasal obstruction, nasal discharge, and sense of smell), facial symptoms (facial congestion, facial pain-pressure, and headache), oropharyngeal symptoms (halitosis, dental pain, cough, and ear pain-pressure), and systemic symptoms (fever and fatigue).

In CRS symptoms are generally the same as those seen in acute rhinosinusitis. However, in some patients, the symptoms might be mild or consist of only a single symptom, such as postnasal drip, or the patient might not be aware of sinus involvement at all (eg, in subjects with concurrent rhinosinusitis and asthma). In CRS the most common symptoms of importance for differential diagnosis are headache, facial pain, nasal obstruction, and discharge.

Headache might even be the only symptom in some patients (eg, those with chronic sphenoiditis). The location of the headache might vary depending on which sinuses are affected. However, headache or facial pain does not generally suggest rhinosinusitis in the absence of other signs and symptoms. Many causes of headaches are manifest in the anterior face. These include tension, migraine, cluster, and rebound headaches and tempromandibular joint dysfunction. Eye diseases and problems with accommodation can also cause periorbital pain. Tension headache is the most common type of headache. It can be described as tightness over the head and neck. It is not aggravated by physical activity, and the typical presenting symptoms of migraine are absent. Patients with tension headaches often believe they have rhinosinusitis because their pain is localized in the forehead and relief is obtained from over-the-counter sinus medications. Migraine headache is an idiopathic recurring disorder with attacks that last approximately 4 to 72 hours. Characteristic of migraine are unilateral location, pulsating quality, moderate-to-severe intensity, associated nausea, and phonophobia or photophobia. Some of the distinctive features of migraine with aura are the complex
toms consistent with the diagnosis of rhinosinusitis.12 Obstruction, nasal discharge, and hyposmia are all symptoms seen with allergic or nonallergic rhinitis.158 Nasal obstruction. Patients with rhinosinusitis and other mucosal diseases most often experience alternating nasal obstruction, usually combined with anterior discharge, postnasal discharge, or both. The mucus might vary in quantity, quality, and color somewhat, depending on the cause of the disorder. Rhinosinusitis symptoms and signs include those seen with allergic or nonallergic rhinitis. Nasal obstruction, nasal discharge, and hyposmia are all symptoms consistent with the diagnosis of rhinosinusitis.12

**TABLE VIII. Acute bacterial rhinosinusitis**

| Major symptoms                  | Minor symptoms       |
|---------------------------------|----------------------|
| Purulent anterior nasal drainage | Headache             |
| Purulent posterior nasal drainage| Facial pain          |
| Cough                           | Periorbital edema    |
|                                 | Earache              |
|                                 | Halitosis            |
|                                 | Tooth pain           |
|                                 | Sore throat          |
|                                 | Increased wheeze     |
|                                 | Fever                |

*A diagnosis of rhinosinusitis probable if 2 or more major symptoms or 1 major symptom and 2 or more minor symptoms are present.

**TABLE IX. Symptoms associated with the diagnosis of rhinosinusitis**

| Major symptoms                  | Minor symptoms       |
|---------------------------------|----------------------|
| Purulent anterior nasal drainage | Headache             |
| Purulent-discolored posterior nasal drainage | Ear pain-pressure-fulness |
| Nasal obstruction-blockage      | Halitosis            |
| Facial congestion-fullness      | Dental pain          |
| Facial pain-pressure-fullness   | Cough                |
| Hyposmia-anosmia               | Fever (all nonacute) |
| Fever (acute only)             | Fatigue              |

*A diagnosis of rhinosinusitis is probable if 2 or more major symptoms or 1 major symptom and 2 or more minor symptoms are present. Facial pain-pressure-fullness alone does not constitute a suggestive history in the absence of another major nasal symptom or sign. Fever alone in acute sinusitis does not constitute a strongly suggestive history in the absence of another major nasal symptom or sign.

2. **Symptom severity scoring.**

Once the relevant rhinosinusitis symptoms have been itemized, they need to be individually quantified. This will help define the magnitude of a patient’s disease and allow for more refined assessments of interventions. The scoring can be as simple as a dichotomy indicating the presence or absence of a given symptom. The most common symptom scoring range in clinical trials of upper respiratory diseases has 4 options: 0, none; 1, mild; 2, moderate; and 3, severe.257 A 6-point Likert scale would range as follows: 0, none-absent; 1, very mild; 2, mild; 3, moderate; 4, severe; and 5, very severe. This scale has been used to identify which symptoms are typically the most problematic for patients with CRS (Table XI).230 Another scoring system option is a visual analogue scale that ranges from 0 (no symptoms) to 100 (maximum severity). The Joint Task Force on Practice Parameters (representing the AAAAI; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology) has developed a method for assessing severity of symptoms of allergic rhinitis. It includes an assessment of nasal symptom severity, an assessment of nonnasal symptom severity, a global assessment of nasal and nonnasal symptom severity, an assessment of QOL issues related to allergic rhinitis, and the effectiveness and adverse profile of current and past rhinitis medications.232 This method for severity assessment of allergic rhinitis symptoms still requires internal and external validation. Nonetheless, it appears to have potential for both assessing patient management and facilitating clinical research. In addition, by using this method as a guideline, a variation of it can be suggested and could be adapted for evaluating rhinosinusitis. Although patients might characterize the severity of rhinosinusitis as mild, moderate, or severe on the basis of one dominating symptom, there is often a mixed degree of severity of the individual symptoms that comprise the full clinical picture.
TABLE XI. Scores of presenting CRS symptoms (range, 0-5)

| Symptom                      | Mean score | 95% CI   |
|------------------------------|------------|----------|
| Major symptoms               |            |          |
| Nasal discharge              | 2.6        | 2.4-2.7  |
| Nasal obstruction            | 3.2        | 3.1-3.3  |
| Facial congestion            | 2.7        | 2.5-2.9  |
| Facial pain-pressure-fullness| 2.5        | 2.4-2.7  |
| Loss of smell                | 2.0        | 1.8-2.2  |
| Minor Symptoms               |            |          |
| Headache                     | 2.6        | 2.4-2.8  |
| Ear pain-pressure            | 1.9        | 1.7-2.1  |
| Halitosis                    | 1.2        | 1.1-1.4  |
| Dental pain                  | 1.3        | 1.1-1.4  |
| Cough                        | 1.7        | 1.5-1.9  |
| Fever                        | 0.7        | 0.6-0.8  |
| Fatigue                      | 2.6        | 2.4-2.8  |

Investigators should strive to report QOL data in a fashion that is most clinically meaningful.

There are several validated rhinosinusitis outcome measures, and the instrument that seems best suited for the particular research question should be selected. QOL is a very important consideration in the evaluation of the severity of rhinosinusitis. QOL measurements reflect the effect symptoms have on the patient’s daily life. Outcomes research studies the effects of diverse therapies on patient outcome and is increasingly recognized by physicians, third-party payers, and the federal government as crucial for the demonstration of treatment effectiveness and the establishment of patient care guidelines. One of the key features of outcomes research is the expanded definition of outcome. The new outcomes measures used in outcomes research include patient-based measures of symptoms, functional status, social and emotional consequences of disease and treatment, and satisfaction with care. Outcomes research refers to the degree of change of the physical, mental, emotional, or social states of being. Generally, outcomes refers to the outcomes of an intervention and the change in these states associated with a treatment or intervention. Outcomes can also change without intervention. Outcome measures can focus on the traditional hard biologic measures, such as blood pressure and laboratory values, or soft measures, such as pain and functional limitations.

Health-related QOL assessment refers to the description of health and disability from the individual’s perspective. QOL instruments generally include measures of physical and emotional impairment, functional disability, and handicap. Over the last 20 years, there has been a dramatic increase in the use of QOL instruments and the reporting of QOL outcomes. Unfortunately, not all results with QOL instruments are easy to understand or can be integrated into the clinical care of patients.

1. Problems in QOL reporting.

There are multiple problems in the published literature regarding the reporting of QOL studies. These problems include (1) the use of unfamiliar scales; (2) failure to explain the clinical importance of the instrument, including the failure to use anchors; (3) failure to describe the minimally clinically important differences; (4) failure to differentiate between inferences for individuals and inferences for individuals versus groups; (5) documenting the responsiveness to change; (6) identifying sample size requirements and statistical power; and (7) multiple QOL end points, longitudinal time frame, and whether the data were analyzed according to an original plan.

2. Health status and health-related QOL in rhinosinusitis.

Health status and health-related QOL instruments can be general or disease specific. General measures allow comparison across different disorders, severities of disease, and interventions, whereas disease-specific scales contain items most relevant to the condition under study.
and that are most likely to change with effective therapy. An example of a general instrument is the Medical Outcomes Study Short Form-36 (SF-36). Examples of disease-specific instruments are the Symptom Score, the Rhinosinusitis Outcome Measure-31, the Sino-Nasal Outcome Test-20, the Chronic Sinusitis Survey, and the Rhinosinusitis Disability Index (RSDI). 

| Table XII. Individual rhinosinusitis symptoms: severity scoring assessment |
|---------------------------------------------------------------|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Nasal obstruction/blockage/congestion | | | | | | |
| Nasal mucoid/purulent drainage: anterior | | | | | | |
| Nasal mucoid/purulent drainage: posterior | | | | | | |
| Facial pain/pressure/fullness | | | | | | |
| Headache | | | | | | |
| Fatigue | | | | | | |
| Decreased sense of smell | | | | | | |
| Ear pain/pain/pressure/fullness | | | | | | |
| Cough | | | | | | |
| Halitosis | | | | | | |
| Dental pain | | | | | | |
| Fever | | | | | | |

**Key to Symptoms**

1 = None – to an occasional limited episode
2
3 = Mild – Steady symptoms but easily tolerable
4
5 = Moderately Botherome – Symptoms hard to tolerate, may interfere with activities of daily living and/or sleep
6
7 = Very severe – Symptoms are so bad, person can not function virtually all the time

and that are most likely to change with effective therapy. An example of a general instrument is the Medical Outcomes Study Short Form-36 (SF-36). Examples of disease-specific instruments are the Symptom Score, the Rhinosinusitis Outcome Measure-31, the Sino-Nasal Outcome Test-20, the Chronic Sinusitis Survey, and the Rhinosinusitis Disability Index (RSDI). 

**Medical Outcomes Study SF-36.** The Medical Outcomes Study SF-36 was originally developed for study of the use of health insurance. It contains 36 items and measures health status in 8 domains: Physical Functioning, Role Physical, Body Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health. Scores range from 0 to 100, with the higher score representing better functioning. Glicklich and Metson showed that patients with sinusitis had significantly lower scores when compared with the general population in the domains of Social Functioning, Body Pain, Vitality, and
b. Symptom Score. The Symptom Score measures the severity of 6 sinusitis-related symptoms: nasal obstruction, problems with sense of smell, anterior rhinorrhea, postnasal discharge, headache, and facial pain. The severity of symptoms is assessed with a visual analogue scale (0-10). In the 24 patients who underwent functional endoscopic sinus surgery, there was a statistically significant difference (improvement) in all 6 symptoms.

c. Rhinosinusitis Outcome Measure-31. This is a 31-item instrument. The items are classified into 7 domains. For each item, there are 2 response scales: Magnitude and Importance. The Magnitude Scale has a 6-category response score, and the Importance Scale has a 4-category response score. The product of the Magnitude and Importance score creates the Symptom-Impact Score, a unique patient-specific score. The Rhinosinusitis Outcome Measure-31 (RSOM-31) requires approximately 20 minutes to complete and has documented response to clinical change.

d. Sino-Nasal Outcome Test-20. The Sino-Nasal Outcome Test-20 (SNOT-20) was derived from the RSOM through the elimination of 11 items. The Importance scale was revised to make scoring easier. The patient is requested to identify which of the 20 items are most important to them and that they hope will get better with therapy (to a maximum of 5). Two scores are derived: (1) Total Score, which is the mean score for all 20 items, and (2) Importance Score, which is the mean score for the items identified as important. The SNOT-20 was validated and demonstrated to be sensitive to change. Items identified as important had higher scores, on average, and showed greater change scores after treatment than items not identified as important.

The SNOT-20 has been used in an outcomes study sponsored by the AAAAI, numerous pharmaceutical-sponsored studies, and is currently being used by Royal College of Surgeons’ (United Kingdom) National Comparative Audit of Sino-Nasal Surgery. The Royal College of Surgeons’ audit is an outcomes study of 3200 patients undergoing sinonasal surgery with a 3-year follow-up (http://www.rcseng.ac.uk/surgical/research/ceu/projects_ongoing/proj_sinosanal.html).

e. Chronic Sinusitis Survey. The Chronic Sinusitis Survey is a 6-item, duration-based monitor of sinusitis-specific outcomes. The symptom-based section contains the following 3 items: pain or pressure, congestion or difficulty breathing through the nose, and nasal discharge or post nasal drip. The medication-based section contains these items: antibiotics, prescription nasal sprays, and sinus medications in pill form. The severity of symptoms are scaled 0 (none) to 4 (severe), and a total score is calculated by using a scoring algorithm that normalized scores from 0 (worst) to 100 (best).

3. Criteria for choosing a particular QOL outcomes measure.

When deciding which QOL outcome measure to use in a particular study, we recommend that the following criteria be used:

1. demonstrated test-retest reliability;
2. validity (measures what it purports to measure);
3. responsiveness to change;
4. ease of interpretability of the results;
5. degree of respondent burden; and
6. intended purpose of the outcome measure, (ie, diagnostic, assess response to therapy, or prognostic).
In summary, for a complete and through assessment of rhinosinusitis and evaluation of treatment, it is imperative that the physical, functional, and emotional problems associated with this condition be measured in a valid way. Without the incorporation of a good QOL instrument, there is no good rhinosinusitis outcomes research. There are many pitfalls in the reporting of QOL information. The investigators should strive to report QOL data in a fashion that is most clinically meaningful. There are several validated rhinosinusitis outcome measures, and the instrument that seems best suited for the particular research question should be selected.

C. Rhinoscopic assessments

Summary Statements:

- Anterior rhinoscopy is the basic tool of the physical examination that relates to determining the existence of pathology in the sinonasal passages. It is best to evaluate the patient after decongestion with topical decongestants. However, even with this method, examination of the nasal passages beyond the anterior portion can be limited.

- Nasal endoscopy helps identify erythema, edema, polyps or polypoid swelling, crusting, eosinophilic mucin, and mucopus or frank pus deep in the nasal cavity. It is most useful in the assessment and treatment of patients with refractory or chronic symptoms and in patients who have impending or existing complications of rhinosinusitis.

- Cultures obtained endoscopically are less invasive and associated with less morbidity; however, this technique is not proved to be equivalent to antral puncture in children with sinus infections.

Rhinosinusitis has been traditionally diagnosed through careful history and physical examination. These techniques reveal important information necessary for diagnosis, treatment, and monitoring. However, symptoms provide information different from and not well correlated with endoscopy or imaging. Patients might be given an improper diagnosis and might be managed improperly on the basis of history alone. Therefore objective measures are increasingly perceived as necessary to accurately determine the presence or absence of rhinosinusitis. The 2 leading methods of objective assessment are nasal endoscopy and sinus imaging with CT. Endoscopy alone cannot be used to determine normalcy because rhinosinusitis can occur in sinus areas that endoscopy cannot detect. Similarly, abnormalities seen in imaging can be present without associated symptoms. Therefore both subjective and objective assessments have value.

1. Anterior rhinoscopy.

Anterior rhinoscopy is the basic tool of the physical examination that most specifically relates to determining the existence of pathology in the sinonasal passages. It is best to evaluate the patient before and after decongestion with topical decongestants, such as oxymetazoline or neosynephrine. Before decongestion, the clinician evaluates the appearance of the anterior nasal passageways. Typically, it is only after decongestion that the middle turbinate can be directly visualized on anterior rhinos-
copy. However, examination of the nasal passages beyond this is very limited when using this method. Septal deviations, seen in up to 79% of the normal population, can obstruct a more complete examination when assessing with anterior rhinoscopy.

2. Nasal endoscopy.

Nasal endoscopy not only plays an important role in the diagnosis of rhinosinusitis but also can assist with its treatment. Most clinicians currently using nasal endoscopy hold 6 tenets to be true: (1) patient symptoms can be an unreliable gauge of disease; (2) endoscopy facilitates proper diagnosis and can detect disease missed on routine history and physical examination or even that missed on imaging studies; (3) discolored drainage (yellow to green) represents a pathologic process draining through the nasal passageways; (4) properly obtained endoscopic cultures are useful in identifying organisms that might be responsible for certain forms of rhinosinusitis; (5) the most important role of endoscopy is in the assessment and treatment of patients with refractory or chronic symptoms and in patients who have impending or existing complications of rhinosinusitis; and (6) endoscopy is well tolerated but is not without risk.

In contrast to anterior rhinoscopy, endoscopy introduces brilliant illumination into the dark cavities and permits magnified direct visualization of the mucosa, the turbinates, and, in postsurgical patients, the sinuses. Nasal endoscopy helps identify erythema, edema, polyps or polypoid swelling, crusting, eosinophilic mucin, and mucopus or frank pus deep in the nasal cavity. The examiner can also identify pus emanating from the middle meatus or sphenoethmoidal recess and in the nasopharynx.

There are 2 types of endoscopes available for evaluating the sinonasal passages: flexible fiberoptic endoscopes and rigid telescopes. They differ mainly in terms of patient comfort and direct access to sinus cavities, flexible endoscopy is generally superior to rigid endoscopy. However, image clarity, the facility to obtain cultures and sample tissues, the ability to control epistaxis, and the ability to perform surgery is superior with rigid endoscopy. Photo documentation of an endoscopic evaluation (photoendoscopy) has been used by some as a research tool. Despite a difference in patient comfort, even rigid nasal endoscopy can be well tolerated. This is evidenced by unpublished data collected during an evaluation of the microbiology of the nasal cavities in 20 healthy medical students. The subjects underwent topical decongestion and anesthesia followed by rigid nasal endoscopy and were asked to rate their overall experience with rigid nasal endoscopy before culture sampling on a 1- to 5-point scale. On average, the subjects rated the experience between tolerable and mildly uncomfortable (2.5).

Although it is generally a very safe and well-tolerated procedure, the most common adverse effects of endoscopy are patient discomfort-pain, epistaxis, and vasovagal events. With regard to patient comfort during endoscopy, it is worth noting that there appears to be decreased sensitivity in the nasal passageways of patients with nasal polyps. This, in part, might be explained by data that

### TABLE XV. Effect of current and past treatment assessments

| Name of Treatment: | | |
|--------------------|-------------------|----------------|
| **Effectiveness:**  | **Complete Relief** | **No Relief** |
|                     | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| **Adverse Effect Profile:** | **No Adverse Effects** | **Severe Adverse Effects** |
|                     | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
suggest that substance P levels are depleted in polyp tissues. This information also helps support the fact that patients can be an unreliable gauge of their own disease. Severe and very rare complications have been reported, albeit rarely, with office endoscopy, including orbital hematoma and death (associated with suctioning near the carotid artery).

Indications for nasal endoscopy during an office evaluation include assessments of symptomatic patients who are refractory to appropriate empiric therapy, who have unilateral disease without septal deviation, or who have severe and disabling symptoms. Endoscopy is also indicated if complications are suspected, if the patient is immunocompromised, or after sinus surgery, trauma, or both.

Although controversy exists over the value of endoscopically obtained cultures, many leaders who study nasal and sinus diseases collect them to guide therapy. Cultures should be obtained by skilled experienced endoscopists. Otherwise, the results from the specimen could be misleading.263-265 Endoscopic sampling can be performed with either a sterile swab or by aspiration into a sterile trap.

3. Techniques for obtaining bacterial cultures.

The sample of sinus secretions must be obtained from one of the paranasal sinuses without contamination by normal respiratory or oral flora to determine the microbiology of rhinosinusitis.267 These specimens can be collected by means of sinus puncture or endoscopically.

a. Sinus aspirates. Traditionally, bacterial specimens of the sinuses have been collected from sinus aspirates. The maxillary sinus is the most accessible. There are 2 nonendoscopic approaches to the maxillary sinus, either through the canine fossa or the inferior meatus. The nasal vestibule is heavily colonized with pathogenic bacteria, especially S. aureus. Accordingly, sterilization of the nasal vestibule and the area beneath the inferior nasal turbinate is recommended. Contaminating nasal flora isolated in the sinus aspirate might be misconstrued as pathogenic. A topical anesthetic is used at the puncture site.

Acute infection is defined as the recovery of a bacterial species in high density (ie, a colony count of at least 10^5-10^6 cfu/mL) to avoid misinterpretation of culture results. This quantitative definition increases the probability that organisms recovered from the maxillary sinus aspirate truly represent in situ infection and not contamination. In fact, most sinus aspirates from infected sinuses are associated with colony counts in excess of 10^4 cfu/mL. If quantitative cultures cannot be performed, Gram staining of aspirated specimens affords semiquantitative data. If bacteria are readily apparent on a Gram stain, the approximate bacterial density is 10^5 cfu/mL. Of 12 cases in which an antral puncture showed at least 10^5 cfu/mL pathogens, the Gram stain demonstrated either organisms or white blood cells in all 12 and organisms and white blood cells in 9 of 12.264 The Gram stain is especially helpful if bacteria are seen on smear and the specimen fails to grow with standard aerobic culture techniques, in which case anaerobic organisms or other fastidious bacteria, such as a bacterial biofilm or an antibiotic-suppressed infection, should be suspected. Performance of a Gram stain will also permit an assessment of the local inflammatory response. The presence of many white blood cells in association with a positive bacterial culture in high density makes it likely that a bacterial infection is present. A Gram stain does not easily differentiate neutrophils from eosinophils, and therefore an eosinophil-rich smear with bacteria would be interpreted as showing many white blood cells by many laboratories. Alternatively, a paucity or absence of white blood cells in association with the presence of a positive culture in low density suggests that the bacteria are contaminating the culture rather than causing infection.

b. Endoscopic specimens. Recently, there has been interest in obtaining cultures of the middle meatus endoscopically as a surrogate for cultures from a sinus aspirate. The endoscopically obtained culture is less invasive and associated with less morbidity.264 Unfortunately, in healthy children the middle meatus has been shown to be colonized with the same bacterial species, S. pneumoniae, H. influenzae, and M. catarrhalis, as are commonly recovered from children with sinus infection.268 Accordingly, this technique is controversial because of the potential for misinterpretation in children.

In 3 recent studies the bacterial species recovered from middle meatal samples of healthy adults were CNS in 35% to 50%, Corynebacterium species from 16% to 23%, and S. aureus from 8% to 20%.64,65,269 The only organism serving both as a commensal and potential pathogen was S. aureus. Several studies in adults have shown a good correlation between cultures of the middle meatus and the sinus aspirate in patients with acute sinusitis, especially when purulence is seen in the middle meatus.264,266,270,271,272 CNS is usually interpreted as a nonpathogen in acute sinusitis. Talbot et al264 correlated the results of endoscopically obtained cultures and cultures obtained from maxillary sinus aspirates. They reported no situations in which the puncture demonstrated CNS of greater than 10^5 cfu/mL; however, a swab of the middle meatus grew CNS in 6 of 53 patients. Interpretation of the pathogenicity of S. aureus is more difficult. Two of 53 patients had greater than 10^5 cfu/mL, which correlated with the endoscopic swab. However, in an additional 6 patients, there was no agreement between sites.264

In rare instances neither a sinus aspirate nor a specimen obtained endoscopically is sufficient for the diagnosis of a sinus infection. In these instances, biopsy of the sinus mucosa and broth culture and appropriate stains might be required to ascertain the microbiology.

D. Imaging assessments

Summary Statements:
- Although rhinosinusitis can be diagnosed in the majority of patients by using only clinical judgment, patients with recurrent or complicated sinus disease might require imaging studies. These studies are an
absolute requirement in patients undergoing functional endoscopic sinus surgery.

- CT has 2 major roles in rhinosinusitis: to define the anatomy of the sinuses before surgery and to aid in the diagnosis and management of recurrent rhinosinusitis or CSR.
- Although MRI does not display the bony anatomy as does CT, it does provide an excellent display of the mucosa, and it is superior in distinguishing between bacterial-viral inflammatory disease and fungal concretions.

A critical assessment of the relative value of various imaging modalities for rhinosinusitis must consider not only the technical merits of each type of study but also the proposed application of the study for disease diagnosis, risk stratification, quantification of disease, response to medical or surgical intervention and disease prognostication.

1. **Standard plain films of the nasal cavity and paranasal sinuses.**

   Although plain film technology might be less costly compared with other diagnostic measures, it falls short of providing adequate diagnostic information. Plain films fail to provide information required on a patient’s anatomy, the paranasal sinus perimeter, and the extent of inflammatory disease. Also, plain films are inadequate to guide surgery.

   Although plain films have limited utility as a screening tool or in children, an appropriate current view would be that the modality is useless in the demonstration of the regional morphology and precludes an accurate representation of the extent of disease. In general, the marginal benefits of sinus plain films are insufficient to justify the exposure to radiation (regardless of how low it might be) afforded by this technology.

2. **CT scanning.**

   CT has 2 major roles in rhinosinusitis: to define the anatomy of the sinuses before surgery and to aid in the diagnosis and management of recurrent rhinosinusitis or CRS. Given its resolution of the regional bony anatomy and mucosa, it has proved to be the optimal modality in providing the anatomic roadmap for the surgeon performing functional endoscopic sinus surgery. Information afforded by the coronal plane has proven to correlate with the endoscopic information and has been the favored plane to study the patient’s anatomy and plan a surgical procedure. The development of image-guided surgical equipment has been based primary on CT information.

   More recently, several authors have attempted to use the CT information, specifically the volume of inflammatory disease within the paranasal sinuses, in an attempt to stage patients with rhinosinusitis. The various staging systems are primarily focused on the presence of and the quantity of the inflammatory disease within the paranasal sinuses. The most accepted staging system is that by Lund-Mackay (Table XVI).

   Unfortunately, no system currently available allows clinicians to show or judge the evolution of this disease or to indicate prognosis. Similarly, to date, a meaningful correlation has not been determined between symptoms and the presence of inflammatory disease within the various sinuses.

3. **Challenges in CT staging.**

   Although results from the Lund-Mackay system appear to be the most reproducible, there are still clinical challenges not addressed by this method of classification. This and other current classification systems lack sufficient levels of gradation for tracking progression or reduction of the disease volume with adequate precision. Another problem is that the classifications currently used do not correlate well with symptoms. It is possible that considering the ostiomeatal channels and quantifying the volume of disease will add to the clinical value of future classification systems.

   A staging system should:

   - provide an objective means of quantifying the volume of inflammatory mucosa and opacification;
   - be easy to use and require no formal training;
   - have high reproducibility, demonstrated by interobserver and intraobserver studies;
   - be able to quantify the patency of the ostiomeatal passageways (ie, specific ostiomeatal tight spots, such as the frontal recess, infundibulum, middle meatus, and sphenoethmoid recess).

   Quantification of the patency of these structures would offer important additional information in staging disease and assessing progression and regression. Ostiomeatal patency might be an important indicator of response to medical or surgical treatment; however, this has not been formally shown. A more precise quantification might also provide a better measure of regression of disease in tight spots in association with a reduction of the volume of inflammatory disease.

4. **MRI.**

   Even though this imaging modality does not display the bony anatomy as does CT, it does provide an excellent display of the mucosa. It is superior in displaying extension of disease beyond the paranasal sinuses into the orbits and intracranial compartment. Bacterial and viral inflammations are indistinguishable; however, MRI is superior in differentiating between infectious inflammatory disease (bacterial or viral) and fungal concretions, and it is the most effective technology in isolating the presence of neoplasia in the morphologic area.

   Given its sensitivity in documenting the presence of fluid, MRI does not distinguish between inflammatory disease and the edematous mucosa seen during the nasal cycle. Additionally, MRI technology is less readily available, more expensive, and lengthier procedure than CT.

5. **Proposals for improving currently available staging systems.**

   Two cross-sectional imaging modalities are available, CT and MRI, and each is able to demonstrate mucosal inflammatory disease and therefore potentially useful in disease staging.

   The Lund-Mackay system is the most objective and most reproducible. A major drawback is its inability to
subgrade the volume of inflammatory disease in grade I, which can represent any degree of sinus involvement from greater than 0% to less than 100%. When evaluating a specific medical therapeutic agent, if grade 1 disease with 10% sinus involvement is cured, it is reduced to grade 0. However, if grade I disease with 90% involvement is reduced to 30%, a substantial improvement, the classification is still grade 1, suggesting there has been no change. Furthermore, this staging system does not take into account the patency of the ostiomeatal channels. These issues can be easily addressed by further stratifying grade I into 1A (1% to 33%), 1B (34% to 66%), and 1C (67% to 99%) and by noting the patency of the tight spots (ie, the frontal recess, middle meatus, infundibulum, and sphenoethmoid recess). These modifications should, of course, be evaluated for reproducibility and prognostic value (Table XVII).

MRI, although more expensive than CT, could be used to assess the volume of inflammatory mucosa. The bright signal intensity of the T2-weighted images can be isolated on a computer workstation and 3-dimensionally reconstructed by the computer to provide a quantitative estimate of volume. A potential confounder is the edematous mucosa of the nasal cycle, which has the same signal as inflammatory disease and cycles from side to side. The edematous mucosa cannot be separated from infected mucosa and must be included in the 3-dimensional reconstruction. However, one would assume (hopefully correctly) that the volume of mucosa that cycles in the nasal cavity is constant in each individual.

E. Nasal-sinus challenge assessments

Summary Statements:

- Nasal and sinus challenges provide a means to study the pathophysiology of disease and the interactions among the nose, sinuses, and lower airway.
- Nasal challenges have also been used to confirm allergy, to assess nasal threshold responses, and to study mediators, inflammatory cells, and cytokines.

Nasal and sinus challenge studies have contributed to understanding the pathophysiology of nasal and sinus disease, as well as understanding the connection between the upper and lower airways. Baroody et al\textsuperscript{218} have been interested in the interaction between the nose and the paranasal sinuses. They first performed a double-blind, placebo-controlled, cross-over trial in 20 healthy nonallergic subjects to assess nasal versus sinus responsiveness to histamine. Subjects were treated with loratadine or placebo for 7 days and then underwent a nasal challenge with histamine. Twenty-four hours later, while receiving the medication, a catheter was placed in the sinus cavity, and the subjects underwent a sinus challenge with histamine. Not surprisingly, in patients receiving placebo, nasal challenge with histamine led to increasing vascular leak indicated by increasing levels of albumin in nasal lavage specimens. When treated with loratadine, an H\textsubscript{1} antihistamine, the effect of histamine challenge was blocked. Although a similar effect was noted in the sinus challenge, the sinus mucosa was 10 times less sensitive to histamine compared with the nasal mucosa. A contralateral response, indicative of a nasonasal reflex, was also evaluated. Although the nasal challenge produced a significant reflex, no effect was noted with sinus challenges. This study showed the feasibility of challenging a sinus directly and suggested differences between the response of the sinus and nasal mucosa to the same stimulus.

Researchers have also investigated whether allergen challenge of the nose has the ability to induce inflammatory changes in the sinuses. Pelikan and Pelikan-Filipek\textsuperscript{289} conducted 73 nasal challenges with antigen in 37 patients with chronic maxillary sinusitis. This resulted in 41 positive nasal responses (in 29 patients), as measured by using rhinometry. Interestingly, 32 of the 41 challenges showed an increase in mucosal edema or opacification of the maxillary sinuses on plain radiographs. They concluded that there was a role of nasal allergy in some patients with chronic maxillary sinusitis. In another study, Baroody et al\textsuperscript{213} evaluated the effect of antigen challenge in the nose on inflammation within the sinus. Using a Sinojet (Atos Medical, distributed by Bivona Medical Technologies, Gary, Ind), an instrument used to obtain sinus lavage fluid from the maxillary sinus, they found that nasal allergen challenge induced an eosinophilic sinus mucosal response that was not seen with control challenge. In another study subjects were challenged to assess the effects of nasal allergen challenge on the ipsilateral versus the contralateral sinus. Although eosinophils were present on both sides, the number of eosinophils was significantly less on the contralateral side.\textsuperscript{290} A significant increase in maxillary sinus eosinophils was also found during the allergy season compared with that seen in patients out of season, confirming the findings of the nasal challenge studies.\textsuperscript{291} Overall, these results suggest that sinus inflammation occurs after nasal allergen challenge.

Adkins et al\textsuperscript{209} studied the ability of inhaled antigen to enter the sinuses. Radiolabeled ragweed pollen was sprayed intranasally in 5 nonallergic subjects. Using a CT scan, radiolabeled ragweed was only detectable in the nose, suggesting in this study that pollen itself was not inhaled into the maxillary sinus. However, as discussed

### TABLE XVI. The Lund-Mackey Staging System

| Sinus systems (0-2) | R | L |
|---------------------|---|---|
| Maxillary           |   |   |
| Anterior ethmoids   |   |   |
| Posterior ethmoids  |   |   |
| Sphenoid            |   |   |
| Frontal             |   |   |
| Ostriomeatal complex|   |   |
| Total               |   |   |
| Anatomic variants (0-1) |   |   |
| Absent frontal sinus|   |   |
| Concha bullosa      |   |   |
| Paradoxic middle turbinate | | |
| Everted uncinate process | | |
| Haller cells        |   |   |
| Agger nasi cells    |   |   |

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earlier, Gwaltney et al\textsuperscript{31} performed a different study in which sinus CT scans were obtained after instillation of radiopaque contrast material into the nasopharynx. The contrast material entered the sinus in 4 of 4 patients after nose blowing, although not after sneezing or coughing. This suggests a mechanism by which allergen or virus could be propelled through secretions into the sinuses.

In addition to advancing the understanding of sinus pathophysiology, nasal-sinus challenges have other important applications in rhinosinusitis research. For instance, nasal challenge with lysine-aspirin has been used to confirm a history of aspirin sensitivity.\textsuperscript{292} Nasal challenges have also been used to confirm allergy, to assess nasal threshold responses, and to study the inflammatory cells and cytokines involved in allergic inflammation. For example, Keith and colleagues\textsuperscript{110} performed allergen challenges on patients with NPs and positive skin test responses and found them to be insensitive to challenge, implying that allergy was not important in the pathophysiology of this group of patients with NPs.

In sum, nasal and sinus challenges provide a means to study the pathophysiology of disease and the interactions among the nose, sinuses, and lower airway. Although not currently indicated, they might, in the future, have value in defining patients to be entered into clinical trials for the study of sinusitis.

\textbf{F. Upper-lower airway assessment}

\textbf{Summary Statements:}

\begin{itemize}
  \item The integrated airway syndrome, also called \textit{chronic inflammatory respiratory syndrome}, has a wide spectrum of severity: at the low end, its manifestations are clinically evident in the form of rhinitis, and at the high end, manifestations include asthma and possibly rhinosinusitis.
  \item The links between the upper and lower respiratory tract are strongly supported: both allergic rhinitis and nonallergic rhinitis are risk factors for asthma; allergic rhinitis is almost ubiquitous in asthma, even in the absence of nasal symptoms; the nasal mucosa of patients with asthma shows evidence of inflammation; and the rhinitis of asthmatic patients tends to be more severe than the rhinitis of nonasthmatic patients.
  \item Allergic reactions and their inflammatory consequences appear to propagate systemically, and therefore the interactions between nasal, sinus, and lower airways might represent the manifestations of such a systemic process.
\end{itemize}

The nasal airways, the sinus cavities, the pharynx, the larynx, the trachea, and the intrathoracic airways are parts of one conduit with a common embryologic origin. Each of these parts appears to have specialized functions, but all parts are highly integrated. Although some illnesses might affect only selected parts, several others manifest themselves over the entire respiratory tract. The chronic allergic respiratory syndrome (and perhaps its nonallergic counterpart) is an example of the panairway affliction. Chronic rhinitis, rhinosinusitis, and asthma should be considered components of this syndrome and not independent nosologic entities.

A model has been proposed to integrate many epidemiologic, pathophysiologic, and clinical observations on rhinitis and asthma.\textsuperscript{293} A similar model could be proposed to integrate rhinitis and rhinosinusitis, as well as rhinosinusitis and asthma. The premise of this model is that the chronic allergic respiratory syndrome has a spectrum of severity. At the low end, its manifestations are clinically evident in the form of rhinitis, and at the high end, manifestations include asthma and possibly rhinosinusitis. The reason why the nose is in the center of the syndrome is because it constitutes the primary deposition site for aeroallergens. In the presence of rhinitis alone, the lack of clinical manifestations of the syndrome in the lower airways and the paranasal sinuses should not be interpreted as a lack of involvement. The lower airways of individuals who only have allergic rhinitis have been repeatedly found to be inflamed or even remodeled (increased thickness of the reticular basement membrane) compared with those of healthy control subjects.\textsuperscript{294} Also, lower airway hyperresponsiveness can be detected in a significant number of individuals with allergic rhinitis but without lower airway symptoms.\textsuperscript{295}

Several observations support the aforementioned model. First, both allergic rhinitis and nonallergic rhinitis are risk factors for asthma in cross-sectional and longitudinal studies.\textsuperscript{296,299} Second, rhinitis is almost ubiquitous in asthma.\textsuperscript{298,300} Furthermore, the nasal mucosa of patients with asthma shows evidence of inflammation,
even in the absence of nasal symptoms. Third, the rhinitis of asthmatic patients tends to be more severe than the rhinitis of nonasthmatic patients. Although this concept has not been adequately investigated and the available data are still in preliminary form, recent epidemiologic evidence provides some support for this theory.

Finally, data from pathologic and clinicoepidemiologic studies suggests that in asthmatic patients the severity of asthma and rhinitis tracks in parallel. An additional aspect of the relationship between nasal and lower airway disease in the context of the chronic allergic respiratory syndrome is that events that take place in the nasal cavities might affect the lower airways. A nasal allergic reaction induced by localized provocation, for example, can result in increased responsiveness in the lower airways or even in late reductions in lung function. Inversely, treatment of allergic rhinitis with topical glucosteroids has been shown, in several studies, to improve various asthma outcomes. However, the mechanisms of this apparent interaction between the nasal and the lower airways are not clear. Obviously, many functions of the nose are known to benefit the lower airways, and it would not be surprising if deterioration or improvement of these functions accounted for the interactions. On the other hand, allergic reactions and their inflammatory consequences appear to propagate systemically, and the interactions between nasal and lower airways might represent the manifestations of such a systemic component.

The data relating sinus disease to asthma are far less extensive; however, they indicate similar relationships between asthma and rhinosinusitis as between asthma and rhinitis. For example, almost ubiquitous presence of paranasal sinus abnormalities in patients with moderate-to-severe asthma has been reported in a study using computed tomography. Because they commonly coexist, testing pulmonary functions in patients with rhinosinusitis should always be considered. Evidence of eosinophilia in the sinus mucosa is stronger in patients with rhinosinusitis and asthma, as opposed to rhinosinusitis alone. Medical and surgical treatment of sinus disease appears to have beneficial effects on asthma outcomes, but the studies reporting such findings are not randomized, and the outcomes are frequently subjective. Thus because the links between the upper and lower airway are not fully understood, additional, careful, mechanistic, and therapeutic studies need to be conducted to further clarify the relationships of rhinosinusitis in these integrated respiratory syndromes.

VII. CLINICAL TRIAL DESIGNS OF RHINOSINUSITIS

A. Issues compromising advances in rhinosinusitis research

Summary Statements:

- Rhinosinusitis definitions for clinical trials or epidemiologic surveys are largely proposed on an ad hoc basis.
- The use of certain markers might be inappropriate as outcome variables in clinical trials because they correlate poorly with clinical end points, such as symptoms.
- Rhinosinusitis trials need to be concerned with timing issues, such as seasonal patterns and the duration of acute versus chronic studies.

1. Definitions.

Several consensus documents have been published in recent years that have attempted to define rhinosinusitis or sinusitis. Individual articles have also attempted to develop definitions. Despite this, disease definitions for clinical trials or epidemiologic surveys are largely proposed on an ad hoc basis. For example, studies designed to demonstrate the efficacy of novel antibiotics frequently study subjects with acute symptoms combined with the presence of fluid in the maxillary sinuses as demonstrated on the basis of air-fluid levels on plain radiography or CT scanning. Given regulatory guidelines by which this class of drug is approved, this definition is understandable. However, many patients present with a similar spectrum of acute symptoms and are treated on an empiric basis without confirmatory imaging tests. On review of published clinical trials, it is clear that even for the acute maxillary paradigm listed above, inclusion and exclusion criteria are inconsistent in regard to the demographics of the populations studied, the medications prohibited during any study, and the range of concomitant medications permitted.

Without a consensus on definitions, it is not surprising that the basic epidemiology is unclear. In large epidemiologic surveys it might be sufficient for a patient to report a diagnosis of CRS to be included in that category. In others, a CT scan or other objective confirmation might be required. Similarly, a variety of outcome scales and instruments have been used. These issues have been discussed in general reviews.

2. Placebos.

There are 2 main issues surrounding placebos: ethics and technical feasibility. There are certain clear situations in which a placebo group would be unethical (e.g., for an acute, severe bacterial infection for which antibiotic treatment is indicated). In this case a standard antibiotic is generally appropriately used as a positive control. In other cases of suspected acute bacterial sinusitis, a placebo-controlled trial might be reasonable if appropriate rescue measures are included to protect the patients in the trial. Discontinuation of patients from such a trial could be a valid efficacy outcome variable. In addition, some clinical trials have demonstrated that antibiotics are not effective for rhinosinusitis. In such cases, a placebo control group might be ethical. Also, when adjunctive or prophylactic agents are being evaluated, it is often possible to design an appropriate placebo-controlled study.

Technical difficulties can occur when evaluating different formulations, such as topical versus systemic agents or oral versus parenteral agents. When it is clear that there
is no infection, the selection of a placebo group might depend on whether that group is adversely affected by allowing the underlying disease processes (eg, inflammation) to continue untreated. If the baseline variability of different study groups is poorly defined or the duration between discrete episodes is long, a placebo run-in period might not be feasible.

3. Topical agents.

The effects of topical agents on the nose and sinuses should be considered during the conduct of a clinical trial. In several European studies evaluating treatment modalities for rhinosinusitis, the use of topical α-adrenergic agonists was permitted as concomitant medication (reference). This will confound the trial data because this class of drug has been shown to increase sinus ostial diameter. Even if the incidence of use of such medications in study groups is similar, their additive effect might not be separable from the effect of the study drug.

There is a large body of literature discussing the effects of preservatives on the nasal mucosa. The overall conclusions, derived from a combination of in vitro and animal studies, are somewhat controversial as applied to clinical practice. Because the ciliary activity might be reduced by infection per se, any added effect caused by preservative-containing topical compounds might be inconsequential when studying infectious rhinosinusitis.

Topical agents introduced into the nose do not pass retrogradely into the paranasal sinuses through an intact osteomeatal unit. Several imaging studies have been conducted that failed to demonstrate retrograde transport. This fact must be considered when interpreting the results of a study of a topical agent in rhinosinusitis. The outcomes might be different for those who have had sinus surgery compared with those who have not.

Studies administering saline by means of nasal instillation demonstrated reduction in nasal blood flow, as measured by means of laser-Doppler velocimetry. Because intranasal saline has been shown to have a mild decongestant action, the use of even seemingly benign sprays should be controlled in studies of rhinosinusitis. In addition, vehicles used in drugs such as polyethylene glycol act as wetting agents and can produce a beneficial effect on nasal symptoms. Testing therapeutic agents that use such vehicles require appropriate controls. Ultimately, the potential beneficial and adverse effects of all components of a drug product other than the drug itself should be taken into consideration when analyzing the value of compounds for the treatment of rhinosinusitis.

4. Systemic agents.

The clinical effect of repeated doses of various medications might be different from the effect seen after administration of a single dose because of such events as receptor downregulation or induction of pharmacologic tolerance. Other issues compromising the use of systemic agents for rhinosinusitis include their adverse effects on other organs and problems with drug-drug interactions.

5. Outcome measures.

The use of certain markers (eg, imaging studies) might be inappropriate as end points in clinical trials because they do not correlate well with clinical end points (ie, symptoms). In studies of therapeutic agents for the treatment of rhinitis, both individual and composite symptom scores are well accepted as end points. In studies of nonantibiotic drugs for the management of rhinosinusitis, a condition for which there is poor correlation between CT findings and symptoms, CT findings alone can not be used as a surrogate in assessing efficacy.

Physicians routinely treat the entities of acute and chronic rhinitis and rhinosinusitis empirically on the basis of symptomatic presentation. In established patients with rhinosinusitis who experience exacerbations, physicians often diagnose and prescribe without physical examination because there is little evidence that physical examination is helpful in establishing the diagnosis in patients who present with typical symptoms of rhinosinusitis. If patients are refractory to therapy or if their symptoms are atypical, a detailed physical examination is generally indicated. In some cases referral to a specialist, with performance of radiographic imaging, flexible or rigid nasal endoscopy, or both, might be appropriate. As experience has evolved with the use of coronal CT imaging of the sinuses, it is now accepted that appropriate timing of a CT scan is crucial. Gwaltney et al showed that positive scans could be demonstrated in acute upper respiratory tract infection. For CRS, a scan taken to demonstrate the extent of residual disease after maximal pharmacotherapy, to define anatomy before surgery, or both is appropriate. There have been several attempts to devise staging systems to define the extent of disease. Most of these have been developed as a guide to surgical staging and have not been validated in the context of assessing the natural history of the disease or in assessing the effect of nonsurgical intervention.

6. Time course.

Clinical trials need to be conducted when there is an increased incidence of upper respiratory tract infections to obtain an adequate number of clinical trial subjects with acute episodes of rhinosinusitis. The seasonal epidemiology of patients with CRS has not been well defined. Patients with an underlying allergic diathesis might experience exacerbations at the time that the allergens to which they are sensitive are present in the environment. There might be acute infectious episodes that present at the time of increased airway reactivity. This could be due to the predisposition induced by allergic inflammation or independent of these effects. For studies conducted in different parts of the world, the duration of seasonal allergies and the specific pollens will vary, leading to disparate clinical effects.

Studies up to 1 year have been reported to study the effects of interventions on the incidence of exacerbations. The environmental and other variables that might change during this prolonged study period could be difficult to assess and control. Similarly, when seeking a past history
of acute rhinosinusitis episodes, it is frequently difficult to pinpoint discrete episodes and even more difficult to document whether they were acute infectious episodes. Such episodes might have been treated empirically or through telephone consultation, and there is rarely objective confirmation of an active pathogen. To be pragmatic, it is often reasonable to define a set of symptoms that are consistent with sinus infection and to assume that the patient can recognize these retrospectively to categorize the sinus infection. Furthermore, because current medical practice includes diagnosing and treating empirically, one option would be to design clinical trial protocols on the basis of this real-life scenario. Because there is limited understanding of the natural history of the various types of rhinosinusitis, the decisions about a specific end point and follow-up time frame after an intervention might be arbitrary.

7. Allergic reactivity.

The effects of allergic inflammation on the paranasal sinuses are of great interest, but their full effect remains poorly understood. However, there is no entity that would be currently characterized as allergic rhinosinusitis. Pelikan and Pelikan-Filipek described a series of cases that demonstrated acute reversible opacification of the maxillary sinuses after topical antigen challenge, but this study did not examine sinus cavities pathologically. Several studies reported a higher incidence of acute sinusitis episodes in patients with allergic rhinitis compared with those without allergic rhinitis. If there was a clear association between allergic rhinitis exacerbations and sinus infections, the effect of allergen immunotherapy would be important to study. Similarly, the effect of other immunomodulating interventions should be studied. Given these facts, there is reason to believe that immunotherapy could confound the assessment of other treatments under evaluation, especially if the allergen dose is not stable. The seasonal effects of immunotherapy on patients who enter long-term clinical trials have not been determined.

8. Surgical therapy.

Assessing the effects of surgery on CRS poses a special challenge. There is a chance that a published case might represent the best results of an individual surgeon or group highly experienced in a given technique. Case series of bilateral intranasal sphenoidectomy have been published. The outcomes of endoscopic surgery have also been well described in several studies. It might be difficult to compare techniques and outcomes from different surgeons. One key point is that the surgical outcome is dependent on the degree of mucosal disease present before the operation. The indications for performing sinus surgery might also vary somewhat by case series, with some patients undergoing surgery despite relatively normal sinus appearance on the preoperative sinus CT scan. It is not clear how these results compare with each other, and it is still difficult for a medical practitioner to decide the basis for referring a given patient to a surgeon other than anecdotal satisfaction. Ethical considerations must be evaluated before doing a parallel-group clinical trial in human subjects, with one group getting sham surgery. One interesting study in nasal polyposis involved operating on an unaffected side. Although it is difficult to blind or sham control surgical treatment, it is possible to and important to consider randomization to surgery versus no surgery with available rescue medication over a period of time.

B. Developing effective drug trial schemes for rhinosinusitis

Summary Statements:

- Most trials for acute rhinosinusitis will likely be carried out in a primary care office setting, where sophisticated diagnostic techniques, such as CT and MRI, might not be readily available, and therefore the medical history in particular, and sometimes the physical examination, should be primarily used to diagnose the condition.
- Therapeutic efficacy must be demonstrated through adequate and well-controlled studies showing that the intervention will have the effect it purports.
- The prospective choice of end points is a critical part of drug development; efficacy end points for trials that will form the basis of approval should be clinically relevant, validated, and direct.

The majority of rhinosinusitis trials for new forms of therapy or new indications for already existing treatments are done in patients with acute rhinosinusitis. CRS is a serious and often debilitating disease; however, the poor pharmacologic response rates seen in this patient population, as well as the lack of understanding about disease classification, have made accurate efficacy assessment difficult. Therefore clearer definitions and categories of CRS are urgently needed.

1. Targeting the appropriate patient population.

Targeting the correct patient population is essential when designing a study for ensuring real-world assessment of an intervention. Researchers developing a clinical trial design need to set diagnostic parameters so that the patients who can provide the most meaningful clinical results can be included. In patients with rhinosinusitis, this might mean distinguishing between viral and bacterial disease, as well as acute rhinosinusitis and CRS. Most trials for acute rhinosinusitis will likely be carried out in a primary care office setting, where sophisticated diagnostic techniques, such as CT and MRI, might not be readily available. For the purposes of research, patients with symptoms lasting less than 10 days should not be included in trials on presumed bacterial infections because symptoms that resolve before 10 days are usually indicative of viral rhinosinusitis. Symptoms that should be evaluated include purulent drainage, nasal congestion, facial pain, and headache. Even if these criteria are applied, consideration must be given to the high rate of spontaneous resolution (approximately 50%) in the population with acute (presumed bacterial) rhinosinusitis. Therefore, unless a sample size is large enough to
effectively power the study, the results might fail to
demonstrate drug efficacy.
2. Study outcome variables.
Pharmacologic studies for rhinosinusitis either involve
symptom-relief drugs or curative drugs. For symptom
relievers, such as corticosteroids, antihistamines, decon-
gestants, or mucolytics, the primary outcome variables
used to evaluate efficacy should be improvement in
symptoms and signs. For curative drugs, such as anti-
biotics, outcome variables could be cure rate or failure or
recurrence rate. Other important outcome measures for
both types of drugs are time to improvement and number
of symptom-free days. Disease burden and QOL can also
be important assessments. Depending on the type of drug,
a study could also be designed to evaluate prophylaxis,
safety, or both.
3. General study design.
Studies are most often designed to focus on efficacy.
Such studies need to be randomized, double-blind, and
controlled. Because a key measure of efficacy in this type
of study is symptom resolution, a control group is essential
to quantify the placebo effect. The duration of treatment
depends on the disease under study. In an acute rhino-
sinusitis study the screening phase would be very short
because of the acute nature of the disease, and the
treatment period should also be brief (eg, 2 weeks).
Studies in patients with CRS will require treatment for
much longer, typically a month or more, and should
differentiate between CRSsNP and CRSwNP, focusing on
different symptom patterns. Studies assessing prophylaxis
need to run at least 12 months. Once the treatment period
has ended, a follow-up period is necessary to ensure
symptoms are truly resolved.
4. Inclusion and exclusion criteria.
Inclusion criteria include predefined age limits (for
either an adult or pediatric study) and clearly defined
symptoms of acute rhinosinusitis for 10 to 28 days.
Common exclusion criteria include immunocompromised
patients, patients with ciliary disorders or any sort of
permanent local obstruction, and, if it is an acute study,
patients with CRS. Other confounding factors that are
usually excluded are seasonal pollen allergy, large nasal
polyps, and atrophic rhinitis.
5. Efficacy and safety outcomes.
Outcome measures will vary depending on the drug
class being studied. Most existing sinusitis studies have
focused on antibiotic therapy. As such, a large body of
information is available as guidance for appropriate
outcome measures for these drugs. However, recent
studies have also been done on nonantibiotic regimens,
such as intranasal steroids. Controlled trials need to show
drug safety for use under labeling conditions and provide
substantial evidence of efficacy for recommended use.
When assessing the safety of a drug, much depends on the
agent and the drug class. Trials evaluating an already
approved medication for a new indication will need much
less focus on safety than trials for new molecular entities
or a drug that is first in that class.

The prospective choice of end points is a critical part
of drug development. Efficacy end points for trials that
will form the basis of approval should be clinically
relevant, validated, and direct. Also, the methods used
to make these measurements should be accurate, pre-
cise, reproducible, and responsive. Choice of efficacy
end points earlier in development might differ and
might even be a surrogate end point, depending on the
phase of development, goals of the study, and rationale
for decision making. Because there is limited experi-
ence with CRS studies, statistically significant differ-
ences from placebo will be important to demonstrate
initially. Clinical relevance might be more difficult to
quantify. A clinically meaningful effect could be the
time to reduce or recover from symptoms when
receiving a study drug versus placebo rather than the
outcome at a certain time point.

A number of potential problems exist when designing
a rhinosinusitis study. Until recently, there has been a lack
of consensus regarding classification and definition of
various types of rhinosinusitis, inability to diagnose
rhinosinusitis with high specificity, and varying standards
of care; all of these factors make design of an effective
clinical study difficult. In many respects acute rhinosinu-
isitis and recurrent rhinosinusitis are easier to study than
CRS. The stage was set for further refinement of the
definitions of CRS, as proposed in this document through
the development of a consensus definition for CRS by the
Chronic Rhinosinusitis Task Force of the Sinus and
Allergy Health Partnership.352

During an acute rhinosinusitis study, evidence of
efficacy depends on the drug itself. For an adjunct therapy,
the study needs to show that the combination is better than
the regimen to which the experimental agent is added. For
a stand-alone nonantibiotic drug, the study needs to show
that the experimental medication is better than placebo.
For a stand-alone antibiotic drug, the study needs to show
that the experimental antimicrobial agent is similar or
superior to an approved antibiotic, as well as showing
some evidence of bacteriological cure ( www.fda.cder/
guidance: Acute Bacterial Sinusitis). For acute bacterial
rhinosinusitis studies, clinical outcomes are measured by
clinical cure or clinical failure, for example, a 20%
difference between an antibiotic and placebo as an
outcome at the end of 10 days of therapy. Microbiologic
outcomes are described as documented eradication, pre-
sumed eradication, documented persistence, or presumed
persistence. During a recurrent rhinosinusitis study,
efficacy variables can include time to recurrence (possibly
primary variable), severity of recurrence (secondary vari-
abe), and frequency of recurrence (secondary variable).
Finally, it is important to determine that end points used to
assess efficacy should be carefully selected to avoid
confounding factors. Investigators need to define the
clinically significant difference for a particular study.
The ways to define clinically significant difference include
a distribution-based approach with a standardized re-
sponse mean and effect size and the preferred anchor-
based approach, using global ratings of change.
VIII. RHINOSINUSITIS CONSENSUS DEFINITIONS AND CLINICAL TRIAL GUIDELINES

What follows are the consensus definitions and disease classifications for acute rhinosinusitis, CRS without nasal polyposis, CRS with nasal polyposis, and classic AFRS, as well as suggested study schemes. Separate definitions are outlined for research and patient care. It is important to keep in mind that the consensus recommendations are based on the experience of the authors, and they should not be assumed to represent the position of any regulatory body or to be complete or final. Much work needs to be done before definitive rhinosinusitis trial schemes are established; therefore future panels should be planned to further define and refine appropriate clinical trials.

A. Definition

The committee decided by consensus to accept the term rhinosinusitis instead of sinusitis throughout the document. Sinusitis is almost always accompanied by concurrent nasal airway inflammation, and in many cases, sinusitis is preceded by rhinitis symptoms. Therefore the use of the term rhinosinusitis more accurately describes the spectrum of infectious and inflammatory conditions previously grouped under the term sinusitis. The group agreed to endorse and adopt the previously developed definition of the Sinus and Allergy Health Partnership Task Force with the following definition for rhinosinusitis: "Rhinosinusitis is a group of disorders characterized by inflammation of the mucosa of the nose and the paranasal sinuses."352

Although the participants recognize the advantages in using the term rhinosinusitis rather than sinusitis, the committee also wants to emphasize that the term rhinosinusitis is not intended to be confused with or replace the term rhinitis, which refers to the various diseases primarily, but not exclusively, confined to the nose. It is important to maintain the distinction between rhinosinusitis and rhinitis both diagnostically and therapeutically, even though the conditions might have overlapping symptoms and signs. For instance, although the use of an antibiotic might be very appropriate for a case of acute rhinosinusitis, it would be unusual for a rhinopathy. Health care professionals are keenly aware of the problem of overuse of antibiotics for upper respiratory tract infections and are committed to adding greater precision to the diagnosis of both acute rhinosinusitis and CRS. In promulgating the definitions proposed in this meeting, experts in the field will need to continually stress the distinguishing features of rhinosinusitis and the importance of applying targeted diagnostic criteria when making therapeutic decisions.

In defining rhinosinusitis, as well as determining the criteria required to secure each of the aforementioned diagnoses, many factors have been considered, including the temporal nature of these disorders, clinical presentation, imaging data, histopathologic findings, causative factors (eg, microorganisms, aspirin sensitivity, and allergy), and differences in therapy.

B. Rhinosinusitis consensus research definitions and clinical trial guidelines

The following sections will discuss the research definitions and clinical trial guidelines as agreed upon by group consensus (≥80% of committee members). For each condition, entrance diagnostic criteria are outlined, including the pattern of symptoms that defines each particular classification, the typical symptoms necessary to diagnose disease, and measures of objective criteria required. These conditions are defined as they typically appear in the community and might not encompass all clinical scenarios encountered (eg, immunocompromised host). Measures for monitoring progress to determine clinical efficacy are also provided. These evaluations include monitoring individual symptoms, rating global symptom severity, assessing QOL, documenting objective clinical trial findings, and rating global response to treatment. A summary of the clinical trial guidelines can be found in Table XVIII.

1. Acute (presumed bacterial) rhinosinusitis.

Acute rhinosinusitis is an inflammatory condition involving the paranasal sinuses, as well as the lining of the nasal passages, and it lasts up to 4 weeks (28 days). In the immunocompetent person living in the general community, acute rhinosinusitis is typically believed to be induced by viruses and does not require antibiotics for the first 10 to 14 days unless complicating features are present, at which point bacteria are presumed to be involved and antibiotics are often employed. These complicating features include severe headache or facial pain, high fever, and impending or actual complications to the eye, lung, or brain. Without any complicating feature present, after 10 to 14 days of symptoms consistent with rhinosinusitis and objective findings, bacteria are presumed to predominate, and the patient might benefit from initiating appropriate antibiotic therapy.\(^335\) Patients with acute rhinosinusitis typically present with varying degrees of the following symptoms: anterior purulent drainage, posterior purulent drainage, or both plus nasal obstruction, facial pain-pressure-fullness, or both. Relative to nasal inflammation, hyposmia can be present. Purulence arising from the sinonasal passages must be present to ensure this diagnosis. The nature of predominating organisms (viruses, bacteria, or fungi) in the immunocompromised host and intensive care unit patient are considered to be more variable, and these patients are not the target population of these definitions and clinical trial recommendations.

a. Research criteria for diagnosis. Patients with acute (presumed bacterial) rhinosinusitis must have symptoms present for a minimum of 10 days up to a maximum of 28 days. Additional individuals who have patterns that might qualify for inclusion are patients with severe disease who have the presence of nasal or postnasal purulent secretions for 3 to 4 days with high fever and patients whose symptoms initially regress but then worsen within the first 10 days. Symptoms required for diagnosis include anterior purulent drainage, posterior purulent drainage, or both plus nasal obstruction or facial pain-pressure-full-
ness. Patients who experience orbital cellulites or intracranial extension of the infection or who require hospitalization are considered to have severe disease and should be excluded automatically from clinical trials of uncomplicated acute (presumed bacterial) rhinosinusitis. Objective documentation for the diagnosis is required by either nasal airway examination for purulent drainage or radiographic evidence of acute rhinosinusitis. Purulent drainage should be noted beyond the nasal vestibule by means of either anterior rhinoscopy or endoscopy or as posterior pharyngeal drainage. Regarding imaging, plain sinus films, although certainly less costly, do have limitations and are generally less reliable than CT or MRI but might be adequate for an acute rhinosinusitis study.

b. Measures for monitoring progress in research setting. Individual symptoms that should be included in outcomes monitoring include drainage (anterior, posterior, or both), nasal obstruction, facial pain-pressure-fullness, diminished sense of smell, headache, ear pain-pressure, halitosis, dental pain-pressure, cough, fatigue, fever, and sleep disturbance. Individual symptoms should be rated on a set categoric scale. Symptom severity should also be rated on a global scale. For example, patients can be asked, “Overall, how bothered are you by your symptoms?” Optional responses would be as follows: 1, not bothered; 2, bothered a little; 3, bothered more than a little but not a lot; 4, bothered a lot; or 5, extremely bothered. Although standardized subjective QOL measurements play an important role in assessing a drug’s effectiveness in clinical trials, there was no consensus agreement as to whether to mandate QOL assessments for all trials of acute (presumed bacterial) rhinosinusitis.

Several objective evaluations should be used for monitoring efficacy. A physical examination is essential. Objective documentation should also be provided on the basis of either (1) a nasal airway examination for purulent drainage beyond the nasal vestibule by means of either anterior rhinoscopy or endoscopy or posterior pharyngeal drainage or (2) imaging by means of plain radiography or CT. Another objective measure that might be useful is obtaining and assessing bacterial cultures. Bacterial cultures were strongly recommended for studies of antibiotic treatment and provide valuable information for any therapeutic trial of acute bacterial rhinosinusitis. Finally, researchers can use the patient’s subjective global rating of response to treatment. For example, in response to the question, “Overall, how would you rate your response to treatment?,” patients could answer using a categorical scale as follows: −4, as bad as can be; −3, a lot worse; −2, more than a little worse; −1, a little worse; 0, same; +1, a little better; +2, more than a little better; +3, a lot better; or +4, as good as can be.

2. CRS with and without nasal polyposis.

These are inflammatory conditions involving the paranasal sinuses, as well as the lining of the nasal passages that persist beyond 12 weeks. The diagnosis of CRS with or without nasal polyposis requires that symptoms must be present for 12 weeks or more. When 2 or more of the following symptoms are present, CRS might be strongly suspected: anterior mucopurulent drainage, posterior mucopurulent drainage, or both; nasal obstruction; facial pain-pressure-fullness; and decreased sense of smell. Objective documentation is required by means of direct visualization of the middle meatus through anterior rhinoscopy (after decongestion) or nasal endoscopy to assert the accurate diagnosis of CRS. Bilateral NPs are recorded as absent or present in the middle meatus to distinguish between CRSwNP and CRSsNP. Although physical examination could reveal unilateral polyposis, and this could represent CRSwNP, this unilateral appearance should always herald the suspicion of inverted papilloma or other sinonasal tumor. Thus in this clinical setting, an imaging study should be strongly considered (see below). In the absence of polyps, signs of inflammation, such as discolored mucus (not blood) or edema of the middle meatus or ethmoid area, must be seen to assert the diagnosis of CRS. A positive sinus CT scan is required for the research definition of both CRSsNP and CRSwNP. Rarely, incidental imaging findings can be used to make the diagnosis of CRS independent of symptoms and physical examination, but imaging studies alone might not be able to determine the presence or absence of polyps.

a. Research criteria for diagnosis of CRSsNP. Again, symptoms must be present for 12 weeks or more. Two or more of the following symptoms are required for diagnosis: anterior mucopurulent drainage, posterior mucopurulent drainage, or both; nasal obstruction; and facial pain-pressure-fullness. Required objective documentation requires endoscopy to exclude the presence of NPs and to document signs of inflammation, such as discolored mucus or edema of the middle meatus or ethmoid area. A positive imaging study by means of sinus CT is also required (see imaging section for criteria set forth).

b. Measures for monitoring progress for CRSsNP. Individual symptoms that should be included in end point monitoring are drainage (anterior or posterior), nasal obstruction, facial pain-pressure-fullness, diminished sense of smell, headache, ear pain-pressure, halitosis, dental pain-pressure, cough, fatigue, fever, and sleep disturbance. Individual symptoms should be rated on a set categoric scale. Global symptom severity should also be rated as outlined in the section “Acute (presumed bacterial) rhinosinusitis.” A validated QOL measurement should be performed to monitor progress. Optional recommended instruments include SF-36, SNOT-20, and RSDI.

Several objective measures can be used for determination of efficacy. A physical examination is essential. Objective documentation requires repeating endoscopy and sinus CT scan. The group did not reach consensus on any particular endoscopic or radiographic scoring system. Other potentially useful objective measures that might be useful include nasal patency measurements (which must be interpreted in light of lung function), such as the peak
nasal inspiratory flow (PNIF); acoustic rhinometry; rhinomanometry; a smell identification test, quantification test, or both; a measure of mucociliary function; assessments of the cytologic pattern; and measurements of inflammatory factors in nasal mucus or epithelial samples. Finally, researchers can use the patient’s subjective global rating of response to treatment as outlined in the section “Acute (presumed bacterial) rhinosinusitis.”

c. Research criteria for diagnosis of CRSwNP. By definition, patients with the diagnosis of CRS with nasal polyposis require the presence of symptoms for 12 weeks or more. Two or more of the following symptoms are

TABLE XVIII. Rhinosinusitis consensus research definitions and clinical trial guidelines

| Type of rhinosinusitis | Acute (presumed bacterial) rhinosinusitis | CRS without nasal polyposis | CRS with nasal polyposis | AFRS |
|-----------------------|------------------------------------------|-----------------------------|-------------------------|------|
| Criteria for diagnosis | Pattern of symptoms                      | Symptoms present for ≥12 wk |                          |      |
|                       | Symptoms present for a minimum of 10 d up until a maximum of 28 d |                          |                          |      |
|                       | Severe disease* (presence of purulence for 3-4 d with high fever) |                          |                          |      |
|                       | Worsening disease (symptoms that initially regress but worsen within first 10 d) |                          |                          |      |
| Symptoms for diagnosis | Requires:                                | Requires ≥2 of the following symptoms: | Requires ≥2 of the following symptoms: | Requires ≥1 of the following symptoms: |
|                       | . Anterior and/or posterior purulent drainage plus nasal obstruction or facial pain-pressure-fullness | . Anterior and/or posterior mucopurulent drainage | . Anterior and/or posterior mucopurulent drainage | . Anterior and/or posterior nasal drainage |
|                       | . Radiographic evidence of acute rhinosinusitis | . Endoscopy to exclude presence of polyps in middle meatus and document presence of inflammation, such as discolored mucus or edema of middle meatus or ethmoid area, and | . Endoscopy to confirm presence of bilateral polyps in middle meatus and | . Endoscopy to document presence of allergic mucin (pathology showing fungal hyphae with degranulating eosinophils) and inflammation, such as edema of middle meatus or ethmoid area or nasal polyps |
| Objective documentation | Requires either nasal airway examination for purulent drainage: | Requires both | Requires both | Requires |
|                       | 1. beyond vestibule by either anterior rhinoscopy or endoscopy, or posterior pharyngeal drainage, or | Endoscopy to exclude presence of polyps in middle meatus and document presence of inflammation, such as discolored mucus or edema of middle meatus or ethmoid area, and | Endoscopy to confirm presence of bilateral polyps in middle meatus and | Endoscopy to document presence of allergic mucin (pathology showing fungal hyphae with degranulating eosinophils) and inflammation, such as edema of middle meatus or ethmoid area or nasal polyps |
|                       | 2. Radiographic evidence of acute rhinosinusitis | . Evidence of rhinosinusitis on imaging by CT | . Imaging by CT with confirmation of bilateral mucosal disease | . Evidence of rhinosinusitis by CT or MRI |
|                       | . Evidence of fungal-specific IgE (skin test or in vitro blood test) | . No histologic evidence of invasive fungal disease | Other possible, but not required, documentation measures: | . Fungal culture |
|                       | . Total serum IgE level | . Imaging by more than one technique (CT or MRI) highly suggestive of AFRS |                          |      |

*Patients who have intracranial extension, have orbital cellulitis, or require hospitalization are considered to have severe disease but should be excluded from clinical trials of uncomplicated acute (presumed bacterial) rhinosinusitis.
required for diagnosis: anterior mucopurulent drainage, posterior mucopurulent drainage, or both; nasal obstruction; and decreased sense of smell. Objective documentation requires both endoscopy to confirm the presence of bilateral polyps and imaging by means of CT with confirmation of bilateral mucosal disease.

d. Measures for monitoring progress of CRSwNP. Individual symptoms that should be included in end point monitoring are drainage (anterior or posterior), nasal obstruction, facial pain-pressure-fullness, diminished sense of smell, headache, ear pain-pressure, halitosis, dental pain-pressure, cough, fatigue, fever, and sleep disturbance. Individual symptoms should be rated on a categoric scale. Global symptom severity should also be rated as outlined previously. A validated QOL measurement should be performed. The group did not reach a consensus on which questionnaire should be used to monitor progress. Optional recommended instruments include SF-36, SNOT-20, and RSDI.

Several objective measures should be used for monitoring efficacy. A physical examination is essential. Required objective measures include endoscopy to assess the magnitude of NPs. Imaging should also be performed by means of CT to measure any changes in extent of disease. Nasal patency measurements (which must be interpreted in light of lung function), such as PNIF, acoustic rhinometry, and rhinomanometry, might also be useful. Other objective measures that might be useful include a smell identification test, a smell quantification test, or both; a measure of mucociliary function; assessments of the cytologic pattern; and measurements of inflammatory factors in nasal mucus or epithelial samples. Finally, the patient’s subjective global rating of response to treatment should be included as outlined previously.

3. Classic AFRS.

AFRS is clinically diagnosed by meeting the criteria for CRS (with or without polyps) while demonstrating the presence of allergic mucin and evidence of fungal hypersensitivity by means of skin testing or in vitro blood testing. Positive fungal cultures, characteristic CT studies, and absence of tissue invasion in the immunocompetent host are not required to secure the diagnosis. However, these tests (cultures, CT, and pathology) are recommended for complete evaluation of these patients. Anecdotally, it is reported that should a patient become immunocompromised, AFRS condition could predispose the patient to acute invasive fungal rhinosinusitis.

a. Research criteria for diagnosis of classic AFRS. The diagnosis of AFRS requires that symptoms must be present for 12 weeks or more. One or more of the following symptoms are required for diagnosis: anterior nasal drainage, posterior nasal drainage, or both; nasal obstruction; decreased sense of smell; and facial pain-pressure-fullness. Required objective documentation includes endoscopy to document the presence of inflammation, such as edema of the middle meatus or ethmoid area, or NPs. Critical to the establishment of the diagnosis of AFRS is the identification of allergic mucin (histologically containing fungal hyphae and degranulating eosinophils). Imaging studies, by means of either CT or MRI, are required. These occasionally show pathognomonic features of AFRS but do so in less than 50% of cases. For consistency, the group agreed that sinus CT or MRI findings of sinus mucosal disease or sinus opacification must be present at some stage, such as preoperatively, but these features do not need to be present postoperatively. This might apply for instance, in a drug treatment trial, in cases in which the disease was clearly present before surgery and the other criteria for disease are met. Other required criteria include evidence of fungal-specific IgE (by means of skin testing or in vitro blood testing) and absence of histologic evidence of invasive fungal disease in sinus tissue. Other potentially useful but not required diagnostic criteria include a positive fungal culture result from sinus mucus, an increased total serum IgE level, and imaging by more than one technique (CT or MRI).

b. Measures for monitoring progress of classic AFRS. Individual symptoms that should be included in outcomes monitoring are drainage (anterior or posterior), nasal obstruction, facial pain-pressure-fullness, diminished sense of smell, headache, ear pain-pressure, halitosis, dental pain-pressure, cough, fatigue, fever, and sleep disturbance. Individual symptoms should be rated on a set scale. Global symptom severity should also be rated as outlined previously. A validated QOL measurement should be performed to monitor progress. Optional recommended instruments include SF-36, SNOT-20, and RSDI. Although a standardized QOL assessment should be included, the group did not reach a consensus on any one specific instrument.

Several objective measures of assessment should be used for determination of efficacy. A physical examination is essential. Objective assessments should include endoscopy, reviewing the initially described characteristics and grading the appearance of NPs. The group did not reach consensus on any particular endoscopic scoring systems. Imaging by means of CT or MRI should also be repeated. The group did not reach consensus for an image scoring system. Other potentially useful objective measures include the use of nasal patency measurements (which must be interpreted in light of lung function), such as PNIF; acoustic rhinometry; rhinomanometry; smell identification testing, smell quantification testing, or both; mucociliary function; assessments of the cytologic pattern; and measurements of inflammatory factors in nasal mucus or epithelial samples. A response to treatment global rating score should be included as outlined previously.

C. Rhinosinusitis patient care definitions

These definitions are summarized in Table XIX. They differ from the research definitions only in terms of the objective documentation required for diagnosis as explained below.

1. Acute (presumed bacterial) rhinosinusitis.

The objective criteria are the same as those for the research definition.
| Criteria for diagnosis | Acute (presumed bacterial) rhinosinusitis | CRS without nasal polyposis | CRS with nasal polyposis | AFRS |
|------------------------|------------------------------------------|-----------------------------|--------------------------|------|
| **Pattern of symptoms** | Symptoms present for a minimum of 10 d up until a maximum of 28 d | Symptoms present for ≥12 wk | Requires ≥2 of the following symptoms: | Requires ≥1 of the following symptoms: |
|                        | Severe disease* (presence of purulence for 3-4 d with high fever) |                            | Anterior and/or posterior mucopurulent drainage | Anterior and/or posterior nasal drainage |
|                        | Worsening disease (symptoms that initially regress but worsen within first 10 d) |                            | Facial pain-pressure-fullness | Nasal obstruction |
| **Symptoms for diagnosis** | Requires: | Requires ≥2 of the following symptoms: | Requires ≥2 of the following symptoms: | Requires ≥1 of the following symptoms: |
|                        | Anterior and/or posterior purulent drainage plus: | Anterior and/or posterior mucopurulent drainage | Anterior and/or posterior nasal polyposis | Anterior and/or posterior nasal drainage |
|                        | Nasal obstruction or | Nasal obstruction | Nasal obstruction | Nasal obstruction |
|                        | Facial pain-pressure-fullness | Facial pain-pressure-fullness | Decreased sense of smell | Decreased sense of smell |
|                      | **Objective documentation** | Requires nasal airway examination of the decongested nose to exclude presence of polyps in middle meatus and document presence of inflammation, such as discolored mucus or edema of middle meatus or ethmoid area | Requires nasal airway examination of decongested nose to confirm presence of bilateral polyps in middle meatus | Requires |
|                      | Requires either | Sinus CT imaging is not essential but should be strongly considered (see text for further discussion). | Sinus CT imaging is not essential but should be strongly considered (see text for further discussion). | |
|                      | Nasal airway examination for purulent drainage: | | | |
|                      | Rarely, incidental imaging findings can be used to make the diagnosis of CRS independent of symptoms and physical examination.† | Rarely, incidental imaging findings can be used to make diagnosis of CRS independent of symptoms and physical examination.† | | Evidence of fungal-specific IgE (skin test or in vitro blood test) |
|                      | 1. beyond vestibule by either anterior rhinoscopy or endoscopy, or | | | |
|                      | 2. posterior pharyngeal drainage, or | | | |

Table Continued on next page
2. CRS with and without nasal polyposis.

For clinical diagnosis, sinus CT imaging is not essential but should be strongly considered. If symptoms or findings are equivocal, a sinus CT scan can confirm the diagnosis. Rarely, incidental imaging findings can be used to make the diagnosis of CRS independent of symptoms and physical examination, but imaging studies alone might not be able to determine the presence or absence of polyps.

3. Classic AFRS.

Sinus CT imaging is not essential but is highly recommended because of the tendency for bony erosions and extension of disease into adjacent anatomic areas.

IX. FUTURE DIRECTIONS

This conference focused on the development of definitions and clinical trial designs for 4 classifications of rhinosinusitis that encompass a large number of patients. However, guidelines still need to be refined and developed for other populations, including patients with acute presumed viral rhinosinusitis, unresolved or subacute rhinosinusitis, recurrent acute rhinosinusitis, acute exacerbations of CRS, and eosinophilic fungal rhinosinusitis. Furthermore, the benefits and risks of various interventions were not a focus of these proceedings.

Rhinosinusitis is complex. The understanding of it is still limited. Developing sound clinical trials that target its various causes will help clinicians gain a better understanding of how to effectively prevent and treat the detrimental health consequences associated with rhinosinusitis.

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