The association between allergy and chronic rhinosinusitis with and without nasal polyps: an evidence-based review with recommendations

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Background: **The relationship between allergy and chronic rhinosinusitis (CRS) remains ill-defined and controversial. The association between the 2 is unclear, making an evidence-based decision of whether to evaluate and treat allergies in CRS patients difficult. The purposes of this systematic review are to (1) examine the relationship between allergy and CRS without nasal polyps (CRSsNP), (2) examine the same for allergy and CRS with nasal polyps (CRSwNP), and (3) recommend evaluation and treatment based on the evidence.**

Methods: **A structured literature search was performed to identify articles examining the link between allergy and CRSsNP and CRSwNP. Pertinent articles were examined for evidence for an association between allergy and CRSsNP and/or CRSwNP.**

Results: **A total of 24 articles were found that met the inclusion criteria; 18 articles examined the relationship between allergy and CRSwNP, with 10 articles showing an association, 7 articles showing no association, and 1 article showing a possible association. Nine articles examined the relationship between allergy and CRSsNP, with 4 articles showing an association and 5 articles showing no association. Four studies directly compared the role of allergy in CRSwNP and CRSsNP, and, again, the results were mixed. No articles examined the outcomes of CRSsNP or CRSwNP following allergy treatment.**

Conclusion: **The role of allergy in CRSwNP and CRSsNP continues to be controversial, with the level of evidence poor. Based on the available data, the recommendation is that allergy testing and treatment are an *option* in CRSwNP and CRSsNP.** © 2014 ARS-AAOA, LLC.

Key Words:
hypersensitivity; allergic; rhinitis; sinusitis; polyp; atopy

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The pathogenesis of chronic rhinosinusitis (CRS) is complex and multifactorial. It is characterized by inflammation of the nasal and sinus mucosa, and studies have suggested several etiologic factors that can provoke, intensify, or perpetuate this inflammation. Alteration or management of these factors could potentially assist in controlling the symptoms of CRS. Therefore, it is important to accurately identify which factors contribute to the development of CRS and to identify a subtype of CRS that may be affected by these factors.

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Allergy as a contributing factor to CRS has been extensively studied, but the relationship remains ill-defined. Some studies have suggested that allergy predisposes patients to CRS, but others have not found a relationship between allergy and CRS.

Part of the difficulty in defining the role that allergy plays in the pathogenesis of CRS is the inconsistency in the use of the terms allergy, atopy, and allergic rhinitis. Atopy is a state in which specific immunoglobulin E (IgE) antibodies to aeroallergens are present in a patient that can be detected by skin prick testing (SPT) or in vitro testing. Allergic rhinitis, on the other hand, is defined by the presence of symptoms in conjunction with atopy. The prevalence of atopy is around 50%,[1,2] whereas the prevalence of allergic rhinitis is usually quoted as 10% to 30%.[3,4] This systematic review uses the term "allergy" to encompass both "atopy" and "allergic rhinitis."

Classification of CRS has more recently been divided into 2 subtypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP).[5] This classification is

based on differences in histopathology, immune response, clinical course, and treatment responses.[6–8]

The purpose of this article is to systematically examine the evidence linking allergy and CRS, specifically CRSsNP and CRSwNP.

Materials and methods

Search strategy

This analysis sought to answer the following 2 questions: (1) Is allergy associated with CRSwNP? (2) Is allergy associated with CRSsNP? A structured search of the literature was performed using Medline (1972 to December 2012), Cochrane Central Register of Clinical Trials, ClincalTrials.gov, and Cochrane Database of Systemic Reviews. A literature search was performed using keywords: "rhinosinusitis," "sinusitis," "allergy," "allergic," and "polyp." The resulting abstracts were screened for English language and full-text availability. These abstracts were then reviewed for suitability by all 3 authors, including only those articles that associated allergy with either CRSwNP or CRSsNP. The references in the retrieved articles were then reviewed in a second pass using the same criteria to maximize the number of pertinent articles. Finally, this list was reviewed to exclude review articles and nonhuman studies. The study design, clinical outcomes, and conclusion of each study were noted.

Inclusion and exclusion criteria

Randomized trials, cohort analyses (with or without controls), reviews, and basic science articles were included in the initial pass to maximize gleaning of the references for additional articles. Articles that discussed an association of allergy with CRS in human subjects were retained for analysis. Other inclusion criteria were full-text availability, English language, and original papers. Papers were then excluded if there was no full-text availability, no original analysis (eg, reviews), or if they described animal or other basic science laboratory studies.

Results

There were 2248 abstracts initially identified, 1776 in English (Fig. 1). Of these, 1603 were subsequently excluded

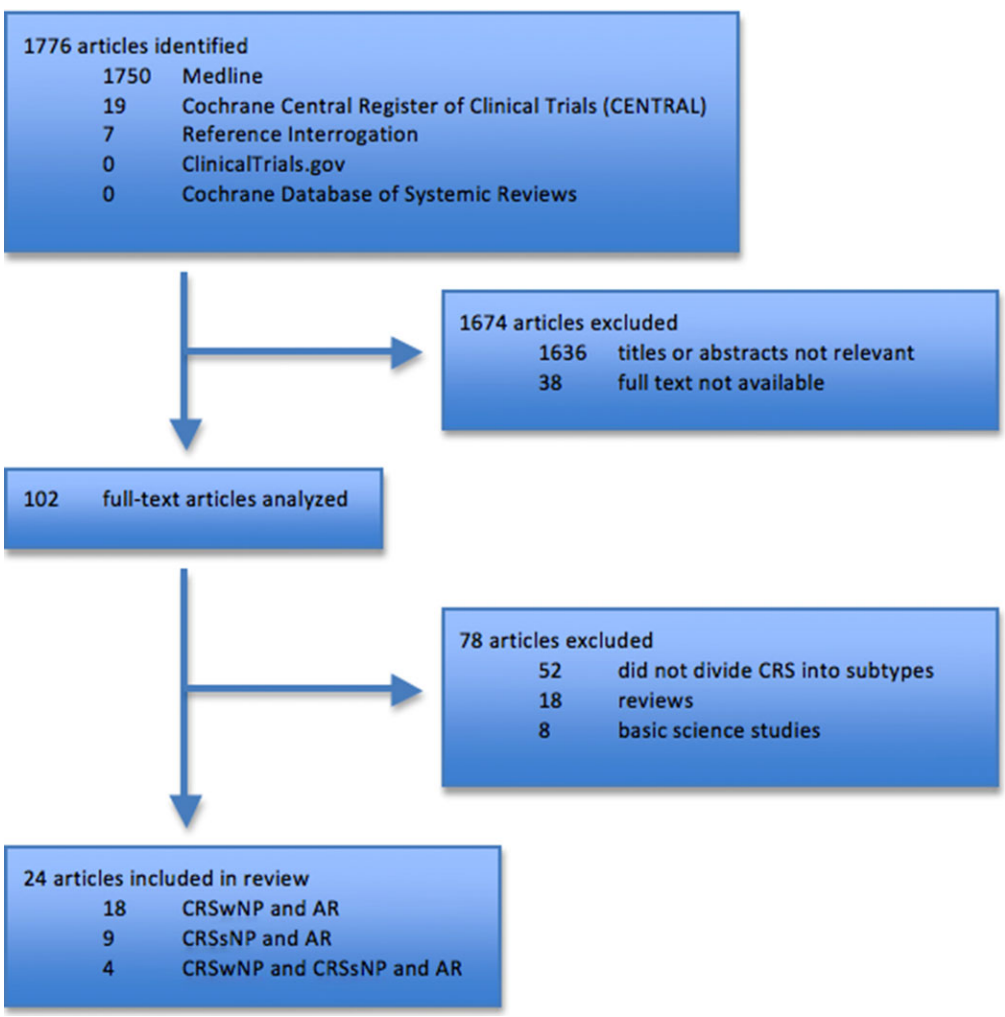

FIGURE 1. Search strategy and article analysis process.

because of irrelevant abstracts or inaccessibility of full text. The full texts of the remaining 102 references were analyzed, and 78 were excluded from further analysis (review articles, basic science studies, or articles that did not divide CRS into subtypes). The 24 remaining articles composed the basis of this review. The articles were divided into those that studied CRSwNP (18 articles), those that studied CRSsNP (9 articles), and those that examined and compared both types of CRS (4 articles).

Allergy and CRSwNP

Twenty articles analyzed the relationship between allergy and CRSwNP. These are summarized in Table 1. Ten articles demonstrated an association, 7 did not, and 1 showed a possible association.

Evidence for an association

Several studies suggest a relationship between allergic disease and nasal polyposis. Tan et al.[9] showed no statistically significant difference in rates of sensitivity on skin prick testing (SPT) between CRSwNP and CRSsNP. However, CRSwNP patients had a higher mean number of positive tests than either CRSsNP or rhinitis patients. This lends indirect evidence to the suggestion that overall immune load contributes to nasal polyp formation.

There is some suggestion that length of exposure to allergens may affect disease progression. Among patients with CRSwNP, Houser and Keen[10] demonstrated that there was an association with hypersensitivity to perennial allergens, though not seasonal allergens by SPT. Muniz del Muñoz del Castillo et al.[11] reported increased rates of positive SPT among CRSwNP patients compared to controls. The most common allergens identified were *Dermatophagoides pteronyssinus* (27.7%), *Dermatophagoides farina* (21.3%), and *Olea europaea* (21.1%). Pumhirun et al.[12] compared CRSwNP patients and controls by SPT, finding higher rates of positive tests among the CRSwNP group ($p < 0.05$). In 2 different studies, Asero and Bottazzi[13,14] found a higher rate of *Candida* and house dust mite sensitivity among CRSwNP patients than among controls. However, the majority of those subjects testing positive did not have correlating nasal symptoms, underscoring the importance of symptoms in addition to sensitivity in the diagnosis of allergy. Taken together, these findings support the suggestion that perennial allergens may play a significant role in nasal polyp formation distinct from that of seasonal allergens.

Another group of studies suggests that allergy to foods contributes to nasal polyp formation. Collins et al.[15] found no significant difference in the sensitivity rates to inhalant allergens between the 2 groups; however, there was a significant difference in the rates of food sensitivity. Pang et al.[16] performed intradermal testing for potential food antigens, finding higher prevalence among CRSwNP patients than controls. However, the technique used may lend itself to false positives, which makes interpretation of this result more challenging. Lill et al.[17] found no significant difference between CRSwNP patients and controls with respect to overall rates of food allergy or rates of wheat sensitivity; however, there was a significantly higher rate of milk sensitivity among CRSwNP patients. Although it is well understood that not all food reactions involve the IgE-mediated pathway, these studies raise the possibility of an association between food allergy and nasal polyp formation.

Finally, there is some suggestion that IgE-mediated response to bacteria and bacterial products may drive some nasal polyp formation. Van Zele et al.[18] studied rates of *Staphylococcus aureus* colonization in the nasal cavities and IgE formation against various *S. aureus*–produced toxins. They found a significantly higher rate of *S. aureus* colonization among CRSwNP patients than among other groups. They also found that specific IgE against *S. aureus* paralleled colonization rates. These data raise the question of whether allergic-type reaction to pathogens, rather than pathogenic infection itself may be responsible for some cases of CRSwNP.

Evidence against an association

There are several studies that would contravene the suggestion of a direct relationship between allergy and nasal polyposis. Erbek et al.[19] found no significant relationship between the presence of allergy and nasal polyp size, symptom scores, or rate of recurrence. Gorgulu et al.[20] reviewed data from CRSwNP patients treated with endoscopic sinus surgery, with smokers and nonsmokers as controls. They did not find a significant difference in the rate of sensitivity to environmental allergens by blood testing. The only risk factor for nasal polyp formation identified in this study was smoking. Bonfils et al.'s group[21,22] has published several investigations into the effect of allergy on CRSwNP. They found no differences in any outcome measure between allergic and nonallergic patients. There was an increased incidence of asthma among the allergy-positive group. In a particularly descriptive study, Keith et al.[23] evaluated 4 groups of patients: patients with both nasal polyps and ragweed allergy, patients with nasal polyps but without ragweed allergy, patients with ragweed allergy but without nasal polyps, and patients with neither nasal polyps nor ragweed allergy. Patients with nasal polyps had high symptom scores and levels of inflammatory mediators throughout the year regardless of allergic status. The ragweed-allergic patients without nasal polyps were the only subgroup that experienced increased symptoms and increased production of inflammatory mediators during the allergy season. Taken together, these papers suggest that other sources of inflammation than allergy may play a role in nasal polyp formation.

Another group of studies explore a possible relationship of nasal polyps with asthma, rather than allergy. Pearlman found that rates of allergy were virtually identical between CRSwNP and CRSsNP groups. However, asthma was significantly more common among CRSwNP patients (57.6%) as compared to patients without allergies (25%).[24] Further

TABLE 1. Studies examining an association between allergy and CRSwNP

Reference	Study design	Population characteristics	Method of diagnosing CRS	Type of allergy	Allergy testing method	Findings	Association
Tan et al.[9]	Prospective case control	n = 62; 29M:34F; mean age 38.2 years	History, endoscopy, CT scan	Seasonal or perennial	SPT	No difference in rates of sensitivity. CRSwNP had higher mean number of antigen sensitivities. Significantly higher rates of asthma were identified in CRSwNP patients than with controls.	Possible
Houser and Keen[10]	Retrospective case series	n = 373; 242F:131M; mean age 39.6 (SD 13.7) years	Met 2003 task force criteria	Seasonal or perennial	In vitro/IDT	Association between PAR and CRS. PAR and tobacco use associated with NP formation.	Yes
Muñoz del Castillo et al.[11]	Prospective case control	n = 190; 69F:121M; mean age 48.2 (SD 15.1) years	EP3OS classification by endoscopy	Seasonal or perennial	SPT	CRSwNP had higher rates of allergy and asthma than controls. *D. pteronyssinus*, *D. farina*, and *Olea europaea* were the most common positives. Significantly higher rates of asthma were identified in CRSwNP patients than with controls.	Yes
Pumhirun et al.[12]	Prospective case control	n = 40; 12F:28M: mean age 34 (range, 15–53) years	Not specified	Perennial	SPT	Increased rates of positive house dust and cockroach tests in CRSwNP compared to controls.	Yes
Asero and Bottazzi[13]	Prospective case control	n = 20; 8F:12M; mean age 50.5 (range, 28–77) years	Not specified	Seasonal or perennial	SPT	Higher rates of *Candida* sensitivity among CRSwNP patients compared to allergic controls.	Yes
Asero and Bottazzi[14]	Prospective case control	n = 68; 30F:38M; mean age 51 (range, 15–78) years	Not specified	Seasonal or perennial	SPT	Higher prevalence of *Candida* and house dust sensitivity among CRSwNP patients compared to nonpolyp controls.	Yes

(Continued)

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TABLE 1. Continued

Reference	Study design	Population characteristics	Method of diagnosing CRS	Type of allergy	Allergy testing method	Findings	Association
Collins et al.[15]	Prospective case control	n = 40; 19F:21M; mean age 51 years (no range given)	History, endoscopy, CT scan	Food	IDT	Higher rate of food sensitivity among CRSwNP patients compared to controls. The top 3 sensitivities among CRSwNP patients were wheat, tomato, and potato. No difference in rates of inhalant sensitivity.	Yes
Pang et al.[16]	Prospective case control	n = 80; 32F:48M; mean age 49 (SD 11) years	Not specified	Food	IDT	CRSwNP patients had a higher number of food sensitivities than controls.	Yes
Lill et al.[17]	Prospective case control	n = 50; 20F:30M; mean age 44 (range, 20–87) years	History, endoscopy, CT scan	Food	In vitro	No difference in overall rate of food sensitivity or rate of wheat sensitivity; however, CRSwNP patients had a higher prevalence of milk sensitivity.	Yes
Van Zele et al.[18]	Prospective case control	n = 55; 19F:36M; mean age 48 years (no range given)	Not specified	*S. aureus* enterotoxin	Tissue homogenates and serum by in vitro	Higher rates of *S. aureus* colonization and formation of IgE to *S. aureus* in CRSwNP patients compared to CRS without NP or controls.	Yes
Erbek et al.[19]	Retrospective case series	n = 83; demographic data not given	History, endoscopy, CT scan	Seasonal and perennial	SPT	No significant relationship was found between presence of allergy and NP size, symptom scores, or rate of recurrence.	No
Gorgulu et al.[20]	Prospective case control	n = 60; 18F:42M; mean age 40.1 (SD 9.8) years	Not specified	Seasonal, perennial, and food	In vitro	No difference in rate of sensitivity to allergens between CRSwNP and controls. Smoking was the only risk factor identified for NP formation.	No
Bonfils et al.[21]	Prospective case series	n = 180; 72F:108M; mean age 48.4 (SD 13) years	Endoscopy and CT scan	Not specified	In vitro	No difference in any outcome measure between CRSwNP patients based on allergic status. Increased incidence of asthma in allergic group.	No

(Continued)

TABLE 1. Continued

Reference	Study design	Population characteristics	Method of diagnosing CRS	Type of allergy	Allergy testing method	Findings	Association
Bonfils and Malinvaud[22]	Prospective case series	n = 63; 27F:36M; mean age 45.8 (SE 1.5) years	Endoscopy and CT scan	Not specified	In vitro	No difference in postoperative course of CRSwNP patients with and without allergy.	No
Keith et al.[23]	Prospective case control	n = 64; 24F:40M; mean age 42 (range, 21–68) years	History and physical exam	Ragweed	SPT	Whether allergic or nonallergic, patients with NPs had high symptom scores and levels of inflammatory mediators throughout the year. Ragweed allergic patients without NPs were the only subgroup that experienced increased symptoms and increased production of inflammatory mediators.	No
Pearlman et al.[24]	Prospective case series	n = 40; demographic data not given	AAO-HNS task force criteria, CT scan, endoscopy	Seasonal and perennial	SPT	Prevalence of CRSwNP was similar between atopic and nonatopic patients. Asthmatic patients were more likely to have CRSwNP.	No
Voegels et al.[25]	Prospective case control	n = 39; 17F:22M; mean age 42.6 (SD 16.9) years	Not specified	Not specified	SPT	Significantly higher rates of asthma in the allergic than the nonallergic patients with CRSwNP.	No
Kirtsreesakul[26]	Prospective cohort study	n = 68; 31F:37M; age not given	History, endoscopy	Seasonal and perennial	SPT	Greater improvements were seen with budesonide nasal spray in CRSwNP patients in sneezing, oral and nasal peak flow, and overall response to therapy among nonallergic subjects than allergic subjects.	Yes

AAO-HNS = American Academy of Otolaryngology–Head and Neck Surgery; CRS = chronic rhinosinusitis; CRSwNP = CRS with NPs; CT = computed tomography; EP3OS = 2007 European Position Paper on Rhinosinusitis and Nasal Polyps; IDT = intradermal dilutional testing; IgE = immunoglobulin E; NP = nasal polyp; PAR = perennial allergic rhinitis; SD = standard deviation; SE = standard error; SPT = skin prick test.

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support for association between CRSwNP and asthma is provided in several additional studies.[9,11,25] In these studies, significantly higher rates of asthma were identified in CRSwNP patients than with controls. Taken together, these data suggest relationships may exist between CRSwNP and asthma as well as asthma and allergic rhinitis, although they do not support a direct relationship between CRSwNP and allergy.

Additional relevant studies

A subset of studies does not directly address the question of association between CRSwNP and allergy; rather, they evaluate the effect of allergy in the evolution of nasal polyp disease. As mentioned above in Evidence Against an Association, Erbek et al.'s[19] group failed to establish concordance between allergic status and polyp size, symptom score, or rate of recurrence. Kirtsreesakul[26] studied nasal polyp patients for response to budesonide therapy. Greater improvements were seen in sneezing, oral and nasal peak flow, and overall response to therapy among SPT-negative subjects than SPT-positive subjects. Although these studies do not give insight into the mechanisms behind therapeutic differences in allergic and nonallergic polyp patients, they suggest that different mechanisms of inflammation are at work.

Allergic rhinitis and CRSsNP

Nine articles were found that analyzed the association of allergy with CRSsNP. On review of the articles, 4 showed evidence of an association whereas 5 did not find an association. These are summarized in Table 2.

Evidence for an association

Two groups examined the effects of allergy on radiologic findings and endoscopy. Berrettini et al.[27] attempted to correlate perennial allergic rhinitis with CRSsNP. They compared 40 patients with perennial allergic rhinitis to 30 control subjects using computed tomography (CT) scans, nasal endoscopy, nasal swab, and rhinomanometry. They found CT evidence of sinusitis in 68% of the allergic patients and 33% of the controls ($p = 0.02$), although the correlation of CT findings to endoscopy, nasal swab, and rhinomanometry were not significant. They concluded that there is an association between perennial allergic rhinitis and chronic sinusitis, but that the mechanism is unclear. Similarly, Kirtsreesakul and Ruttanaphol[28] divided 198 CRSsNP patients into allergic (52%) and nonallergic (48%) groups, based on skin prick reactivity. The 2 groups then underwent nasal endoscopy (looking for discharge from the middle and/or superior meatus) and sinus radiography (plain films). They found that allergic patients were more likely to have abnormal sinus X-rays ($p < 0.001$), but there was no difference in the endoscopy results ($p = 0.55$). Among patients with abnormal radiographs, the allergic patients were less likely to have a positive nasal endoscopy compared to the nonallergic patients ($p = 0.006$). They concluded that allergic patients were more likely to have sinus inflammation and recommended that patients with suspected rhinosinusitis should be evaluated for allergy.

Baroody et al.[29] took a more basic approach. This group evaluated the relationship between allergy and maxillary sinus inflammation. Eighteen subjects with ragweed allergy were examined in and out of ragweed season. Subjects became symptomatic during the season, reported worse quality of life, and had increased nasal reactivity to methacholine. There were significantly more eosinophils on maxillary sinus lavage during the ragweed season (median = 4248) compared with the out-of-season samples (median = 370, $p \leq 0.02$). They concluded that exposure to pollen in allergic subjects leads to sinus inflammation.

Alho et al.[30] also studied sinus inflammation, specifically whether sinus functioning during viral colds is affected by allergic rhinitis. This group examined 48 volunteers during the first few days of a cold and again 3 weeks later, evaluating them with CT scans, mucosal biopsies, and microbiological specimens. Subjects were then divided into allergic (9 patients, 19%) and nonallergic (39 patients, 81%) groups based on SPTs and history of intermittent or persistent rhinitis. The allergic subjects were more often sensitized to *S. aureus* enterotoxin than nonallergic subjects (33% vs 3%, $p = 0.02$). The allergic subjects had higher CT scores (16 vs 6, $p = 0.004$). This study concluded that allergic subjects had more severe paranasal sinus changes and were at more risk of impaired sinus functioning leading to sinusitis.

Evidence against an association

In contrast to the findings in the previous section, several groups found no correlation between CRSsNP and allergic rhinitis. Robinson et al.[31] examined the relationship between atopy and CRS in 193 CRS patients. Atopic status was determined by in vitro testing to dust mites, mixed molds, grass pollens, and cat and dog dander. They found that atopy was equally prevalent in patients with CRSwNP (27.5%) and CRSsNP (32.3%). Atopic status was not associated with Lund symptom scores. Neither were the CT scores different in atopic vs nonatopic patients. They concluded that the clinical features of CRS are not influenced by atopy. Gelincik et al.[32] studied 115 patients with persistent rhinitis to determine whether allergic or nonallergic rhinitis is more predisposing to CRS. The allergic status was evaluated using SPT, and sinusitis was diagnosed with symptoms, nasal endoscopy, and CT scan. They found that CRS was equally prevalent in patients with allergic (43%) as well as nonallergic (50%) rhinitis. Additionally, nasal polyps were equally present between the 2 groups.

Pearlman et al.[24] examined the effect of asthma and atopy on the severity of CRS and the presence of polyps. One hundred and six patients underwent allergy SPT, of which 52 (49%) were atopic and 54 (51%) were nonatopic. Subset analysis of the 66 CRSsNP patients (62%) showed the expected finding that atopy was more prevalent in those who

TABLE 2. Studies examining an association between allergy and CRSsNP

Reference	Study design	Population characteristics	Method of diagnosing CRS	Type of allergy	Allergy testing method	Findings	Association
Berrettini et al.[27]	Prospective case control	n = 70; demographic data not given	History, endoscopy, CT scan	Perennial	SPT	Increased CT evidence of sinusitis in allergic (68%) compared to nonallergic (33%) patients. No difference in endoscopy, nasal swab, or rhinomanometry.	Yes
Kirtsreesakul and Ruttanaphol[28]	Retrospective case series	n = 198; 128F:70M; mean age 35 (range, 16–64) years	History, endoscopy, CT scan	Seasonal and perennial	SPT	Allergic patients more likely to have abnormal sinus X-rays, but no difference in endoscopy.	Yes
Baroody et al.[29]	Randomized control trial	n = 18; demographic data not given	Not applicable	Seasonal and perennial	SPT	Subjects with ragweed allergy have more symptoms, greater reactivity, and more sinus inflammation during ragweed season.	Yes
Alho et al.[30]	Prospective case series	n = 48; adults (age and gender not otherwise specified)	Not applicable	Seasonal and perennial	SPT	During a viral cold, allergic subjects had higher CT scores and were more often sensitized to *S. aureus* enterotoxin. Allergic subjects have more severe sinus changes during a cold.	Yes
Robinson et al.[31]	Prospective case series	n = 193; 68F:125M; mean age 47.5 years	History, endoscopy, CT scan	Seasonal and perennial	In vitro	Atopic status was not associated with Lund symptom or CT scores.	No
Gelincik et al.[32]	Prospective case series	n = 115; 78F:37M; mean age 31.9 (range, 14–64) years	History, endoscopy, CT scan	Seasonal and perennial	SPT	CRS was equally prevalent in patients in allergic (43%) and nonallergic (50%) rhinitis.	No
Pearlman et al.[24]	Prospective case series	n = 66; demographic data not given	AAO-HNS task force criteria, CT scan, endoscopy	Seasonal and perennial	SPT	Atopy more prevalent in asthmatic subjects. No difference in CT scores between the atopic and nonatopic patients.	No
Tan et al.[9]	Prospective case control	n = 63; 34F:29M; mean age 38.2 years	History, endoscopy, CT scan	Seasonal and perennial	SPT	Nonsignificant trend toward increasing atopy rates going from rhinitis (72%) to CRSsNP (79%) to CRSwNP (86%). Concluded that atopy does not predispose patients toward CRS or any specific subtype.	No
Van Zele et al.[18]	Prospective case control	n = 31; 16F:15M; mean age 45.9	Not specified	*S. aureus* enterotoxin	In vitro	*S. aureus* colonization rates similar in CRSsNP patients and controls. IgE antibody prevalence mirrored colonization rates. Local allergic response to bacteria does not play a role in CRSsNP.	No

AAO-HNS = American Academy of Otolaryngology–Head and Neck Surgery; CRS = chronic rhinosinusitis; CRSsNP = CRS without NPs; CRSwNP = CRS with NPs; CT = computed tomography; IgE = immunoglobulin E; NP = nasal polyp; SPT = skin prick test.

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had asthma ($p = 0.001$). However, there was no difference in Lund-Mackay scores between the atopic and nonatopic CRSsNP groups. They concluded that the association between systemic atopic status and CRS severity is weak and that CRS is an inflammatory disease that occurs independently of systemic IgE-mediated pathways.

Tan et al.[9] analyzed patients failing medical therapy for CRSwNP and CRSsNP for allergen sensitivity and compared them to rhinitis patients without CRS and the general population. Of 125 CRS patients who had failed maximal medical therapy and had completed a sinus and allergy workup, 63 had CRSsNP based on endoscopic and CT findings. There was a trend toward increasing atopy rates going from rhinitis (72%) to CRSsNP (79%) to CRSwNP (86%), but the overall atopy rates were not significantly different. They concluded that atopy does not predispose patients toward CRS or any specific subtype.

Van Zele et al.[18] looked at the local IgE and eosinophilic immune response to *S. aureus* colonization by examining middle meatus tissue homogenates. Although they found increased *S. aureus* colonization of nasal polyps (64%), this phenomenon was not found in CRSsNP (27%) or controls (33%). The prevalence of IgE antibodies to *S aureus* enterotoxins in the tissue paralleled colonization rates, suggesting that the local immune response to the bacteria may play a role in the formation of polyps but not in CRSsNP.

Direct comparison of CRSsNP and CRSwNP

Four studies examined the role of allergy in both CRSwNP and CRSsNP and directly compared the 2 groups. These studies are summarized in Table 3.

Three studies[9,24,31] directly compared allergy status in both CRSsNP and CRSwNP subjects. All 3 found no difference in the prevalence of allergy in these 2 patient subpopulations using SPT to common allergens.

One study[18] examined local IgE specific to *S. aureus* and found significantly higher levels in CRSwNP subjects compared to CRSsNP subjects. These findings mirrored colonization differences between the 2 subgroups as well, although colonization was more prevalent than IgE presence, suggesting a 2-stage process of colonization followed by another event generating local allergy.

Discussion

To our knowledge, this is the first evidence-based review to evaluate the association of allergy with the subtypes of CRS (CRSwNP and CRSsNP). The number of articles in this systemic review testifies to the interest in the role of allergy in CRSwNP and CRSsNP. The review also shows that conflicting data exist regarding this role. A nearly equal number of studies support and refute the role of allergy in CRSwNP and in CRSsNP. Moreover, there appears to be little data supporting the concept that allergy plays a differing role in whether polyps are manifested as a part of CRS. As a result, it is not clear whether allergy and CRS (with or without nasal polyps) are associated, much less whether allergy causes either form of CRS.

Because of varied study designs, subject groups, and controls, direct comparison among studies cannot be done in a meaningful way, and a meta-analysis is not feasible. Given that many studies were retrospective case series, the risk of bias exists. Additional complexity is introduced by changing rates of allergic disease across time, which makes even comparison of incidence of allergy identified in different periods of time difficult.

As with so many other aspects of CRS, the question of allergy's role may be more subtle than whether it is an etiology or not. Some evidence exists that indicates allergy may have a disease-modifying role in CRS. Tan et al.[9] studied CRSwNP patients who had failed medical therapy compared to CRSsNP medical treatment failures, and allergic rhinitis patients without CRS. Patients with CRSwNP were equal to CRSsNP and allergic rhinitis patients without CRS in the binary presence or absence of allergy. But on closer inspection, CRSwNP patients did show a higher median number of allergens present. They postulated that allergies do not have an etiologic role, but rather that an impaired epithelial barrier may allow increased exposure to, and thus reaction to, antigens. In this theory, allergy is a modifier of disease as part of its pathophysiology, but allergy is not a root cause of the disease. It bears noting that the patients in this study had failed medical therapy and therefore may represent the most severe or "end-stage" CRS patients, not all CRS patients.

These conflicting and unclear data beg the question of whether allergy should be assessed in CRSwNP and CRSsNP patients and, if found, should be treated as part of their CRS management? Assessing and addressing allergy status has theoretical support in that allergy is a potential trigger for nasal and sinus inflammation. CRS appears to have many possible pathophysiologic routes involving inflammation. Nevertheless, CRS is a highly prevalent condition with significant treatment expense. Allergy testing and management are moderately costly and therefore necessitate evidence to support their use. Unfortunately, there is no evidence that addresses the efficacy of allergy management in CRSwNP or CRSsNP, leaving us to extrapolate from the conflicting data reviewed.

Summary

1. Aggregate quality of evidence: D (Expert opinion and reasoning from first principles and conflicting prevalence data).
2. Benefit: Allergy evaluation and management are generally well tolerated. Management theoretically reduces triggers and modifies symptoms of chronic rhinosinusitis.
3. Harm: Mild local irritation associated with testing and immunotherapy, mild sedation seen with

TABLE 3. Studies examining an association between allergy and CRS with direct comparison between CRSwNP and CRSsNP

Reference	Study design	Population characteristics	Method of diagnosing CRS	Type of allergy	Allergy testing method	Findings
Gelincik et al.[32]	Prospective case series	n = 115; 78F:37M; mean age 31.9 (range, 14–64) years	History, endoscopy, CT scan	Seasonal or perennial	SPT	Polyps found in equal prevalence in allergic and nonallergic subjects. Asthma and CRS found in equal prevalence in allergic and nonallergic subjects.
Pearlman et al.[24]	Prospective case series	n = 106; demographic data not given	AAO-HNS task force criteria, CT scan, endoscopy	Seasonal or perennial	SPT	Presence of allergy was not associated with nasal polyps (38% of allergic, 37% of nonallergic). Allergy was associated with asthma in the CRSwNP subset, but not overall.
Tan et al.[9]	Prospective case control	n = 125; 58F:67M; mean age 41.1 years	History, endoscopy, CT scan	Seasonal or perennial	SPT	Presence of allergy was equal in CRSwNP (85.5%) and CRSsNP subjects (79.4%), as well as in rhinitis subjects without sinusitis (72.0%). CRSwNP subjects had a higher number of median allergens on testing than CRSsNP and rhinitis subjects.
VanZele et al.[18]	Prospective case control	n = 77; 30F:47M; mean age 48 years	Not specified	*S. aureus* enterotoxin	In vitro	Colonization with and local IgE to *S. aureus* were higher in CRSwNP than CRSsNP subjects (colonization: 63.6% vs 27.3%; local IgE paralleled these rates but was lower [specific percentages not given])

AAO-HNS = American Academy of Otolaryngology–Head and Neck Surgery; CRS = chronic rhinosinusitis; CRSsNP = CRS without NPs; CRSwNP = CRS with NPs; CT = computed tomography; IgE = immunoglobulin E; NP = nasal polyp; SPT = skin prick test.

some antihistamine drugs; severe complications are rare.
4. Cost: Moderate direct costs for testing and treatment; some therapies require significant patient time (eg, office-administered subcutaneous immunotherapy).
5. Benefits-Harm assessment: Preponderance of benefit over harm.
6. Value Judgments: None.
7. Policy level: Allergy testing and treatment are an option in CRSwNP and CRSsNP.
8. Intervention: Allergy testing (skin or in vitro) and allergy management (avoidance, pharmacotherapy, and/or immunotherapy).

Conclusion

In summary, the data supporting an association between allergy (ie, allergic rhinitis and atopy) and CRS (both CRSwNP and CRSsNP) are mixed. No data exists that examines the role of allergy therapy in improving the symptoms and quality of life of CRS patients. This review makes obvious the need for more studies to better understand the role of allergy in the pathophysiology and presentation of CRSwNP and CRSsNP. Those who care for these patients need to better understand which patients should be tested and treated, and whether the cost-benefit relationship supports allergy treatment.

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