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Endotypes and phenotypes of chronic rhinosinusitis: A PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology

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Abstract

Chronic rhinosinusitis (CRS) is a complex disease consisting of several disease variants with different underlying pathophysiologies. Limited knowledge of the mechanisms of these disease subgroups is possibly the greatest obstacle in understanding the causes of CRS and improving treatment. It is generally agreed that there are clinically relevant CRS phenotypes defined by an observable characteristic or trait, such as the presence or absence of nasal polyps. Defining the phenotype of the patient is useful in making therapeutic decisions. However, clinical phenotypes do not provide full insight into all underlying cellular and molecular pathophysiologic mechanisms of CRS. Recognition of the heterogeneity of CRS has promoted the concept that CRS consists of multiple groups of biological subtypes, or “endotypes,” which are defined by distinct pathophysiologic mechanisms that might be identified by corresponding biomarkers. Different CRS endotypes can be characterized by differences in responsiveness to different treatments, including topical intranasal corticosteroids and biological agents, such as anti-IL-5 and anti-IgE mAb, and can be based on different biomarkers that are linked to underlying mechanisms. CRS has been regarded as a single disease entity in clinical and genetic studies in the past, which can explain the failure to identify consistent genetic and environmental correlations. In addition, better identification of endotypes might permit individualization of therapy that can be targeted against the pathophysiologic processes of a patient's endotype, with potential for more effective treatment and better patient outcomes.

Keywords

Chronic rhinosinusitis; endotypes; phenotypes; cytokines; biological agents; treatment; diagnosis; IgE; nasal polyps; pathophysiology

The definition of *rhinosinusitis* has been proposed in consensus documents by expert panels worldwide.¹⁻³ The term rhinosinusitis is preferred because sinusitis rarely occurs in the absence of rhinitis, and the nose and sinuses are contiguous structures sharing vascular, neuronal, and interconnecting anatomic pathways. As proposed by the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) expert committee,¹ rhinosinusitis is defined as inflammation of the nose and the paranasal sinuses characterized by 2 or more symptoms, one of which should be either nasal blockage/obstruction or nasal discharge (anterior/posterior nasal drip). Other symptoms can be facial pain/pressure, reduction or loss of smell, or both. Acute rhinosinusitis (ARS) is clinically defined as symptoms lasting less than 12 weeks with complete resolution.¹ Chronic rhinosinusitis (CRS), which is the focus of this document, is defined as symptoms on most days lasting at least 12 weeks without complete resolution.

The incidence and prevalence of CRS have not been extensively studied, and comparing data between studies is challenging because of inconsistent definitions. The prevalence of physician-diagnosed CRS ranges from approximately 1% to 9% of the general population. In 2011, a large-scale adult population study showed the prevalence of CRS to be 10.9% in Europe. Chronic rhinosinusitis with nasal polyps (CRSwNP), a clinical phenotype, is found in up to 4% of the population. In contrast to the clinical definition of CRS, including the presence of symptoms and consistent endoscopic or radiologic criteria, the EPOS proposed a

symptom-based definition for epidemiologic studies of CRS.⁵ This epidemiologic definition correlated with endoscopic findings.⁵

Most clinicians and investigators accept the existence of clinically relevant CRS phenotypes, as defined by an observable characteristic or trait, such as the absence or presence of nasal polyps (NPs). Existing evidence suggests an individual therapeutic approach for patients with CRSwNP and patients with chronic rhinosinusitis without nasal polyps (CRSsNP). However, these broad phenotypes do not provide full insight into the potential underlying cellular and molecular mechanisms of CRS. CRS is a complex disease with several variants caused by different cellular and molecular mechanisms. The characterization of this heterogeneity supports the concept that CRS consists of multiple biological subtypes, or endotypes, which are defined by distinct pathophysiologic mechanisms that might be identified by corresponding biomarkers.⁶⁻⁸ CRS endotypes potentially differ in therapeutic responses and stimulate the development of modified diagnostic criteria to better define CRS. In addition, their elucidation might stimulate the development of more precise criteria to define CRS. In retrospect, some clinical trials of therapeutic agents in patients with CRS might have been unsuccessful because they have been performed by including patients without any consideration given to classification of patients according to endotypes.⁶ Within the whole CRS population, there are good responders, weak responders, and nonresponders to any given therapeutic agent. Better insight into different endotypes might allow the identification of subgroups in relation to response to treatment.⁹ Limited knowledge on the pathophysiology of CRS and its endotypes, with inclusion of multiple subtypes, might have contributed to the failure to identify consistent genetic and environmental correlations with CRS.^{7,8} In the whole field of medicine, recognition of endotypes of chronic inflammatory diseases is becoming more and more important because it is apparent that a traditional management approach of “one size fits all” does not adequately treat many patients whose symptoms remain uncontrolled and who have severe disease.^{7,8,10}

This PRACTALL consensus report on CRS produced by experts from the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology summarizes the existing knowledge of CRS phenotypes and endotypes and clarifies the questions requiring additional research. The goal of this PRACTALL document is to improve patient outcomes by assisting in the current therapy of CRS and to identify research needs to advance clinical understanding. The current state of understanding does not permit strict definitions of CRS endotypes, but this PRACTALL document suggests various directions for additional research to better define pathophysiologic mechanisms and ultimately better characterize endotypes.

Pathophysiology of CRS

The pathophysiology of CRS is complex and includes local, systemic, microbial, environmental, genetic, and iatrogenic factors (Fig 1).

Role of microorganisms in patients with CRS

ARS is triggered by infectious organisms. In contrast, the role of infectious agents in patients with CRS is less clear. Diverse hypotheses about the cause of CRS have focused on

bacteria, viruses, and fungi, and each hypothesis has some supporting data. In general, studies searching for a unifying disease-causing entity are disappointing. The study of the bacteriology of the sinonasal cavities in patients with CRS has yielded highly variable results, although many have found evidence for greater prevalence of certain bacteria, such as *Haemophilus*, *Moraxella*, *Pseudomonas*, and *Streptococcus* species and *Staphylococcus aureus*, particularly in patients with acute exacerbations of CRS.^{2,11} Interestingly, certain phyla of bacteria, such as proteobacteria, are more common in the lower airways of patients with asthma or chronic obstructive pulmonary disease based on deep sequencing of 16S RNA on biopsy samples.¹² Consistent with the unclear role of bacterial infection in many cases of CRS, CRS can be relatively unresponsive to most antibiotics. Modest improvement in some patients with CRS can occur with antibiotic therapy, supporting a possible role of microorganisms at least in selected subsets or an endotype of CRS. Macrolides and doxycycline have been recommended for the treatment of CRS because these agents have not only antibacterial but also anti-inflammatory properties.¹

A number of investigators have studied the role of bacterial biofilms, communities of bacteria encased within a protective extracellular matrix that protect the organisms from exogenous and host-derived antimicrobial agents.¹³⁻¹⁵ Biofilms occur frequently, but not always, in patients with CRS but also occur in healthy subjects. The most robust detection techniques require electron microscopy or fluorescent *in situ* hybridization. More insight into the pathophysiologic contribution of biofilms is needed, and investigations are warranted to determine whether biofilms define specific endotypes. Novel therapies might have clinical applications to prevent and destabilize biofilms.

Suggestions of a viral cause of CRS have largely been disappointing because of the lack of convincing evidence for such a cause. Considerable efforts have been expended on a fungal cause of CRS, the tenets of which are that the burden of mucosal fungal colonization is not increased in patients with CRS (other than allergic fungal sinusitis) but that the immunologic sensitivity to ambient fungi is increased.¹⁶ This hypothesis is questioned because of the failure of antifungal therapeutics to improve symptoms. However, clinical response in a limited fraction of cases sustains the possibility of a credible fungal endotype (Figs 1 and 2).^{17,18}

S aureus is among the most frequently found bacteria in patients with CRS, as confirmed by using culture-independent techniques.¹⁹ *S aureus* is particularly associated with eosinophilic inflammation and NPs.²⁰ *S aureus* can form biofilms, which allow the microorganism to survive antibiotic treatment, or it might penetrate into the mucosa and reside intramucosally and intracellularly.²¹ *S aureus* can initiate the T_H2 response through staphylococcal exotoxins (SEs) or other staphylococcal proteins, or a pre-existing T_H2 milieu might facilitate the persistence of *S aureus* in the sinonasal mucosa. These possibilities might be 2 distinct endotypes or a single endotype. At least 2 T_H2 cytokines, IL-4 and IL-13, compromise the immune response to *S aureus*.²² Thus clarifying the role of *S aureus* in CRS as an initiator, augmentor, or both is challenging.

S aureus residing in or on the sinonasal mucosa can continuously form enterotoxins with superantigenic activity. In human subjects superantigens can induce activation and strong

cytokine release from both CD4 and CD8 T cells,²³ amplifying the T_H2 response in the tissue and impairing the function of regulatory T cells.²⁴ In addition, this T-cell activation induces granulocyte migration and survival and is associated with increased synthesis of IgE, IgG/IgGz, and IgA.²⁵ Specifically, staphylococcal enterotoxin A and toxic shock syndrome toxin 1 have the potential to induce a polyclonal IgE response against multiple allergens, including inhalant allergens and SEs. Tissue-based IgE antibodies occur even in nonatopic subjects, confirming the potential of SEs to regulate IgE.²⁶

Innate immune responses in patients with CRS

As described above, CRS is linked to frequent infections and colonization of the upper airways and sinuses with bacteria or fungi. Although the rate of colonization with *S aureus* is likely higher in patients with CRS than healthy control subjects, not all affected subjects are colonized with *Staphylococcus* species, and no single organism or class of organisms has emerged to explain CRS. Rather, the colonizing organisms are diverse, suggesting that a host factor, such as reduced immunity, might be involved. Studies suggest the decreased presence of the antimicrobial enzymes lysozyme and lactoferrin in patients with CRS.^{27,28} Investigations using analysis of mRNA and protein demonstrated reduced release of host defense molecules, such as psoriasin/S100A7, and decreased expression of members of the palate, lung, nasal epithelium clone (PLUNC) family of LPS-binding antimicrobial peptides (also called the bacterial permeability-inducing family).²⁹⁻³¹ Most of these molecules are produced by epithelial cells; some of them, such as psoriasin and defensins, are produced by mucosal epithelial cells, especially in the anterior region of the nasal cavity (eg, the inferior turbinates), whereas others, such as many PLUNC family members, lysozyme, and lactoferrin, are produced by glandular epithelium and then secreted into the sinus or airway lumen along with either serous or mucous secretions. The action of dozens of constitutive and inducible host defense molecules is responsible for the maintenance of an antimicrobial state in the airways, and compromise of the release of a number of these molecules has been the basis of the “immune barrier hypothesis” for CRS.¹⁷ In the case of PLUNC (and probably lysozyme and lactoferrin), the reduced expression is restricted to the NP tissue, whereas psoriasin levels are reduced in epithelium throughout the nasal cavity in patients with CRS.³⁰⁻³³

Several studies have implicated blunting of Toll-like receptor (TLR) responses, especially TLR2 and TLR9, in patients with recalcitrant disease, particularly in patients with early recurrence of polyps after surgery.^{34,35} The molecular mechanisms responsible for reductions of host defense molecules from the epithelium are unknown, but one hypothesis is a blunting of signaling through the transcription factor signal transducer and activator of transcription 3 (STAT3). STAT3 has been strongly linked to immunity because patients with defects in STAT3 manifest the hyper-IgE syndrome (Job disease), which is characterized by frequent infection with bacteria (especially *S aureus*) and fungi.³⁶ Studies demonstrate that epithelial host defense molecule release is mediated frequently by activation of STAT3, and a local decrease in STAT3 phosphorylation in tissues from patients with CRS might be mechanistically linked to a blunted innate immune response.³⁷

Epithelial barrier function in patients with CRS

The barrier function of the sinus and NP mucosal epithelium is an essential component of host defense (Fig 1). Epithelial tight junctions (TJs) form the most apical intercellular junctions between sinonasal epithelial cells. These TJs result from homodimeric interactions of several families of molecules, such as occludins, claudins, and other junctional adhesion molecules.³⁸ TJs are responsible for the regulation of epithelial permeability by controlling paracellular flux, the movement of substances across an epithelium by passing between cells. In addition, TJs also prevent foreign particles, such as allergens, from entering the immunoactive subepithelial layers. In contrast, opening of TJs can also mitigate an immunologic or inflammatory process through the egress of inflammatory cells into the lumen and away from tissue inflammation, supporting the resolution of inflammatory processes. Thus TJs can be considered gatekeepers that contribute to either the initiation and augmentation or resolution of inflammation-related tissue damage.

Screening assays of TJ mRNAs, performed with a microfluidic card PCR with sinus tissue, show decreased TJ barrier function of the sinus mucosa in patients with CRS. TJ expression is decreased and inconsistent in CRSwNP samples.³⁹ Additional support for the abnormal epithelial barrier function in patients with CRS is provided by 3-dimensional *ex vivo* cultures of sinus mucosal samples. Transepithelial resistance is reduced in the air-liquid interface in cultures derived from patients with CRSwNP compared with those from patients with CRSsNP and healthy control subjects. This resistance is decreased *in vitro* by IFN- γ and IL-4 through opening the TJs in the cultured tissue, whereas IL-17 had no effect.³⁸

Epithelial cell interaction with activated T cells is potentially a biphasic phenomenon in patients with CRS.⁴⁰ Initially, activated T cells stimulate and lead to induction of the proinflammatory functions of epithelial cells, which substantially contribute to inflammation through release of multiple cytokines and chemokines. This is followed by the apoptotic death of highly activated epithelial cells by IFN- γ and interactions of Fas ligand with Fas and TNF-related apoptosis-inducing ligand (TRAIL) with TRAIL receptor II.⁴⁰ Apoptosis and shedding of the epithelium likely compromise the barrier function of the epithelium and increase susceptibility to bacterial colonization, biofilm formation, and continued inflammation. This process is analogous to the role of spongiosis in the skin observed in patients with atopic dermatitis and epithelial shedding in the bronchial mucosa in asthmatic patients.⁴¹ Apoptotic death and shedding of epithelial cells in patients with CRS might also decrease inflammation by eliminating highly activated proinflammatory cytokine- and chemokine-secreting cells.⁴² Similarly, marked reductions in expression levels of several genes involved in epithelial barrier maintenance and repair occur in patients with CRS.²⁹ Expression levels of calcium-binding cellular regulatory proteins, S100A7 (psoriasin), and S100A8 (calgranulin A) are significantly decreased in both patients with CRSwNP and patients with CRSsNP. S100A9 (calgranulin B) expression is significantly decreased in patients with CRSsNP, and SPINK5 expression is significantly decreased in patients with CRSwNP. In summary, the nasal and sinus epithelium and the TJs between these cells likely have important roles in the initiation and regulation of inflammation in patients with CRS and might provide a new window for defining disease endotypes.

Adaptive immune responses in patients with CRS

As a consequence of chronic inflammation in a microenvironment colonized by bacteria and fungi with or without biofilms, the affected tissues of patients with CRS manifest an increase in numbers of cells of the adaptive immune response, especially T cells, B cells, and plasma cells.⁴³ These are associated with increases in local production of several immunoglobulin isotypes, especially IgE and IgA.^{25,44}

Local immunoglobulin synthesis—Plasma cells producing IgE and IgA are particularly prominent within NP tissue, and it is possible that locally produced IgE and IgA are involved in activation of mast cells and eosinophils, which in turn contribute to inflammation in these tissues.⁴⁵ Total IgE levels in NPs are often highly increased independent of atopy and related to the degree of eosinophilic inflammation. Specific IgE to SEs usually can be found locally within the mucosa but not necessarily in the serum.⁴⁶ Follicle-like structures can be identified frequently in NP tissues, which highly express IgE antibodies binding to SEs.⁴⁷ In addition to IgE, NPs have increased IgA levels.²⁵ The observation of increased local immunoglobulin production is supported by the expression of the immunoglobulin diversification enzyme activation-induced deaminase, indicating local immunoglobulin class-switching to IgE and IgA.⁴⁸ Local IgE antibodies, although polyclonal and directed against a range of inhalant and SE-related allergens, are functional and capable of degranulating mast cells.⁴⁹ The presence of SE-IgE antibodies and the increase in local IgE suggests an association with the comorbidity of asthma.^{50,51} The role of IgA in the pathology of CRS is unknown, but the presence of IgA in patients with most types of chronic mucosal inflammation, such as periodontitis, suggests that IgA is important and might identify a unique endotype of CRS.⁵²

A proof-of-concept study confirms the functionality of local polyclonal IgE in the upper and lower airways by assessing anti-IgE therapy.⁵³ A substantial decrease in total polyp scores after 16 weeks in the omalizumab group compared with baseline values was confirmed by means of computed tomographic (CT) scanning. Omalizumab significantly improved upper and lower airway symptoms (nasal congestion, anterior rhinorrhea, loss of sense of smell, wheezing, and dyspnea) and asthma-related quality-of-life scores, irrespective of atopy.⁵⁴ The demonstration of direct IgE switching and the existence of cellular IgE memory suggest the possibility of targeting these mechanisms for the treatment of IgE-mediated diseases.^{55,56} More research is required to clarify whether local IgE production and memory IgE B cells can be considered a CRS endotype.

Autoimmunity in patients with CRS—Regulation of locally produced immunoglobulins might be dependent on tissue production of B cell-activating factor of the TNF family (BAFF). Increased BAFF levels in NPs correlate with the local expansion of B cells and plasma cells.⁵⁷ In addition, levels of chemokines that attract B cells, such as CXCL12 and CXCL13, are also increased in patients with CRS.⁵⁸ The specificities of locally produced immunoglobulins from NP tissues of patients with recalcitrant CRSwNP include self-antigens. This local autoimmune response in patients with CRS is potentially a significant disease modifier, suggesting that future studies are warranted to clarify the role

of autoimmunity in its pathogenesis.⁵⁹ CRS with autoantibodies might identify another endotype.

T-cell subsets in patients with CRS—In general, NPs are considered eosinophilic; however, most polyps have variable numbers of neutrophils and eosinophils. Primarily neutrophilic types of adult bilateral polyps do occur, predominantly in Asian subjects and some populations in North America. Evidence is accumulating that there are varying patterns of inflammation in NPs throughout the world^{60,61} and that these patterns are influenced by factors such as the bacterial colonization of the nasal mucosa.^{20,62} In a subset of patients, the presence of tissue eosinophilia is related to IL-5. T cells are the most likely source of IL-5,⁵⁰ and anti-IL-5 treatment can reduce eosinophil-related inflammation and polyp size.⁶³ T_H2-type inflammation with expression of IL-5 is associated with an increased risk of having asthma comorbidity.⁵⁰ Consequently, the differentiation of NPs with IL-5-expressing T_H2-biased versus non-T_H2-biased polyps is of clinical relevance (Fig 1).⁶⁴ In contrast, neutrophilic polyps are associated mainly with increased levels of IFN- γ , IL-17, or both.⁶¹ IFN- γ and IL-17 are also predominant in neutrophilic, cystic fibrosis-related polyp disease.⁶⁰ A mixed cytokine profile, which can be classified as a T_H0 profile, has been demonstrated,⁶⁵ and the possible existence of T_H22 and T_H17 cells as novel subsets requires further investigation in patients with different forms of CRS.⁶⁶ Future research on better classification of T_H subsets in patients with CRS might lead to a better understanding of disease mechanisms, response to treatment, and the role of chronicity.

Remodeling patterns in patients with CRS

Chronic inflammation in patients with CRS results in structural changes that can be referred to as remodeling, including different types of polyps, angiogenesis, goblet cell hyperplasia, epithelial shedding, and subepithelial fibrosis. The remodeling pattern in patients with CRS does not always show a consistent profile in patients with CRSwNP or CRSsNP. NPs are grape-like, translucent, edematous structures, whereas the ethmoidal mucosa from patients with CRSsNP is rather firm. These differences suggest different types of mucosal remodeling, which are regulated by factors such as the TGF- β family and their receptors, matrix metalloproteinases (MMPs; enzymes responsible for extracellular matrix degradation contributing to edema formation), and tissue inhibitors of metalloproteinase (TIMPs).^{64,67} For example, expression of TGF- β 1 and TGF- β 2 protein, expression of the receptors TGF- β R1 and TGF- β R3, and related collagen deposition are upregulated in patients with CRSsNP, whereas TGF- β 1 protein expression and expression of the receptors TGF- β R1, TGF- β R2, and TGF- β R3, as well as collagen deposition, are downregulated in patients with CRSwNP.⁶⁸ This differential regulation was confirmed in Asian patients with CRS. MMP-7 and MMP-9 levels are upregulated in both patients with CRSsNP and patients with CRSwNP, whereas TGF- β protein, TIMP-1 and TIMP-4, collagen formation, and forkhead box P3 mRNA values are decreased in NPs compared with mucosal samples from subjects without NPs.⁶⁹

Another cytokine of regulatory importance that differs among CRS phenotypes is IL-32, a modulating cytokine involved in various chronic inflammatory diseases. IL-32 acts as an inhibitor of angiogenesis and of the secretion of the proangiogenic factors vascular

endothelial growth factor and platelet-derived growth factor *in vitro*.⁷⁰ IL-32 mRNA is upregulated by TNF- α and IFN- γ in primary sinus epithelial cells, whereas IL-1 β , IL-4, IL-13, and IL-17 do not influence IL-32 expression.^{70,71} IL-32 protein and message levels are significantly increased in patients with CRSwNP compared with levels seen in patients with CRSsNP and control subjects.^{71,72} The importance of the difference in IL-32 among CRS endotypes is not defined. Other potential remodeling and inflammatory factors that differ among specific CRS phenotypes include eosinophils, mast cells, local complement activation, and the presence of fibrinolytic components.^{73,77} In summary, an array of immunomodulators and repair process regulators vary among CRS variants, potentially defining pathogenic endotypes.

Diagnosis of Rhinosinusitis

CRS endotypes depend on definition of pathophysiologic mechanisms; however, phenotypes are recognized by clinical findings. Internationally, there is consensus concerning the clinical diagnosis of rhinosinusitis.^{1,75,76} Rhinosinusitis represents a symptomatic inflammation of the paranasal sinuses involving the sinonasal tract. The diagnosis of CRS is based on the presence of at least 2 sinonasal symptoms and should be supported by objective clinical or radiologic evidence of sinonasal inflammation. At least 1 symptom should be either nasal secretion or nasal obstruction. Other symptoms can be facial pain or dysosmia.^{75,76} Supportive objective evidence includes the following:

- Rhinoscopic/endoscopic findings of:
 - polyps and/or
 - mucopurulent discharge and/or
 - edema/mucosal obstruction (at the level of the middle meatus) and/or
- CT scan findings of significant mucosal changes within the paranasal sinuses.

Nasal endoscopy is the preferred method to demonstrate pathology at the level of the osteomeatal complex, which cannot be well visualized by means of simple anterior nasal examination/rhinoscopy or posterior rhinoscopy. Nasal endoscopy might reveal swelling of the mucosa, secretions, and/or NPs at the osteomeatal complex or sphenoidal recess. Alternatively, radiologic imaging by using CT scanning is the preferred method for confirming inflammation within the paranasal sinus cavities. Caution is necessary in the interpretation of the CT scan because asymptomatic subjects or patients with allergic rhinitis or acute viral infections might show CT scan abnormalities of the sinonasal cavities, potentially lasting for several weeks.^{77,78} The timing of a CT scan and relating the symptoms and CT scan abnormalities are crucial for a correct clinical diagnosis. On the basis of the duration of symptoms, patients with rhinosinusitis are divided into groups with a viral common cold, bacterial ARS, and CRSwNP or CRSsNP. Both the common cold and most cases of ARS or intermittent sinusitis are generally considered self-limiting diseases with durations of less than 10 days or 12 weeks, respectively. Patients can have recurrent ARS with complete resolution of symptoms between episodes. CRS is considered to be present when symptoms persist for more than 12 weeks.^{75,76} In addition to the clinical definition of rhinosinusitis, a European expert panel^{75,76} has proposed a

simplified definition for epidemiologic studies relying on symptoms and their duration, as well as a more complex definition for research of rhinosinusitis and NPs. An important question remains whether diagnosing disease endotypes by using biomarkers, histology, and anatomic assessment will improve the management of CRS.

Contributing Factors, Differential Diagnosis, and Comorbidities of Patients with CRS

There are a variety of contributing factors and comorbid conditions that should be considered when diagnosing and managing CRS or defining endotypes. The symptoms of rhinosinusitis can be aggravated by anatomic deformities, such as nasal septal deviations, nasal valve dysfunction, concha bullosa (enlarged nasal turbinate caused by internal ethmoid air cell), adenoid hyperplasia, nasal choanal narrowing, nasal or sinus mucocoeles, scarring from prior nasal or sinus surgery, and septal perforations. A nasal foreign body, particularly in children or subjects with mental disorders, might suggest CRS or predispose to the development of CRS. Deficient mucociliary transport resulting from primary ciliary dyskinesia or increased mucous viscosity can cause or aggravate CRS, often resulting in NPs with pathophysiologic features, which differ from the more common CRSwNP.

Chronic nasal infections, such as nasal vestibulitis and atrophic rhinitis (ozena associated with *Klebsiella* species, staphylococcal, streptococcal, or other local bacterial infection), can suggest CRS. A variety of immunodeficiencies, particularly humoral immunodeficiencies but also some cellular deficiencies, increase the risk of CRS. These include total IgG deficiency, some cases of IgA deficiency and IgG subclass deficiency, and defects in specific antibody production. Systemic inflammatory disorders can affect the nose and sinuses, and in some of these conditions, CRS might be the predominant presenting symptom complex. These include Churg-Strauss vasculitis, granulomatosis with polyangiitis (Wegener polyarteritis), microscopic polyangiitis, polychondritis, sarcoidosis, and Sjögren syndrome or disease. Finally, a variety of malignancies can affect the anatomy and physiology of the upper airways, predisposing to CRS or aggravating or mimicking the symptoms. These include squamous cell carcinoma, upper airway lymphoma, inverted papilloma, esthesioneuroblastoma (olfactory neuroblastoma), juvenile angiofibroma (primarily affecting teenage males), hemangioma, and hemangiopericytoma.

Inhalant allergen sensitization and exposure can result in an allergic immune response after allergen encounter, aggravating or resulting in sinonasal inflammation with or without NPs.⁷⁹ Aspirin-intolerant patients often have NPs and asthma (ie, aspirin-exacerbated respiratory disease). This unique endotype is associated with tissue eosinophilia and an increase in the production of leukotrienes, as evidenced by an increase in urinary leukotriene E₄ concentrations. Sensitivity to fungal elements in a subject with fungal colonization in the mucus within the sinus cavity might lead to an endotype of CRS termed allergic fungal rhinosinusitis. Environmental factors, including cigarette smoke and occupational exposure to both allergens and irritants, might contribute to CRS with or without NPs.⁸⁰ Chronic topical application of cocaine and, less commonly, therapeutic vasoconstrictors can result in chronic rhinitis medicamentosa and possibly CRS. All of these factors should be taken into account when evaluating suspected CRS or assessing inadequate response to treatment.

In addition to the comorbidities and contributing factors, the differential diagnosis of CRS includes any condition that can result in 1 or more of the 4 cardinal symptoms: nasal secretions, nasal obstruction, facial pain, and smell dysfunction.⁷⁵ Nasal obstruction and secretions are characteristic of allergic and nonallergic rhinitis and can also occur with anatomic deformities. Endonasal tumors or foreign bodies often present with unilateral symptoms. Clear nasal discharge might be a manifestation of a posttraumatic leakage of cerebrospinal fluid. Detection of increased β_2 -transferrin or glucose levels in nasal secretions suggests this potentially life-threatening source of nasal symptoms. Olfactory dysfunction (dysosmia), ranging from hyposmia (decreased sense of smell) to parosmia (pleasant or common smell misinterpreted as unpleasant aroma) to anosmia, could be a key symptom of NPs, as well as neurodegenerative diseases or intracranial lesions. Olfactory disorders can also be congenital or the result of prior trauma. Facial pain or headache can have a dentogenic, vascular, arthritic, or neurologic origin. In addition to the differential diagnosis, one should bear in mind that CRS represents a complex pathology, with many factors affecting disease severity. Any underlying sensitization to inhalant allergens might give rise to an allergic immune response aggravating the inflammation in patients with CRSsNP^{79,81} Environmental factors, including cigarette smoke, as well as occupational factors, can contribute to the disease process as well.

Treatment of CRS

Treatment of CRS is straightforward in most cases of acute exacerbations, but a significant group of subjects have persistent or recurrent disease. This challenge is most probably due to multiple phenotypes and endotypes with different underlying mechanisms that lead to chronicity and severity. The number of different treatment options and modalities in the literature is large, but there are limited treatment options with evidence of benefit. Apart from nasal irrigation/douching, nasal and oral corticosteroids, and antibiotics, most other treatment options do not have proved efficacy in prospective, randomized, placebo-controlled, double-blind trials.

The proposed algorithms for CRSwNP and CRSsNP are shown in Fig 3. As evident throughout this document, current guidelines tend to divide CRS into forms with and without polyps.^{76,82-85} The available guidelines base treatment on the severity of the disease, whereas guidelines do not consider the response to prior treatment. Within the EPOS 2012 update, the first proposal for control of disease in patients with CRS was introduced based on subjective and objective parameters of sinonasal inflammation.^{1,86} Certain subtypes of CRS, such as cystic fibrosis, primary ciliary dyskinesia, antrochoanal polyps, and fungal disease (allergic and invasive), are not specifically mentioned in the evidence-based guidelines for medical treatment because their medical treatment might not differ substantially from other phenotypes of rhinosinusitis and because surgery is the usual treatment for unilateral disease, such as antrochoanal polyps. Furthermore, children might differ from adults in their pathophysiology because their immune system is not fully mature, and hypertrophy of the structures that constitute the Waldeyer ring might modify the disease phenotype.⁷⁹ Therefore modified treatment strategies for children have been incorporated into the recent update of EPOS.^{1,76,87}

The general therapeutic approach to CRS consists of medical treatment and surgery in cases of medical failures with persistent symptoms. Because of their anti-inflammatory properties, corticosteroids are the most effective anti-inflammatory option for both CRSwNP and CRSsNP. However, topical intranasal corticosteroids are more effective for CRSwNP⁸⁸ than for CRSsNP^{89,90}. Optimal delivery strategies for both nasal and sinus disease have not been developed.⁹¹ This is highlighted by the delivery of corticosteroid nasal solution or suspension (drops),⁹² which reduced the need for surgical intervention in a group of patients who had previously received conventional nasal corticosteroid sprays.⁹³ Oral corticosteroids administered over 2 to 4 weeks temporarily reduce NP size and CRS symptoms, but the optimum dose and duration are not established.⁹⁴ In children oral methylprednisolone improved the efficacy of amoxicillin/clavulanate in the treatment of CRS, reducing symptoms and the inflammatory changes on CT scans.⁹⁵ Controlled delivery of mometasone furoate to the sinus mucosa through bioabsorbable implants deployed at the time of endoscopic sinus surgery improved surgical outcomes by reducing synechiae formation, polyposis, and the need for postoperative interventions.⁹⁶

The currently recommended treatment of NPs consists of nasal saline irrigation, nasal corticosteroids, and/or oral corticosteroids in severe cases. A multitude of other strategies have been suggested with minimal or no supportive evidence. These include oral and topical antihistamines, leukotriene receptor antagonists, 5-lipoxygenase inhibitors, immunotherapy specific for fungi or other aeroallergens, large-volume irrigations with or without topical medications,^{97,98} methotrexate,⁹⁹ topical and oral antifungal drugs,¹⁰⁰ decongestants, mucolytic agents, phototherapy, protein pump inhibitors,¹⁰¹ capsaicin, furosemide, vitamin D, Manuka honey, bromelain, n-acetylcysteine, quercetin, undecylenic acid, urtica dioica, massage of the sinus ostia with swabs of botanical essential oils, air purifiers, and diets,¹⁰² as well as aspirin desensitization orally¹⁰³ or with intranasal lysine aspirin.¹⁰⁴ Unmet needs in treatment and advances in molecular biology and immunology have also spurred the development of new biological immune response modifiers to treat CRS.⁹ Biological agents include therapeutic antibodies, soluble receptors, cytokines, small molecules, and combinations of these approaches that can target effector molecules at various points in the immune/inflammatory pathways on different immune cells.⁹ Two biological agents, anti-IgE and anti-IL-5, have been studied in patients with CRS.^{54,63} Response to these targeted therapies is variable, suggesting benefit in select subsets, possibly because of heterogeneity of the subjects within the whole group with anti-IL-5-responsive and anti-IgE-responsive CRS endotypes.

Surgery is indicated for intracranial and intraorbital complications, mucoceles, significant anatomic variations (eg, severe septal deviation and choanal atresia), allergic fungal disease, obstructive polyps with bony remodeling, and antrochoanal polyps. The most common reason for surgery is persistent symptoms despite medical treatment. The degree of symptom control with medical treatment is variable and not well characterized. Therefore no statement can be made about the percentage of patients requiring sinus surgery for CRS. However, several studies have compared outcomes of prolonged medical treatment with endoscopic sinus surgery, showing that short-term outcomes were not significantly different between the 2 treatment groups.^{105,106} Unilateral surgery showed better CT findings, olfaction, polyp scores, and relief of symptoms on the side undergoing surgery compared

with the medically treated side. Smith et al¹⁰⁷ compared the outcomes for patients electing continued medical therapy with the outcomes for those electing surgery. Several quality-of-life instruments showed better improvement in patients electing surgery.

The best surgical approach is a matter of debate. The currently favored procedure aims at removing inflamed sinus tissue and bony septae between the nasal and sinus cavities, as well as within the sinus cavities.¹⁰⁸ Up to 85% of patients report subjective benefit from surgery, with outcomes depending on surgical skills, preoperative findings, and postoperative care. Worse outcomes are found in those patients with aspirin-exacerbated respiratory disease (or Samter triad), asthma, frontal sinus disease, and occupational exposure to environmental agents.^{80,109} Surgery in children is generally accepted for persistent disease in patients with cystic fibrosis and in those with orbital and intracranial complications. In summary, the design and interpretation of CRS clinical trials have been hindered by the inherent heterogeneity of the disease, a lack of uniform definitions for the various subtypes, an incomplete understanding of the underlying pathologies, use of rescue medications, and a lack of useful and standardized clinical and laboratory end points for measurement of the response to therapy.⁸⁴

Phenotypes and Endotypes of CRS

CRS is a heterogeneous collection of diseases.^{82,85} In clinics CRS can be phenotyped according to duration (acute vs chronic), NPs (with and without), recurrent disease, severity (mild vs moderate vs severe), conventional therapy response, mucus color, presence of peripheral specific IgE, nature of triggering events, and presence of a complication (Fig 2). However, extensive scientific evidence is accumulating that justifies a differentiation of sinus disease not only by phenotype (ie, defined by an observable characteristic, such as the presence of absence of NPs) but also by recognition of more detailed endotypes (ie, defined by differences in pathogenetic mechanisms that can be discerned by the presence of particular patterns of biomarkers; Fig 2 and Box 1). Definition of different endotypes is mandatory for the development of a better understanding of the pathophysiology of CRS and holds promise for guiding the development of innovative therapeutic approaches based on that knowledge. In addition, different endotypes might define different treatment responses, such as anti-IL-5-responsive patients, anti-IgE-responsive patients, or differential response to topical intranasal corticosteroids between patients with CRSwNP and patients with CRSsNP. Moreover, the presence of different inflammation and remodeling patterns, such as more inflammatory- or remodeling-dominant pathologies, might reflect different pathophysiologic mechanisms and are associated with different responses to treatment.^{63,67} Therefore better identification of endotypes might permit individualization of therapy that can be targeted against the pathophysiologic processes of a specific endotype, with potential for more effective treatment and better patient outcomes.

The phenotypic differentiation of CRS into CRSwNP and CRSsNP has been supported recently by endotypic differences found in remodeling patterns, including the expression of TGF- β proteins and their receptors, expression of MMPs and TIMPs, and, finally, collagen deposition. Whereas in patients with CRSsNP, TGF- β proteins and TGF- β receptors are overexpressed, resulting in an upregulation of phospho-Smad-positive cells and collagen

deposition, this pathway is downregulated in NPs.^{68,69} Because TGF- β regulates MMPs and TIMPs, the balance between those factors is biased toward an overactivity of MMPs in patients with CRSwNP but not in patients with CRSsNP.⁶⁹ These different endotypes associated with CRSwNP and CRSsNP appear to be valid worldwide, independent of the type of inflammation present (ie, with or without eosinophil predominance). Moreover, the endotype associated with CRSsNP seems to be expressed early in patients with CRSsNP.⁶⁷

Defining other endotypes on the basis of inflammatory profile, the vast majority of NPs in Europe and the United States are T_H2 biased, with IL-4, IL-5, and IL-13 being released and orchestrating an eosinophilic type of inflammation.⁵⁸ However, in places such as mainland China, only a minority of NP tissues are T_H2 biased, whereas the majority express IFN- γ , T_H17, or other neutrophil-related cytokines.¹¹⁰ Related to a low TGF- β expression, regulatory T-cell function is suppressed in both polyps of both European and Asian patients.^{65,69} Further endotyping can be based on TGF- β expression, T_H2 bias, and SE-specific IgE (eg, low TGF- β expression with a T_H2 bias in the presence or absence of SE-specific IgE). This method of endotyping can be an important prognostic factor because inflammation in a T_H2-biased NP can be amplified further by the effect of staphylococcal superantigens, resulting in local polyclonal IgE and eosinophil activation.^{26,111}

Successful interventional studies with mAbs, such as anti-IL-5 and anti-IgE, emphasize the importance of a further differentiation of NPs based on pathogenesis, such as the expression of IL-5 and SE-specific IgE.⁶³ The probability of the development of specific new therapies for CRS is dependent on defining the endotypes so that the therapy can be targeted, particularly for biological agents.

Current data are insufficient to propose a full characterization of endotypes in patients with CRS. Accordingly, a framework for proposed criteria that could define endotypes is presented (Box 1).

Conclusion

In this report we propose that one of the major obstacles to understanding the causes of CRS and improving treatment is the failure to understand the underlying disease mechanisms in patients with different underlying pathophysiologies (Box 2). It will be necessary to classify patients into endotypes according to the underlying disease mechanism to improve our understanding of CRS. We propose that the classification of patients with CRS according to endotype will facilitate the development of future knowledge to establish genetic associations, demonstrate biomarkers for disease subgroups, and test novel therapeutic targets. In addition, the use of endotypes in clinical practice in the future is expected to identify patient groups that will benefit most from new and existing treatments to substantially improve the patient-tailored care of patients with CRS. Although we proposed endotypes according to circulating biomarkers, histopathologic findings, cytokine profile, cellular dominance, and therapy response, their clear definition remains to be demonstrated in prospective clinical studies. The expectation is that better understanding of CRS endotypes will ultimately translate into improved patient care. In the long term, this should

lead to optimized and individualized treatment for CRS that will be appreciated by those patients with severe persistent and comorbid disease.

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Abbreviations used

ARS	Acute rhinosinusitis
BAFF	B cell–activating factor of the TNF family
CRS	Chronic rhinosinusitis
CRSwNP	Chronic rhinosinusitis with nasal polyps
CRSsNP	Chronic rhinosinusitis without nasal polyps
CT	Computed tomography
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps

MMP	Matrix metalloproteinase
NP	Nasal polyp
SE	<i>Staphylococcus aureus</i> exotoxin/enterotoxin
STAT3	Signal transducer and activator of transcription 3
TIMP	Tissue inhibitor of metalloproteinases
TJ	Tight junction
TLR	Toll-like receptor
TRAIL	TNF-related apoptosis-inducing ligand

Box 1**Criteria that can be used to define endotypes of CRS**

- A.** Presence of NPs with specific immune inflammatory and remodeling profiles, such as CRSsNP (high TGF- β level and fibrosis) or CRSwNP (low TGF- β level, edema, regulatory T-cell deficit, and TIMP1 deficit), and IL-5- and or IL-17-expressing NPs
- B.** Endotypes defined according to circulating biomarkers (specific IgE, blood eosinophils, SE-specific IgE, fungus [*Aspergillus* species]-specific IgE and IgG, allergic fungal sinusitis)
- C.** SE-specific IgE-expressing NPs (greater eosinophilia, high polyclonal IgE levels, increased risk of asthma)
- D.** Endotypes defined according to therapeutic responsiveness to novel biological agents, such as anti-IL-5-responsive and anti-IgE-responsive
- E.** Aspirin sensitivity: aspirin-sensitive versus aspirin-tolerant CRS
- F.** Endotypes defined according to control of disease by currently recommended treatment, with resistance to antibiotics and corticosteroids possibly defining a severe endotype

Box 2**Questions remaining for improving our knowledge in CRS include the following**

- What specific treatment should be given for what specific phenotype or endotype?
- Can high-resolution CT or other imaging define subtypes?
- What is the precise contribution of allergens and environmental factors to the inflammatory cascade in patients with CRS?
- What is the effect of the microbiome on airway inflammation?
- What is the role of defects in mucosal defense and barrier function?
- Does the presence of asthma define a unique CRS phenotype?
- Is autoimmunity involved in the pathophysiology of recalcitrant CRS?
- Which specific biomarkers are useful to differentiate endotypes and predict treatment response?
- How should exacerbations of CRS be defined and managed?
- Does aspirin-exacerbated respiratory disease define a separate endotype of CRS?
- Is allergic fungal rhinosinusitis a separate endotype of CRS?
- What is the best therapeutic option when surgery, antibiotics, and corticosteroids do not resolve CRS (the true unmet clinical need)?

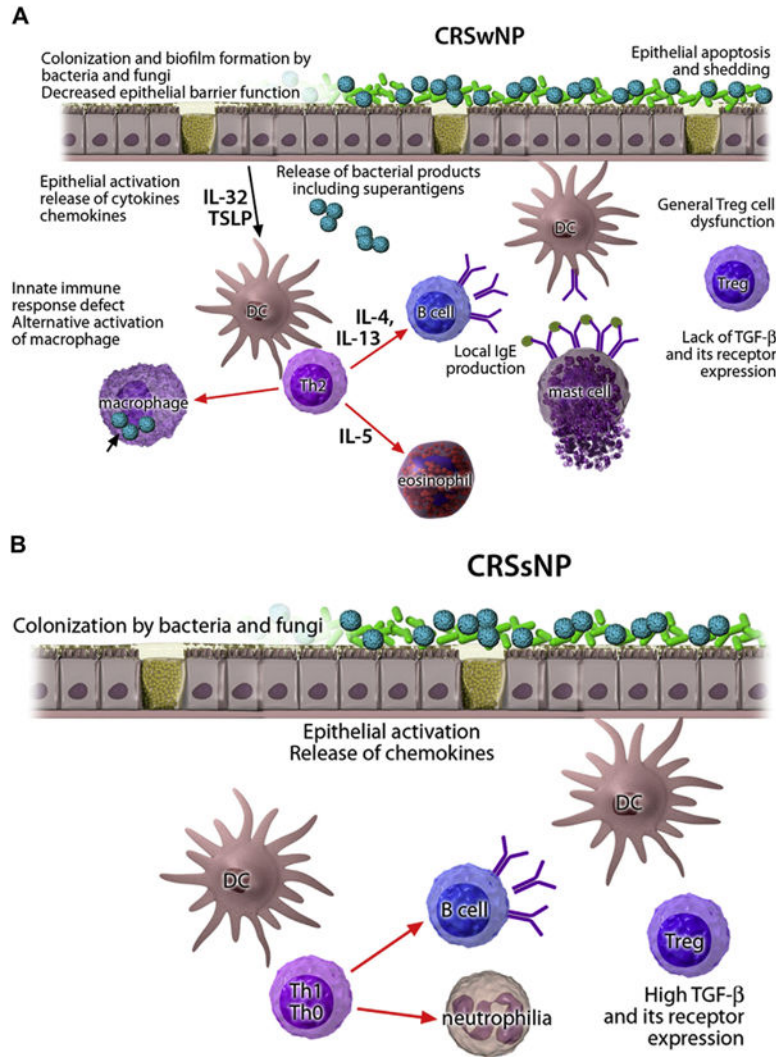


FIG 1. Pathomechanisms of CRS. **A**, CRSwNP. In a T_H2 -type microenvironment with general lack of regulatory T (*Treg*) cell function, IL-5 induces eosinophilia, and IL-4 and IL-13 induce local IgE production. An alternatively activated macrophage subset contributes to the inflammation. The activation of epithelium colonized by bacteria and fungi leads to release of proinflammatory chemokines and cytokines with increased thymic stromal lymphopoietin (*TSLP*) and IL-32 levels. Activated epithelial cells die, with apoptosis resulting in a compromised epithelial barrier. **B**, CRSsNP. Instead of a T_H2 -skewed T-cell response, a T_H1 or a mixed T_H0 response predominates, neutrophilia is often associated, and expression of TGF- β and its receptors is increased. *DC*, Dendritic cell.

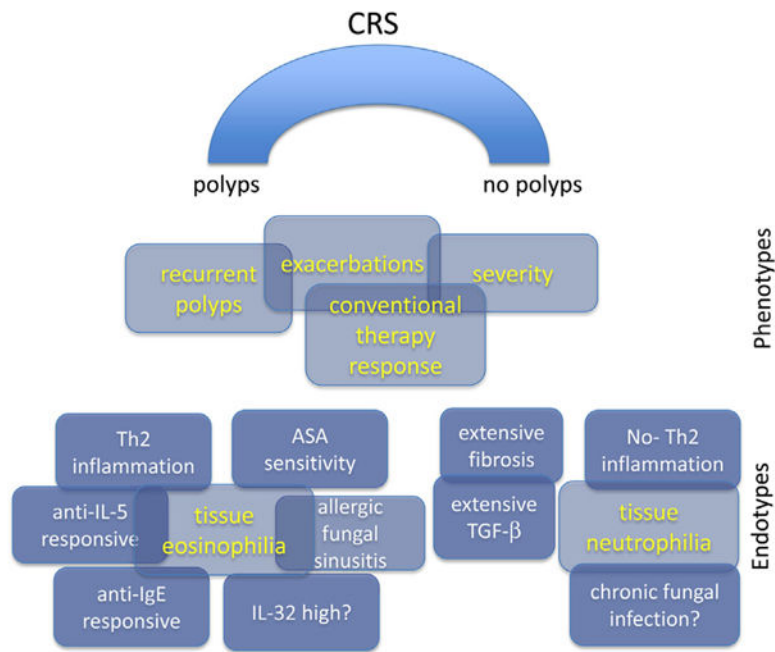


FIG 2. Key phenotypes in relationship to proposed endotypes and their possible associations are shown. ASA, Aspirin.

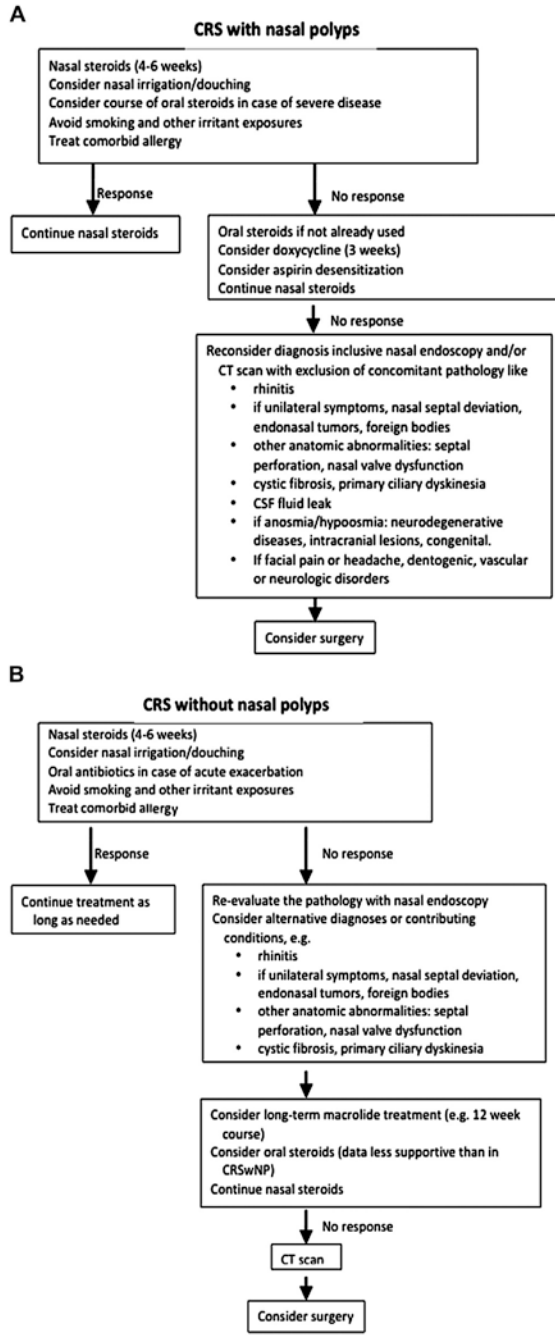


FIG 3. Algorithm for the follow-up of patients with CRSwNP (A) and CRSsNP (B). CSF, Cerebrospinal fluid.