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Asthma, Rhinitis, and Sinus Disease

LEARNING OBJECTIVES

- Examine the evidence of lower airway inflammation in patients with rhinitis.
- Describe four possible mechanisms to explain the effect of the upper airway on the lower airways.
- Contrast the roles of mechanical factors and inflammatory processes in chronic sinusitis.

INTRODUCTION

A wide variety of studies covering epidemiology, pathophysiology, and clinical conditions strongly suggest that allergic rhinitis and asthma are related.

In several reports, an average of 40% of patients with allergic rhinitis also had asthma. Rhinitis is also commonly present in patients with asthma; in one study, it was present in 99% of patients with allergic asthma. Rhinitis has also been reported to

be an independent risk factor for developing asthma. Similarities in nasal and bronchial mucosa have been noted.¹ Chronic sinusitis occurs in patients with rhinitis and/or asthma. Researchers have investigated relationships among allergic rhinitis, sinusitis, and asthma and suggested possible mechanisms for the effect of upper airway disease on the lower airways.

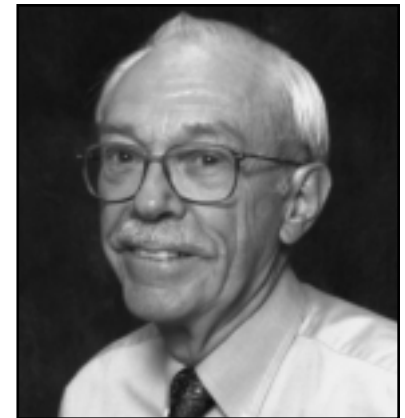
EVIDENCE OF LOWER AIRWAY INFLAMMATION IN PATIENTS WITH RHINITIS

Perennial eosinophilic rhinitis

To isolate the effect of rhinitis alone (without allergy) on the lower airways, Leone studied whether patients with nonallergic eosinophilic rhinitis exhibited bronchial responsiveness to methacholine and evidence of airway inflammation.²

Leone studied patients with a history of perennial rhinitis referred to an outpatient clinic. Patients with a history of lower respiratory symptoms or evidence of atopy by skin tests or RAST were excluded. Potential study participants underwent nasal lavage. Researchers selected patients with perennial rhinitis and eosinophilia, characterized by year-round rhinorrhea, nasal obstruction, and sneezing, and chose a diagnostic threshold of 10% eosinophils in the nasal lavage fluid. Thirty-nine subjects were enrolled in the study. All subjects underwent bronchial challenge with methacholine. Serum IgE and blood eosinophil count were measured. Twenty-two of the subjects underwent sputum induction successfully, and differential cell counts were performed on the sputum samples.

Forty-six percent of the subjects had measurable bronchial responsiveness (methacholine PD₂₀ range, 0.32 to 22.56 µmol) (Table 1). The subjects in this group (I) were similar in several respects to the 21 patients who did not have measurable methacholine PD₂₀ (results > 24 µmol; Group II); values for age, gender, serum eosinophil count, and total IgE showed no statistically



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Table 1. Characteristics of all patients with perennial rhinitis without atopy and those with (Group I) and without (Group II) measurable bronchial responsiveness

	All Patients (n=39)	Group I (n=18)	Group II (n=21)
Methacholine PD₂₀ range (μmol)	0.32 to >24	0.32 to 22.56	>24
Baseline FEV₁ (% predicted)	98.1 ± 2.0	91.3 ± 1.8	104.0 ± 2.9*
Length of clinical history (yr)	3.3 ± 0.7	1.8 ± 0.4	4.5 ± 1.3†
Eosinophils, blood (cells/mm ³)	350.6 ± 40.2	363.3 ± 66.7	336.1 ± 42.2
Eosinophils, nasal lavage fluid (%)	32.6 ± 3.3	29.3 ± 5.1	35.5 ± 4.2
Eosinophils, induced sputum (%)	9.3 ± 2.9 (n = 22)	16.8 ± 5.6 (n = 10)	3.1 ± 1.3† (n = 12)

Data from Leone et al.²

*P <.001 compared with Group I

†P <.05 compared with Group I

significant differences between the two groups. However, baseline FEV₁ values were higher in the Group II than in I (P<.001), and the duration of nasal symptoms was longer in Group II (P<.05). Mean values for percentage eosinophils in a differential cell count of nasal lavage fluid demonstrated no significant difference between the groups (I, x = 29.3 ± 5.1; II, x = 35.5 ± 4.2), but values for eosinophils in induced sputum were significantly lower in group II than group I (3.1 and 16.8, respectively; P<.05). Methacholine values significantly correlated with the number of eosinophils in sputum over the entire population of subjects (n=22; r=-0.63, P <.002).

Leone's study showed that patients with perennial nonallergic eosinophilic rhinitis have evidence of bronchial inflammation. In addition, nearly half demonstrated bronchial hyperresponsiveness, an important predisposing condition for asthma, even though they had no history of lower respiratory symptoms. The results also may indicate that eosinophilic inflammation is associated with bronchial hyperresponsiveness, since elevated sputum eosinophil values correlated with increased methacholine sensitivity. As the authors point out, other factors are likely involved, including genetic predisposition, but this provides important evidence for asymptomatic lower airway inflammation in many patients with perennial rhinitis.

Allergic Rhinitis

Seasonal pollen exposure produces increased methacholine sensitivity in patients with seasonal allergic rhinitis, even in the absence of asthma symptoms.³ Also, treatment of patients with seasonal allergic rhinitis with nasal corticosteroids has blocked the development of lower airway symptoms.⁴

A study by Chakir extends this information in patients with allergic rhinitis.⁵ Researchers took bronchial biopsy specimens from eight subjects with seasonal pollen-induced rhinitis with no history of asthma. Biopsies were performed in and out of the pollen season, and specimens were tested immunochemically for cytokine expression and numbers/activation of inflammatory cells. Spirometry and airway responses to methacholine challenge were also assessed in and out of pollen season.

All subjects had normal FEV₁ and FVC values at baseline (**Table 2**). Responses to methacholine challenge decreased from a mean of 64 mg/mL out-of-pollen-season to about half that value (33 mg/mL) during the period of natural pollen exposure, but values did not reach the asthmatic range. Lymphocyte counts rose during pollen season, with statistically significant increases seen in CD4⁺, CD8⁺, and CD45RO⁺ counts. No increases were noted in mast cells, EG2⁺ cells, CD25⁺ cells, or HLA-Dr⁺ cells, and the increase in eosinophils was not statistically significant. No correlations were

Table 2. Airway responsiveness, bronchial mucosal inflammatory cells, and cytokine expression in and out of pollen season in pollen-sensitive subjects with allergic rhinitis

	Out of Pollen Season	In Pollen Season
FEV ₁ (% predicted)	112 ± 5	not tested
FVC (% predicted)	108 ± 5	not tested
Methacholine challenge (PC ₂₀ , mg•mL ⁻¹)	65 ± 15	33 ± 8*
Lymphocyte subpopulations (cells/mm ²)		
CD4+	4 ± 0.7	12 ± 6*
CD8+	2 ± 0.4	8 ± 2*
CD45RO+	34 ± 4	55 ± 10†
Eosinophils , (cells/mm ²)	7 ± 1	12 ± 3
Cytokine expression (cells/mm ²)		
IL-4 ⁺	10 ± 3	15 ± 4
IL-5 ⁺	35.7 ± 9.5	75.7 ± 6.4*
IFN-γ ⁺	21 ± 7	19 ± 4

Data taken from Chakir et al.⁵ Values expressed as mean ± SEM

*P <.01 v. out-of-pollen-season value

†P <.04 v. out-of-pollen-season value

found between changes in individual inflammatory cells and changes in methacholine challenge results. Bronchial samples were also stained for immunoreactivity to IL-4⁺, IL-5⁺, and IFN-γ⁺. Mean IL-5⁺ expression doubled from 35.7 cells/mm² to 75.7 cells/mm², but IL-4⁺ and IFN-γ⁺ values did not change significantly.

The results indicate the upregulation of inflammatory responses in the bronchial mucosa of nonasthmatic subjects with allergic rhinitis after natural exposure to pollen during the pollen season. IL-5 immunoreactivity and recruitment of inflammatory cells were specifically increased.

Airway responsiveness also increased in the subjects during pollen season but did not enter the asthmatic range. The increase may be due to the increase in lower airway inflammation, but the authors found no correlation between increases in inflammatory cell counts and methacholine challenge results. The authors suggest that inflammatory responses may increase the risk of developing asthma in these subjects.

UPPER AIRWAY EFFECT ON LOWER AIRWAYS: POSSIBLE MECHANISMS

The effect of the upper airway on the lower airways may be explained by one of four proposed mechanisms (**Table 3**).

Table 3. Possible Mechanisms of Upper Airway Effect on Lower Airways

- Mouth breathing
- Drainage of inflammatory cells, mediators into lungs
- Nasal-bronchial reflex
- Systemic absorption of upper airway cells and cytokines

Mouth breathing

The nose conditions inspired air, warming it to within 10°C of body temperature. It also humidifies the air to 100% relative humidity. The cilia in the nose trap particulates; those greater than 10 mm in diameter are completely filtered out. Gases are also absorbed, with water-soluble gases such as SO₂ and formaldehyde completely removed. Patients breathing preferentially through their mouths because of rhinitis-related nasal obstruction may, therefore, be exposed to inhaled environmental pollutants in addition to dry, cold air; all of these contribute to lower airway symptoms in predisposed individuals.

Drainage of inflammatory cells, mediators into lung

Bardin investigated whether pulmonary aspiration of the contents of maxillary sinuses could be demonstrated in patients with chronic maxillary sinusitis or sinusitis and asthma.⁶ Thirteen subjects participated; four with sinusitis only, three with sinusitis and moderate asthma, and six with sinusitis and severe asthma with recurrent airway obstruction. A radionuclide (^{99m}Tc millimicrospheres) was placed in the maxillary sinus of each subject during therapeutic puncture. This particular radiopharmaceutical was selected because it was not likely to be absorbed by the sinus, respiratory, or GI mucosa; it had been shown in a pilot study to stay in place for at least 24 h after placement bronchoscopically in the bronchial tree. In all subjects, immediate aspiration of the radionuclide into the nasopharynx and swallowing were demonstrated, and the radionuclide moved through the entire GI tract. However, no pulmonary aspiration was demonstrated in any of the patients with sinusitis alone or with sinusitis and asthma. The authors concluded that aspiration of purulent secretions from the maxillary sinus probably plays at most a minor role in the effect of upper airway disease on lower airways.

Another study attempted to quantitate aspiration during sleep in normal subjects. Gleason studied 10 healthy male volunteers during two full-night sessions.⁷ Radioactive tracer (^{99m}Tc sulfur colloid, 2 mL/hr) was introduced into the nasopharynx during EEG-documented sleep, and lung scans were conducted immediately after the subjects awoke. Five of the 10 subjects had tracer evident in the pulmonary parenchyma following one of the two nights, with amounts aspirated ranging from 0.01 to 0.2 mL. The authors speculate that, since sleep impairs the cough reflex, aspiration occurs passively during normal sleep and may provide a mechanism for the introduction of organisms from the upper airway into the lung. It is also possible that cells or inflammatory mediators present in aspirated nasal secretions may play a role in the effect of rhinitis on the development of lower airway hyperresponsiveness. This contrasts with the lack of pulmonary aspiration of maxillary sinus contents into the lung in the study by Bardin.

Nasal-bronchial reflex

Fontanari investigated the changes in lower airway resistance induced by nasal inhalation of various samples of air to see whether the nasal-

bronchial reflex might play a role in the effect of upper airway disease on lower airways.⁸ Researchers analyzed the changes in interruption resistance (R_{int}), a measure of lower airway resistance, in normal individuals, during nasal inhalation of either moderately cold and dry air, very cold and dry air, or room temperature air was that either dry or moist. Twelve subjects participated. Nasal inhalation of cold (-4°C) dry air or dry air at room temperature increased baseline R_{int} values by 17 and 21%, respectively (Table 4). This response was even greater when colder (-10°C) air was inhaled. Moist air did not increase R_{int}. Both nasal anesthesia with Lidocaine and inhalation of ipratropium bromide, a cholinergic antagonist, blocked the effect of cold air inhalation on R_{int} values. Breathing cold dry air through the mouth produced no changes in R_{int}.

These results indicate that activation of cold or osmoreceptors in the nasal mucosa induces protective bronchoconstrictive responses in normal individuals, and that this reflex originates only in the nose, not the mouth. This may be a protective mechanism to reduce penetration into the lungs of air insufficiently conditioned by the nose. The study demonstrates the potential for stimulation of receptors in the upper airway in subjects with allergic rhinitis to adversely affect lower airways.

Systemic absorption of cells and cytokines

Other researchers have looked at the effect of nasal or bronchial allergen provocation on the number of eosinophils and the production of inflammatory molecules in the nose and lung.

Braunstaal enrolled nine nonasthmatic patients with seasonal allergic rhinitis due to grass pollen and nine nonallergic controls in a study of nasal allergen provocation.⁹ Nasal provocation was performed using 10,000 BU of grass pollen extract delivered as a fixed dose in each nostril. Blood samples and bronchial and nasal biopsy samples were collected before the provocation and 24 hours later. Levels of eosinophils, IL-5, eotaxin, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin, and human endothelium marker (CD31) were measured in the biopsy samples. Total numbers of eosinophils were measured in blood samples.

At 24 hours after nasal allergen challenge, increased nasal and bronchial symptoms and reduced pulmonary and nasal function were noted in the subjects with allergic rhinitis but not in the control subjects. Eosinophils were increased in the epithelium and lamina propria of the nose and bronchi of the subjects with allergic rhinitis. Blood eosinophils were also increased at 24 hours in these subjects. Biopsy samples from patients with allergic rhinitis showed increased staining for ICAM-1, VCAM-1, and E-selectin in nasal tissue as compared to baseline and increased ICAM-1 in bronchial tissue (Table 5). Increased percentages of vessels staining for ICAM-1, VCAM-1, and E-selectin vessels were present in nasal and bronchial specimens at 24 hours in subjects with allergic rhinitis versus baseline and versus controls.

Table 4. Change in interruption resistance (Rint) in healthy subjects during nasal breathing of treated air compared to untreated room air

Air Treatment	% Increase in Rint	P value v. beginning of test period (untreated room air)
-4°C, dry	17%	P<.001
-10°C, dry	42%	P<.001
Dry, room temperature	21%	P<.01
Moist, room temperature	No change	NS

Data from Fontanari et al.⁸

Table 5. Blood eosinophils, serum IL-5, and biopsy results for ICAM-1, VCAM-1, and E-selectin in patients with allergic rhinitis and controls, measured at baseline and 24 h after nasal provocation

	Allergic Rhinitis T ₀ N=9	Controls T ₀ N=9	Allergic Rhinitis T ₂₄ N=9	Controls T ₂₄ N=9
Eosinophils, whole blood Median (range) 10 ⁶ /L	140 (10-360)	110 (30-180)	300 (140-555)*†	140 (40-180)
IL-5,% serum Median, pg/mL	—	—	27.7†	14.6
Nasal lamina propria, % area staining positive				
ICAM-1	4	7	12#	6
VCAM-1	2	2	4**	4
E-selectin	0	0	1#	0
Bronchial lamina propria, % area staining positive				
ICAM-1	2	2	3††	3
VCAM-1	2	1	1	1
E-selectin	0	0	0	0
Nasal subepithelium, % area vessels staining positive				
ICAM-1/CD31	13	28	44##	19
VCAM-1/CD31	13	19	65##	19
E-selectin/CD31	42	44	54##	39
Bronchial subepithelium, % area vessels staining positive				
ICAM-1/CD31	50	30	82##	38
VCAM-1/CD31	0	6	45##	11
E-selectin/CD31	0	0	35##	0

Data from Braunstahl et al.⁹

*P <.008 v. allergic rhinitis at T₀

†P <.001 v. controls at T₂₄

#P <.02 v. allergic rhinitis at T₀; NS v. controls at T₂₄

**P <.008 v. allergic rhinitis at T₀; NS v. controls at T₂₄

††P <.05 v. allergic rhinitis at T₀; NS v. controls at T₂₄

P <.05 v. allergic rhinitis at T₀; P <.05 v. controls at T₂₄

The authors conclude that nonasthmatic patients with allergic rhinitis show increased expression of endothelial adhesion molecules in the nasal and bronchial mucosa after nasal allergen provocation; this is accompanied by eosinophilic allergic inflammation. These data support the hypothesis that local allergen exposure in the upper airway contributes to lower airway inflammation. The authors further suggest that repetitive stimulation of the nose by allergens produces a constant release of systemic inflammatory mediators that are carried to the lower airways, and this could be a significant contributing factor in the development of asthma in predisposed individuals.

Braunstahl also evaluated the effect of segmental bronchial allergen provocation (SBP) on nasal inflammation in patients with allergic rhinitis.¹⁰ The study compared allergic inflammation in upper and lower airways after SBP with grass pollen in eight controls and eight nonasthmatic, grass-pollen-sensitive patients with allergic rhinitis. Blood samples and bronchial and nasal biopsies were obtained before and 24 hours after SBP. The procedure induced nasal and bronchial symptoms and a reduction in pulmonary and nasal function in the allergic rhinitis group but not the controls. The allergic rhinitis subjects also had increases in eosinophils in the blood and in both challenged and unchallenged bronchial mucosa after SBP. At 24 hours after SBP, the subjects with allergic rhinitis also demonstrated increased BMK13-positive cells (eosinophils) and eotaxin-positive cells in the nasal lamina propria and increased expression of IL-5 in the nasal epithelium. No such changes were demonstrated in the healthy controls.

These results demonstrate an interconnection between the lower and upper airways. In patients with allergic rhinitis without asthma, SBP can induce allergic inflammation in the nose accompanied by peripheral blood eosinophilia and eosinophilic infiltration in the bronchi, including sections that were not involved in the allergen challenge. There is a clear systemic effect of allergen challenge in these subjects.

CHRONIC SINUSITIS IN PATIENTS WITH RHINITIS AND/OR ASTHMA

Chronic sinusitis is a condition that occurs in many patients with rhinitis and/or asthma, and several studies have evaluated the role of mechanical factors and markers of inflammatory processes in these patients.

Mechanical factors

Sinus computed tomography (CT) is often used to assess the severity of sinusitis; CT plays a central role in diagnosis and treatment planning as well as in research into the relationship between upper and lower respiratory disease. Bhattacharyya evaluated the test-retest reliability of CT in chronic rhinosinusitis to see if CT results were stable over time.¹¹ Forty-five patients scheduled for endoscopic sinus surgery received two CT scans, an initial scan during diagnostic evaluation and a second scan as part of image-guided sinus surgery. Mean time between scans was 123 days, and no surgical intervention occurred during this time. The average Lund scores for the first and second scans were 13.56 and 13.27, respectively, not significantly different. Scores remained the same in five patients, increased in 22 patients, and decreased in 18 patients. These results indicate that CT findings in patients with chronic rhinosinusitis remain stable over time and serve as a reliable assessment of disease.

Berrettini evaluated 40 adults with perennial allergic rhinitis with sinus CT and compared the results to sinus CT of 30 control subjects.¹² Sixty-eight percent of the perennial allergic rhinitis group had radiographic abnormalities compared to 33% of the controls (Table 6). Of 22 adults with perennial allergic rhinitis who had abnormalities of the maxillary sinuses, 13 had no obstruction of the osteomeatal complex. The authors concluded that factors other than mechanical obstruction must contribute to the development of chronic sinusitis in patients with perennial allergic rhinitis.

Table 6. Prevalence of abnormalities on CT scans in selected populations

Author	Population	CT abnormalities %
Berrettini et al ¹²	40 subjects with perennial allergic rhinitis	68
	30 controls	33
Havas et al ¹³	666 patients without clinical suspicion of sinus disease	43

Another study looked at the prevalence of incidental abnormalities in sinus CT scans of asymptomatic adults.¹³ The study population comprised 666 patients who referred for cranial CT for reasons such as tumors, seizures, headaches, head injuries, and visual disturbances. Patients with active sinus disease under treatment, suspicion of active sinus disease, or a history of sinus disease within the prior three months were excluded. Researchers discovered abnormalities of one or more paranasal sinuses in 42.5% of scans, most commonly in the ethmoid sinuses (28%) and maxillary sinuses (25%) (Table 6) and concluded that clinical correlation with radiologic findings is necessary when interpreting sinus CT scans.

Markers of inflammatory processes

Researchers have also investigated potential relationships between severity of sinus disease as indicated on CT scans and markers of inflammatory processes. Baroody looked more specifically at the degree of sinus mucosal thickening indicated on CT scans in patients with sinusitis and compared it to patients' total and specific IgE levels.¹⁴ Eighty-six patients who had total and specific serum IgE determinations for nasal complaints and a sinus CT scan within one to two months of the IgE tests were selected. Forty-four subjects had allergy, and 42 did not. Severity of disease on CT scan was graded in a blind fashion and compared to IgE values. A significant positive correlation was noted between severity of disease on CT and serum IgE levels, and patients with allergy had as a group both higher mean IgE and higher mean CT scores (Table 7). Baroody hypothesized a role for IgE in sinusitis resulting from allergic inflammation or as a phenotypic marker for genes associated with the inflammatory response in the sinus mucosa. Genes for cytokines that regulate IgE levels are located in the same chromosomic region as genes for other cytokines, such as IL-5, that influence eosinophils, leading the authors to propose that genetic control of host inflammatory response could contribute to sinusitis.

Another study by Bhattacharyya used retrospective review to evaluate peripheral eosinophilia in chronic sinusitis.¹⁵ Results from 87 patients undergoing endoscopic sinus surgery, 32 undergoing septoplasty, and a nonrhinologic control group (n=92) were compared (Table 7). The endoscopic surgery group had significantly higher percentages of peripheral eosinophil count when compared with the other groups; the specificity of peripheral eosinophil count for chronic sinusitis was 85%. However, the sensitivity was low (49%). The elevated eosinophil counts were associated with chronic sinusitis but not chronic rhinitis alone, suggesting sinusitis is an inflammatory condition with potential systemic manifestations.

Hoover also evaluated CT score and peripheral eosinophilia in patients with chronic sinusitis.¹⁶ Eighty patients with chronic sinus symptoms had a complete blood count with differential, CT scan of the sinuses, and serum assays for IgE and other antibody classes. A highly significant correlation between extent of disease and peripheral eosinophil count was noted; this association was independent of asthma, atopy, and age (Table 7). Although total IgE and IgG4 also correlated with disease, multiple stepwise regression analysis revealed that these factors did not add to the predictive value of the eosinophil count in identifying patients with disease. Hoover concluded that chronic sinusitis may involve immune activation of the TH2 type, which would involve cytokines such as IL-3, IL-4, IL-5, and GM-CSF.

The role of tissue eosinophilia in sinusitis was studied by Harlin, who evaluated sinus tissue removed from 26 patients undergoing surgery for chronic sinusitis.¹⁷ Of these, 13 had asthma (5 had asthma and sinusitis while 8 had sinusitis, asthma, and allergic rhinitis), 7 had sinusitis and allergic rhinitis without asthma, and 6 had only chronic sinusitis. Significant tissue eosinophilia was present in all of the patients with asthma, 6 of the 7 with rhinitis alone, and none of the

Table 7. IgE, peripheral eosinophilia, and sinusitis

Author	Key Findings
Baroody et al ¹⁴	A significant positive correlation between severity of disease on CT and serum IgE levels in patients with sinusitis
Bhattachayya et al ¹⁵	Elevated peripheral eosinophil counts associated with chronic sinusitis but not chronic rhinitis alone; significantly higher than control groups
Hoover et al ¹⁶	Highly significant correlation between extent of disease on CT scan and peripheral eosinophil count
Harlin et al ¹⁷	Significant sinus tissue eosinophilia in patients with asthma or with rhinitis alone, but not in patients without asthma or rhinitis
Newman et al ¹⁸	Significant sinus tissue eosinophilia in patients with asthma; significantly correlated with extensive sinus disease on CT scan. Serum IgE correlated with CT score

6 without asthma or rhinitis (**Table 7**). A characteristic finding was desquamation of ciliated epithelial cells. Little evidence of neutrophil infiltration was observed. These results suggest that the tissue eosinophil is an important effector cell in sinus disease in patients with rhinitis and/or asthma.

Newman assessed the possible correlation between peripheral and tissue eosinophilia, IgE, and sinus disease assessment by CT scan in 104 patients undergoing endoscopic sinus surgery.¹⁸ Blood samples were drawn and analyzed for complete blood cell count and differential, and IgE was measured in the sera. Biopsy specimens of diseased areas were obtained at surgery and evaluated for tissue eosinophilia. Patients with asthma had significantly higher mean CT score. The best predictive test for extensive sinus disease was peripheral eosinophilia, but 21% of patients without eosinophilia had extensive disease, limiting the test's usefulness in predicting severity of disease (**Table 7**). Serum IgE also correlated with CT score. Tissue eosinophilia was significantly associated with asthma, extensive sinus disease on CT scan, elevated total serum IgE, and peripheral eosinophilia. These results are in agreement with those of Harlin,¹⁷ again indicating the potential role of eosinophils in sinus disease in patients with asthma.

Researchers led by ten Brinke looked at the relationship between the extent of inflammation in the nasal mucosa and bronchial inflammation in severe asthma.¹⁹ Eighty-nine outpatients with severe asthma received CT scans and measurements of lung function, NO in exhaled air, and sputum and blood eosinophils. The CT scans were graded in a blind fashion on a 0 to 30 scale to identify mucosa thickening in the sinuses osteomeatal complexes and nasal cavities. Abnormalities in the CT scans were noted in 84% of patients, with 24% demonstrating severe disease. These abnormalities were noted even in patients without nasal symptoms. The CT scores correlated significantly with peripheral blood eosinophils ($r = .46$), sputum eosinophils ($r = .40$), exhaled NO ($r = .45$), and FRC ($r = .47$) and inversely with diffusion capacity ($r = -.53$) (**Table 8**). These data demonstrate a direct relationship between sinus mucosa thickening and bronchial inflammation in patients with sinusitis and severe asthma, suggesting either a role for eosinophilic inflammation in the

sinuses contributing to inflammation in the lower airways, or that inflammation in both organs reflects the same diffuse disease of the respiratory tract.

Eosinophils can release cationic proteins, oxygen free radicals, and proinflammatory cytokines, which can lead to respiratory tissue damage. Apoptosis, a form of programmed cell death that is distinct from necrosis, involves clearance of inflammatory cells without release of toxic contents. Eosinophilic apoptosis is inhibited during persistent eosinophil inflammation by the upregulation of cytokines such as IL-5 that enhance eosinophil survival. Fan investigated whether apoptosis of eosinophils might be inhibited in persistent tissue eosinophilia in allergic sinusitis.²⁰ Patients with nonallergic sinusitis were used as controls. Numbers of eosinophils, numbers of IL-5+ cells, and an eosinophilic apoptosis index were calculated in samples of ethmoid and maxillary sinus mucosa before and after prednisolone treatment. EG2+ and IL-5+ cells were abundant in samples from patients with allergic sinusitis (**Table 9**); slightly more than half of the IL-5-producing cells were eosinophils. Prednisolone treatment was followed by an induction of eosinophilic apoptosis with a marked decrease in EG2+ and IL-5+ cells. Fan concluded that IL-5 secretion by eosinophils helps to make the management of eosinophilic disease difficult, since it reduces apoptosis, and that therapeutic intervention to induce eosinophilic apoptosis is crucial for the reversal of tissue eosinophilia in chronic sinusitis.

Taken together, the results of these studies suggest that chronic sinusitis in patients with asthma and/or rhinitis represents an extension of the eosinophilic inflammatory process into the sinus mucosa. These patients are probably prone to recurrent infections more because of the presence of diseased tissue than because of obstruction to drainage. Emphasizing osteomeatal complex obstruction as the basis of chronic sinusitis in patients with asthma is not consistent with the known histopathology. Surgical intervention is rarely of lasting benefit to these patients and sometimes increases infections by removing barriers to bacterial entry into the sinuses.

Table 8. Correlation between sinus CT-scan and other measures in patients with severe asthma

Blood eosinophils (log)	Sputum eosinophils (log of %)	Exhaled NO (log of ppb)	FRC (ppb)	K _{co} (% predicted)
Rs = 0.46	Rs = 0.40	Rs = 0.45	Rs = 0.47	Rs = -0.53
P < .001	P = .007	P < .001	P = .002	P = .001

Data from ten Brinke et al.¹⁹

Table 9. EG2⁺ cells, IL-5⁺ cells, and apoptotic index in patients with allergic or nonallergic sinusitis

	Disease	Superficial layer (mean)	Deep layer (mean)
Eosinophils EG2 ⁺ cells per HPF	AS	114*	47*
	NAS	15	8
IL-5 ⁺ cells per HPF	AS	112*	51*
	NAS	8	4
Eosinophils/IL-5 cells, %	AS	58.1	54.9
	NAS	55.8	51.1
Eosinophil apoptotic index, %	AS	0.98*	3.99*
	NAS	0.64	2.24

Data from Fan et al²⁰; HPF, high-power field; AS, allergic sinusitis, n = 13; NAS, nonallergic sinusitis, n = 16; *P <.01 v. same layer in patients with NAS

SUMMARY

- The respiratory tract shares a similar mucosa and probably an integrated immune system.
- Inflammation and treatment of inflammation in one portion of the respiratory tract can influence the other regions.
- The primary mechanisms of these reciprocal effects are reflexes from the upper airway and a direct effect on the inflammatory process.

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POST TEST | Asthma, Rhinitis and Sinus Disease

1. Which of the following statements about the relationship between rhinitis and bronchial inflammation is (are) correct?

- a. Inflammatory responses can be demonstrated in the bronchial mucosa of pollen-sensitive, nonasthmatic subjects with allergic rhinitis after exposure to pollen.
- b. Bronchial inflammation can be demonstrated in patients with perennial nonallergic eosinophilic rhinitis.
- c. Most pollen-sensitive, nonasthmatic subjects with allergic rhinitis develop airway responsiveness (PC₂₀ values) in the asthmatic range after exposure to pollen.
- d. Both (a) and (b) are correct.
- e. Both (a) and (c) are correct.

2. Mouth-breathing has been proposed as a possible mechanism for the effect of rhinitis on lower airways because:

- a. Mouth-breathing exposes the patient to environmental pollutants that the nose would typically filter out of the airstream.
- b. Mouth-breathing increases mechanical stress on bronchial air sacs.
- c. Mouth-breathing increases the moisture in the inhaled air, triggering increased lower airway responsiveness.
- d. Only (a) and (b) are correct.
- e. (a), (b), and (c) are correct.

3. Activation of receptors in the nasal mucosa triggers a protective bronchoconstriction in normal individuals; this nasal-bronchial reflex may adversely affect lower airways in patients with allergic rhinitis.

- True
- False

4. Which of the following statements correctly describe(s) the responses seen in nonasthmatic patients with allergic rhinitis after nasal allergen challenge?

- a. Eosinophilic allergic inflammation increases in the nose and bronchi.
- b. Blood eosinophils increase initially but return to baseline within 24 hours.
- c. Inflammatory mediators are released in the upper airway and carried to the lower airways.
- d. (a) and (c) are correct.
- e. (b) and (c) are correct.

5. Which of the following statements correctly describe(s) computed tomography (CT) scans of the sinus?

- a. CT scans are a sensitive and specific measure of abnormalities in patients with perennial allergic rhinitis.
- b. CT findings in a typical patient with chronic rhinosinusitis will vary widely over time, making their use as a reliable assessment of sinus disease very problematic.
- c. CT scans detect abnormalities in a significant portion of healthy controls, making their use as a diagnostic tool for determining the presence of sinus disease unreliable.
- d. Both (c) and (d) are correct.

6. Over 40% of healthy controls without clinical suspicion of sinus disease have abnormalities on sinus CT scans.

- True
- False

7. Severity of sinus disease as indicated by CT scan correlates with which of the following factors?

- a. Peripheral eosinophil counts in patients with sinusitis
- b. Serum IgE in patients with sinusitis
- c. Sinus tissue eosinophilia in patients with rhinitis
- d. Only (a) and (c) are correct.
- e. (a), (b), and (c) are correct.

8. A direct relationship between sinonasal mucosal thickening and bronchial inflammation can be demonstrated in patients with sinusitis and severe asthma. Which of the following conclusions may be drawn from these results?

- a. Eosinophilic inflammation in the sinuses contributes to lower airway inflammation.
- b. The same diffuse disease of the upper and lower airways may cause inflammation in both the sinuses and the bronchi.
- c. Patients with asthma may have coincidental sinusitis, but sinusitis cannot be said to directly impact their asthma.
- d. Either (a) or (b) could explain these results.
- e. (a), (b), and (c) are all probable conclusions that can be drawn from these data.

9. Eosinophilic apoptosis, a form of programmed cell death that is distinct from necrosis, is increased in the sinus mucosa of patients with allergic sinusitis.

- True
- False

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