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Contemporary Classification of Chronic Rhinosinusitis Beyond Polyps vs No Polyps
A Review

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IMPORTANCE Chronic rhinosinusitis (CRS) is a broadly defined process that has previously been used to describe many different sinonasal pathologic conditions from odontogenic sinusitis and allergic fungal sinusitis to the more contemporary definition of broad inflammatory airway conditions. Previous classification systems have dichotomized these conditions into CRS with nasal polyps and CRS without nasal polyps. However, clinicians are learning more about the inflammatory subtypes of CRS, which can lead to improved delivery and effectiveness of treatment.

OBSERVATIONS In clinical practice, treatment decisions are often based on observable findings, clinical history, presumed disease, and molecular pathophysiologic characteristics. A proposed classification system is simple and practical. It proposes that the functional anatomical compartments involved create the first level of separation into local and diffuse CRS, which are usually unilateral or bilateral in distribution. Diffuse does not imply "pansinusitis" but simply that the disease is not confined to a known functional anatomical unit. This classification takes into account whether local anatomical factors are associated with pathogenesis. Then the inflammatory endotype dominance is separated into a type 2 skewed inflammation, as this has both causal and treatment implications. The non–type 2 CRS encompasses everything else that is not yet known about inflammation and may change over time. The phenotypes or clinical examples are CRS entities that have been described and how they align with this system.

CONCLUSIONS AND RELEVANCE Although research continues to further define the subtypes of CRS into phenotypes and endotypes, the proposed classification system of primary CRS by anatomical distribution and endotype dominance allows for a pathway forward.

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Supplemental content

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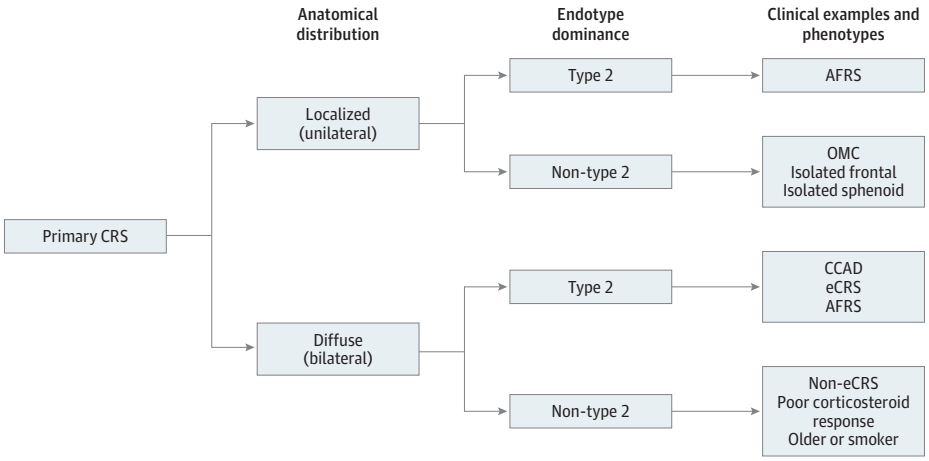
Chronic rhinosinusitis (CRS) is a broadly defined process that has previously been used to describe many different sinonasal pathologic conditions from odontogenic sinusitis and allergic fungal sinusitis to the more contemporary definition of broad inflammatory airway conditions. Previous classification systems have dichotomized these conditions into CRS with nasal polyps and CRS without nasal polyps.[1,2] Although this classification system is simple, it relies heavily on clinical findings for diagnosis without accounting for the pathophysiologic differences between CRS subtypes and therefore may not be able to assess response to different treatment regimens. Furthermore, inflammatory nasal polyps are seen as an end point of inflammation and fibrin deposition rather than specific for any underlying pathophysiologic cause.[3,4] Current therapies are now chosen on the basis of presumed underlying causal pathogenesis or endotypic subtype of CRS. Many different phenotypes of CRS, as well as the inflammatory disorders underlying them, have been proposed.[5]

In clinical practice, treatment decisions are often based on observable findings, clinical history, presumed disease, and molecular pathophysiology. These treatment algorithms used in inflammatory sinonasal disease have largely been associated with research in the lower respiratory tract and applied to the upper airway given the unified airway theory.[6,7] Determination of endotypes originated with asthma and has been further extrapolated to the management of CRS.[6,8-11] An endotype in CRS is defined as a distinct pathophysiologic mechanism that may be identified by specific biomarkers.[4,5,12] The delineation of these endotypes has the ability to streamline and improve treatment in patients with CRS as well as allow for better analysis of treatment results.

Although all subtypes and causes of CRS have previously been grouped together on the basis of the presence or absence of polyps, we propose instead that CRS may be indicative of primary or secondary sinus pathologic characteristics. These subtypes (primary vs secondary) can be further delineated by their anatomical locations and endotype or inflammatory predominance (or causal mechanism). These further classifications ultimately result in the constellation of a phenotype with clinical and radiographic findings. The classification is a proposed system, based on our rhinologic practices, that provides a framework in which to move forward and provide further data to support such a new classification system and

Figure 1. Classification of Primary Chronic Rhinosinusitis (CRS)



The functional anatomical compartments involved create the first level of separation into localized and diffuse. These compartments are usually unilateral or bilateral in distribution. Diffuse does not imply pansinusitis but simply that the disease is not confined to a known functional anatomical unit, taking into account whether local anatomical factors are associated with pathogenesis. Then the inflammatory endotype dominance separates into a type 2 skewed inflammation because this delineation has both causal and treatment implications. The non–type 2 classification encompasses everything else not yet known about inflammation and may change over time. The phenotypes or clinical examples are CRS entities that have been described and how they align with this system. AFRS indicates allergic fungal rhinosinusitis; CCAD, central compartment atopic disease; eCRS, eosinophilic CRS; and OMC, ostiomeatal complex.

to evolve beyond the presence or absence of polyps. Although this system has not been fully tested, it provides a working classification on which we can continue to build.

We propose a CRS classification that allows for integrating contemporary scientific knowledge on the known causes of CRS, which is based on anatomical distribution and the endotype dominance or mechanisms that produce previously described phenotypes of CRS. The proposed classification system is integral in the European Position Paper on Rhinosinusitis 2020.[13]

Primary CRS

Primary CRS is contemporarily defined as a primary inflammatory disorder of "the airway" or respiratory system (**Figure 1**). Patients are defined as having primary CRS if they have a disorder that is limited to their airway or respiratory system only. Thus, patients who have CRS in the setting of immunodeficiencies (eg, selective immunoglobulin deficiency), autoimmune conditions (eg, granulomatosis with polyangiitis or sarcoidosis), genetic abnormalities (eg, cystic fibrosis), odontogenic sinusitis, or local neoplasm do not have primary CRS, as their sinonasal mucosal disease is secondary to another process.

Anatomical Distribution

Localized

Local airway inflammation occurs at the level of the sinonasal mucosa without direct involvement of the lower airway or even the contralateral paranasal sinuses. The key feature is that the sinus cavities involved are anatomically discrete and almost always follow the known ostial or functional drainage pathways. Examples are isolated sphenoid, isolated frontal, or the ostiomeatal unit group of sinuses: maxillary, anterior ethmoid, and frontal. These are examples of a localized disease process and are usually unilateral conditions, although there may be circumstances in which a localized or discrete process may occur synchronously on both sides, although it would be very uncommon. Surgery is likely to be a part of the first-line management of localized CRS.

Diffuse

Diffuse airway inflammation describes a broader inflammatory disorder that may affect both the upper and lower airways. Involvement of the sinuses may be patchy or diffuse on results of radiologic assessment and does not have to have complete opacification of all sinuses but will not be limited by functional sinonasal units or spaces. There will be variability in the degree to which the upper and lower airway are involved in a single patient, as one part of the airway may dominate the clinical presentation. It is common that some degree of disease often exists across the entire airway. It is important to delineate whether or not the patient has lower airway symptoms, as these symptoms may differentiate between a local sinus process or broader airway disease and thus the underlying mechanism associated with the disease process.

Endotype Dominance

At the sinus mucosal level, the adaptive immune response is typically divided into a T-cell response and a B-cell response; these will be discussed as they relate to CRS. Several patterns of inflammatory immune response have been described, but the most recognized are the helper T cell, type 1 (T_H1), T_H2, and T_H17 immune responses.[14] These are sometimes referred to as type 1, type 2, and type 3. In the pathogenesis of CRS, these immune responses may go awry.

Type 2

The type 2 inflammatory response seen in CRS is likely associated with T_H2 cells, cytotoxic T cells, and innate lymphoid cells.[4] Type 2 immune responses are associated with upregulated production of interleukin

4 (IL-4), IL-5, IL-13, local immunoglobulin E (IgE), and profound eosinophilia. The threshold of eosinophilia (or other markers) that might define type 2 responses is likely to change over time and has been intentionally avoided.[15,16] Type 2 responses are also associated with high asthma comorbidity. Interleukin 5 is a key activator and factor for survival of the eosinophil. Interleukin 4 and IL-13 are responsible for mucus production in epithelial cells. A presumed mechanism of this inflammation is through stimulation of nasal epithelial cells to secrete thymic stromal lymphopoietin, IL-25, and IL-33. Interleukin 25 is in the IL-17 family; however, it is responsible for inducing a type 2 immune response. Thymic stromal lymphopoietin, IL-25, and IL-33 induce the release of IL-4, IL-5, and IL-13 from the epithelial and mucosal mast cells. These interleukins then go on to stimulate immunoglobulin class, switching to IgE and IgG4 and mast cell degranulation into eosinophils.[17] Mast cell and eosinophil degranulation trigger inflammation and subsequent tissue damage, which may have long-term negative consequences. Treatment interventions are being developed that are based on inhibition of these type 2 inflammatory mediators, including duplimab (IL-4 and IL-13), mepoluzimab (IL-5), benralizumab (IL-5 receptor), and omalizumab (IgE).[18]

Non–Type 2

Non–type 2 inflammation in the setting of CRS is a mix of type 1 and type 3 inflammation. Interleukin 6, IL-8, and tumor necrosis factor have been shown to stimulate the production of interferon gamma (IFN-γ) and IL-8, which further recruit immune responses. Interleukin 8 recruits neutrophils to the area, which then release further cytokines, including IL-1β, IL-6, IL-8, and myeloperoxidase. The release of IFN-γ leads to the differentiation of CD4-positive T cells into the T_H1 inflammatory response through further production of IL-2 and IFN-γ.[17] The immune-modulating effects of macrolides are an example of the anti–IL-8 effect that have been shown to benefit patients with this skew in inflammation.[19,20]

The proposed mechanism of type 1 inflammation involves an epithelial response to environmental stimuli that leads to osteopontin stimulation of dendritic cells, which induce T_H1-cell differentiation and T_H17-cell differentiation. This mechanism further orchestrates noneosinophilic inflammation through production of IFN-γ and tumor necrosis factor and lymphotoxin α. This production leads to macrophage activation with enhancement of phagocytic properties, class switching to production of IgG subclasses with complement-fixing abilities, antigen presentation to macrophages, and local tissue inflammation and neutrophil activation.[21]

The proposed mechanism of type 3 inflammation involves T_H17 responses that are preferentially invoked with the production of large amounts of IL-17A, IL-17F, and IL-22, with several protective effects that include neutrophil recruitment, activation, and proliferation and innate antimicrobial production by airway epithelial cells.[22]

Clinical Phenotype

Localized, type 2 pathologic conditions associated with inflammation can include examples such as allergic fungal rhinosinusitis, a local response to common fungal species including *Alternaria*, *Bipolaris*, and *Curvularia*. Diagnosis requires eosinophilic mucin, which has a typical appearance of peanut butter, fungal hyphae with Charcot-Leyden crystals on histologic examination, and serum-specific IgE to fungal pathogens.[23-25] It is uncommon for patients with localized type 2–dominant disease, such as allergic fungal rhinosinusitis, to have broader airway disease and bronchpulmonary aspergillosis.[26] Although classically unilateral, allergic fungal rhinosinusitis can be diffuse (eFigure 1 in the Supplement). The mainstay of treatment for these diseases includes early surgical intervention with creation of a "neo-sinus" cavity in addition to adequate postoperative medical management (ie, corticosteroid irrigations).

Localized, non–type 2 pathologic conditions include the following: isolated frontal disease (**Figure 2**A), isolated sphenoid disease (Figure 2B), and ostiomeatal complex involvement (Figure 2C and D). These clinical entities are not associated with eosinophils or IgE. The remodeling events that occur with inflammation (fibrosis, basement membrane thickening, fibrin deposition, and metaplasia) may not be fully reversible with medical therapy.[27] When these remodeling events occur with functional drainage pathways, they create anatomically discrete or localized sinus disease. These conditions usually require surgical intervention and have a good prognosis from surgery as a single-modality intervention.

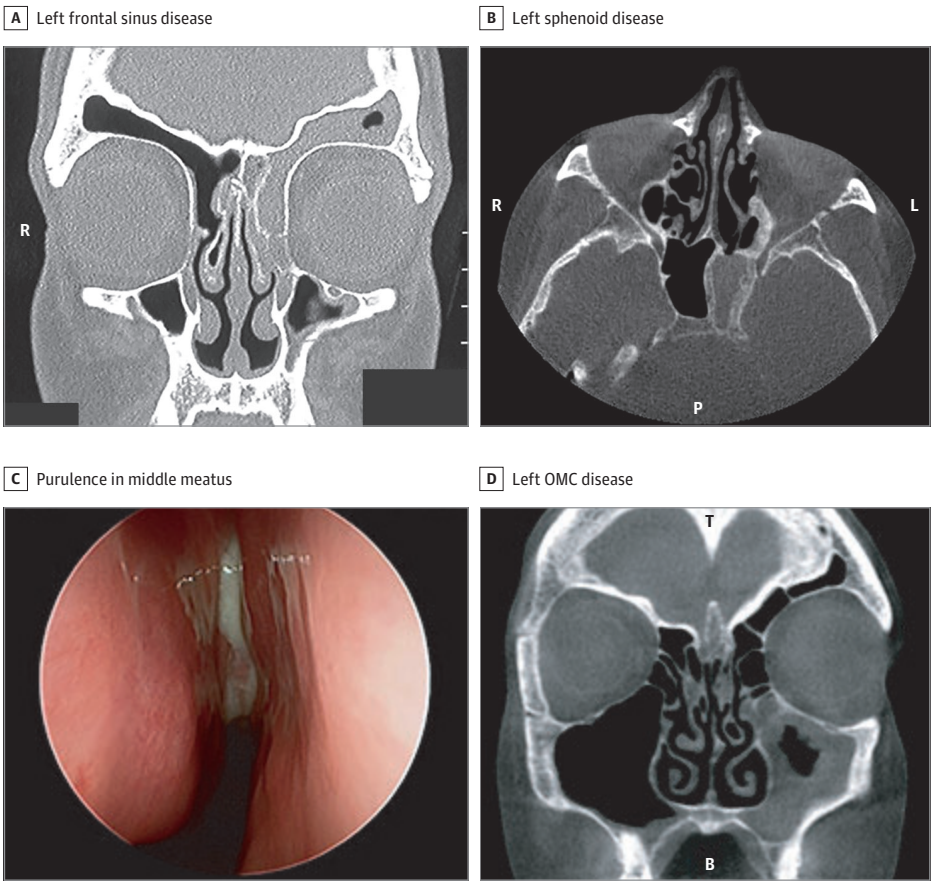
Diffuse type 2 pathologic conditions include central compartment atopic disease, eosinophilic CRS, and allergic fungal rhinosinusitis. A newly described phenotype is central compartment atopic disease, which is an IgE-associated disease process that is associated with inhalant allergy.[28,29] Patients with central compartment atopic disease will have specific radiographic findings, including central thickening of the turbinates and septum with superior and lateral sparing of the sinus cavities.[30] This centralized inflammation with otherwise normal surrounding mucosa has been described as a halo sign[31] (eFigure 2 in the Supplement). The sinus dysfunction is mainly postobstructive with mucus trapping. Barotrauma and pressure symptoms are common for individuals with central compartment atopic disease. In contrast, eosinophilic CRS is associated primarily with tissue and serum eosinophila, and patients will have or go on to develop concomitant lower airway disease (adult-onset eosinophilic asthma). These patients typically have nasal polyps and severe olfactory dysfunction, and their symptoms are sensitive to corticosteroids.[32] Their loss of smell is often profound and very sensitive to corticosteroids. They will have thick, glue-like eosinophilic mucin (**Figure 3**). These patients' symptoms are not associated with inhalant allergy in contrast to central compartment atopic disease, and serum IgE is not directly associated with eosinophilic response.[33] Diffuse allergic fungal rhinosinusitis is similar to the previously described localized allergic fungal rhinosinusitis except that there is broad paranasal sinus involvement (eFigure 3 in the Supplement).

Diffuse non–type 2 pathologic conditions include non–eosinophilic CRS. Patients with non–eosinophilic CRS are often older (age, 50-60 years)[5] and do not have the same benefit from the use of corticosteroids.[19] These patients may have polyps or polypoid edema, but they will lack the eosinophilic mucin seen in patients with eosinophilic CRS.[16,34] These patients will less often have smell loss as a presenting symptom and may have an uncontrolled lower airway when using corticosteroid inhalers.[19,20,32] They will often have postobstructive infective phenomena with purulence noted on endoscopic evaluation[35] (**Figure 4**).

Secondary CRS

Less commonly, CRS is secondary to an established systemic disease or local pathologic condition (odontogenic or neoplasm)

Figure 2. Primary Localized Non–Type 2 Chronic Rhinosinusitis



A, Coronal computed tomography (CT) scan showing isolated left frontal sinus disease. B, Axial CT scan showing isolated left sphenoid disease. C, Nasal endoscopy with purulence within the middle meatus for this non–type 2 disease process. D, Coronal CT scan showing isolated left ostiomeatal complex (OMC) disease. These images are examples of traditional ostial occlusion chronic rhinosinusitis disease or isolated sinusitis.

(**Figure 5**). Secondary CRS represents a group of clinical entities in which the sinus disease observed is part of another disease process. Secondary CRS is simply an expression of another condition, and correction of that mechanism will result in resolution of the CRS.

Anatomical Distribution

Localized

Local sinus pathologic conditions, such as periapical dental abscess, neoplasm, facial trauma, and foreign bodies, are all examples of CRS that may occur locally in anatomically discrete sinus cavities as a result of these pathologic conditions.[36] These conditions are usually unilateral, but uncommon situations may arise, such as advanced neoplasms,[37] in which both sides are involved, but the CRS and pathologic condition remain anatomically related. Surgery will likely play a role in first-line therapy in the management of these conditions.

Diffuse

Secondary CRS that is diffuse is almost always the result of a broader systemic disorder. Examples include cystic fibrosis, selective immunodeficiency, and granulomatosis with polyangiitis; these are diseases in which inflammation in the sinus cavity is an expression of the underlying disease and are thus considered secondary CRS.

Mechanism

Although the list and categorization here is not designed to be comprehensive, most systemic conditions that are associated with the development of mucosal inflammation predominantly fall into conditions that impair the mechanical function of the sinuses to clear mucus (mucociliary), the development of an abnormal immune response (autoimmune), and the lack of an appropriate immune response (immunodeficiency). It is important to highlight that these are processes that occur outside the respiratory system as well.

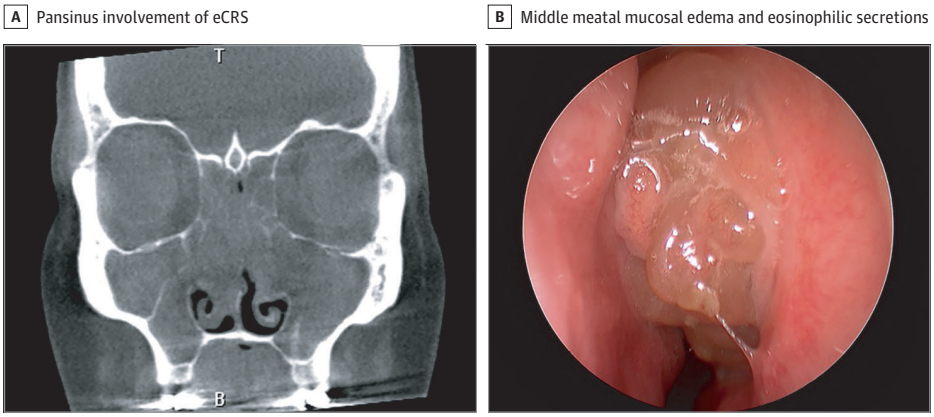
Mucociliary

Conditions that fit under this classification will affect the clearance of mucus from the paranasal sinuses and will lead to mucostasis. Mechanical clearance of mucus is an important part of the innate immune defense, and mucostasis can serve as a source for secondary infection. *Pseudomonas* and *Staphylococcus aureus* are common bacteria that colonize those with mucostasis. The mechanical clearance of mucus is an important part of the innate immune defense. Cystic fibrosis is a disorder of impaired mucociliary clearance. Primary ciliary dyskinesia is an example of loss of mechanical action of the cilia.[38]

Autoimmune

Autoimmune pathologic conditions arise from autoantibodies that lead to vasculitis or systemic deposition of inflammatory cells. These pathologic conditions occur systemically and can have effects in the upper

Figure 3. Primary Diffuse Type 2 Dominant Chronic Rhinosinusitis (CRS): Eosinophilic CRS (eCRS) or Adult-Onset Eosinophilic Nasal Polyposis



A, Coronal computed tomography scan showing the typical pansinus involvement of eCRS. B, Nasal endoscopy showing extensive middle meatal mucosal edema and eosinophilic secretions. The size of the polyps does not always reflect the severity of the inflammatory process. This type of CRS is often associated with adult-onset asthma. These patients obtain significant relief from corticosteroid use.

and lower airways. Examples include granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) and eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome).[39,40]

Immunodeficiency

Immunodeficiencies lead to the inability to clear pathogens and persistence or recurrence of infections. The upper airway serves as a filter for some of these pathogens and can be inoculated easily given the route of transmission. Classic immunodeficiencies identified with sinus involvement include selective immunoglobulin deficiencies, common variable immune deficiency (CVID), and type 1 and 2 diabetes.[41]

Clinical Phenotype

Localized involvement of the paranasal sinuses may occur due to certain local pathologic conditions (eg, odontogenic sources, fungal ball, or neoplasia). Fungal ball affects the maxillary sinus most often; however, it can be seen in other isolated sinuses.[42-44] Given the predilection of fungal ball for the maxillary sinus, patients undergoing endodontic treatment are at higher risk.[45] These patients may also have purulence draining from the sinus owing to postobstructive infective phenomena. Odontogenic sinusitis is typically seen in patients older than 40 years with a history of previous dental work or need for dental work. These patients may also report cachosmia. When the maxillary sinus is the primary sinus affected, the anterior ethmoid and frontal sinus can be involved in a postobstructive manner; however, the disease is anatomically discrete or localized to a functionally related group of sinuses (eFigure 4 in the Supplement). Benign and malignant neoplasia can affect the sinus from which it arises by causing local obstruction for normal mucociliary flow but also increased inflammation in the area. The sinuses surrounding the neoplasia may experience postobstructive mucus trapping. Patients with localized but secondary CRS usually require surgery, but the intervention needs both drainage and reventilation of the sinuses as well as the underlying pathologic condition to be treated for the CRS to resolve.

Diffuse disease due to mucociliary defects includes primary ciliary dyskinesia and cystic fibrosis, which are caused by different autosomal recessive genetic mutations. Primary ciliary dyskinesia is highlighted by defective respiratory cilia; however, other cilia are defective as well. These patients have poor mucociliary clearance and experience upper and lower airway disease.[46,47] They often have polypoid edema or polyps on results of endoscopy and have diffuse sinus involvement[48,49] (eFigure 5 in the Supplement).

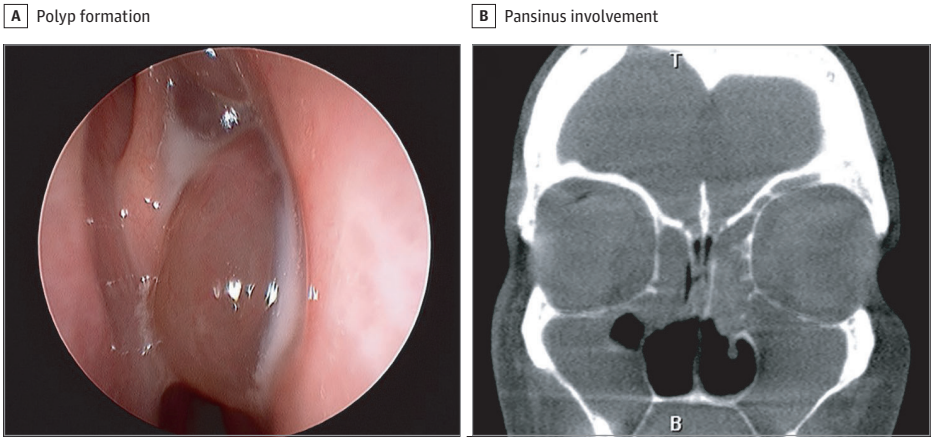
Patients with cystic fibrosis have impaired chloride transport leading to decreased air-surface liquid interface, which leads to mucociliary clearance defects owing to defective ciliary beat frequency. These patients often have polypoid edema or true middle meatal polyps on results of endoscopy with universal pansinus involvement on results of imaging. In many cases, depending on the specific genetic mutation, there is hypoplasia of the maxillary and frontal sinuses on results of radiography.[50]

Diffuse disease due to autoimmune disease includes eosinophilic granulomatosis with polyangiitis. Patients with eosinophilic angiitis have eosinophilia, asthma, and evidence of vasculitis. The upper airway of these patients will look similar to the upper airway of those with eosinophilic CRS; however, patients with eosinophilic angiitis have other organ involvement such as skin, cardiac, gastrointestinal, and musculoskeletal.[51]

Patients with granulomatosis with polyangiitis will experience nasal ulcers and crusting, saddle-nose deformity, and/or other systemic symptoms (fatigue, weight loss, and night sweats). Septal ulcerations and perforations may be present in patients with active disease and those with disease in remission. Nasal crusting is common in patients with active disease.[52] Patients with granulomatosis with polyangiitis will have other organs involved such as skin, kidney, musculoskeletal, ophthalmologic, central nervous system, and/or cardiac.[53-55]

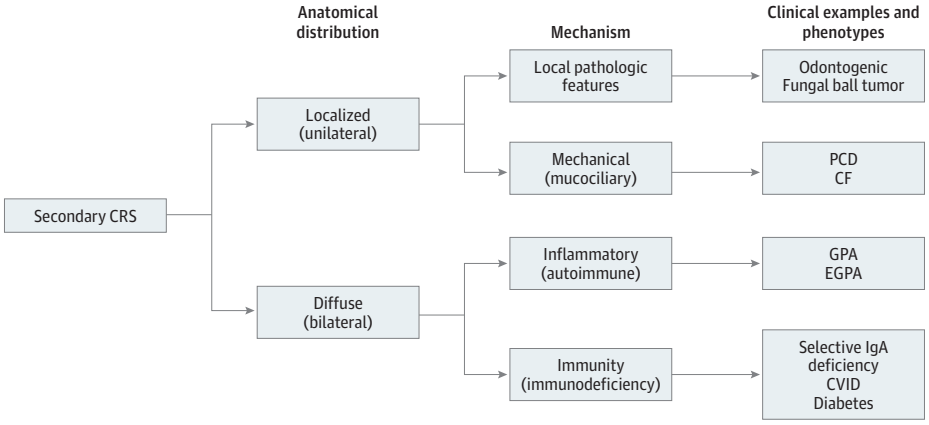
Diffuse disease associated with immunodeficiencies includes selective IgA deficiency, CVID, and diabetes. The prevalence of selective IgA deficiency is different across different races/ethnicities and can be a clinical challenge to diagnose. These patients may present with recurrent sinopulmonary infection, allergic symptoms, and autoimmune illnesses. However, most patients are asymptomatic. These patients will have a serum IgA level less than 7 mg/dL (to convert to grams per liter, multiply by 0.01) in individuals older than 4 years with otherwise normal

Figure 4. Primary Diffuse Non–Type 2 Chronic Rhinosinusitis (CRS): Non-Eosinophilic CRS (eCRS)



A, Nasal endoscopy demonstrating that polyp formation occurs in different inflammatory subtypes. The secretions are distinctively different from those in eCRS. B, Coronal computed tomography scan demonstrating the diffuse or pansinus involvement. This patient (age, >50 years) was poorly responsive to corticosteroids with disease in both upper and lower airways but had complete remission with long-term macrolide therapy.

Figure 5. Classification of Secondary Chronic Rhinosinusitis (CRS)



Secondary CRS implies that another local or systemic pathologic condition or disease process is the factor associated with the sinus changes. The functional anatomical compartments involved create the first level of separation into local and diffuse. These compartments are usually unilateral and bilateral in distribution. Diffuse does not imply pansinusitis but simply that the disease is not confined to a known anatomical unit, taking into account whether local anatomical factors are associated with pathogenesis. The mechanism for diffuse disease implies that another process is associated with the CRS and either a mechanical (mucociliary), an inflammatory (usually autoimmune), or an immunodeficiency dysfunction is present. The phenotypes or clinical examples are CRS entities that have been described and how they align with this system. CF indicates cystic fibrosis; CVID, common variable immunodeficiency; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; IgA, immunoglobulin A; and PCD, primary ciliary dyskinesia.

immunoglobulins and normal responses to vaccinations. Patients may present with allergic symptoms including conjunctivitis, rhinitis, urticaria, eczema, food allergies, and asthma. The IgE concentration is often elevated in these patients.[56] Common variable immunodeficiency is often not diagnosed until adulthood despite being one of the most common primary immunodeficiencies. Patients with CVID have a normal number of B immune cells; however, the cells do not mature appropriately. Patients with CVID present with a broad range of symptoms including recurrent bacterial infections, autoimmunity, interstitial lung disease, and allergic symptoms. Recurrent sinusitis is found in half the patients with CVID.[57] Some of these patients may have already undergone multiple sinus operations, and their sinusitis may not have been well controlled with conventional therapy; therefore, investigations into immunodeficiencies should be considered.

Conclusions

With scientific advances in the understanding of CRS, a working classification system for CRS should move away from the dichotomy of CRS with nasal polyps and CRS without nasal polyps to change clinical practice. The proposed classification has been left intentionally simple (local or diffuse and type 2 or non–type 2) to give it the flexibility to incorporate future research and allow phenotypes to be defined. The proposal allows for current therapies, from balloons to macrolides to surgery and biologics, to be more appropriately directed. Although research continues to further define the subtypes of CRS into phenotypes and endotypes, the proposed classification system of primary CRS by anatomical distribution and endotype dominance allows for a pathway forward.

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Acquisition, analysis, or interpretation of data: Grayson, Senior, Harvey.
Drafting of the manuscript: Grayson.
Critical revision of the manuscript for important intellectual content: All authors.
Administrative, technical, or material support: Grayson.
Supervision: Hopkins, Mori, Senior, Harvey.

Conflict of Interest Disclosures: Dr Hopkins reported completing board work for Sanofi, AstraZeneca, Smith & Nephew, and Olympus. Dr Harvey reported serving as a consultant with Medtronic, Olympus, and NeilMed Pharmaceuticals and serving on the speakers bureau for GlaxoSmithKline, Seqiris, and AstraZeneca. No other disclosures were reported.

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