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Phenotypes of Chronic Rhinosinusitis

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Abstract

Chronic rhinosinusitis (CRS) is a complex heterogeneous disease with different phenotypes and endotypes. Recent advances in our understanding of the pathogenetic mechanisms of CRS endotypes have led to the introduction of effective biologic agents for CRS management. Traditionally, CRS phenotypes have been divided into with or without nasal polyps depending on the presence of polyps. Although this classification does not reflect the various endotypes that are recently emerging, it is simple and easily recognized by clinicians. Other phenotypes of CRS are fungal rhinosinusitis (including invasive and noninvasive subtypes), infectious rhinosinusitis, aspirin-exacerbated respiratory disease, cystic fibrosis, pediatric CRS, and CRS associated with systemic diseases. This article reviews the diagnostic approaches and up-to-date treatment strategies for each CRS phenotype with the hope that a better understanding of endotypes will result in a more scientific understanding of phenotypes and precise, personalized treatments.

Keywords

Chronic rhinosinusitis; Nasal polyps; Fungal rhinosinusitis; Aspirin-exacerbated respiratory disease; AERD; Cystic fibrosis

INTRODUCTION

The clinical and pathologic heterogeneity of chronic rhinosinusitis (CRS) has been appreciated for several decades (Figure 1). In 2004, a rhinosinusitis consensus group convened to define CRS on the basis of prevailing evidence.[1] This group concluded that there are 3 main clinical phenotypes of CRS, namely, CRS without nasal polyps (NP) (CRSsNP), CRS with nasal polyps (CRSwNP), and allergic fungal rhinosinusitis (AFRS)

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plus certain well-defined subphenotypes within this context, such as “cystic fibrosis CRS” and “aspirin-exacerbated respiratory disease (AERD)” as well as many other less well-defined subtypes, such as “CRS vasculitis” and “CRS sarcoidosis.”

Since 2004, significant progress has been made toward understanding the host-microbial interactions involved in CRS.[5] This work has helped elucidate the key role of mucosal innate immunity in maintaining sinus health and certain genetically defined conditions predisposing to sinus infection and CRS.[6] Other defects in innate immunity or epithelial barrier function have also been described. In addition, given the advent of targeted biologic therapies for allergic and immunologic diseases, there has been an emergence of studies to define CRS “endotypes” on the basis of patterns of inflammatory cell and cytokine expression in sinus tissues.[7] This work is leading toward a reclassification of CRS also based on endotypes and offers promise toward discovery of more targeted and effective treatments for CRS (Figure 1). This review describes our current understanding of CRS subtypes based on existing information and strategies for treatment of each subtype.

CRSsNP VERSUS CRSwNP

There are several classifications in CRS to date, but until recently, CRS was primarily defined as CRSsNP versus CRSwNP depending on whether or not patients had NP. Although this classification is simple and intuitive, it does not explain the underlying pathophysiology. CRSsNP is a variable chronic inflammatory disease. The main treatment options include intranasal corticosteroids and nasal irrigation, although antibiotics can be used in treating acute exacerbations of CRSsNP.[8] In addition, long-term macrolide treatment, which has antimicrobial as well as anti-inflammatory effects,[9,10] is used by some clinicians. Oral corticosteroids are often not recommended for the treatment of CRSsNP unless there is a high suspicion that the disease involves T_H2-predominant inflammation.[8] Patients not responding to medical therapy for CRSsNP often undergo endoscopic sinus surgery (ESS).[10]

CRSwNP is usually a T_H2-predominant eosinophilic-driven disease. Medical treatment options for CRSwNP include intranasal corticosteroids, nasal saline irrigation, a short course of oral corticosteroids, and dupilumab (anti-IL-4Rα mAb) in severe cases. Intranasal mometasone, fluticasone, budesonide, and triamcinolone (up to 2 sprays twice daily) are the treatments of choice in patients with CRSwNP with mild symptoms. However, they are often insufficient to control symptoms, a main reason for which could be ineffective drug delivery to the middle meatus, where NP originates. Different glucocorticoid delivery systems have been tried to overcome this drug delivery issue and in 2017 the US Food and Drug Administration (FDA) approved a new delivery system using fluticasone (Xhance; Optinose, Yardley, Pa). This system uses breath-actuated exhalational assistance to deliver intranasal fluticasone to the middle meatus. Another FDA-approved device to effectively deliver corticosteroids is a mometasone-eluting stent (Sinuva; Intersect ENT, Menlo Park, Calif), which can be inserted endoscopically in the outpatient setting for recurrent NP, usually after ESS. The Sinuva stent is bioabsorbable and elutes mometasone for 90 days. However, the device can cause excessive secretions, mucosal crusting, and a bad odor and is temporary in its effectiveness. Another treatment modality is the use of aqueous corticosteroids,

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budesonide, 0.5 to 1 mg, mixed in 240 mL of normal saline, and insufflating it into the nose.[11] Use of an aqueous glucocorticosteroid for sinus irrigation is more effective than a simple nasal spray in post-ESS patients to reduce NP regrowth and control symptoms, ultimately decreasing the use of oral glucocorticosteroids.[12,13] In 2019, the FDA approved dupilumab, an anti-IL-4Rα antibody, for this disease. Its success is based on 2 successful phase III clinical trials in which patients with NP received dupilumab plus intranasal mometasone furoate versus placebo plus intranasal mometasone furoate. Although dupilumab is a great option for refractory CRSwNP, with or without ESS history, it is expensive, costing tens of thousands of dollars per year. Therefore, cost-effectiveness should be considered when making recommendations for ESS versus dupilumab. Regardless, patients with this disease should understand that thorough postoperative care is very important because of the recurrence rate of NP in CRSwNP.

INFECTIOUS CRS

Presently, the only recognized form of infectious CRS is “acute exacerbations of CRS,” which is often associated with either viral or bacterial infections.[14,15] Consensus guidelines on CRS treatment generally favor the use of antibiotics only for acute exacerbations of CRS.[16] These consensus papers also recommend, when possible, that antibiotic treatment should be guided by endoscopically obtained cultures. This is illustrated in a recent study demonstrating that cultures obtained at the time of acute exacerbations of CRS vary and showed a range of organisms, including *Staphylococcus aureus* and coagulase-negative staphylococci, most frequently followed by *Haemophilus influenza*, *Pseudomonas aeruginosa*, and Enterobacteriaceae. Antibiotic resistance was detected in isolates from 46% of patients.[15] In contrast, bacterial infection is not generally regarded as an important component of the pathogenesis of CRS, although there remains considerable controversy centered around the relative contribution of bacterial biofilm, defects in innate immunity, and dysbiosis to the full CRS pathogenic picture.[17] Infectious aspects and their impact on CRS are discussed below.

Much attention has been given to bacterial biofilm as a feature of CRS.[18–27] Studies examining surgically obtained sinus tissue have demonstrated an abnormal biofilm in 54% of cases.[5] The presence of polymicrobial biofilm or biofilm containing *Staphylococcus aureus* in sinus tissue at the time of surgery is associated with more severe disease and a poorer postoperative course.[28] The presence of bacterial biofilm is also strongly associated with persistent mucosal inflammation after ESS.[24] In another study, Bendouah et al[29] found that increased biofilm-forming capacity of bacteria (specifically *P aeruginosa* and *S aureus*) isolated from patients with CRS at the time of surgery is a predictor of poor evolution of CRS symptoms and endoscopic severity in patients followed at least 1 year post-ESS. What is less clear is the extent to which the biofilm persists after sinus surgery with restoration of sinus ventilation and mucociliary clearance.

The sentinel work of Lee et al[30] identified a loss of function in bitter taste receptor T2R38 as an important innate immune defect in patients with CRS. The initial observation was that patients with CRS who were either homozygous or heterozygous for the nonfunctional T2R38 receptor had an increased tendency for *Pseudomonas* infection compared with

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patients with CRS who were homozygous for the functioning receptor. A specific acylhomoserine lactone quorum-sensing molecule secreted by *P aeruginosa* was found to be responsible for activating the normal receptor.[30] Subsequent work identified a range of additional volatile bacterial metabolites produced by other pathogens including *S aureus, P aeruginosa*, and *Streptococcus pneumoniae* that elicit a T2R-dependent nitric oxide response.[31] This loss of function in bitter taste receptors (AVI genotype) is the best-described defect in innate immunity responsible for persistent bacterial infection in patients with CRS. Three other bitter taste receptors (T2Rs) with similar ability to stimulate nitric oxide production have since been found to be expressed on the sinonasal tract, raising the possibility that additional functional deficiencies in T2Rs will be discovered.[32]

A deficiency in certain antimicrobial peptides in sinus secretions has also been described in patients with CRS, most notably deficiency in lactoferrin or short palate, lung, and nasal epithelial clone (SPLUNC1) protein in sinus secretion (reviewed in Hamilos[5]), but it remains unknown whether these represent primary or secondary deficiencies.

Many patients with CRS have persistent sinus inflammation after surgery even in the absence of overt infection. The extent to which a disturbance in the sinus microbiome ("dysbiosis"), defects in mucosal innate immunity, or persistence ofmucosal biofilm account for this inflammation is presently unclear. Studies comparing the healthy sinus microbiome with the CRS-associated microbiome suggest that CRS behaves as a state of "dysbiosis" that favors the presence of inflammation-tolerant pathogens.[33] Pathologic biofilm can be viewed as a type of dysbiosis. Whether therapies directed at restoring a normal sinus microbiome would be useful for the treatment of CRS remains an exciting but unanswered question.

In a study of 100 consecutive patients seen by one of the authors (D.L.H.) at Massachusetts General Hospital, 9.1% of patients with CRSsNP and 8.8% of patients with CRSwNP had a history of culture-proven infection with either *P aeruginosa*, other unusual Gram-negative pathogens, or *S aureus*.[34] It is presently unknown to what extent defects in local innate immunity, abnormal mucociliary clearance, defective epithelial barrier function, or overzealous antibiotic use accounts for this subset of patients, but it is clear that patients in this category are often the most refractory to medical and surgical management.

Patients with AFRS who undergo sinus surgery are often also infected with *S aureus*.[35,36] It is likely that the staphylococcal infection is secondary to the disease, because the bacterial infection typically does not persist after antibiotic treatment and AFRS-directed anti-inflammatory treatment.

FUNGAL RHINOSINUSITIS: INVASIVE FUNGAL RHINOSINUSITIS, AFRS, FUNGAL BALL

"Fungal rhinosinusitis" is an overarching term describing fungal diseases of the sinonasal tract. These diseases are further subdivided into invasive and noninvasive forms.

Invasive fungal sinusitis is a condition in which fungal hyphae invade the mucosal tissue of the nose and paranasal sinuses.[37] Acute, chronic, and granulomatous invasive forms exist.[38]

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Invasive fungal sinusitis is usually found in patients who are immunocompromised or have uncontrolled diabetes mellitus. In a systematic review, patients with advanced age or intracranial extension, or those who do not receive surgery as a part of therapy, had poor survival rates.[39]

AFRS is a unique disorder characterized by intense T_H2 inflammation in response to a colonizing fungus in sinus mucus. Dematiaceous species and Aspergillus species account for most cases.[38,40] AFRS is strictly an allergic inflammatory disorder that is not associated with fungal tissue invasion. AFRS can be unilateral or bilateral and causes thick inflammatory exudates called “allergic mucin” or “eosinophilic mucin.” Eosinophilic mucin is defined as tenacious-appearing mucus laden with clumps of eosinophils and free eosinophilic granules.[41] This highly viscous brown-green mucus can lead to compressive expansion to adjacent structures like orbits. The treatment of choice is ESS, followed by postoperative oral corticosteroids and topical intranasal steroids or corticosteroid irrigations, rather than antifungal agents.[10,42]

Fungus ball is the other noninvasive form of fungal rhinosinusitis. Patients tend to be middle-aged or older women and the disease presents in the form of unilateral sinusitis most commonly in the maxillary sinus with typical patterns of microcalcification on computed tomography scan.[43] It is often asymptomatic and can be found incidentally on computed tomograph or magnetic resonance imaging. ESS is the treatment of choice if the patient is symptomatic, with a low rate of recurrence and no need for treatment with antifungal agents.[44]

ASPIRIN-EXACERBATED RESPIRATORY DISEASE

AERD is a syndrome characterized by CRS with recurrent eosinophilic nasal polyps, asthma, and respiratory reactions induced by aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit the cyclooxygenase-1 enzyme. The disease is usually one with onset in adulthood,[45–47] and the prevalence of AERD is about 30% of patients with asthma and CRSwNP.[48] Aspirin and other NSAID-induced respiratory reactions typically cause increased nasal congestion and rhinorrhea and can be accompanied by bronchoconstriction and wheezing or occasionally by skin rash and gastrointestinal symptoms.[46] It is important that patients are educated to avoid aspirin and other NSAIDs, but even in the absence of these medications, the upper and lower respiratory tract symptoms of AERD persist. Appropriate diagnosis of AERD is critical to initiate disease-specific treatments and to ensure patient safety. Oral aspirin challenge is the criterion standard diagnostic for AERD because there are no validated *in vitro* diagnostic tests. However, in patients who present with adult-onset asthma, recurrent nasal polyps, and a history of 2 or more NSAID-induced reactions that caused consistent respiratory symptoms, the diagnosis can be made clinically, without requiring an aspirin challenge. For patients in whom the clinical history is less clear, or for whom NSAID sensitivity is unknown, a provocative drug challenge is warranted to establish the diagnosis, with several published protocols available.[49,50]

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In addition to symptom-driven treatments for asthma and NP, a protocol of aspirin desensitization to initiate daily high-dose aspirin therapy can be beneficial for many patients with AERD. Aspirin desensitization is achieved by administering increasing doses of aspirin until a reaction occurs and is treated, and then once reaction symptoms have abated, escalating doses are administered until the patient is able to take aspirin daily.[51] For many patients with recalcitrant AERD, high-dose (325–1300 mg per day) daily aspirin therapy reduces the rate of nasal polyp regrowth and the need for additional polyp surgeries, and improves sense of smell and decreases the need for systemic corticosteroids.[52,53] Other than high-dose aspirin, there are currently no disease-specific therapies for AERD, and the symptoms are treated with usual medical and surgical care, following guidelines for asthma and CRSwNP treatment. Of note, the recently FDA-approved biologic therapy dupilumab for CRSwNP has also been shown to work well in patients with AERD for reduction of nasal polyp burden, improvement in sense of smell, and improvement in lung function. This suggests a reliance on the IL-4Rα pathway in patients with this phenotype.[54]

CYSTIC FIBROSIS

CRS is highly prevalent in patients with cystic fibrosis (CF), and mutations of the CF transmembrane conductance regulator gene are also more prevalent in non-CF patients with CRS.[55,56] There is an increased prevalence of NP in patients with CF of all ages. CRS is highly challenging to treat in patients with CF, owing to the increased mucus viscosity, chronic sinus infection, and biofilm formation; the presence of distinctive sinus pathogens, including *S aureus* (children), *P aeruginosa* (children, adults), and unusual pathogens, such as *Burkholderia cepacia* or *Achromobacter (Alcaligenes) xylosoxidans*; and the greater severity and poorer outcomes of CRS in patients with CF versus without CF.[57]

Dysfunctional CF transmembrane conductance regulator chloride channels lead to markedly impaired mucociliary clearance.[58] Large amounts of DNA released from the degeneration of neutrophils also contribute to high viscosity of CF airway secretions.[59] Other factors also contribute to reduced local innate immunity in CF sinuses (reviewed in Hamilos[57]) including reduced airway surface liquid pH resulting in impaired antimicrobial peptide activity and reduced nasal nitric oxide levels.[60–64]

Nasal polyps from patients with CF have a barely visible epithelial basement membrane, relatively sparse eosinophils, and a preponderance of acid mucin in glands and cysts of the polyp and in their surface mucus.[65] In comparison, non-CF nasal polyps in adults have extensive epithelial basement membrane thickening, high stromal eosinophil counts, and mainly neutral mucin in mucous glands, cysts, and mucus.[65] In pediatric patients with CF who underwent ESS, the prevalence of polypoid CRS was 18% in those younger than 6 years and increased to 45% in adolescents aged 13 to 18 years.[66] The histology of CF polypoid lesions typically shows dilated glandular ducts and a predominance of mucous glands, with an increased number of plasma cells and mast cells[67] with fewer eosinophils compared with non-CF polyps.[65,66] However, the histology is variable, and 42% of CF polyps have an eosinophilic infiltrate usually admixed with neutrophils.[67]

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Nasal polyps are rare in children younger than 6 years but can occur in CF at any age, with the youngest noted being 2.5 years old.[68]

Mainstays of medical treatment include isotonic saline irrigations and topical intranasal glucocorticoids, with some evidence that topical intranasal glucocorticoids reduce NP size.[57] Mucolytics have received little attention as a treatment for CRS in CF. Nasally nebulized dornase alfa (recombinant human deoxyribonuclease) after sinus surgery shows promise but is not approved by the FDA for use in CRS.[59,69] There are studies supporting the use of topical antibiotics, including colistimethate sodium or tobramycin, administered as a saline irrigation or antral lavage in patients after sinus surgery when susceptible bacteria are cultured.[70–72] Key components of CF sinus surgical management include extensive surgery to ensure that the sinus cavities are widely opened with smoothing of bony overhangs to prevent mucus retention and bacterial recolonization, meticulous postoperative daily nasal irrigations, and appropriate use of culture-directed topical antibiotics. Combined surgical and medical management of CF CRS has received attention toward its impact on lung transplantation.[70–72] A common practice is to perform sinus surgery after lung transplantation to improve long-term outcomes from the lung transplantation,[73] although not all centers adhere to the practice of performing ESS posttransplantation.[74] No data exist yet on whether the CF-targeted therapies, including ivacaftor or ivacaftor combined with lumacaftor, have an impact on CF CRS.

PEDIATRIC CRS

Children may experience the symptoms of CRS differently than adults, and persistent cough, prolonged nasal drainage, low-grade fever, and irritability are commonly observed in children.[75] In addition, the diagnosis of CRS is rarely made in isolation in children, and appropriate initial evaluation may include assessment of possible comorbidities, including allergy, CF, primary ciliary dyskinesia, and immunodeficiency. A careful nasal examination must be done to examine for nasal foreign body if the symptoms are unilateral. The physical examination must also include a thorough oral and otic examination, because dental infections can present with sinus discomfort in children, and otitis media with effusion can commonly accompany rhinosinusitis in these patients. Two histopathology studies comparing pediatric versus adult CRS histopathology found that neutrophilic inflammation is more common in pediatric CRS and eosinophilic inflammation is more common in adult CRS.[76,77] Therapeutic interventions for pediatric CRS generally include a combination of nasal saline irrigation and intranasal corticosteroids, in addition to antihistamines when symptoms are related to environmental allergies. In some cases, treatment can be further advanced by eliminating an allergic component so that avoidance therapy and possible allergen immunotherapy can be initiated. When an infection is suspected, on the basis of nasal purulence, fetid breath, or the presence of a maxillary sinus airfluid level, a course of antibiotics may be useful, especially when guided by an endoscopically obtained middle meatus or antral puncture culture. However, there are very few randomized, placebo-controlled trials to guide treatment recommendations for CRS in children, and much of the medical management is based on the known efficacies of these therapies for adults with CRS.[78] When medical management has failed to provide improvement, pediatric patients with persistent symptoms of CRS should be referred to an otolaryngologist for possible

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surgical management.[79] Adenoidectomy alone or combined with sinus lavage is the most common initial intervention selected by otolaryngologists in the United States, with endoscopic surgery often reserved for children who fail these modalities.[80]

SINONASAL TRACT INVOLVEMENT IN SYSTEMIC DISEASES

In addition, systemic inflammatory disorders, rheumatic diseases, or vasculitis affect the nose and paranasal sinuses. These include sarcoidosis, IgG_4-related systemic disease, granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and other types of vasculitis.

Nose and/or sinus involvement is rare in sarcoidosis (1%–4% of cases) and typically presents with nonspecific symptoms. Histologic confirmation is needed to establish the diagnosis.[81,82] Likewise, IgG_4-related systemic disease rarely involves the sinuses but is not uncommon in certain contiguous structures, including the lacrimal ducts, orbits, Eustachian tubes, and nasopharynx.[83] The rare infiltrative disease involving the sinuses, lacrimal glands, and ducts previously known as “eosinophilic angiocentric fibrosis” was recently discovered to be a subtype of IgG_4-related systemic disease.[84]

GPA, formerly known as Wegener granulomatosis, is a systemic inflammatory disease that mainly involves the nasal cavity and the paranasal sinuses, lungs, and kidneys, but any other organ and site can be affected. In a retrospective study of 120 patients with GPA referred for otolaryngology consultation, the most common nasal symptom was nasal mucosal crusting (69.2%) and the most common finding was CRS (60.8%), followed by septal perforation (32.5%).[85] The use of immunosuppressive agents and rituximab leads to the improvement of nasal symptoms and can even lead to disease resolution. EGPA, formerly known as Churg-Strauss syndrome, is characterized by severe asthma, rhinitis, and CRS often accompanied by NP. In the UK study, 80% of patients with EGPA had active sinonasal symptoms at the time of the study, 40% of patients had undergone nasal polypectomy and 20% had undergone ESS.[86]

Although oral corticosteroids are the first line of treatment for EGPA, recently, an anti-IL-5 mAb, mepolizumab, showed a significant clinical benefit in the management of the disease.[87] Mepolizumab treatment led to more weeks of remission than placebo and a higher percentage of participants in remission at both weeks 36 and 48. Benralizumab, an anti-IL-5-Rα agent, has also received FDA approval for the indication of refractory EGPA.

FUTURE RESEARCH DIRECTIONS

There are currently more than 50 active clinical trials in the United States to test the efficacy of various therapeutic interventions to treat CRS, with or without NP. Many of these will improve our mechanistic understanding of currently available treatments, including topical corticosteroids and antibiotics, and existing biologics that are used for the treatment of asthma. Extensive laboratory and basic science work over the past decade has led to a deeper understanding of the role of type 2 inflammation in CRS. The results of these findings are clearly reflected in the upcoming clinical trials for patients with CRS or CRSwNP, including anti-IL-33 and anti-thymic stromal lymphopoietin biologics, small orally bioavailable anti-

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CRTH2 medications, and several drugs aimed at inhibiting eosinophil and mast cell activation. Furthermore, the mechanistic research into understanding the initiating immune triggers has continued, with ongoing work into the role of microRNAs and the microbiome, as well as more precision-focused research to better characterize patients into specific cytokine-classified endotypes of disease. Each of these approaches holds promise and ultimately should help better define the phenotypes and endotypes of CRS and result in more focused treatment.

CONCLUSIONS

Work over the past 15 years has sharpened the focus on the different clinical and endotypic subtypes of CRS. Progress in this area is likely to proceed much more rapidly going forward, given the growing array of technologies that can be used to more precisely define CRS subtypes. In addition, the ever-expanding list of targets for biologic agents, such as thymic stromal lymphopoietin, IL-33, and IL-25, will further focus and define CRS endotypes as has occurred with asthma.[88,89] Additional therapeutic research will likely result in better identification of patients who are “responders” or “nonresponders” to these agents.

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Abbreviations used

AERD	Aspirin-exacerbated respiratory disease
AFRS	Allergic fungal rhinosinusitis
CF	Cystic fibrosis
CRS	Chronic rhinosinusitis
CRSsNP	Chronic rhinosinusitis without nasal polyps
CRSwNP	Chronic rhinosinusitis with nasal polyps
EGPA	Eosinophilic granulomatosis with polyangiitis
ESS	Endoscopic sinus surgery
FDA	Food and Drug Administration
GPA	Granulomatosis with polyangiitis
NP	Nasal polyps
NSAID	Nonsteroidal anti-inflammatory drug

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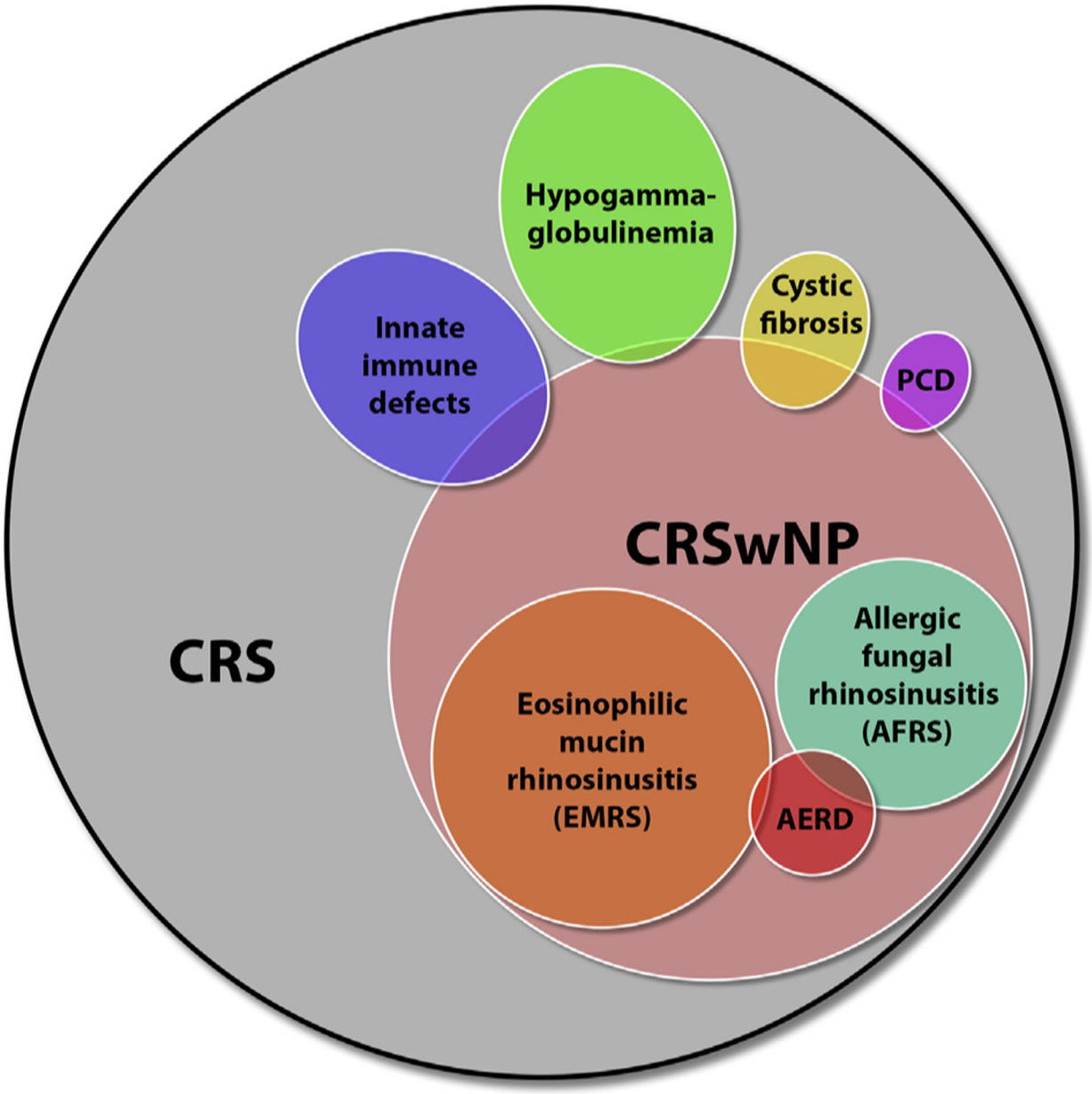

FIGURE 1.

Venn diagram depicting the major clinical subsets of CRS. CRS is currently classified as either with nasal polyps (CRSwNP) or without nasal polyps (CRSsNP). AFRS is a subset of CRSwNP.[1] Eosinophilic mucin rhinosinusitis (EMRS) is a subset of CRSwNP characterized by the presence of eosinophilic mucin without fungal hyphae.[2] EMRS is more common than AFRS.[3] Subsets of patients with CRS with an innate immune defect, hypogammaglobulinemia, CF, or PCD, are depicted as overlapping subsets of CRSsNP and CRSwNP, although the proportion of cases within CRSsNP and CRSwNP is variably reported and not intended to be precisely depicted in the Venn diagram. Certain phenotypes of CRS, including infectious, fungal, antrochoanal polyps and associated with systemic

disease, are not depicted in the diagram but are discussed in the text. *PCD*, Primary ciliary dyskinesia. Adapted from Hamilos.[4]

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