

Chronic Rhinosinusitis with Nasal Polyps



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List of Design Committee Members: Whitney W. Stevens, MD, PhD, Robert P. Schleimer, PhD, and Robert C. Kern, MD.

Learning objectives:

1. To describe the clinical characteristics of patients with chronic rhinosinusitis with nasal polyps (CRSwNP).
2. To identify clinical comorbidities commonly associated with CRSwNP.
3. To understand the underlying cellular and molecular mechanisms contributing to CRSwNP pathogenesis.
4. To review current medical and surgical treatment options for CRSwNP patients.

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Chronic rhinosinusitis with nasal polyps (CRSwNP) is an important clinical entity diagnosed by the presence of both subjective and objective evidence of chronic sinonasal

inflammation. Symptoms include anterior or posterior rhinorrhea, nasal congestion, hyposmia, and/or facial pressure or pain that last for a duration of more than 12 weeks. Nasal polyps are inflammatory lesions that project into the nasal airway, are typically bilateral, and originate from the ethmoid sinus. Males are more likely to be affected than females, but no specific genetic or environmental factors have been strongly linked to the development of this disorder to date. CRSwNP is frequently associated with asthma and allergic rhinitis, but the cellular and molecular mechanisms that contribute to the clinical symptoms are not fully understood. Defects in the sinonasal epithelial cell barrier, increased exposure to pathogenic and colonized bacteria, and dysregulation of the host immune system are all thought to play prominent roles in disease pathogenesis. Additional studies are needed to further explore the clinical and pathophysiological features of CRSwNP so that biomarkers can be identified and novel advances can be made to improve the treatment and management of this disease. © 2016 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2016;4:565-72)

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Abbreviations used

AERD- Aspirin-exacerbated respiratory disease
CRS- Chronic rhinosinusitis
CRSsNP- Chronic rhinosinusitis without nasal polyps
CRSwNP- Chronic rhinosinusitis with nasal polyps
CT- Computed tomography

Nasal polyps are inflammatory outgrowths of sinonasal tissue that are estimated to occur in 1% to 4% of the US general population.¹ Although nasal polyps are observed in various clinical conditions including cystic fibrosis and malignancy, they are more frequently associated with a subset of chronic rhinosinusitis (CRS) aptly named chronic rhinosinusitis with nasal polyps (CRSwNP). In this condition, nasal polyps are benign and typically develop bilaterally in the sinonasal cavity. Among all patients with CRS, only approximately 25% to 30% have CRSwNP. However, CRSwNP is associated with significant morbidity and decreased quality of life, making this disease clinically important to identify, evaluate, and treat.

DEMOGRAPHIC CHARACTERISTICS

CRSwNP is a disease of middle age, with the average age of onset being 42 years and the typical age of diagnosis ranging from 40 to 60 years.^{1,2} Most commonly, nasal polyps present as bilateral inflammatory lesions originating in the ethmoid sinuses and projecting into the nasal airway beneath the middle turbinate. In contrast, isolated nasal lesions that present medial to the middle turbinate are concerning for neoplasm. Presumptive nasal polyps found in patients younger than 20 years or older than 80 years also raise suspicion for other clinical conditions. In children, cystic fibrosis becomes a concern^{3,4} and unilateral nasal growths suggest a possible encephalocele. In adults, new-onset polyps at an advanced age or in atypical locations suggest the possibility of neoplasm.

Males are more likely than females to have CRSwNP.¹ However, a 2015 study by Stevens et al⁵ examining patients with CRSwNP undergoing sinus surgery at a tertiary care center found that females with CRSwNP had more severe disease than did males. In this study, CRSwNP was diagnosed in 38% and 62% of females and males, respectively. When compared with males, females had significantly enhanced radiographic evidence of sinus disease, were more likely to be taking systemic corticosteroids at the time of sinus surgery, and more often required revision sinus surgeries.⁵ Additional studies are needed to better understand the underlying pathophysiological and societal factors that could be contributing to these observations.

CLINICAL CHARACTERISTICS

By definition, patients with CRSwNP must report the presence of anterior or posterior rhinorrhea, nasal congestion, hyposmia, and/or facial pressure or pain lasting for a duration of more than 12 weeks.¹ However, these subjective findings are neither sensitive nor specific for CRSwNP alone and are used to also characterize patients who have chronic rhinosinusitis without nasal polyps (CRSsNP).¹ On average, patients with CRSwNP are thought to have more severe sinonasal symptoms compared with patients with CRSsNP.^{6,7}

To improve the ability to clinically distinguish CRSwNP from CRSsNP, several studies have compared symptom profiles of

affected patients as a means to identify possible clinical factors unique to each condition. In a cohort of 126 patients with CRS, Banerji et al⁸ found that nasal obstruction and hyposmia/anosmia were more significantly associated with CRSwNP while facial pain/pressure was more prevalent in patients with CRSsNP. Additional studies of patients with CRS at separate tertiary care centers found that patients with CRSwNP were more likely than patients with CRSsNP to report rhinorrhea, severe nasal congestion, and loss of smell/taste.^{9,10} However, in both studies, there was still a considerable overlap in symptoms reported by both patients with CRSsNP and patients with CRSwNP, thus emphasizing the need for additional criteria to diagnose CRSwNP.

In addition to subjective assessments of CRSwNP, there must be objective evidence of sinonasal inflammation and nasal polyps on sinus computed tomography (CT) scan and/or nasal endoscopy (Figure 1). Patients with CRSwNP on average have more extensive sinus disease than do patients with CRSsNP as measured by worse sinus CT and endoscopic scores.^{7,8,11} Even after sinus surgery, patients with CRSwNP can continue to have more severe objective measures of sinus disease than do patients with CRSsNP who also underwent surgery.^{6,12} It is thus not surprising that patients with CRSwNP on average are more likely to require revision sinus surgeries than do patients with CRSsNP.⁶

COMORBIDITIES

CRSwNP is often associated with other important medical conditions that can influence disease severity. In a large retrospective study evaluating more than 400,000 primary care patients, those diagnosed with CRSwNP had a significantly higher premorbid prevalence of acute rhinosinusitis, allergic rhinitis, chronic rhinitis, asthma, gastroesophageal reflux disease, and sleep apnea.¹³ How these conditions could contribute to the development of CRSwNP remains unclear.

The role of atopy in CRSwNP has been the focus of numerous studies. Although the percentage of patients with allergic rhinitis with nasal polyps is similar to that of the general population (0.5%-4.5%),¹ 51% to 86% of patients with CRSwNP are sensitized to at least 1 aeroallergen.^{11,14} No study to date has established a relationship between sensitization by a particular aeroallergen and the development of CRSwNP, but sinus disease can worsen during allergen season.¹⁵

Further complicating the understanding of CRSwNP are conflicting reports regarding the relationship between atopy and sinus disease severity. Some studies report that sinus CT and endoscopic scores are significantly worse in patients sensitized to inhalant allergens,^{11,16} whereas other studies found no difference in sinus severity in sensitized and nonatopic patients.^{14,15,17} In summary, future investigations are needed to better explore how atopy may contribute to CRSwNP.

The association between asthma and CRSwNP has been more extensively defined. A large majority of those with asthma (~88%) have at least some radiographic evidence of sinonasal inflammation.¹ More specifically, CRSwNP is estimated to occur in 7% of all those with asthma whereas asthma is reported to occur in 26% to 48% of patients with CRSwNP.^{1,18} Pearlman et al¹⁵ found the prevalence of nasal polyps to be significantly greater in those with asthma than in those without asthma within a tertiary care population. In addition, patients with CRSwNP were more likely than patients with CRSsNP to have asthma

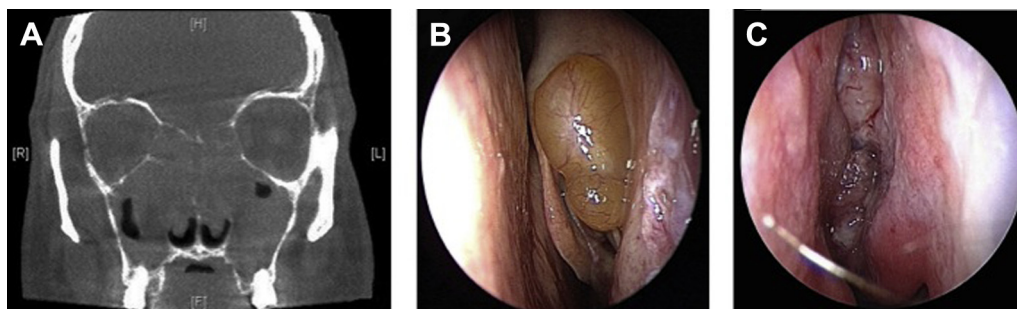


FIGURE 1. Imaging studies of nasal polyps. Sinus CT scan of a patient with CRSwNP (A). Benign nasal polyps (B) and malignancy (C) are directly visualized in the nasal cavity by endoscopy.

(odds ratio = 7.5).^{11,19} Increased asthma severity has also been shown to be associated with enhanced sinonasal inflammation.²⁰

There is a subset of patients with CRSwNP and asthma who also develop upper and/or lower respiratory tract symptoms following the ingestion of medications that inhibit the cyclooxygenase-1 enzyme. Such patients have aspirin-exacerbated respiratory disease (AERD). It is estimated that approximately 10% of patients with nasal polyps and 9% of patients with CRS have AERD,²¹ but the true prevalence of this disease remains unknown. Furthermore, patients with AERD on average have more severe sinus disease and undergo more sinus surgeries than do patients with CRSwNP alone.²² There have been several important studies characterizing the clinical profiles of patients with AERD as well as defining unique underlying mechanisms in disease pathology.^{23,24} As such, AERD will not be further discussed in this review.

PATHOPHYSIOLOGY

The underlying mechanisms that contribute to the chronic sinonasal inflammation observed in CRSwNP are not completely defined. Various research groups have focused on exploring the role sinonasal epithelial cells, the host immune system, and pathogens may play in CRSwNP pathogenesis (Figure 2). It is hypothesized that an impaired sinonasal epithelial barrier could lead to increased exposures to inhaled pathogens, antigens, and particulates that, in the setting of a dysregulated host immune response, could promote chronic inflammation.

In healthy conditions, the epithelial cells that line the sinonasal mucosa not only form a physical barrier to protect the host from inhaled respiratory pathogens and particulates but also play critical roles in mucociliary clearance and host defense. In CRSwNP, the sinonasal epithelial barrier is defective, leading to increased tissue permeability, decreased epithelial resistance, acanthosis, and acantholysis. Why the epithelial barrier is defective in CRSwNP remains unclear. It may be that epithelial cells are inherently abnormal in CRSwNP.²⁵ Alternatively, extrinsic factors unique to CRSwNP could impair an otherwise intact epithelial barrier and induce the breakdown observed in CRSwNP. To this end, Pot-hoven et al²⁶ noted that oncostatin M, an IL-6 family member, was elevated in CRSwNP nasal polyps and could induce tissue permeability, disrupt tight junctions, and decrease electrical resistance in cultured human epithelial cells.

Other aspects of epithelial host defense are also impaired in CRSwNP. For example, levels of epithelial-derived antimicrobial proteins including lysozyme, S100A7, S100A8/9, beta-defensins,

and Palate, Lung, and Nasal Epithelial Clone proteins were reduced in patients with CRSwNP compared with healthy controls.²⁷⁻³⁰ Pendrin, an epithelial ion transporter that can increase mucus production, and Muc5AC, a type of mucin, were elevated in CRSwNP versus controls.^{31,32} These findings suggest that impairment in mucociliary clearance, reduction in antimicrobial defense protein secretion, and breakdown in the physical barrier can lead to chronic exposure of pathogenic and nonpathogenic mediators and the development of a chronic inflammatory response.

The dysregulation of the host immune system has also been extensively evaluated in patients with CRSwNP. Originally, this disease was categorized by a type 2 inflammatory response with enhanced tissue eosinophilia. Levels of eosinophilic granule proteins (eg, eosinophil cationic protein), the eosinophilic survival factor (IL-5), and eosinophil chemotactic proteins (eg, eotaxin-1, eotaxin-2, eotaxin-3, and monocyte chemotactic protein 4 [MCP-4]) are all elevated in nasal polyps of patients with CRSwNP compared with healthy controls.³³⁻³⁸ Studies have also reported patients with CRSwNP to have increased numbers of basophils,³⁹ innate type 2 lymphoid cells,⁴⁰ and mast cells.⁴¹ In addition, levels of type 2 cytokines including IL-5 and IL-13³⁶ as well as the epithelial cell–derived thymic stromal lymphopoietin⁴² are elevated in patients with CRSwNP. Although the inflammatory environment in CRSwNP has been extensively characterized, the specific events and signals that initiate this response are not well defined.

Further complicating the study of CRSwNP pathogenesis is the observation that not all nasal polyps have the same histological appearance. The original studies of type 2 inflammation and nasal polyps were completed in patients with CRSwNP of European descent. However, an article published in 2008 indicated that nasal polyps of Asian patients living in Asia lack enhanced tissue eosinophilia, have lower levels of IL-5, and increased levels of the type 1 cytokine IFN- γ when compared with nasal polyps from European patients.⁴³ As a result, genetic factors may also be contributing to CRSwNP pathology as discussed below.

In addition to innate immune response, the host adaptive immune system is also dysregulated in patients with CRSwNP. Naive B cells and activated plasma cells are elevated in patients with nasal polyps compared with healthy controls.⁴⁴⁻⁴⁶ This is most likely in response to nasal polyps also having increased levels of CXCL-12 and CXCL-13 (factors important for B-cell chemotaxis) as well as B-cell Activating Factor (BAFF) and IL-6 (factors that induce B-cell proliferation and activation).⁴⁶⁻⁴⁸

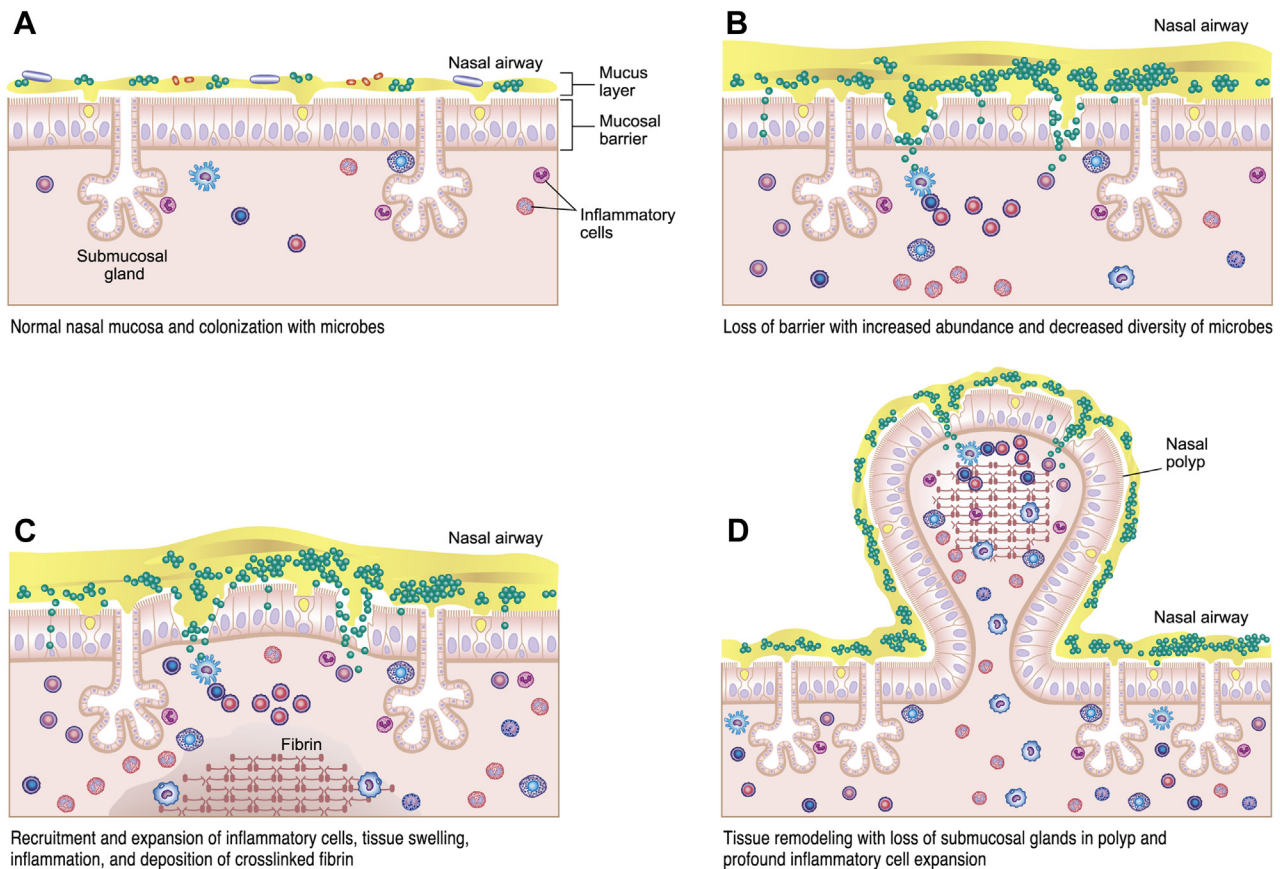


FIGURE 2. Overview of CRSwNP pathogenesis. Colonization with microbes and accumulation of immune cells can lead to tissue injury, inflammation, and mucosal barrier loss in CRS (A-D).

Levels of IgG₁, IgG₂, IgG₄, IgA, IgE, and IgM are increased in nasal polyps but not in the circulation of patients with CRSwNP, suggesting that local factors within the nasal polyps can activate B cells.⁴⁵ The exact specificity of the antibodies detected in CRSwNP remains unclear but is the focus of ongoing investigations. Studies have provided evidence that some of the antibodies detected in polyps of patients with CRSwNP are directed against nuclear antigens and cytokines.^{49,50} How such autoantibodies contribute to the clinical symptoms of CRSwNP remains unclear.

The adaptive immune system is also composed of T cells that are important not only for their direct cytotoxic functions but also for their ability to mediate an ongoing immune response. In nasal polyps from European patients, a significant fraction of CD4 T cells can produce type 2 cytokines compared with controls, whereas T cells isolated from nasal polyps from Asian patients are more likely to release type 1 and type 17 inflammatory mediators.^{38,43} Some studies suggest that regulatory T cells are impaired in patients with CRSwNP as determined by reduced levels of the transcription factor Foxp3 and increased levels of SOCS3, a known negative regulator of Foxp3 expression.^{36,51} This imbalance in regulatory T cells could lead to a subsequent lack of immune suppression that, in turn, could promote the chronic inflammation seen in patients with CRSwNP. However, more research is indicated in this area especially since a

study published in 2014 reports that regulatory T cells are increased in nasal polyps.⁵²

Finally, pathogens can directly and indirectly contribute to CRSwNP pathogenesis. Both *Pseudomonas aeruginosa* and *Staphylococcus aureus* disrupt the epithelial barrier in cultured human nasal epithelial cells.^{53,54} This impaired barrier could lead to heightened exposure to pathogens as well as increased bacterial colonization. To this end, it is estimated that as many as 63% of patients with CRSwNP are colonized with *S aureus* and a subset of these patients can develop specific IgE antibodies against *S aureus* enterotoxins.⁵⁵ Levels of specific IgE significantly correlate with levels of IL-5 and total number of eosinophils in nasal polyps, suggesting that these antibodies may be important in driving pathogenesis.⁵⁶

The sinonasal cavity has a mixture of pathogenic and commensal bacteria, and the properties of this microbiome have been explored in patients with CRS, but not specifically in patients with CRSwNP. To date, a reduced diversity of bacteria has been reported in patients with CRS compared with healthy controls but no specific organism has yet been linked to causing CRS.^{57,58} In addition, traditional pathogenic microbes including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* have been found in sinonasal cavities of patients without CRS, thus obscuring the role these organisms may play in disease.⁵⁹ Therefore, further investigations are necessary to

fully characterize and define the role of pathogenic and commensal bacteria in patients with CRSwNP.

GENETICS

Given the clinical heterogeneity of CRSwNP, the genetics of this disease are not well understood. A 2015 study indicates that first-degree relatives of a patient with CRSwNP have a 4.1-fold increased risk of developing nasal polyps.⁶⁰ However, no single polymorphism or genetic mutation has been consistently or reproducibly associated with CRSwNP to date with the exception of the cystic fibrosis transmembrane regulator mutation in cystic fibrosis.⁶¹ For example, flaggrin mutations have been associated with other atopic diseases with epithelial barrier dysfunction including atopic dermatitis and asthma. However, a recent study found no association between the presence of a common flaggrin null mutation and CRSwNP.⁶²

It is tempting to speculate that there is some currently unidentified genetic element responsible for the histologic differences observed between nasal polyps from Asian and Western patients. In support of this concept, a study found that second-generation Asian patients living in the United States still had reduced nasal polyp eosinophilia compared with white or black patients within the same surgical cohort.⁶³ However, prospective studies in Asia have suggested that the prevalence of eosinophils in nasal polyps is increasing especially in urban areas.^{64,65} Taken together, the development of CRSwNP may be dependent on both a genetic predisposition and exposure to specific albeit unclear environmental factors.

BIOMARKERS

There is no single validated biomarker that can reliably predict whether a patient has CRSwNP versus CRSsNP, acute sinusitis, or no sinus disease at all. Eosinophil markers such as eosinophil cationic protein, IL-5, or eotaxin may be useful in confirming CRSwNP but not all patients with CRSwNP will have elevated type 2 inflammatory markers and vice versa. There are no biomarkers to date that predict who will respond to medical versus surgical treatment. However, Lou et al⁶⁶ reported that having an absolute tissue eosinophil count of more than 55 eosinophils per hpf or having more than 27% eosinophils out of the entire cells counted in a sinonasal tissue specimen predicted the recurrence of nasal polyps within 2 years of sinus surgery.⁶⁶

When seeking a biomarker, it is important to consider the clinical specimen from which it will be measured. Peripheral blood, while easy to obtain, may not reflect the inflammatory changes observed locally in nasal polyps. A recent study examined whether there was a direct correlation between levels of inflammatory mediators measured in nasal lavage fluid versus nasal polyp tissue within the same individuals. Of the 20 mediators evaluated (including eosinophil cationic protein, IL-5, IL-13, and eotaxin), only IL-10 was found to have a significant and positive correlation between nasal lavage and polyp tissue.³⁷ This finding supports a previous observation that there is regional variability in inflammatory mediator expression within a single sinonasal cavity.⁶⁷ Therefore, the chronic inflammation in nasal polyps may not necessarily be reflected when sampling the entire nasal cavity by lavage.

DEFINITION OF CRS

According to the European position paper on rhinosinusitis and nasal polyps (EPOS) 2012 guidelines, CRS is defined as inflammation of the nose and paranasal sinuses characterized by the presence of 2 or more of the following symptoms for a duration of more than 12 weeks: (1) nasal blockage/obstruction/congestion, (2) nasal discharge, (3) facial pain/pressure, and (4) reduction or loss of smell.¹ Objective confirmation of the diagnosis is made by sinus CT scan or nasal endoscopy, which will also determine the phenotype: CRSsNP or CRSwNP. In adults, nasal polyps should be seen in both nasal passages and any unilateral polyps should be concerning for an alternative etiology such as malignancy.

Recommendation for information to be obtained to determine the phenotype

When evaluating patients for CRSwNP, it is important to evaluate for the presence of the 4 cardinal symptoms: rhinorrhea, nasal congestion, facial pressure/pain, and hyposmia. Although not definitive, hyposmia is more classically associated with CRSwNP whereas facial pain/pressure is more suggestive of CRSsNP.^{8,9} It remains difficult to distinguish eosinophilic and noneosinophilic nasal polyps by clinical symptoms alone. A recent study examining 57 patients with CRS who underwent surgery at a tertiary care facility found that ear pain, sneezing, severe difficulty breathing through the nose, severe nasal congestion, and bothersome loss of taste/smell were significantly more likely to be reported in patients with eosinophilic nasal polyps than in patients with noneosinophilic nasal polyps.¹⁰ The duration of sinus symptoms is also critical to ascertain, as symptoms lasting for more than 12 weeks are consistent with CRS whereas those lasting for less than 4 weeks are more concerning for an acute infectious process.

In addition to addressing sinonasal complaints, a detailed clinical history should be obtained to establish the presence of an underlying lower respiratory tract disease such as asthma. Past reactions to any cyclooxygenase-1 inhibitors should be documented so as to not miss the diagnosis of AERD. Finally, symptoms such as sneezing, itching, and ocular involvement are suggestive for underlying allergic rhinitis and should be evaluated given the association with CRSwNP.

Treatment

Medical treatment options for patients with CRSwNP remain limited. According to the most recent US guidelines, both topical corticosteroids and nasal saline irrigations are recommended as initial medical therapies for affected patients.⁶⁸ Intranasal corticosteroids can decrease nasal polyp size, lessen sinonasal symptoms, and improve patients' quality of life.^{69,70} Oral corticosteroids can also reduce polyp size and improve symptoms but should always be administered cautiously given their association with serious systemic side effects.⁷¹ Antibiotics may be useful in treating infectious exacerbations of CRSwNP, but clinically significant efficacy (ie, polyp shrinkage) in large, randomized trials is lacking.

Patients with significant sinonasal disease and/or those who fail medical management should be evaluated for sinus surgery. In a retrospective analysis, a delay of more than 5 years from initial CRS diagnosis to sinus surgery was associated with greater postoperative health care utilization compared with when surgery was performed within 12 months of diagnosis.⁷² Functional

endoscopic sinus surgery can improve sinonasal symptoms as well as objective evidence of sinonasal inflammation on sinus CT scan.^{22,73} However, nasal polyps can still reoccur despite sinus surgery,⁷⁴ with patients having both CRSwNP and asthma requiring, on average, significantly more sinus surgeries than do patients with CRSwNP alone.⁷⁵

In 2011, the US Food and Drug Administration approved the use of Propel implants, biodegradable stents that elute mometasone over a 30-day period.⁷⁶⁻⁷⁸ When inserted at the time of sinus surgery, these stents significantly reduced post-operative surgical interventions by 51%, oral corticosteroid use by 40%, and frank nasal polyposis by 46%⁷⁹ after 1 month. Given these findings, a longer-lasting variant of Propel is currently being evaluated in a Food and Drug Administration trial, with initial results suggesting that this stent can significantly improve polyp size and nasal symptoms 3 months following insertion.⁸⁰

There have also been several promising clinical trials evaluating the safety and efficacy of various biologics in CRSwNP. Notably, these drugs target factors associated with the type 2 inflammation observed in the polyp tissue. Omalizumab, a fully humanized anti-IgE mAb, significantly reduced nasal polyp size and improved symptoms when compared with placebo in patients with CRSwNP independent of atopic status.⁸¹ In patients with CRSwNP with severe nasal polyposis refractory to corticosteroid therapy, mepolizumab, a humanized anti-IL-5 antibody, also significantly reduced nasal polyps and improved sense of smell, postnasal drip, and nasal congestion (but not rhinorrhea) when compared with placebo-treated controls.⁸² Finally, dupilumab, a human mAb that binds to the IL-4 receptor alpha subunit and inhibits signaling of IL-4 and IL-13, significantly reduced nasal polyp burden and improved nasal symptoms when used in conjunction with intranasal steroids in patients with CRSwNP with refractory disease.⁸³ It should be noted that omalizumab, mepolizumab, and dupilumab are currently not approved for the treatment of nasal polyps. However, given the separate observations that omalizumab, mepolizumab, and dupilumab can also reduce asthma exacerbations,⁸⁴⁻⁸⁶ it is possible that these biological agents could have potentially even greater beneficial effects in patients with both asthma and CRSwNP.

Research questions and future directions

Over the past decade, there have been very important advances made in both the clinical and pathophysiological understanding of CRSwNP. However, many important questions still remain unanswered including the following:

- What is the true prevalence of CRSwNP within the general population or even among patients with CRS with or without asthma?
- What are the factors (environmental or genetic) that trigger the development of CRSwNP?
- What role does bacteria (pathogenic or commensurate) play in CRSwNP?
- What are the precise cellular and molecular events that lead to epithelial barrier dysfunction and immune dysregulation in CRSwNP?
- What are unique biomarkers in CRSwNP that could serve as targets for potential clinical and therapeutic interventions?

- What are the underlying mechanisms by which omalizumab, mepolizumab, and dupilumab exert their clinical effects?

CONCLUSIONS

CRSwNP is an important clinical entity diagnosed on the basis of the presence of subjective and objective evidence of chronic sinonasal inflammation. Nasal polyps occur bilaterally within the nasal cavity and are benign in patients with CRSwNP. Men are more likely to be affected than women, but no specific genetic or environmental factors have been linked to the development of the disorder to date. CRSwNP is frequently associated with asthma and allergic rhinitis, but the cellular and molecular mechanisms that contribute to the clinical symptoms are not fully understood. Defects in the sinonasal epithelial cell barrier, increased exposure to pathogenic and colonizing bacteria, and dysregulation of the host immune system are all thought to play prominent roles in disease pathogenesis. Additional studies are needed to further explore the clinical and pathophysiological features of CRSwNP so that biomarkers can be identified and novel advances can be made to improve the treatment and management of this disease.

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