

Allergic Rhinitis and Rhinosinusitis

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Although conventionally considered as distinct clinical entities, allergic rhinitis and rhinosinusitis are increasingly being regarded as interrelated and part of a spectrum of upper airway inflammatory disease. A recent article by Krouse and colleagues [1] illustrated the concept of a “unified airway” with inflammatory processes affecting and coexisting in the upper and lower airways and underscored the importance of understanding this relationship to effectively diagnose and treat illnesses within this spectrum. Despite the lack of a clearly established causal link between allergic rhinitis and rhinosinusitis, an increasing body of evidence published in both the otolaryngology and allergy literature is strongly suggestive of a shared pathophysiologic relationship. Both conditions are characterized by an inflammatory response leading to an altered milieu within the nose and paranasal sinuses, thus rendering normal host defenses weakened and susceptible to further inflammatory insult. Although the inciting agents or factors leading to the inflammatory response, and the immunologic mechanisms driven by this response, may differ, it is logical to infer that an allergic-mediated inflammation within the nasal lining could lead to or contribute to the development of a sustained inflammatory state within the paranasal sinuses, especially if the allergic response occurs repeatedly and chronically.

Undoubtedly, the role of allergy in the pathogenesis of rhinosinusitis has been the subject of much scrutiny, debate, and controversy over the past several years. However, the compelling notion of a “unified airway” would lead one to argue that distinct clinical entities do not exist in a mutually exclusive vacuum, but rather that one entity could variably affect the development of or alter the course of another. This article will discuss both allergic rhinitis and rhinosinusitis as separate entities and will then go on

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to explore them as part of a spectrum of upper airway disease with a common pathophysiologic link.

Allergic rhinitis

Allergic rhinitis is a prevalent disease, estimated to affect approximately 20% of the adult population in the United States, and up to 40% of children [2]. These statistics are even more astounding when one considers the impact that allergic rhinitis has on quality-of-life measures and societal costs. Allergic rhinitis accounts for approximately 16.7 million physician office visits annually, and its treatment with over-the-counter and physician prescriptions result in direct costs of approximately \$4.5 billion/year in the United States. Furthermore, an estimated 3.8 million lost work and school days occur annually as a result of allergic rhinitis [3]. Previous studies have demonstrated that patients with allergic rhinitis have a statistically diminished quality of life as compared with the normal population [4,5]. An extensive list of allergy and allergic rhinitis statistics is available on the American Academy of Allergy, Asthma, and Immunology Web site, www.aaaai.org [6]. Regardless of the different statistics cited in various reports, it is clear that allergic rhinitis has had a profound impact on our society.

The hallmark of allergic rhinitis is an IgE-mediated, type 1 hypersensitivity reaction to an inciting inhaled antigen and, in some cases, an ingested food that causes a cross-reaction because of antigenic similarities between the inhalant and the food. The result of this reaction is a cascade of immunologic events leading to the clinical expression of the disease, which includes both nasal and non-nasal symptoms (Box 1). The basic immunologic mechanisms underlying the “allergic reaction” within the nose and paranasal sinuses are well characterized. In general, allergic sensitization and response occur in a series of steps with the first step involving an Antigen Processing Cell (APC) or macrophage incorporating and processing the antigen that has entered the host. After processing the antigen, the APC contacts a $CD4^+$ T_H2 T-helper cell via HLA Class II receptors on its cell surface. This interaction activates the T_H2 cell, resulting in the release of various cytokines, such as interleukin (IL)-4 and IL-13, which stimulate more T_H2 cells to respond to the antigen load and also cause B cells to differentiate into plasma cells that elaborate IgE antibodies specific to the antigen (Fig. 1). These antibodies then attach to the surface of mast cells, rendering them “sensitized.” This phase of the immunologic response resulting in mast cell sensitization is also known as the priming phase. Subsequent allergen provocation from further allergen exposure results in mast cell degranulation and the release of pre-formed mediators, such as histamine, kinins, and proteases. This “early-phase response” occurs about 10 to 30 minutes after allergen exposure. The increased number of degranulating mast cells in the nasal epithelium produces significant vascular leakage and interstitial edema resulting in irritation of sensory nerves, nasal pruritis,

Box 1. Nasal and non-nasal symptoms of allergic rhinitis*Nasal*

Sneezing
Rhinorrhea
Pruritis
Congestion
Smell impairment
Postnasal drip
Eustachian tube dysfunction

Non-nasal

Lacrimation
Conjunctivitis
Itching eyes
Fatigue
Sleep disturbances
Depression
Headache
 Palatal pruritis
 Ear fullness/otalgia
 Midface pressure
 Cognitive impairment

rhinorrhea, nasal congestion, and sneezing. The “late phase” of this allergic response occurs approximately 4 to 8 hours after antigen exposure as a result of chemotaxis and migration of neutrophils, basophils, eosinophils, T-lymphocytes, and macrophages across the mucosal endothelium into the nasal submucosa (Fig. 2). Further cytokine and chemokine release from these cells results in increased nasal inflammation and end organ damage. With repetitive allergen exposure, a priming effect occurs, where progressively smaller amounts of allergen are required to elicit an early-phase response.

Allergic rhinitis has been conventionally divided into seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). SAR, also known as “hay fever,” is the more common form, occurring during different seasons depending on the inciting inhalant antigen. Typical seasonal allergens include tree pollens in the spring, grass pollens in the summer, and weed pollens in the fall. Nasal and ocular symptoms are prominent during these exposures. PAR is the more chronic form of allergic rhinitis where symptoms occur to some degree year-round. Molds, cockroaches, mites, and animal dander are the typical inciting agents.

Irrespective of the plethora of classification systems used to describe allergic rhinitis, the evaluation and treatment algorithms for this disease are relatively straightforward. A thorough history will in most cases be able to

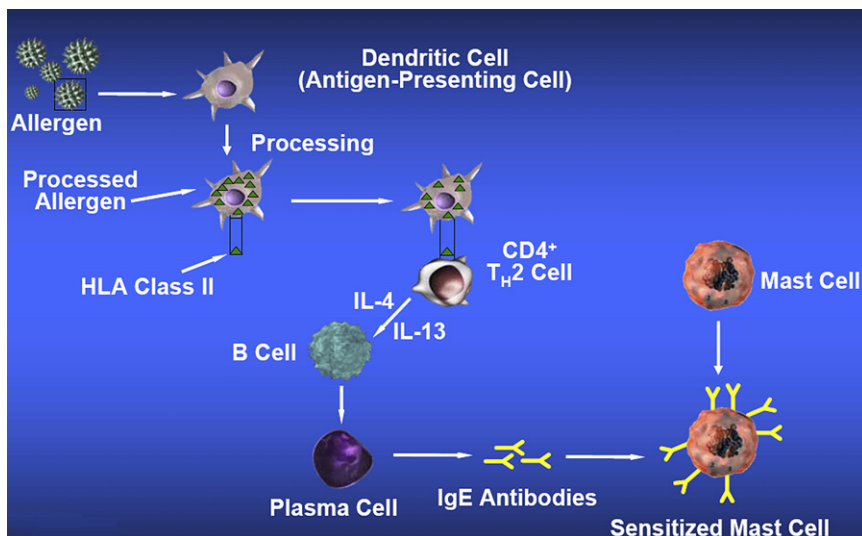


Fig. 1. Immunologic mechanism underlying allergic rhinitis. Initiation of the allergic response. (Adapted from Gwaltney JM Jr, Jones JG, Kennedy DW. Medical management of sinusitis: educational goals and management guidelines. The International Conference on Sinus Disease. Ann Otol Rhinol Laryngol Suppl 1995;167:22–30; and Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngol Head Neck Surg 2000;123: S1–32; with permission.)

distinguish allergic rhinitis and its subtypes from other common types of rhinitis (ie, infectious, occupational, chemical/irritative, anatomic, vasomotor, nonallergic with eosinophilia, medication-induced, hormonal, atrophic, and gustatory rhinitides). Several physical exam findings further corroborate the diagnosis of allergic rhinitis (Box 2). Once a presumptive diagnosis of allergic rhinitis is made, then management entails educating and counseling a patient and his or her family about the disease and its treatment (Fig. 3). Avoidance of triggering allergens and environmental modification are the initial measures taken to prevent or mitigate the symptoms of allergic rhinitis. Environmental measures often entail the modification of factors that are known to be or are potentially the source of the allergic response in areas such as the home, school, and workplace. Pharmacotherapy, with oral or topical antihistamines, oral or topical steroids, leukotriene inhibitor agents, mast cell stabilizers, anticholinergics, and limited use of oral or topical decongestants, plays a significant role in the management of allergic rhinitis. The unifying theme among these agents is the modulation of the immune response to the inciting agent. In some cases, the pharmacologic agent targets specific sites in the immunologic pathway (mast cell destabilizers, antihistamines) and in others, the agent has a generalized mode of action in mitigating the immune response (steroids). The efficacy and safety of these various agents have been extensively studied, and is beyond the scope of this article.

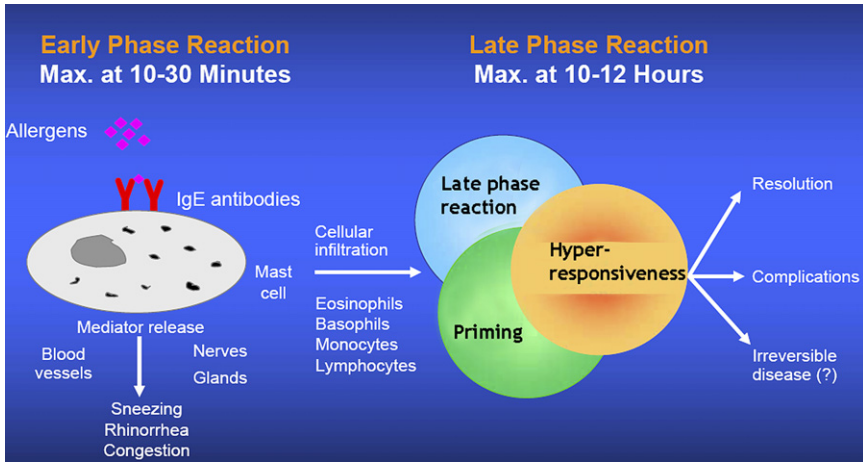


Fig. 2. The early and late phase responses in allergic rhinitis. Pathophysiology of allergic inflammation: clinical disease. (Adapted from Gwaltney JM Jr, Jones JG, Kennedy DW. Medical management of sinusitis: educational goals and management guidelines. The International Conference on sinus Disease. Ann Otol Rhinol Laryngol Suppl 1995;167:22–30; and Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngol Head Neck Surg 2000;123:S1–32; with permission.)

The use of laboratory and skin testing enables a definitive diagnosis to be established and is required before the onset of immunotherapy, which is employed and warranted when the above measures are insufficient to attain symptom control. Documentation of specific allergen sensitivities by in vivo skin testing or in vitro serum testing allows for targeted immunotherapy. Immunotherapy involves the injection of increasing amounts of allergen every 5 to 7 days until a “maintenance dose” is achieved that relieves symptoms or is maximally tolerated. This dose is then given once every 2 to 4 weeks based on the length of symptom control. Immunotherapy is typically continued for 3 to 5 years and results in long-term symptom control in up to 75% of patients. There has been considerable interest regarding sublingual immunotherapy or SLIT, which has been widely used in Europe. This therapy entails the sublingual deposition of the allergen (in most cases many times the dose of injected allergen in conventional immunotherapy) and has been noted to achieve symptom relief after 2 years of institution. This therapy is starting to gain widespread acceptance in the United States based on many studies touting its efficacy and safety.

This basic overview of allergic rhinitis serves to illustrate the important point that immune responses to various allergens lead to predictable and distinct histopathologic changes in the nasal and paranasal sinus epithelium (as both are contiguous) that can impair and overwhelm host defenses and create a milieu where further inflammatory insult would occur more readily and on a more sustained level.

Box 2. Physical exam findings in allergic rhinitis*Ocular*

Conjunctivitis

Allergic shiners—venous stasis from persistent nasal congestion leading to lower eyelid edema

Dennie's lines—creases in lower eyelid occurring from Mueller's muscle spasm

Allergic lashes—long, silky, full eyelashes

Nasal

Turbinate congestion/bogginess and hypertrophy

Other

Posterior pharyngeal cobblestoning

Adenoid hypertrophy

Lateral pharyngeal bands

Crowded teeth/high-arched palate

Vocal cord edema

Rhinosinusitis

Perhaps no other topic in the field of otolaryngology has engendered as much heated debate and conflicting opinions as that of rhinosinusitis. Its definition, classification, and management have spawned countless task forces, consensus statements, clinical studies and review articles, basic science research studies, and roundtable discussions. Ultimately, rhinosinusitis is an inflammation of the nose and paranasal sinuses, attributed to many potential factors. The term “rhinosinusitis,” as opposed to “sinusitis,” is a more accurate reflection of the anatomic and pathophysiologic relationship that occurs as a result of these instigating factors. The statistics pertaining to rhinosinusitis are no less staggering than that of allergic rhinitis, with estimates of more than 30 million Americans affected by this disease yearly [7]. In terms of its significance as a major public health concern, it ranks similar in prevalence to hypertension and diabetes [8]. Direct and indirect costs attributable to this diagnosis are also estimated in the billions of dollars, and the personal and societal burden from decreased productivity and diminished quality of life further attest to the negative impact of this disease.

The typical pathophysiologic schema leading to the development of rhinosinusitis starts with some inciting agent (viral, bacterial, fungal, allergen) or predisposing factor (anatomic, immunologic) leading to generalized mucosal edema and inflammation. The specific immunologic mechanisms set into motion by these agents or factors may be different, but ultimately, the basic histopathologic responses are similar. In some cases, the effect of the infectious or allergic agent may be limited to generalized mucosal edema

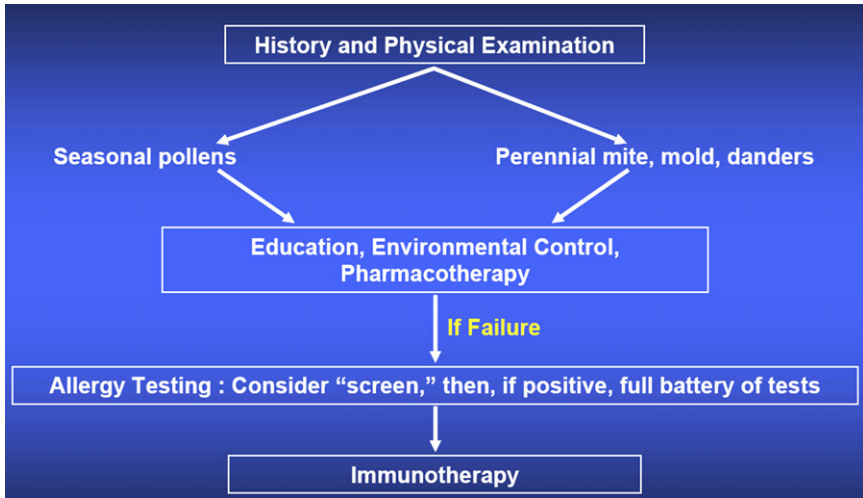


Fig. 3. Evaluation and treatment algorithm for allergic rhinitis. (Adapted from Gwaltney JM Jr, Jones JG, Kennedy DW. Medical management of sinusitis: educational goals and management guidelines. The International Conference on sinus Disease. *Ann Otol Rhinol Laryngol Suppl* 1995;167:22–30; and Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg* 2000;123:S1–32; with permission.)

and inflammation, and with conservative or pharmacologic measures, the inflammation dampens or subsides. In rhinosinusitis, the events subsequent to mucosal inflammation and edema are more elaborate and likely occur due to the interplay of many factors occurring in concert, rather than in the case of allergic rhinitis where the inciting agent and immune response are directly related to each other both spatially and temporally. In the development of rhinosinusitis, mucosal inflammation leads to ciliary dysfunction and mucus stasis, as well as edema of the sinus ostia. The stasis of secretions within the sinuses serves as a nidus for bacterial colonization and growth. These events coupled with the impairment of host defenses as a result of the inflammatory mediators released in response to the inciting agent, create a cycle of sustained inflammation that can chronically damage the nasal and paranasal sinus linings (Fig. 4). This vicious cycle will go unabated unless antibiotics, anti-inflammatory agents, and various conservative measures are used to restore the normal sinus cycle.

The myriad classification systems, physical exam findings, diagnostic workup, and treatment options in rhinosinusitis have been extensively documented and well characterized; however, what remains elusive is a broad agreement as to the degree of contribution of various factors in the development of rhinosinusitis. Although a broad and general definition of rhinosinusitis put forth by The Task Force for Defining Adult Chronic Rhinosinusitis of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) in 2002 [9,10] has met with relative agreement,

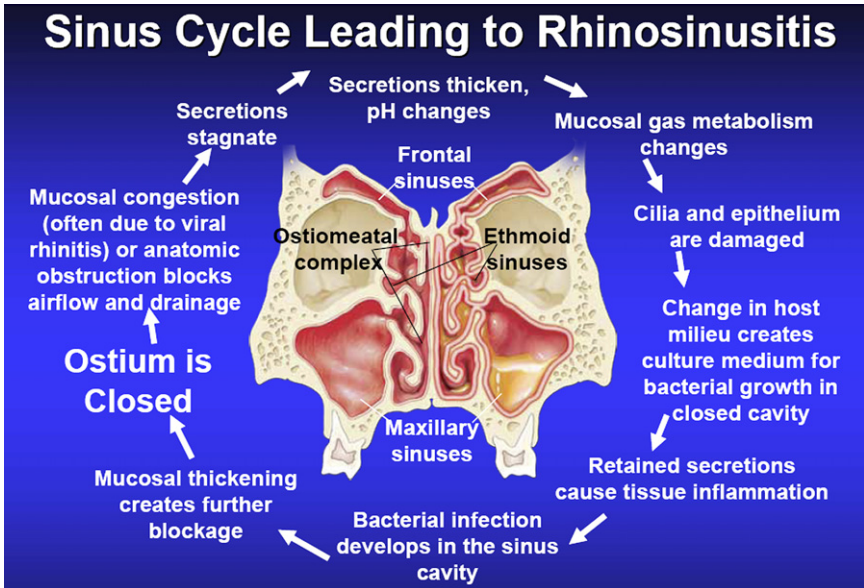


Fig. 4. Sinus cycle leading to rhinosinusitis. (*Adapted from* Gwaltney JM Jr, Jones JG, Kennedy DW. Medical management of sinusitis: educational goals and management guidelines. The International Conference on sinus Disease. *Ann Otol Rhinol Laryngol Suppl* 1995;167:22–30; and Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg* 2000;123:S1–32; with permission.)

the degree of influence and impact of various factors such as allergic disease, fungal colonization, chronic bacterial infection, environmental agents, and immunologic and nonimmunologic mechanisms in the pathogenesis of rhinosinusitis is debatable. Adult chronic rhinosinusitis was defined as a “group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses of at least 12 weeks’ duration.” This definition was not only endorsed by the AAO-HNS, but also by the American Rhinologic Society, the American Academy of Otolaryngic Allergy, and the Sinus and Allergy Health Partnership. The Task Force recognized that various host, systemic, and environmental factors play a role in the etiology of chronic rhinosinusitis, but that definitive associations between these factors and the development of chronic rhinosinusitis were not yet determined.

This increased recognition of the role of chronic inflammatory processes in the pathogenesis of chronic rhinosinusitis leads us to an examination of the role and relationship of allergy in the development and symptom expression of chronic rhinosinusitis.

The role of allergy in rhinosinusitis

In the past, chronic rhinosinusitis was characterized as a disease process caused by an anatomic obstruction of the sinus ostia, specifically

osteomeatal occlusion. The factors leading to this obstruction included viral infection aided by anatomic factors, leading to mucosal inflammation and edema, with thickening of mucus secretions and secondary bacterial infection. Our understanding of this disease process has evolved considerably with the publication of numerous studies on the etiology of chronic rhinosinusitis. It has become clear that the pathogenic mechanisms are more complex than would be explained by a simple model and that there are other chronic inflammatory processes that contribute to the development of chronic rhinosinusitis. A cause-and-effect relationship between allergy and chronic rhinosinusitis has been proposed in many anecdotal studies, and has stimulated considerable research efforts in recent years to define a specific relationship. However, the exact mechanism by which allergy predisposes to the development of chronic rhinosinusitis remains elusive. Nevertheless, a growing body of literature is strongly suggestive of a causal relationship.

An emerging and evolving model of the pathogenesis of chronic rhinosinusitis is one that is similar to the pathophysiologic mechanisms underlying chronic asthma, with persistent and progressive injury to the respiratory epithelium. In this model, described by Christodouloupolous and colleagues [11], chronic rhinosinusitis is characterized by "basement membrane thickening, subepithelial fibrosis and edema, goblet cell hyperplasia, and persistent inflammation." Remodeling of the mucosa occurs in response to this chronic and progressive inflammation. In an article by Ponikau and colleagues [12], a similar chronic mucosal injury and remodeling occur in the paranasal sinuses as a result of chronic inflammation induced by fungal organisms, eosinophils, and T-cell cytokine release, paralleling the observations seen in chronic asthma. Both of these studies are reflective of a new paradigm, shifting thought away from a simple and linear series of events that lead to persistent and chronic inflammation within the nose and paranasal sinuses. These models of pathogenesis also lend further support to the notion of a unified airway with similar histopathologic changes and immunologic mechanism occurring as a result of inflammatory insult.

In the past, the specific role of allergy in the etiology of rhinosinusitis was largely inferred on the basis of epidemiologic studies and anecdotal reports. Allergy was considered to have a probable role in the pathogenesis of rhinosinusitis, but a specific causative relationship was not elaborated. A 25% to 75% concordance between allergy and rhinosinusitis has been noted in various studies. In a 1989 study by Savolainen [13], skin testing in two groups of young adults, one with acute maxillary sinusitis, and another, a matched group without sinusitis, revealed that the prevalence of positive allergen testing was greater (45% versus 33%) in the group with sinusitis. The author thus concluded that allergy did play a role in the development of acute rhinosinusitis, and that it was more common among atopic individuals. Similar inferences were made by Suzuki and colleagues

[14], who documented an increased prevalence of allergy in individuals with chronic rhinosinusitis and higher levels of eosinophils and IL-5 in the sinus aspirates of these allergic individuals. In an article by Kennedy [15], positive inhalant allergy testing was present in over 50% of the 120 patients undergoing endoscopic sinus surgery, which led him to conclude that “allergy may well be a predisposing cause of chronic sinusitis.” Other studies have also shown a greater prevalence of allergy in patients with rhinosinusitis, and an increased severity of exam and CT findings and symptoms in these patients [16–19]. Review articles by Zacharek and Krouse provide further confirmation and elaboration of these reports and their findings [20,21].

The contribution of allergy in the pathophysiology of both acute and chronic rhinosinusitis has been supported by studies examining the role of the ethmoid sinuses in terms of immunologic, histopathologic, and post-surgical changes. The ethmoid mucosa affected by rhinosinusitis demonstrates an increased CD4/CD8 ratio and increase in the number of eosinophils and mast cells present as well as extracellular matrix deposition, basement membrane disruption, and denudation of the epithelium [11]. These findings are similar to the effect of allergy on other parts of the respiratory tract. Interleukin expression (such as IL-13) is increased in both acute and chronic rhinosinusitis, and the finding of elevated numbers of cells expressing IL-5 mRNA in tissue samples collected during endoscopic sinus surgery has been thought to be a predictor of poor response to surgery. This is suggestive of a role for allergy in this patient population, as IL-5 expression plays a central role in the allergic response. The negative impact of chronic allergic inflammation on surgical outcomes has also been documented in other studies [22,23]. Nishioka and colleagues [24] observed less scarring and fewer abnormalities in endoscopic appearance after functional endoscopic sinus surgery (FESS) in allergic patients treated with immunotherapy after FESS versus allergic patients who refused immunotherapy. Their conclusion was that post-FESS immunotherapy could reduce inflammation related to allergic disease and hence, improve surgical outcomes. A study by Nayak and colleagues [25] examined the effect of allergic inflammation on surgical outcomes in patients with chronic rhinosinusitis. The authors of this study compared a limited endoscopic sinus surgical technique, termed “FENS” (functional endoscopic nasosinus surgery) to traditional FESS. They argued that the FENS technique was more suitable in patients with an allergic component to their rhinosinusitis. This limited and conservative technique was considered more appropriate since an uncinectomy and extensive ethmoid sinus exenteration were avoided and, hence, a theoretically lessened exposure to allergens and bacteria in the inspired airflow would be achieved. The retained uncinate process and limited ethmoid cell removal via a transbullar approach was postulated to protect the sinuses from allergen exposure and contamination. In this study, 64 allergic patients (documented positive skin allergy

testing) with chronic rhinosinusitis, and CT-confirmed disease, were prospectively randomized to undergo either FENS or FESS. The authors noted a significant improvement in headache, nasal obstruction, and postnasal drip in the FENS group as compared with the FESS group. On nasal endoscopy, the FENS group also had less residual disease and fewer synechiae. The authors concluded that conservative surgical resection would limit the sinus mucosa from inciting allergens and improve surgical outcomes in conjunction with aggressive postoperative medical management. The limitations of this study are readily apparent, but strongly suggestive of a role for allergy in modulating disease expression in chronic rhinosinusitis.

Research into the pathophysiologic link between allergy and rhinosinusitis has yielded many interesting insights. Bhattacharyya and colleagues [26] attempted to correlate tissue histopathology in chronic rhinosinusitis with immune mechanisms in allergic disease. In this study, a method was proposed to reliably quantify tissue eosinophilia in chronic rhinosinusitis and examine its relationship with CT staging in a cohort of 71 surgical patients with refractory disease. Preoperative CT scans were obtained and mucosal specimens and eosinophil counts were obtained at surgery. The results revealed a moderate degree of correlation between CT stage and eosinophilia. The conclusions of this study were that the proposed method for quantifying tissue eosinophilia in sinus mucosa was reliable and valid and that a relatively strong correlation existed between CT scan stage and tissue eosinophilia in chronic rhinosinusitis. A study by Newman and colleagues [27] in 1994 examined the relationship between allergy and severity of disease in chronic rhinosinusitis. One hundred and four patients undergoing FESS completed symptom questionnaires, CT evaluation, in vitro allergy testing, sinus cultures, and evaluation of tissue and peripheral eosinophilia. The study demonstrated a strong correlation between the extent of disease on CT evaluation and the amount of eosinophils within the sinus tissue, as well as the presence of IgE antibodies specific to one or more inhalant allergens. This association appeared to be limited to patients with extensive disease. In 1997, the same group hypothesized that chronic rhinosinusitis involved a T_H2 -type immune response, similar to what occurs in allergic inflammation [28]. Another study suggesting a strong link between allergy and rhinosinusitis was conducted by Krouse [22]. In this study, 50 patients undergoing FESS for chronic rhinosinusitis were assessed with allergy skin testing, CT evaluation, and two quality-of-life instruments. The results of this study revealed that the severity of allergy (determined to be intradermal end points on skin testing) had an inverse relationship to quality-of-life measures. Interestingly, quality of life was not associated with severity of CT scan stage of disease. The conclusion of this study was that the presence and severity of allergy was a better predictor of quality of life than severity of disease by CT scan staging.

Studies examining the relationship between allergen exposure or provocation and rhinosinusitis exacerbation have also suggested a common mechanism in allergic rhinitis and rhinosinusitis [29–31]. Slavin and colleagues [31] demonstrated an increase in metabolic activity of the maxillary sinus mucosa in chronic rhinosinusitis patients during ragweed season, using single-photon emission CT scanning.

There has been increasing interest in the association between upper and lower airway diseases, exemplified by the recent article by Krouse and colleagues [1] on the unified airway theory.

Brinke and colleagues [32] studied the association between sinonasal disease and lung function, eosinophilia, and exhaled nitrous oxide in 89 non-smoking patients with severe asthma. Among these patients, 84% had CT abnormalities and 24% were noted to have extensive disease. Positive correlations were found between sinus mucosal thickening on CT scan and serum and induced sputum eosinophilia, exhaled nitrous oxide, and decreased functional residual capacity. An inverse correlation between sinus mucosal thickening and diffusion capacity was observed. Furthermore, patients with extensive sinus disease were noted to be afflicted more commonly with adult-onset asthma. These findings argue for a common inflammatory mechanism in upper and lower airway disease. Senior and colleagues [33] demonstrated improvements in pulmonary function in asthmatic individuals following medical and surgical treatment of chronic rhinosinusitis. The implications of this study were that common systemic mediators existed to account for the coexistence of allergic-induced inflammation of the sinus mucosa and pulmonary tissue eosinophilia with exacerbation of reactive airway disease.

A study conducted by Riccio and colleagues [34] further illustrated the association between upper and lower airway disease, and proposed that allergic inflammation was the etiologic factor in both anatomic sites. The cytokine levels were measured in 35 asthmatic children, aged 5 to 12 years, with chronic rhinosinusitis and correlated to findings in those with and without allergic disease. Of these 35 children, 20 were determined to be allergic to either dust mite antigen or pollens on skin-prick testing, with 15 being considered nonallergic. Using enzyme-linked immunosorbent assay (ELISA) methods, cytokine levels from nasal cytology and lavage specimens were measured, including IL-3, IL-4, IL-5, IFN- γ , tumor necrosis factor (TNF)- α , IL-1 β , IL-8, and IL-12. High levels of IL-4 and low levels of IFN- γ and IL-12 in allergic asthmatic children with chronic rhinosinusitis were consistent with a T_H2-dependent immune mechanism, similar to that seen in allergic rhinitis. The authors of this study reason that allergy is not a discrete entity but rather a disease process that can affect the entire respiratory epithelium, resulting in a spectrum of disease including chronic rhinosinusitis and asthma.

A review article by Vinuya [35] provided epidemiologic, pathophysiologic, and treatment outcomes data as evidence to support a link between upper airway and lower airway disease. From this article, 28% to 94% of

patients with asthma manifest rhinitis symptoms and 19% to 38% of patients with rhinitis have asthma. There appears to be a temporal sequence in the development of inflammation, with rhinitis preceding the development of asthma. This may indicate that allergic inflammation in the nose and paranasal sinuses may induce or aggravate inflammation in the lower respiratory tract. Several studies have supported this notion by demonstrating an improvement in asthma symptoms after sinus surgery and successful medical treatment of allergic rhinitis [36,37]. Vinuya's article presents evidence of a link between upper and lower airway disease based on several factors including the contiguous nature of upper and lower airway anatomy, loss of the protective function of allergen clearance in the chronically inflamed nose, a common systemic inflammatory process, and the nasobronchial reflex. Studies that have shown an improvement in asthma symptoms and bronchial hyper-responsiveness after treatment of allergic rhinitis further strengthen this link [38–40].

Summary

Evidence of a common pathophysiologic mechanism linking allergic rhinitis and rhinosinusitis is compelling and continues to evolve and be elaborated. Although a clear and definitive causal relationship leading from allergy to the development of rhinosinusitis remains to be elucidated, an increasing number of studies support the plausibility of this link. The paradigm shift to a “unified airway” and the evidence to support this concept further strengthen this link.

References

- [1] Krouse JH, Brown RW, Fineman SM, et al. Asthma and the unified airway. *Otolaryngol Head Neck Surg* 2007;136(5 Suppl):S75–106.
- [2] Dykewicz MS, Fineman S, Skoner DP, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology. *Ann Allergy Asthma Immunol* 1998;81:478–518.
- [3] Summary of health statistics for U.S. adults: national health interview survey, 2002. Available at: <http://www.cdc.gov/nchs/fastats/allergies.htm>. Accessed August 1, 2007.
- [4] Kremer B. Quality of life scales in allergic rhinitis. *Curr Opin Allergy Clin Immunol* 2004;4: 171–6.
- [5] Bousquet J, Bullinger M, Fayol C, et al. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. *J Allergy Clin Immunol* 1994;94:182–8.
- [6] American Academy of Allergy, Asthma, and Immunology Web site. Available at: www.aaaai.org.
- [7] Slavin RG. Management of sinusitis. *J Am Geriatr Soc* 1991;39:212–7.
- [8] Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. *Otolaryngol Head Neck Surg* 1995;113:104–9.
- [9] Benninger M, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg* 2003;129(Suppl 3): S1–32.

- [10] Lanza DC, Kennedy DW. Adult rhinosinusitis defined. *Otolaryngol Head Neck Surg* 1997; 117:S1–7.
- [11] Christodoulopoulos P, Cameron L, Durham S, et al. Molecular pathology of allergic disease II: upper airway disease. *J Allergy Clin Immunol* 2000;105:211–23.
- [12] Ponikau JU, Sherris DA, Kephart GM, et al. Features of airway remodeling and eosinophilic inflammation in chronic rhinosinusitis: is the histopathology similar to asthma? *J Allergy Clin Immunol* 2003;112:877–82.
- [13] Savolainen S. Allergy in patients with acute maxillary sinusitis. *Allergy* 1989;44:116–22.
- [14] Suzuki M, Watanabe T, Suko T, et al. A clinical and pathologic study of chronic rhinosinusitis: the role of the eosinophil. *Am J Otolaryngol* 1999;20:112–5.
- [15] Kennedy DW. Prognostic factors, outcomes and staging in ethmoid sinus surgery. *Laryngoscope* 1992;102(12 Pt 2 Suppl 57):1–18.
- [16] Berrettini S, Carabelli A, Sellari-Franceschini S, et al. Perennial allergic rhinitis and chronic rhinosinusitis: correlation with rhinologic risk factors. *Allergy* 1999;54:242–8.
- [17] Emmanuel IA, Shah SB. Chronic rhinosinusitis: allergy and sinus computed tomography relationships. *Otolaryngol Head Neck Surg* 2000;123:687–91.
- [18] Ramadan HH, Fornelli R, Ortiz AO, et al. Correlation of allergy and severity of sinus disease. *Am J Rhinol* 1999;13:345–7.
- [19] Yaritkas M, Doner F, Demirci M. Rhinosinusitis among the patients with perennial or seasonal allergic rhinitis. *Asian Pac J Allergy Immunol* 2003;21:75–8.
- [20] Krouse J. Allergy and chronic rhinosinusitis. *Otolaryngol Clin North Am* 2005;38:1257–66.
- [21] Zacharek M, Krouse J. The role of allergy in chronic rhinosinusitis. *Curr Opin Otolaryngol Head Neck Surg* 2003;11:196–200.
- [22] Krouse JH. Computed tomography stage, allergy testing, and quality of life in patients with sinusitis. *Otolaryngol Head Neck Surg* 2000;123:389–92.
- [23] Stewart MG, Donovan DT, Parke RB Jr, et al. Does the severity of sinus computed tomography findings predict outcome in chronic sinusitis? *Otolaryngol Head Neck Surg* 2000;123: 81–4.
- [24] Nishioka GJ, Cook PR, Davis WE, et al. Immunotherapy in patients undergoing functional endoscopic sinus surgery. *Otolaryngol Head Neck Surg* 1994;110:406–12.
- [25] Nayak DR, Balakrishnan R, Murty KD. Endoscopic physiologic approach to allergy-associated chronic rhinosinusitis: a preliminary study. *Ear Nose Throat J* 2001;80(6): 390–403.
- [26] Bhattacharyya N, Vyas DK, Fechner FP, et al. Tissue eosinophilia in chronic sinusitis: quantification techniques. *Arch Otolaryngol Head Neck Surg* 2001;127:1102–5.
- [27] Newman LJ, Platts-Mills TA, Phillips CD, et al. Chronic sinusitis: relationship of computed tomographic findings to allergy, asthma, and eosinophilia. *JAMA* 1994;271:363–7.
- [28] Hoover GE, Newman LJ, Platts-Mills TA, et al. Chronic sinusitis: risk factors for extensive disease. *J Allergy Clin Immunol* 1997;100:185–91.
- [29] Pelikan Z, Pelikan-Filipak M. Role of nasal allergy in chronic maxillary sinusitis—diagnostic value of nasal challenge with antigen. *J Allergy Clin Immunol* 1990;86:484–91.
- [30] Conner BL, Roach ES, Laster W, et al. Magnetic resonance imaging of the paranasal sinuses: frequency and type of abnormalities. *Ann Allergy* 1989;62:457–60.
- [31] Slavin RG, Zilliox AP, Samuels LD. Is there such an entity as allergic rhinosinusitis? [abstract] *J Allergy Clin Immunol* 1988;81:S284.
- [32] Brinke AT, Grootendorst DC, Schmidt JT, et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. *J Allergy Clin Immunol* 2002;109(4):621–6.
- [33] Senior BA, Kennedy DW, Tanaboddee J, et al. Long-term impact of functional endoscopic sinus surgery on asthma. *Otolaryngol Head Neck Surg* 1999;121(1):66–8.
- [34] Riccio AM, Tosca MA, Cosentino C, et al. Cytokine pattern in allergic and non-allergic chronic rhinosinusitis in asthmatic children. *Clin Exp Allergy* 2002;32:422–6.
- [35] Vinuya RZ. Upper airway disorders and asthma: a syndrome of airway inflammation. *Ann Allergy Asthma Immunol* 2002;88(4 Suppl 1):8–15.

- [36] Dunlop G, Scadding GK, Lund VJ, et al. The effect of endoscopic sinus surgery on asthma: management of patients with chronic rhinosinusitis, nasal polypsis, and asthma. *Am J Rhinol* 1999;139(4):261–5.
- [37] Dhong H, Jung YS, Chung SK, et al. Effect of endoscopic sinus surgery on asthmatic patients with chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2001;124(1):99–104.
- [38] Corren J, Harris AG, Aaronson D, et al. Efficacy and safety of loratidine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. *J Allergy Clin Immunol* 1997;100:781–8.
- [39] Wilson A, Orr LC, Sims EJ, et al. Antiasthmatic effects of mediator blockade versus topical corticosteroids in allergic rhinitis and asthma. *Am J Respir Crit Care Med* 2000;162:1297–301.
- [40] Osguthorpe J, Derebery J. Otolaryngic allergy. *Otolaryngol Clin North Am* 2003;36(4):xi–xii.