



Practical clinical management strategies for the allergic patient with chronic rhinosinusitis

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Purpose of review

Allergic rhinitis often coexists with chronic rhinosinusitis (CRS). The purpose of this review is to provide a practical algorithm for the treatment of patients with allergic rhinitis and CRS.

Recent findings

Despite conflicting literature on the causative association of allergic rhinitis with CRS, recent research shows a higher incidence of allergic rhinitis in CRS patients refractory to medical therapy. Local IgE is hypothesized to play a role in the inflammation characteristic of both disorders, even in patients who test negative for inhalant allergies.

Summary

As allergic rhinitis and CRS symptoms overlap, medications appropriate for one disorder may also be appropriate for the other. The exception would be allergen immunotherapy in the absence of allergy and antibiotics in the absence of infection. Given these principles, we have developed and provide a personalized management strategy for patients with symptoms of allergic rhinitis and CRS based on the individual's response to therapy.

Keywords

allergic rhinitis, asthma, atopy, chronic rhinosinusitis, immunotherapy

INTRODUCTION

Both allergic rhinitis and chronic rhinosinusitis (CRS) are characterized by inflammation. The symptoms of allergic rhinitis and CRS overlap and mimic each other, blurring the diagnostic and therapeutic considerations between the two disorders. Immunotherapy provides effective symptom control and reduction in medication use in allergic rhinitis with the potential to cure patients of the disease [1[•],2[•]]. For most patients with CRS, the underlying cause of inflammation remains elusive and requires chronic anti-inflammatory therapy. Moreover, many patients with CRS exhibit dysfunction in innate and adaptive immune pathways [3–5]. Therapy targeted to such dysfunction, with the exception of IgG deficiencies, does not yet exist for CRS. CRS is broadly classified by the presence or absence of polyps (CRS with nasal polyps and CRS without nasal polyps), but the disorder is heterogeneous and presents with a spectrum of phenotypes. By and large, CRS is an inflammatory condition not driven by bacterial infection [6[•]]. Many of the therapeutic options for allergic rhinitis are directed at controlling inflammation, and as a result can be effective in CRS patients. A trial of

medications appropriate in allergic rhinitis, therefore, is frequently beneficial in the patient with CRS. Even in the patient with negative allergy testing, the possibility that the patient has IgE hypersensitivity localized solely to the upper or lower airway exists. The goal of this review is to examine the current evidence and provide a practical algorithm to help manage allergic rhinitis in the setting of CRS.

EPIDEMIOLOGY AND DEFINITIONS

Atopy predisposes patients to adverse outcomes in asthma and CRS, but the clinical relevance to these disorders is complex. Studies show increased likelihood of clinically manifest allergic rhinitis in patients with higher number of positive allergen

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KEY POINTS

- Patients with CRS should be considered candidates for allergy testing and appropriate therapy.
- Allergy and CRS commonly coexist and immunotherapy may improve patient outcome.
- A symptom-based treatment algorithm is outlined for managing patients with allergic rhinitis and CRS.

sensitizations. Furthermore, clinical relevance depends on the allergen class and the exposures in the patient's environment [7[■],8]. Definitions of atopy vary in the literature and include a personal or familial tendency to produce IgE antibodies, propensity to developing specific IgE to common allergens, and association with a symptom or disease. Nevertheless, it is clear that the incidence of atopy is increasing worldwide. A recent cross-sectional National Health and Nutrition Examination Survey study showed a 43.7% prevalence of atopy in the USA [7[■]], in this case defined as at least one positive specific IgE to at least one of the tested allergens, compared with 20.2% 2–3 decades earlier [9].

The correlation between atopy and CRS remains an active area of investigation. A recent GA²LEN survey showed that 56.7% of those reporting symptoms that fulfilled the EP³OS criteria for CRS also reported symptoms of allergy [10[■]]. Elevated levels of serum-specific IgE and peripheral eosinophilia correlate with CRS severity [11,12], and patients requiring endoscopic sinus surgery for CRS show a higher prevalence of atopy in comparison to the general population [13,14[■]].

RELATIONSHIP BETWEEN CHRONIC RHINOSINUSITIS AND ATOPY

Although CRS with nasal polyps is thought to be largely a Th2-biased profile with eosinophils, evidence showing a cause and effect relationship between a classic type I hypersensitivity and CRS is absent. Eosinophilia is often present in allergy, but is not exclusive to allergy, and many of the most problematic and symptomatic CRS patients demonstrate peripheral and histologic eosinophilia in the absence of allergy. In a subset of CRS patients with allergic fungal rhinosinusitis, IgE-mediated hypersensitivity is generally accepted as one of the driving factors of inflammation [15].

Coexisting or comorbid conditions that contribute to CRS include allergy, asthma, immunodeficiency, environmental pollutants, cigarette smoke exposure, and gastroesophageal reflux disease

(GERD). Although the pathophysiology of CRS is currently unknown, it is logical that targeted and symptom-specific therapy and avoidance can potentially improve conditions that mimic CRS or ameliorate potential drivers of inflammation.

Studies that show a correlation are confounded by variability in testing methods, the interpretation and diagnosis of allergy, and patient selection (Table 1). A positive allergy test does not reliably predict clinically significant allergy, nor does a negative allergy test preclude local IgE hypersensitivity; test results are a guide and must be interpreted in the context of the patient's history.

Recently, Tan *et al.* [14[■]] found that, in a group of CRS patients who failed medical therapy, 82% were positive on skin prick testing, with higher rates of multiple allergen sensitivity and asthma in the patients with CRS with nasal polyps.

In a Spanish study evaluating 121 patients with nasal polyps, 63% had positive skin prick testing compared with 31% of controls. Dust mite was the most common allergen eliciting a response [16]. The authors suggested that IgE-mediated hypersensitivity might play a role in the development of polyps. Similarly, Gutman *et al.* [17] reported a 57.4% prevalence of allergen hypersensitivity via in-vitro or intradermal endpoint titration in CRS patients. A total of 92% of these patients also showed sensitivity to perennial allergens, particularly mold and dust mites.

Almost a decade ago, Emanuel and Shah [18] showed that 84% of 200 patients requiring surgery for CRS were positive on either skin prick or in-vitro testing, chiefly to dust mites. The authors concluded that perennial allergy contributes to the development of CRS. Paradoxically, the group of patients with the highest degree of inflammation on sinus computed tomography (CT) in that study showed the lowest degree of allergy sensitivity. In contrast, other studies show that patients with allergic rhinitis show increased disease severity on CT and increased skin end point titration scores correlate with advanced CT stage [19,20].

The lack of correlation between atopy and CRS has also been demonstrated. Studies show that atopic status does not significantly impact quality of life or CT findings in the CRS patient. Wormald and colleagues reported a far lower incidence of atopy than most studies, with only 30% of 193 CRS patients showing in-vitro allergen positivity [21]. Pearlman *et al.* [22] reported allergen skin test positivity, a more sensitive assay for allergy than in-vitro techniques, in 49% of 106 CRS patients. This did not correlate, however, with CRS severity. The authors concluded that inflammation in CRS occurs independently of systemic IgE-mediated pathways.

Table 1. Studies examining the relationship between AR and CRS

Author(s)	Year	AR diagnostic method	CRS diagnostic method	Study population	Correlation	Study design
Studies showing a correlation between AR and CRS						
Tan <i>et al.</i> [14]	2011	Clinical history in conjunction with SPT or IDT	Sinus CT, nasal endoscopy	62 CRS with NP, 63 CRS without NP, 50 AR controls	Higher rate of atopy in CRS patients failing sinus surgery.	Prospective cohort
Munoz del Castillo <i>et al.</i> [16]	2009	SPT	Nasal endoscopy	190 NP patients and 190 controls	63.2% positive on skin testing in NP patients compared with 31.1% controls.	Case control
Houser and Keen [13]	2008	SPT, IDT, or RAST	Operative records and CRS diagnosis per 2003 task force	474 patients undergoing sinus surgery	Association of perennial AR and tobacco use with NP. 56.4% prevalence of atopy in CRS patients.	Retrospective review
Ramadan and Hinerman [23]	2006	Unknown	Sinus CT	141 children undergoing sinus surgery	Immunotherapy before surgery improved surgical success rate at 1-year follow-up (84% compared with 62% who were not treated).	Retrospective cohort
Gulman <i>et al.</i> [17]	2004	IDT or RAST	Clinical criteria	48 with CRS or recurrent acute rhinosinusitis with prior surgery	57.4% had positive allergy testing, and, of the patients with positive testing, 92% had sensitivity to perennial allergies (mold and dust mites).	Retrospective review
Alho <i>et al.</i> [24]	2003	Allergy questionnaire, SPT, or RAST	CT scan during a cold and 3 weeks later	9 AR patients, 39 nonallergic patients	AR patients had poorer paranasal sinus functioning as demonstrated with CT scan during viral infections. There was a significant correlation between serum IgE, nasal subepithelial eosinophil counts, and CT scores.	Prospective cohort
Emanuel and Shah [18]	2000	SPT, IDT, or in-vitro test	Sinus CT	200 CRS patients requiring sinus surgery	84% of CRS patients had atopy, with 58% with multiple allergen sensitivities, lower percentage of allergic patients in patients with most severe sinus disease on CT. Over 60% of patients had sensitivity to dust mites.	Retrospective review
Krouse [19]	2000	Allergy questionnaire, IDT	Sinus CT, nasal endoscopy	48 CRS patients	Correlation between CT score and mean end point as well as symptom scores. Increased skin end point titration scores correlated with advanced CT stage.	Case series
Berretini <i>et al.</i> [25]	1999	Clinical history, SPT	Sinus CT, nasal endoscopy	40 with perennial AR, 30 controls	Dust mite sensitivity correlated with pathologic CT. 67.5% of AR patients had sinus inflammation on CT vs. 33.4% of controls.	Case control
Ramadan <i>et al.</i> [20]	1999	Modified RAST	Sinus CT	42 CRS patients without prior surgery	Higher mean LMS in atopic patients than nonatopic patients.	Retrospective Review
Nishioka <i>et al.</i> [26]	1994	Clinical history in conjunction with SPT or in-vitro test	Sinus CT	283 CRS patients, 72 atopic and 211 nonatopic	Allergic patients had higher incidence of polyp recurrence after surgery.	Retrospective cohort
Newman <i>et al.</i> [11]	1994	Allergy questionnaire, in-vitro test, eosinophil count	Sinus CT	104 CRS patients undergoing sinus surgery	Antigen-specific IgE and eosinophilia correlated with increased severity on sinus CT.	Prospective cohort
Studies showing no correlation between AR and CRS						
Pearlman <i>et al.</i> [22]	2009	SPT	Sinus CT	40 CRS with NP, 66 CRS without NP	Among atopic patients, mean LMS or presence of CRS with NP was not affected by sensitivity to any allergen except cockroach.	Prospective cohort
Leo <i>et al.</i> [27]	2007	SPT or in-vitro test	Clinical history meeting two of major criteria	351 children meeting clinical criteria for CRS	Children with CRS had a comparable rate of allergic sensitization compared with general public.	Retrospective review

Table 1 (Continued)

Author(s)	Year	AR diagnostic method	CRS diagnostic method	Study population	Correlation	Study design
Robinson <i>et al.</i> [21]	2006	In-vitro test	Sinus CT	66 CRS with NP, 127 CRS without NP, failing medical therapy	Prevalence of atopy was 30% and no difference in QOL found between atopic and nonatopic rhinosinusitis patients or need for surgical revision. Atopic status had modest effect on CT findings.	Prospective cohort
Smith <i>et al.</i> [28]	2005	Clinical history	Sinus CT	119 CRS patients undergoing sinus surgery	History of allergy had no impact on preoperative or postoperative CT, endoscopy, or quality of life.	Prospective cohort
Keith <i>et al.</i> [29]	1994	Skin prick test or in-vitro test	Physical exam of nasal cavity for polyp size	16 control patients, 16 with NP allergic to ragweed, 16 NP not allergic to ragweed, 16 allergic to ragweed	Seasonal allergy exposure in CRS with NP did not affect disease severity.	Prospective cohort
Savolainen <i>et al.</i> [30]	1989	Allergy questionnaire, skin testing, and nasal smears	Sinus X-ray	224 patients with acute maxillary sinusitis	Prevalence of AR was 25% and 16.5% in non-AR patients and no difference found between AR and non-AR patients in previous sinusitis episodes.	Case control

AR, allergic rhinitis; CRS with NP, chronic rhinosinusitis with nasal polyps; CRS without NP, chronic rhinosinusitis without nasal polyps; CT, computed tomography; IDT, intradermal test; LMS, Lund–Mackay score; QOL, quality of life; RAST, radioallergen sorbent test; SPT, skin prick test.

It is possible, however, that IgE-mediated mechanisms are responsible for a subset of CRS patients. It has been hypothesized that increased total and specific IgE in the mucosal lining without a positive skin prick test or obvious serum-specific IgE may contribute to the pathophysiology of CRS [31,32]. Intriguingly, this ‘local allergy’ independent of systemic positivity may be associated with *Staphylococcus aureus* enterotoxins that act as superantigens inducing T-cell activation and local IgE formation. As a result, this local response may contribute to the inflammation seen in CRS in the absence of obvious atopy on current testing methods [33²²]. A subset of CRS patients with high total IgE with negative inhalant testing may have a significant hypersensitivity to Staphylococcal superantigens which is currently not amenable to testing except in research settings.

Finally, a correlation has been seen with nasal polyps and food allergy, but the data is not robust. Studies have reported from 70 to 81% prevalence of food hypersensitivity on skin testing in nasal polyp patients [34,35]. Whether exposure to the foods found positive on testing resulted in worsening symptoms or whether elimination diets would lead to resolution of sinonasal inflammation remains unknown.

BENEFITS OF IMMUNOTHERAPY IN CHRONIC RHINOSINUSITIS PATIENTS

Concomitant medical treatment of allergic rhinitis may improve surgical outcome [8,26]. Atopy patients have a higher polyp recurrence rate after surgery, although other outcome parameters such as postoperative maxillary antrostomy patency and synechiae rates have not shown a statistically significant difference between patients treated with and without immunotherapy [26]. The six allergic CRS patients who did not undergo immunotherapy had a four-fold worse outcome. The study, however, was retrospective and included a very small number of allergic patients who did not receive immunotherapy. In an earlier study by Schlenter and Mann [36], of 31 allergic and 34 nonallergic CRS patients undergoing surgery, the 15 allergic patients who underwent concomitant allergen-specific immunotherapy had surgical outcomes comparable to the nonallergic patients, but the allergic patients who did not undergo immunotherapy, despite medical treatment, had significantly worse outcomes. In a retrospective cohort study, immunotherapy and medical allergy treatment before surgery improved the surgical success rate at a 1-year follow-up in children with CRS from 64 to 84% [23].

In a retrospective review of over 20 years of data in a tertiary academic practice, those allergy patients

undergoing immunotherapy who felt most improved had a history of recurrent rhinosinusitis. In this same report, approximately 50% of the patients with a history of prior sinus surgery believed that surgery alone did not completely resolve recurrent episodes of sinusitis, and over 30% of patients had undergone prior nasal or sinus procedures. The authors concluded that failure to address allergy, when present as a contributing factor to sinus disease, diminishes the probability of a successful surgical intervention [37].

THE UNIFIED AIRWAY

With a more global understanding of how CRS fits into the inflammatory picture, links between rhinitis, sinusitis, and asthma are being more clearly defined. Over 80% of patients with asthma manifest rhinitis symptoms and, furthermore, up to 40% of patients with rhinitis symptoms have asthma [38,39]. A recent survey of 52 000 adults across 12 European countries revealed strong and independent associations between asthma and both allergic rhinitis and CRS [10[¶]]. Symptoms of allergic rhinitis often precede the onset of asthma and the treatment of allergic rhinitis and CRS can improve asthma outcomes [39,40]. Inflammatory mediators and cytokines released at one site can result in recruitment of eosinophils into circulation and ultimately into the sinonasal as well as the bronchial mucosa [41[¶]]. The interdependence of the upper and lower airways should be considered in the comprehensive management of the allergic rhinitis and CRS patient.

ALLERGY TESTING AND IMMUNOTHERAPY IN CHRONIC RHINOSINUSITIS PATIENTS

Current guidelines vary regarding the role of allergy testing in the management of CRS patients (from optional to recommended) [42^{¶¶}]. Nevertheless, as symptoms overlap and, if allergic rhinitis is diagnosed, an additional armamentarium of therapeutic options becomes available, we advocate the assessment for allergy by either history or testing in all CRS patients. It is logical that concurrent management of allergic rhinitis could potentially decrease sinonasal inflammation and the severity of CRS symptoms. In our tertiary practice, many patients have already undergone endoscopic sinus surgery with recurrence of inflammatory disease prior to being referred for further management of allergy. It is reasonable that the diagnosis and management of allergy in a proactive manner may improve patient symptoms, medication usage, and outcome after surgery or even lead to sufficient symptom

improvement such that surgery is not required. We recommend that CRS patients failing to improve with an initial trial of medical therapy be considered for allergy evaluation and treatment. Even patients responding to initial therapy may benefit from allergy therapy by removing the source of antigenic stimulation or by immunotherapy, which has the potential to cure the patient of allergic inflammation. We generally recommend immunotherapy for those patients with inadequate relief with environmental controls in conjunction with medical therapy or for patients with symptoms for at least 6 months of the year.

MANAGEMENT ALGORITHM

It is often difficult to differentiate allergic rhinitis from sinusitis because of overlapping symptomatology. The diagnosis is made by history and physical exam including nasal endoscopy, and confirmed by allergy testing. In our practice, all patients who meet the criteria for CRS undergo allergy testing, whether by skin testing or in-vitro testing. The patient is assessed for medications that have already been tried (Table 2), comorbid conditions, such as asthma and GERD, and immunodeficiency.

Endoscopic evaluation of the sinonasal mucosal lining may aid in the diagnosis of allergy and even immunodeficiency. Allergic rhinitis is characterized by pale and boggy mucosa, whereas patients with food allergy usually have erythematous swollen inferior turbinates. In immunodeficiency patients, even in the absence of infection, white or clear viscous mucous drainage is often seen.

Comprehensive management includes environmental controls, medical therapy, frequently immunotherapy, and referral for treatment of asthma if appropriate. Several drug classes are commonly used to treat allergic rhinitis, including oral antihistamines, nasal steroids, nasal antihistamines, leukotriene inhibitors, and nasal saline irrigation. Allergic rhinitis is a symptom-driven disease, with nasal congestion and blockage the most common. Other symptoms include sneezing, rhinorrhea, postnasal drainage, fatigue, and facial pressure. As perennial allergens, such as dust mites and molds, can cause predominately nasal congestion in the absence of classical symptoms considered allergic, such as sneeze and itch, we usually recommend allergy testing in all patients with chronic nasal congestion refractory to initial medical therapy and frequently even with a response to medical therapy. It may be more cost-effective and beneficial to treat the patient with environmental controls and immunotherapy rather than with prescription medications long-term. In patients with obstructing nasal

Table 2. Example of documentation of a patient's response to prior therapy, allowing a quick overview of the patient's profile of effective and ineffective medications as well as potential medications that can be added to the patient's regimen

Medications/interventions	Date	Effective	Ineffective	Not tried
Nasal steroid spray			X	
Antihistamine nasal spray			X	
Montelukast/Zafirlukast		X		
Zileuton				X
Oral antihistamine				X
Decongestant				X
Guaifenesin				X
Proton pump inhibitor				X
Oral antibiotic				X
Topical antibiotic				X
Nasal saline irrigation				X
Nasal steroid irrigation				X
Oral corticosteroid				X
Immunotherapy				X
IVIG				X
Omalizumab				x

IVIG, intravenous immunoglobulin.

polyps, however, topical therapy will be ineffective and a course of systemic corticosteroids may be necessary to control the patient's inflammation.

THE RATIONAL PATIENT EXPERIMENT

Patients with a history and physical exam findings consistent with allergic rhinitis are prescribed a treatment algorithm that includes progressive addition or replacement of medications individualized to the patient's symptoms, an algorithm we term the 'Rational Patient Experiment' (Table 3). Prior medications that have failed to bring relief despite appropriate use are eliminated from the patient's regimen. In an experiment, one variable is changed at a time and the impact of that variable on outcome, namely the patient's improvement in symptoms, is assessed. Patients are instructed to initiate one medication or intervention at a time, so that efficacy can be determined independently. If complete relief is attained, the patient is instructed to continue that medication and no further medications are added. If the medication provides no relief, then it is discontinued and the next medication is started in the order prescribed. If a partial response is attained, then the patient continues that medication and adds the next. A more detailed description of this treatment plan is outlined in a previous publication [43].

Written instructions and literature are provided to the patient explaining the order, length, and

potential side-effects of each intervention necessary to assess efficacy. After symptoms are controlled with a given regimen, patients are instructed to de-escalate therapy in a similar manner, again with removing one intervention at a time, and to reinitiate therapy if symptoms return.

We have found that this management outline requires more extensive education at the first office consultation in reviewing the 'Rational Patient Experiment', but having written educational material available, and an outline that can be personalized to the patient, facilitates understanding and compliance. This plan of care reduces follow-up visits for medication adjustments and limits the number of medications that a patient is ultimately prescribed.

In addition to the medications approved for the treatment of allergic rhinitis, we include medications in our treatment algorithm that treat conditions which can cause symptoms often misdiagnosed as resulting from allergic rhinitis or CRS, such as postnasal drainage. In a double-blind, randomized controlled study, Vaezi *et al.* [44] showed that, in patients with symptoms of postnasal drainage but no CT evidence of sinusitis or allergies by testing, an 8-week trial of a proton pump inhibitor significantly improved postnasal drainage symptoms. Moreover, none of the extensive gastrointestinal testing, including pH-probe studies, manometry, and esophagoscopy, correlated with response to treatment. In patients who complain

Table 3. The rational patient experiment

Order to be tried	Medication/intervention	Dose and considerations	Symptoms which should improve	Time to achieve noticeable effect	Length of trial
	Nasal steroid spray	Two sprays in each nostril once daily. Direct spray using right hand to left nose, and vice versa to maximize delivery laterally.	Nasal congestion, postnasal drainage	1 week	2–4 weeks
	Antihistamine nasal spray	As above. Do not sniff for one minute after spray to minimize bad taste. Rarely causes somnolence.	As above plus allergy symptoms	30 min	3–5 days
	Montelukast/Zafirlukast	10 mg pill.	As above plus cough	1 day	3–5 days
	Oral antihistamine	Over the counter, may cause somnolence.	As above plus cough Itching, sneezing	1–4 h	3–5 days
	Decongestant	May cause insomnia, elevated blood pressure and heart rate.	Nasal congestion	30 min	3–5 days
	Guaifenesin	1200 mg twice daily.	Thick mucous drainage	1 day	3–5 days
	Oral antibiotic	As prescribed. Eat yogurt or take a probiotic to replenish good bacteria in your system.	Thick mucous drainage, nasal congestion, facial pressure	1–2 days	As prescribed
	Proton pump inhibitor	As prescribed, take 30 min to 1 h before major meal.	Acid reflux symptoms, postnasal drainage	3 days	8 weeks
	Topical antibiotic	As prescribed.	Thick mucous drainage, nasal congestion, facial pressure	1–2 days	As prescribed
	Nasal saline irrigation	1–2 times daily, water should be distilled or purified.	Thick mucous drainage, crusting	1 week	2–4 weeks
	Nasal steroid irrigation	As prescribed.	Nasal congestion, postnasal drainage, loss of smell	1 week	2–4 weeks
	Mupirocin	2% nasal ointment, can be applied to inside of nose or mixed with saline and used as a spray (if nasal culture positive for <i>Staphylococcus aureus</i>).	Crusting, dryness, bleeding	3–5 days	2–4 weeks
	Queen Helene's Cocoa Butter Cream	Apply as needed to inside of nose.	Crusting, dryness, bleeding	3–5 days	2–4 weeks

Try each checked medicine one at a time in the order listed. If the medicine does not make you feel better in 3–5 days, then stop the medicine and try the next medicine listed.

If the medicine makes you *partially* better, but not completely symptom free, then add the next medicine listed. If the medicine relieves your symptoms, then continue it for at least several days or weeks as instructed. If you are feeling back to normal, then stop the medicine, but restart if your symptoms return.

Adapted with permission [43].

of significant postnasal drip without significant improvement on allergy therapy, an 8-week trial of a proton pump inhibitor is considered.

FOOD ALLERGY AND ELIMINATION CHALLENGE DIET

Other considerations include recommendation of an elimination challenge diet if the patient has coinciding gastrointestinal symptoms that may indicate a non-IgE-mediated food allergy. This includes the elimination of wheat, dairy, corn, and soy in a stepwise fashion. The food is eliminated for 5–10 days and then the patient is asked to reintroduce the food into the diet with close monitoring of symptoms 15 min to 24 h after ingestion. Symptoms such as headache, fatigue, nasal congestion, bloating, muscle or joint aches/swelling may indicate a non-IgE-mediated food allergy. If a food is identified as causing symptoms, patients are advised to eliminate the food from the diet for 2–3 months, at which point in most patients it can be safely reintroduced on a restricted schedule in which it is not eaten more than once every 5 days. Most patients tolerate a reintroduced food at this level once the desensitization period has been reached.

THE FUTURE OF IMMUNOTHERAPY

Further understanding of the interaction between allergen-specific IgE, mast cells, eosinophils, and T-cells has fueled targeted immunotherapy research for allergic rhinitis, asthma, and potentially CRS. Currently, anti-IgE therapy (omalizumab) [45] and anti-IL-5 therapy (mepolizumab) [46] show promise in treating patients with refractory inflammatory disease. The current paradigm of traditional allergy testing and immunotherapy will probably continue to be of value in treating allergic rhinitis. In the future, we predict that specific therapy to correct dysregulated pathways in the innate and adaptive immune systems, which underlie much of chronic upper and lower airway disease, will be developed for patients with uncontrolled inflammation seen in allergic rhinitis, asthma, and CRS.

CONCLUSION

The data is currently mixed on the role of allergy in CRS. Recent studies show that local IgE-mediated responses could contribute to the inflammation characteristic of both disorders. Patients undergoing sinus surgery have improved outcomes when allergies are managed. Comprehensive management of the CRS patient, including incorporation of allergy

and asthma treatment strategies, could help improve patient outcome and also provide a better understanding of the interdependence of these disorders.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 218).

1. Calderon MA, Boyle RJ, Penagos M, Sheikh A. Immunotherapy: the meta-analyses. What have we Learned? *Immunol Allergy Clin North Am* 2011; 31:159–173; vii.

A meta-analysis demonstrating that allergen immunotherapy is effective for treating allergic rhinitis and asthma.

2. Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). *Allergy* 2011; 66:740–752.

This Cochrane review supports the efficacy of sublingual immunotherapy for treatment of allergic rhinitis and provides a comprehensive evaluation of current studies.

3. Lane AP. The role of innate immunity in the pathogenesis of chronic rhinosinusitis. *Curr Allergy Asthma Rep* 2009; 9:205–212.

4. Ramanathan MJ, Lee WK, Spannhake EW, Lane AP. Th2 cytokines associated with chronic rhinosinusitis with polyps down-regulate the antimicrobial immune function of human sinonasal epithelial cells. *Am J Rhinol* 2008; 22:115–121.

5. Van Bruaene N, Perez-Novo CA, Basinski TM, et al. T-cell regulation in chronic paranasal sinus disease. *J Allergy Clin Immunol* 2008; 121:1435–1441; 1441.e1431–e1433.

6. Lee S, Lane AP. Chronic rhinosinusitis as a multifactorial inflammatory disorder. *Curr Infect Dis Rep* 2011; 13:159–168.

This study examines the current evidence and the pathophysiology of chronic rhinosinusitis as a heterogeneous inflammatory disorder.

7. Salo PM, Calatroni A, Gergen PJ, et al. Allergy-related outcomes in relation to serum IgE: results from the National Health and Nutrition Examination Survey 2005–2006. *J Allergy Clin Immunol* 2011; 127:1226–1235; e1227.

The most current iteration of NHANES, this study provides updated data on atopic prevalence in the USA as well as allergy-related outcomes.

8. Burbach GJ, Heinzerling LM, Edenharter G, et al. GA(2)LEN skin test study II: clinical relevance of inhalant allergen sensitizations in Europe. *Allergy* 2009; 64:1507–1515.

9. Gergen PJ, Turkeltaub PC, Kovar MG. The prevalence of allergic skin test reactivity to eight common aeroallergens in the U.S. population: results from the second National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 1987; 80:669–679.

10. Jarvis D, Newson R, Lotvall J, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA(2) LEN survey in Europe. *Allergy* 2012; 67:91–98.

This study surveyed 52 000 adults and examines the relationship between CRS, asthma, and allergic rhinitis.

11. Newman LJ, Platts-Mills TA, Phillips CD, et al. Chronic sinusitis. Relationship of computed tomographic findings to allergy, asthma, and eosinophilia. *JAMA* 1994; 271:363–367.

12. Poznanovic SA, Kingdom TT. Total IgE levels and peripheral eosinophilia: correlation with mucosal disease based on computed tomographic imaging of the paranasal sinus. *Arch Otolaryngol Head Neck Surg* 2007; 133:701–704.

13. Houser SM, Keen KJ. The role of allergy and smoking in chronic rhinosinusitis and polyposis. *Laryngoscope* 2008; 118:1521–1527.

14. Tan BK, Zirkle W, Chandra RK, et al. Atopic profile of patients failing medical therapy for chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2011; 1:88–94.

This study evaluated the atopic status of patients who required sinus surgery and examined allergen sensitivity between CRS patients refractory to medical therapy and allergic rhinitis patients.

15. Chakrabarti A, Denning DW, Ferguson BJ, et al. Fungal rhinosinusitis: a categorization and definitional schema addressing current controversies. *Laryngoscope* 2009; 119:1809–1818.

16. Munoz del Castillo F, Jurado-Ramos A, Fernandez-Conde BL, *et al.* Allergenic profile of nasal polyposis. *J Investig Allergol Clin Immunol* 2009; 19:110–116.
 17. Gutman M, Torres A, Keen KJ, Houser SM. Prevalence of allergy in patients with chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2004; 130:545–552.
 18. Emanuel IA, Shah SB. Chronic rhinosinusitis: allergy and sinus computed tomography relationships. *Otolaryngol Head Neck Surg* 2000; 123:687–691.
 19. Krouse JH. Computed tomography stage, allergy testing, and quality of life in patients with sinusitis. *Otolaryngol Head Neck Surg* 2000; 123:389–392.
 20. Ramadan HH, Fornelli R, Ortiz AO, Rodman S. Correlation of allergy and severity of sinus disease. *Am J Rhinol* 1999; 13:345–347.
 21. Robinson S, Douglas R, Wormald PJ. The relationship between atopy and chronic rhinosinusitis. *Am J Rhinol* 2006; 20:625–628.
 22. Pearlman AN, Chandra RK, Chang D, *et al.* Relationships between severity of chronic rhinosinusitis and nasal polyposis, asthma, and atopy. *Am J Rhinol Allergy* 2009; 23:145–148.
 23. Ramadan HH, Hinerman RA. Outcome of endoscopic sinus surgery in children with allergic rhinitis. *Am J Rhinol* 2006; 20:438–440.
 24. Alho OP, Karttunen TJ, Karttunen R, *et al.* Subjects with allergic rhinitis show signs of more severely impaired paranasal sinus functioning during viral colds than nonallergic subjects. *Allergy* 2003; 58:767–771.
 25. Berrettini S, Carabelli A, Sellari-Franceschini S, *et al.* Perennial allergic rhinitis and chronic sinusitis: correlation with rhinologic risk factors. *Allergy* 1999; 54:242–248.
 26. Nishioka GJ, Cook PR, Davis WE, McKinsey JP. Immunotherapy in patients undergoing functional endoscopic sinus surgery. *Otolaryngol Head Neck Surg* 1994; 110:406–412.
 27. Leo G, Piacentini E, Incorvaia C, *et al.* Chronic rhinosinusitis and allergy. *Pediatr Allergy Immunol* 2007; 18 (Suppl. 18):19–21.
 28. Smith TL, Mendolia-Loffredo S, Loehrl TA, *et al.* Predictive factors and outcomes in endoscopic sinus surgery for chronic rhinosinusitis. *Laryngoscope* 2005; 115:2199–2205.
 29. Keith PK, Conway M, Evans S, *et al.* Nasal polyps: effects of seasonal allergen exposure. *J Allergy Clin Immunol* 1994; 93:567–574.
 30. Savolainen S. Allergy in patients with acute maxillary sinusitis. *Allergy* 1989; 44:116–122.
 31. Bachert C, Gevaert P, Holtappels G, *et al.* Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. *J Allergy Clin Immunol* 2001; 107:607–614.
 32. Pant H, Ferguson BJ, Macardle PJ. The role of allergy in rhinosinusitis. *Curr Opin Otolaryngol Head Neck Surg* 2009; 17:232–238.
 33. Bachert C, Zhang N, Holtappels G, *et al.* Presence of IL-5 protein and IgE antibodies to staphylococcal enterotoxins in nasal polyps is associated with comorbid asthma. *J Allergy Clin Immunol* 2010; 126:962–968; e961–e966.
- Examining the role of local IgE to *Staphylococcus aureus* enterotoxins, this study evaluated levels of IgE and IL-5 in both Belgian and Chinese patients with nasal polyps and asthma.
34. Pang YT, Eskici O, Wilson JA. Nasal polyposis: role of subclinical delayed food hypersensitivity. *Otolaryngol Head Neck Surg* 2000; 122:298–301.
 35. Collins MM, Loughran S, Davidson P, Wilson JA. Nasal polyposis: prevalence of positive food and inhalant skin tests. *Otolaryngol Head Neck Surg* 2006; 135:680–683.
 36. Schlenter WW, Mann WJ. Operative therapy in chronic sinusitis - results in allergic and nonallergic patients. *Laryngorhinootologie* 1983; 62:284–288.
 37. Lane AP, Pine HS, Pillsbury HC 3rd. Allergy testing and immunotherapy in an academic otolaryngology practice: a 20-year review. *Otolaryngol Head Neck Surg* 2001; 124:9–15.
 38. Vinuya RZ. Upper airway disorders and asthma: a syndrome of airway inflammation. *Ann Allergy Asthma Immunol* 2002; 88:8–15.
 39. Bousquet J, Khaltaev N, Cruz AA, *et al.* Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008; 63 (Suppl. 86):8–160.
 40. Dhong HJ, Jung YS, Chung SK, Choi DC. Effect of endoscopic sinus surgery on asthmatic patients with chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2001; 124:99–104.
 41. Tomassen P, Van Zele T, Zhang N, *et al.* Pathophysiology of chronic rhinosinusitis. *Proc Am Thorac Soc* 2011; 8:115–120.
- This study evaluates the diverse phenotypes in chronic rhinosinusitis as well as the interdependence of the upper and lower airways.
42. Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. *Mayo Clinic proceedings*. *Mayo Clin* 2011; 86:427–443.
- This comprehensive review examines the divergence as well as similarities between several consensus guidelines including the Rhinosinusitis Initiative, the Joint Task Force on Practice Parameters, the Clinical Practice Guideline, the European Position Paper 2007, and the British Society for Allergy and Clinical Immunology.
43. Ferguson BJ, Otto BA, Pant H. When surgery, antibiotics, and steroids fail to resolve chronic rhinosinusitis. *Immunol Allergy Clin North Am* 2009; 29:719–732.
 44. Vaezi MF, Hagaman DD, Slaughter JC, *et al.* Proton pump inhibitor therapy improves symptoms in postnasal drainage. *Gastroenterology* 2010; 139:1887–1893; e1881; quiz e1811.
- This double-blind, placebo-controlled study examined the role of proton pump therapy in patients with postnasal drainage symptoms in the absence of sinusitis or allergy.
45. Verbruggen K, Van Cauwenberge P, Bachert C. Anti-IgE for the treatment of allergic rhinitis – and eventually nasal polyps? *Int Arch Allergy Immunol* 2009; 148:87–98.
 46. Gevaert P, Van Bruaene N, Cattaert T, *et al.* Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol* 2011; 128:989–995; e981–e988.
- This study examined the effect of mepolizumab in patients with recalcitrant CRS with polyposis and provides evidence for use of this novel therapy to reduce inflammation in these patients.