Rhinitis and sinusitis

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Rhinitis and sinusitis are among the most common medical conditions and are frequently associated. In Western societies an estimated 10% to 25% of the population have allergic rhinitis, with 30 to 60 million persons being affected annually in the United States. It is estimated that sinusitis affects 31 million patients annually in the United States. Both rhinitis and sinusitis can significantly decrease quality of life, aggravate comorbid conditions, and require significant direct medical expenditures. Both conditions also create even greater indirect costs to society by causing lost work and school days and reduced workplace productivity and school learning. Management of allergic rhinitis involves avoidance, many pharmacologic options, and, in appropriately selected patients, allergen immunotherapy. Various types of nonallergic rhinitis are treated with avoidance measures and a more limited repertoire of medications. For purposes of this review, *sinusitis* and *rhinosinusitis* are synonymous terms. An acute upper respiratory illness of less than approximately 7 days' duration is most commonly caused by viral illness (viral rhinosinusitis), whereas acute bacterial sinusitis becomes more likely beyond 7 to 10 days. Although the mainstay of management of acute bacterial sinusitis is antibiotics, treatment of chronic sinusitis is less straightforward because only some chronic sinusitis cases have an infectious basis. Chronic rhinosinusitis (CRS) has been subdivided into 3 types, namely CRS without nasal polyps, CRS with nasal polyps, and allergic fungal rhinosinusitis. Depending on the type of CRS present, a variety of medical and surgical approaches might be required. (J Allergy Clin Immunol 2010;125:S103-15.)

Key words: *Rhinitis, sinusitis, rhinosinusitis, allergic, fungal sinusitis, nasal polyposis*

Rhinitis and sinusitis are among the most common medical conditions and are frequently associated.[1-4] An estimated 10% to 25% of the population in Western societies has allergic rhinitis.[1,2]

Abbreviations used

ABRS:	Acute bacterial rhinosinusitis
AERD:	Aspirin-exacerbated respiratory disease
AFRS:	Allergic fungal rhinosinusitis
AR:	Allergic rhinitis
CRS:	Chronic rhinosinusitis
CRScNP:	Chronic rhinosinusitis with nasal polyposis
CRSsNP:	Chronic rhinosinusitis without nasal polyposis
CT:	Computed tomography
FDA:	US Food and Drug Administration
FESS:	Functional endoscopic sinus surgery
INS:	Intranasal corticosteroids
LTRA:	Leukotriene receptor antagonist
NARES:	Nonallergic rhinitis with eosinophilia syndrome
PAR:	Perennial allergic rhinitis
PRN:	As required
SAR:	Seasonal allergic rhinitis
URI:	Upper respiratory tract infection

Sinusitis affects an estimated 31 million persons annually in the United States.[3] Both rhinitis and sinusitis can significantly decrease quality of life, aggravate comorbid conditions, and require significant direct medical expenditures. Both conditions also create even greater indirect costs to society by causing lost work and school days, as well as reduced workplace productivity and school learning.

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RHINITIS

Background

Although semantically, the term rhinitis implies inflammation of the nasal mucous membranes, inflammatory cell infiltrates are not characteristic of all disorders considered to be rhinitis. As a clinical term, rhinitis refers to a heterogeneous group of nasal disorders characterized by 1 or more of the following symptoms: sneezing, nasal itching, rhinorrhea, and nasal congestion.[1] Rhinitis can be caused by allergic, nonallergic, infectious, hormonal, occupational, and other factors.[1,2] Allergic rhinitis is the most common type of chronic rhinitis, but 30% to 50% of patients with rhinitis have nonallergic triggers. Preliminary data suggest that 44% to 87% of patients with rhinitis might have mixed rhinitis, a combination of allergic and nonallergic rhinitis.[1,2,5] Worldwide, the prevalence of allergic rhinitis continues to increase. Studies suggest that seasonal allergic rhinitis (hay fever) is found in approximately 10% to 20% of the general population,[1,2] with an even greater prevalence in children. Overall, allergic rhinitis affects 30 to 60 million subjects in the United States annually.[1,6] Severe allergic rhinitis has been associated with diminished quality of life, disordered sleep (in as many as 76% of patients), obstructive sleep apnea, and impairment in work performance.[1,2] In addition, rhinitis can contribute to sinusitis (see the section below on Sinusitis, comorbidities, and allergic rhinitis) and is frequently associated with asthma.

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Pathogenesis

Nasal anatomy and physiology. The nasal cavity (Fig 1) is divided by the nasal septum, which is composed of bone more proximally and cartilage more distally. The inferior, middle, and superior turbinates in the nasal cavity promote air filtration, humidification, and temperature regulation. The nasal cavity and turbinates are lined with mucosa comprised of pseudostratified columnar ciliated epithelium that overlies a basement membrane and the submucosa (lamina propria). The submucosa consists of serous and seromucous nasal glands, nerves, extensive vasculature, and cellular elements. Overlying the nasal epithelium is a thin layer of mucus that dynamically moves by means of ciliary action to the posterior nasopharynx. Infections (viral or bacterial) and allergic inflammation impair mucociliary clearance. Because nasal tissues are highly vascular, vascular changes can lead to significant nasal obstruction. Vasoconstriction and consequent decreases in nasal airway resistance result from sympathetic nerve stimulation. Parasympathetic nerve stimulation promotes secretion from nasal airway glands and nasal congestion. The nasal mucosa also contains nerves of the nonadrenergic noncholinergic system. Neuropeptides from the latter nerves (substance P, neurokinin A and K, and calcitonin gene–related peptide) are thought to play some role in vasodilatation, mucus secretion, plasma extravasation, neurogenic inflammation, and mast cell nerve interactions, but the relative clinical importance of neuropeptides needs further definition.[7]

Allergic rhinitis

Pathophysiology. Common allergens causing allergic rhinitis include proteins and glycoproteins in airborne dust mite fecal particles, cockroach residues, animal danders, molds, and pollens. On inhalation, allergen particles are deposited in nasal mucus, with subsequent elution of allergenic proteins and diffusion into nasal tissues. In addition, small-molecular-weight chemicals in occupational agents or drugs can act as haptens that react with self-proteins in the airway to form complete allergens. Evidence extrapolated from asthma studies suggests that once in nasal tissues, common aeroallergens not only undergo antigen processing to elicit allergen-specific allergic responses but also promote development of allergic airway disease through their inherent properties. For example, protease activities of several common aeroallergens can facilitate allergen access to antigen-presenting cells by cleaving tight junctions in the airway epithelium and activation of protease-activated receptors on epithelial cells.[8] Activated epithelial cells then produce cytokines, chemokines, and thymic stromal lymphopoietin, which interact with interepithelial and subepithelial dendritic cells to skew T-cell development and adaptive allergic sensitization. The house dust mite allergen Der p 2 mimics MD-2, the LPS-binding component of the Toll-like receptor 4 signaling complex,[2] and facilitates Toll-like receptor 4 signaling and airway T_H2-type inflammation.[9]

In the nose allergens are processed by antigen- presenting cells (dendritic cells expressing CD1a and CD11c and macrophages) in the nasal epithelial mucosa, with subsequent presentation of allergenic peptides by MHC class II molecules to T-cell receptors on resting $CD4^+$ T lymphocytes in regional lymph nodes. With costimulatory signals, allergen-stimulated T cells proliferate into T_H2-biased cells that release IL-3, IL-4, IL-5, IL-13, and other cytokines. These cytokines then lead to a cascade of events that promote B-cell isotype switching with subsequent local and systemic production of allergen-specific IgE antibody production by plasma cells, eosinophilic infiltration into the nasal epithelium and mucosa, and mast cell proliferation and infiltration of airway mucosa.

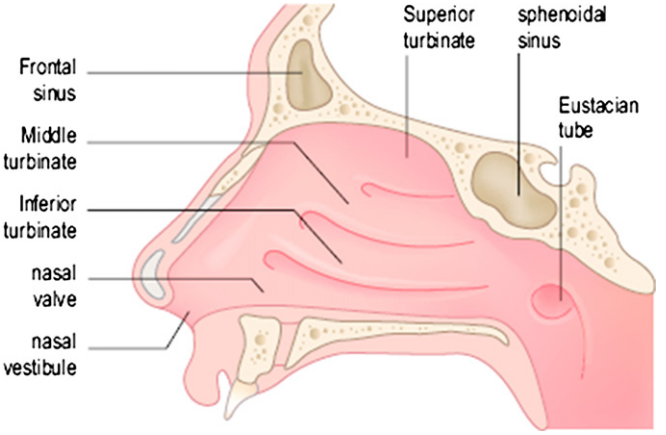

FIG 1. Nasal anatomy. Reprinted with permission from Dykewicz MS. Rhinitis and sinusitis. In: Rich RR, Fleischer TA, Shearer WT, Schroeder HW Jr, Frew AJ, Weyand CM, editors. *Clinical Immunology*. 3rd ed. London: Mosby Elsevier; 2008. p. 626-39.

Early/immediate allergic response. Within minutes of inhalation of allergen in sensitized subjects, deposited allergens are recognized by IgE antibody bound to mast cells and basophils, causing degranulation and release of preformed mediators, such as histamine and tryptase, and the rapid *de novo* generation of mediators, including cysteinyl leukotrienes (leukotrienes C_4, D_4, and E_4) and prostaglandin D_2. Mediators cause plasma leakage from blood vessels and dilation of arteriovenous arteriole venule anastomoses, with consequent edema, pooling of blood in the cavernous sinusoids (the principal cause of the congestion of allergic rhinitis), and occlusion of the nasal passages. Mediators also stimulate active secretion of mucus from glandular and goblet cells. Histamine elicits itching, rhinorrhea, and sneezing, whereas other mediators, such as leukotrienes and prostaglandin D_2, likely have more important roles in the development of nasal congestion. Stimulation of sensory nerves results in the perception of nasal congestion and itching and can provoke systemic reflexes, such as sneezing paroxysms.[1,10]

Late-phase response. Mediators and cytokines released during the early phase set off a cascade of events over the ensuing 4 to 8 hours that lead to an inflammatory response called the late response. Although clinical symptoms during the late phase might be clinically similar to those of the immediate reaction, nasal congestion is more prominent. The cysteinyl leukotrienes also play an active role in recruitment of inflammatory cells. Mediators and cytokines released during the early response act on postcapillary endothelial cells to promote expression of adhesion molecules, such as intercellular adhesion molecule 1, E-selectin, and vascular cell adhesion molecule 1, that promote adherence of circulating leukocytes, such as eosinophils, to endothelial cells. Factors with chemoattractant properties, such as IL-5 for eosinophils, promote the infiltration of the superficial lamina propria of the mucosa with many eosinophils, some neutrophils and basophils, and eventually $CD4^+$ (T_H2) lymphocytes and macrophages.[1] These cells become activated and release more mediators, which in turn activate many of the proinflammatory reactions seen in the immediate response.