Rostrum

Allergic rhinobronchitis: The asthma–allergic rhinitis link

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Allergic rhinitis and asthma are linked by epidemiologic, histologic, physiologic, and immunopathologic characteristics and by a common therapeutic approach. Epidemiologically, the disorders often coexist. Histologically, the upper and lower airways are lined, and linked, by the respiratory epithelium. Physiologically, they may be linked by the nasobronchial reflex. Pathologically, they are linked by similar early- and late-phase allergic responses throughout the airways and by the systemic immunologic response to airborne allergens. Uncontrolled allergic rhinitis may be associated with worsening of coexisting asthma, and optimal treatment of allergic rhinitis may improve coexisting asthma. The key to managing both disorders is prevention and relief of chronic allergic inflammation in both the upper and lower airways. The similarities between allergic rhinitis and asthma outweigh the differences. To facilitate appropriate recognition and treatment of the common inflammatory process throughout the airways, consideration should be given to introducing the new term "allergic rhinobronchitis." (J Allergy Clin Immunol 1999;104:534-40.)

Key words: *Allergic rhinitis, asthma, bronchitis, chronic allergic inflammation, inhaled glucocorticoids, intranasal glucocorticoids, bronchial hyperresponsiveness*

Although the clinical association of allergic rhinitis and asthma has been recognized for centuries,[1] along with specialization in medicine and increased use of inhaled medications targeted to either the upper airway or the lower airway, there has been an increased focus on allergic rhinitis and asthma as separate disease entities. It is now time to address this situation. Introduction of a new term, allergic rhinobronchitis, might facilitate recognition of the concept of chronic allergic inflammation throughout the airways, and at the very least, might remind physicians who focus primarily on the lower airways to consider the importance of the upper airways, and vice versa. A precedent exists in that croup infection–induced inflammation common to both the upper and lower airways is described as acute laryngotracheobronchitis.[2]

Patients may come to a physician because of either allergic rhinitis or asthma, or both. One disorder often predominates, and the other may remain undiagnosed unless the physician actively determines whether it is present. This obviously involves asking pertinent questions, examining the chest, and performing spirometry before and after bronchodilator in patients with allergic rhinitis, and asking pertinent questions, examining the nose, and searching for eosinophils in the nasal secretions or mucosa in patients with asthma. Physicians who care for children, adolescents, and young adults and those who care for adults with occupational airways disease or aspirin-induced airways disease are more likely than other physicians to see patients who have overt clinical manifestations of both allergic rhinitis and asthma and may accept the concept of allergic rhinobronchitis more readily than others.

Whether allergic rhinitis and asthma develop sequentially or concurrently, once established they often have similar natural histories and similar seasonal exacerbations. They also have similar provoking factors, although pollen allergy is more clearly associated with rhinitis than with asthma and some nonspecific provoking factors such as cold, dry air are more clearly associated with asthma than with rhinitis. The clinical observation that allergic rhinitis often precedes asthma[3] and that asthmatic patients with severe allergic rhinitis tend to have worse asthma than those with mild allergic rhinitis[4] have been confirmed in epidemiologic studies.

Sinusitis also commonly coexists with asthma and may eventually be recognized as part of the allergic rhinobronchitis syndrome. Despite the strong clinical association between severe chronic sinusitis and asthma,[5] however, there is considerably less published epidemiologic, physiologic, immunopathologic, or therapeutic evidence supporting the link than there is for allergic rhinitis and asthma, a current challenge for generation of hypotheses and clinical investigations.

EPIDEMIOLOGY

In early epidemiologic studies up to 40% of patients with allergic rhinitis were reported to have asthma, and 30% to 80% of asthmatic patients were reported to have allergic rhinitis.[6] These percentages are probably underestimates because in recent studies in which asthmatic patients were interviewed in a standardized fashion by using questionnaires with improved sensitivity the preva-

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TABLE I. Allergic rhinitis and asthma: links and differences

	Links	Differences
Epidemiology	Coexistence, natural history, triggers, seasonal exacerbations	—
Embryology/histology	Chronology	—
	Respiratory epithelium: posteriorly from the septum and lateral walls of the fossa to the nasopharynx, larynx, trachea, bronchi and bronchioles	Keratinized and nonkeratinized stratified squamous epithelium in nasal vestibule. Venous sinusoids in lamina propria of nasal fossa. Cartilage is found from nasal fossa to bronchi only. No muscle in nasal cavity, skeletal muscle in nasopharynx and larynx, smooth muscle in lower airway
Physiology	Nasal and bronchial hyperresponsiveness to environmental and chemical stimuli. Nasobronchial reflex, especially from environmental stimuli	Objective tests for obstruction and nasal hyperresponsiveness in allergic rhinitis are not widely used, in contrast to pulmonary function tests and tests for bronchial hyperresponsiveness in asthma
Immunopathology	Type I and type IVa_2 allergic responses occur in both the upper and lower airways. There is a systemic immune response to airborne allergens.	Nasal immunopathologic response can be more readily monitored, at least for presence of eosinophils, than lower airway immunopathologic response
Therapeutics*	Prevention/relief of allergic rhinitis and asthma symptoms with control of airborne allergens, medications, and, in selected patients, immunotherapy	Vasoconstrictor effects of α-adrenergics in upper airway; bronchodilator effects of β-adrenergics in lower airway

*Most interventions have been studied separately in the upper and lower airways but, in fact, have similar effects throughout the airways.

lence of allergic rhinitis was found to be higher. For example, in a study in which 475 adults and adolescents with asthma were interviewed regarding the recurrence of one or more nasal symptoms (congestion, rhinorrhea, sneezing, pruritus) in the same temporal pattern every year, rhinitis was found in 98.9% of allergic subjects with asthma and in 78.4% of nonallergic subjects with asthma. The investigators concluded that a "chronic allergic total airway disease syndrome" exists.[7]

EMBRYOLOGY AND HISTOLOGY

The chronology of the embryologic development of the upper and lower airways is similar, beginning during the fourth week of gestation and continuing for years after birth, with the nose developing from the nasal placodes and the nasal prominences, and the larynx, trachea, bronchi, and lungs developing from the laryngotracheal groove in the ventral wall of the primitive pharynx[8] (Table I).

Keratinized and nonkeratinized stratified squamous epithelium and transitional epithelium are found in the nasal vestibule. The remainder of the airways, including the nasal fossa, the nasopharynx, and the lower airways, is lined with respiratory epithelium, which consists of ciliated pseudostratified columnar epithelium with goblet cells. This epithelium gradually loses height, goblet cells, and cilia as it approaches the alveolar ducts. The lamina propria of the nasal fossa, but not the rest of the airways, is characterized by venous sinusoids. The presence of skeletal muscle in the nasopharynx and larynx contrasts markedly with the prominent role of smooth muscle in the trachea, bronchi, and bronchioles[9] (Table I).

PHYSIOLOGY

Nasal challenge with environmental stimuli such as cold air inhalation leads to bronchoconstriction. This response can be abolished by suppression of the afferent arc of the nasopulmonary reflex with local anesthesia or by suppression of the efferent reflex arc with a cholinergic antagonist.[10] Nasal challenge with chemical stimuli such as histamine or methacholine also leads to bronchoconstriction; however, the possibility of systemic absorption from the nasal mucosa contributing to the bronchoconstriction has been difficult to rule out.[11]

Many patients with allergic rhinitis who have no perceived asthma symptoms have bronchial hyperresponsiveness to natural stimuli such as exercise or to bronchial challenge with chemical stimuli such as histamine and methacholine,[12] especially during allergic rhinitis exacerbations. The proportion of these patients who will be eventually diagnosed with asthma is unknown, and only prospective longitudinal studies lasting many years will provide this information. In a study in which upper and lower airway responsiveness was explored concurrently, bronchial challenge with histamine was given to subjects with allergic rhinitis or some other upper airway disorder who had persistent cough and other asthma-like symptoms but a normal chest examination and normal spirometry. Extrathoracic airway hyperresponsiveness alone was found in 26.5% of the subjects and combined extrathoracic airway and bronchial hyperresponsiveness was found in 40.6% (Fig 1).[13]

In practical terms, a patient with complete nasal blockage resulting from severe allergic rhinitis must resort to mouth breathing, and this may adversely affect

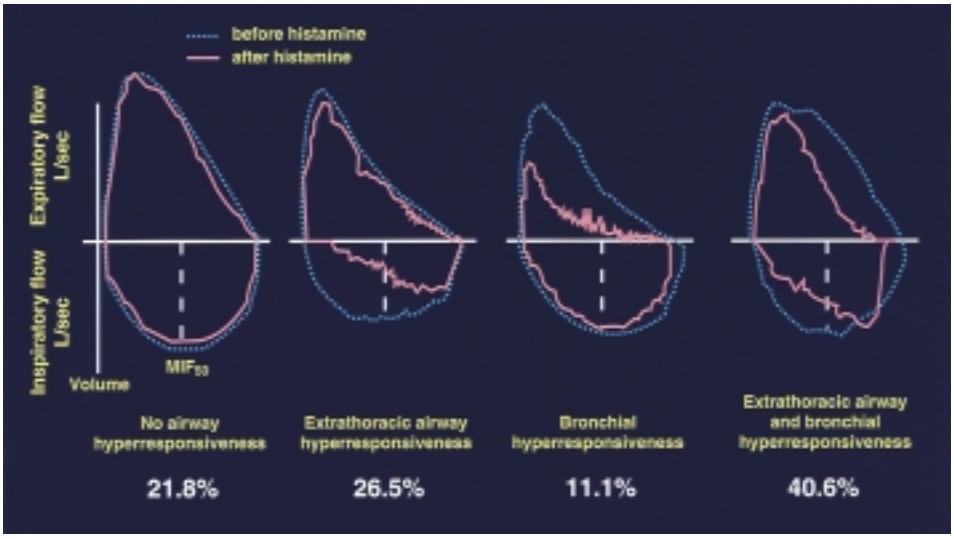


FIG 1. Extrathoracic airway dysfunction, including rhinitis, may account for and sustain asthma-like symptoms. A total of 441 consecutive subjects with cough and other asthma-like symptoms, but no history of asthma and normal pulmonary function tests, had a histamine bronchial challenge test; 21.8% of them had no airway hyperresponsiveness, 26.5% had extrathoracic airway hyperresponsiveness, 11.1% had bronchial hyperresponsiveness, and 40.6% had both extrathoracic airway and bronchial hyperresponsiveness. (Modified from Bucca C, Rolla G, Brussino L, DeRose V, Bugiani M. Are asthma-like symptoms due to bronchial or extrathoracic airway dysfunction? Lancet 1995;346:791-5.)

the lower airways because of lack of nasal "air-conditioning" and warming, humidification, and filtration of inspired air. Direct linkage of the upper and lower airways by postnasal drip of upper airway contents into the lower airway, although known to occur in individuals with suppressed consciousness, has not been convincingly documented in healthy individuals or in those with rhinitis or sinusitis.[14]

The upper airway is the primary site of the initial encounter between airborne allergens and the human body. During processing on the upper respiratory tract mucosa, the allergenic activity of pollens and possibly of other allergens may be enhanced (Fig 2).[15]

IMMUNOPATHOLOGY

Allergic rhinitis is characterized by integrity of the respiratory epithelium and by lack of basement membrane thickening; in asthma epithelial fragility and subepithelial collagen deposition may be found.[16,17] Apart from these differences in immunopathology, both disorders are characterized by a similar early allergic response and by similar chronic allergic inflammation of the epithelium and submucosa as evidenced by a predominance of eosinophils, mast cells, and basophils. The underlying pathologic processes, type I (immediate-type, IgE-dependent hypersensitivity) and type IVa_2 (chronic allergic inflammation or cell-mediated eosinophilic hypersensitivity in the revised Gell and Coombs classification),[18] are similar in the upper and lower airways. These processes involve the respiratory epithelial cells, Langerhans cells, dendritic cells and other antigen-presenting cells; recruitment and activation of $CD4^+$ helper cells with the Th2-type phenotype; and the effector cells: eosinophils, basophils, and mast cells. IgE plays a prominent role. There is increased expression of cytokines such as IL-4 and IL-13, which are important in local IgE production and in mast cell and basophil allergic responsiveness, and IL-5, which has eosinophil modifying properties, as well as GM-CSF, RANTES, and IL-3. Preformed mediators of inflammation such as histamine, tryptase, kinase or other proteases, newly generated mediators such as leukotrienes, PGs, and platelet-activating factor, and neurotransmitters are similar in the upper and lower airways, although their effects may differ in the different target organs.

In addition, allergic rhinitis and asthma are unified by a systemic immunologic response to airborne allergens. At a practical level, this is evident in the frequent finding of eosinophilia in peripheral blood as well as in nasal secretions and sputum. It is also evident in the antigen-specific responses of allergic subjects' PBMCs, resulting in increased IL-4 production and reduced IFN-γ production compared with PBMCs from healthy control subjects (Fig 3).[19] Although these cells play an important role in attracting, priming, and activating other cell types, little is known about their trafficking from the blood to the respiratory tract and vice versa. Furthermore, in patients with allergic rhinitis, asthma, and other atopic diseases, IgE receptor–positive inflammatory cells (eosinophils, basophils, and mast cells) are derived from a common progenitor in the bone marrow, move to the systemic circulation, and are recruited to sites of mucosal inflammation.[20] Seasonal fluctuations

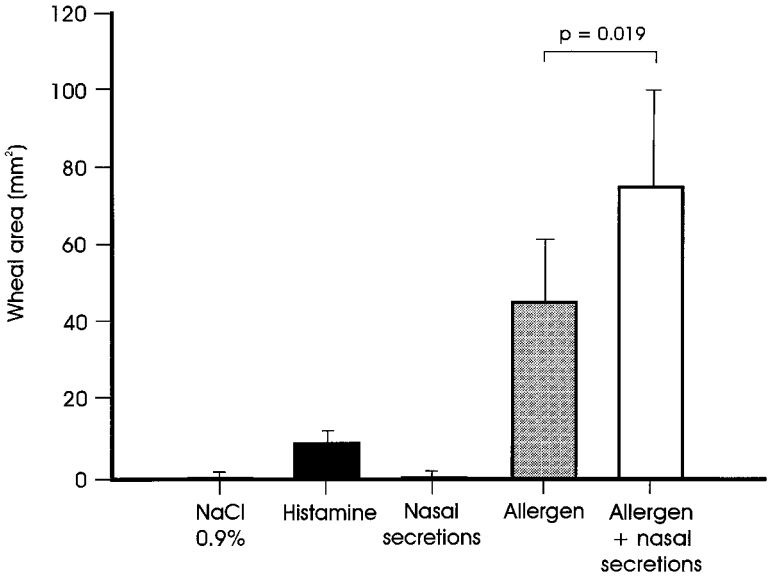


FIG 2. Nasal secretions may increase the allergenic activity of inhaled antigens. Two isoforms of a major Timothy grass allergen, Phl p5, were expressed in *Escherichia coli,* purified, and converted to stable, low-molecular-weight 10 to 20-kd peptides. In the presence of nasal secretions obtained from healthy subjects and from patients with allergic rhinitis, these recombinant allergens produced larger skin wheals (ie, had increased biologic activity) compared with allergen alone. (Modified from Bufe A, Gehlhar K, Schramm G, Schlaak M, Becker W-M. Allergenic activity of a major grass pollen allergen is elevated in the presence of nasal secretion. Am J Respir Crit Care Med 1998;157:1269-76.)

of progenitor cells in peripheral blood have been documented.

Improved understanding of the integration of the systemic and local immunologic responses in the upper and lower airways is needed. The presence of the systemic response, and of multiorgan disease, has made it difficult to depend absolutely on peripheral blood markers such as eosinophil-, mast cell–, or neutrophil-derived substances; T cells; cytokines or adhesion molecules; or exhaled nitric oxide as hallmarks of inflammation in the lower airways.[21]

TREATMENT

Allergic rhinitis and asthma are generally studied as separate disorders and treated as separate disorders, as reflected in current guidelines for the diagnosis and management of each disorder.[22,23]

Avoidance of environmental allergens and immunotherapy

Avoidance of airborne allergens and, in some patients, immunotherapy with these allergens likely benefits the entire airway, although few studies have been concerned with both allergic rhinitis *and* asthma.[24,25] Whether allergen avoidance and immunotherapy are effective because they prevent or relieve the early and late allergic responses in the upper and lower airways, or because they downregulate the systemic allergic response, or both, is not entirely clear at this time.

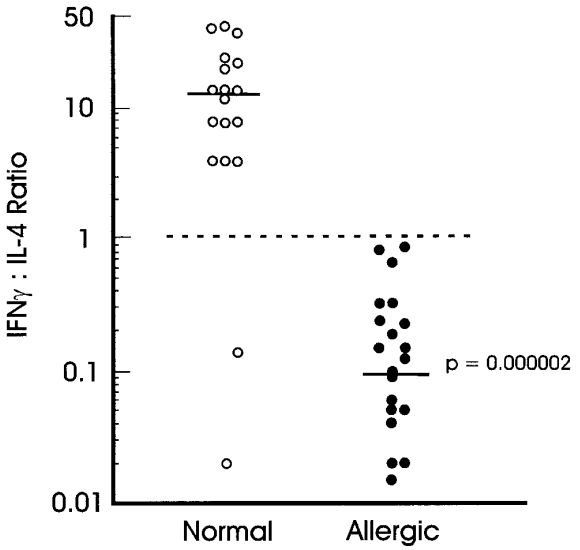


FIG 3. Allergic subjects have a systemic response to allergen. Primary cultures of fresh PBMCs from grass pollen–sensitive patients and nonallergic control subjects were stimulated with different grass pollen concentrations in the absence of exogenous cytokines or polyclonal activators. In allergic subjects mean IL-4 production was 13 pg/mL compared with less than 1 pg/mL in control subjects ($P < .000001$) and IFN-γ was lower ($P = .008$), providing direct evidence for an imbalance in both IL-4 and IFN-γ production. A ratio of 1.0 *(dashed line)* reflects balanced IFN-γ/IL-4 production. (Modified from Imada M, Simons FER, Jay FT, Hay-Glass KT. Allergen-stimulated interleukin-4 and interferon-gamma production in primary culture: responses of allergic subjects and normal controls. Immunology 1995;85:373-88.)

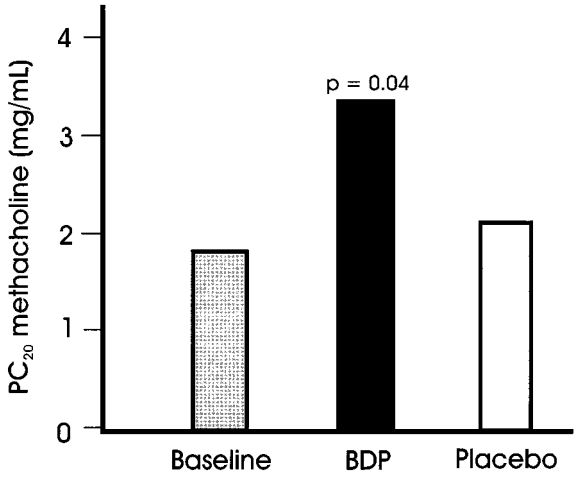


FIG 4. Treatment of allergic rhinitis indirectly improves asthma symptoms and decreases bronchial hyperreactivity. In a double-blind cross-over study, children were treated with intranasal aqueous beclomethasone dipropionate *(BDP)* or placebo, each given for 4 weeks. Compared with placebo treatment, after beclomethasone dipropionate treatment, although peak expiratory flows did not differ, rhinitis and asthma symptom scores were lower and bronchial hyperresponsiveness to methacholine improved significantly (shown). (Modified from Watson WTA, Becker AB, Simons FER. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. J Allergy Clin Immunol 1993;91:97-101.)

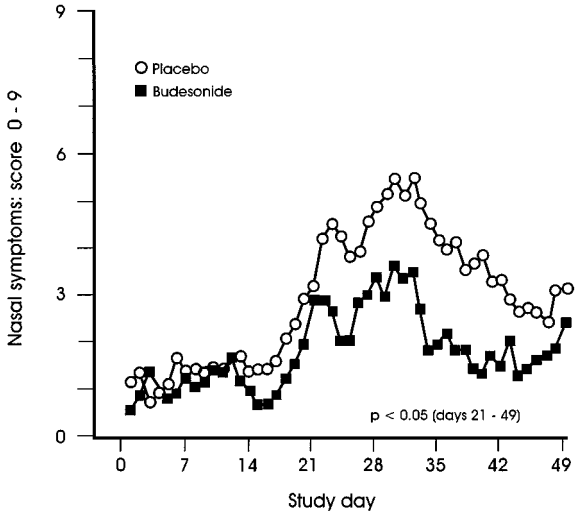


FIG 5. Treating subclinical asthma with an orally inhaled glucocorticoid may improve allergic rhinitis. In a placebo-controlled, double-blind, parallel-group 7-week study during the birch pollen season, patients with allergic rhinitis and bronchial hyperresponsiveness to methacholine, but no clinical asthma, orally inhaled budesonide 600 μg twice daily by Turbuhaler dry-powder inhaler (Astra). Budesonide prevented seasonal development of increased bronchoconstrictor responsiveness to methacholine ($P < .05$), and also reduced nasal symptoms (shown), nasal brush eosinophils, nasal lavage fluid eosinophilic cationic protein, and peripheral blood eosinophilia. The mechanism for its significant anti-inflammatory effects throughout the entire airway, including the nasal mucosa, which was not exposed topically to it, could be either systemic absorption or communication between the lower airways and the bone marrow involving cytokines such as IL-5 and GM-CSF and chemokines such as eotaxin or unselected airways migration of T lymphocytes. (Modified from Greiff L, Andersson M, Svensson C, Linden M, Wollmer P, Brattsand R, et al. Effects of orally inhaled budesonide in seasonal allergic rhinitis. Eur Respir J 1998;11:1268-74.)

Pharmacology

The only major difference between the pharmacologic treatments for allergic rhinitis and asthma relates to differences in adrenergic control in the upper and lower airways, with α-adrenergic agonists acting as vasoconstrictors in allergic rhinitis and β_2-adrenergic agonists acting as bronchodilators in asthma[26] (Table I).

During the past few decades the focus has been on administration of medications such as glucocorticoids in high concentrations directly to receptor sites in the target organ to minimize systemic absorption of the medication and to reduce or eliminate potential adverse effects. This approach has been extremely successful in reducing morbidity but also has had the unanticipated effect of reinforcing the artificial distinction between allergic rhinitis and asthma as separate disorders. With use of exquisitely sensitive gas chromatography–mass spectroscopy assays, it is possible to measure glucocorticoid concentrations in plasma after intranasal or oral inhalation,[27] and evidence for at least some systemic effect of many intranasally or orally inhaled glucocorticoids is mounting.

In the initial studies in which an intranasal glucocorticoid was found to reduce nasal symptoms significantly and concurrently to reduce asthma symptoms or decrease bronchial hyperresponsiveness significantly, the possibility of intrapulmonary deposition of the intranasally administered medication could not be ruled out. In later placebo-controlled, double-blind studies this concern was addressed and satisfactory evidence was obtained that intranasal solutions not only decreased nasal symptoms but also improved asthma symptoms, pulmonary function test results, and bronchial hyperresponsiveness without entering the lower airways (Fig 4).[28,29] In one study beclomethasone dipropionate aqueous solution labeled with technetium 99 was placed in the anterior nares of volunteers, after which radionucleotide scan revealed 63% of radioactivity over the abdomen, 35% over the nasopharynx, and only 2% over the chest.[28] In another study the subjects inhaled to total lung capacity before the beclomethasone dipropionate solution was introduced intranasally; in addition, laser analysis of the size of the particles in the nasal solution revealed a mean diameter of 30 μm, making it unlikely that much beclomethasone dipropionate reached the lower airways.[29] The lower airway effects of intranasal glucocorticoids are small, consistent, and probably dose dependent because they are not found when low doses are administered.[30] The same dose of glucocorticoid may provide more protection against bronchial hyperresponsiveness when administered intranasally than when administered directly into the lower airways.[31]

In contrast to the above, orally inhaled glucocorticoids not only have anti-inflammatory effects in the lower airways as expected but also in the nasal mucosa that has not been exposed topically to them (Fig 5).[32]

Currently available classes of oral medications are generally used in *either* allergic rhinitis *or* asthma, and their potential has seldom been fully explored in both disorders. For example, theophylline, used for more than 6 decades in the treatment of asthma, is not generally considered to be useful in allergic rhinitis treatment, although it has been documented to prevent symptoms of allergic rhinitis.[33] Conversely, although H_1-receptor antagonists have a well-established role in the treatment of allergic rhinitis, they are generally considered to be ineffective in asthma treatment unless given in high and potentially unsafe doses. Recently, however, in doses ordinarily used for seasonal allergic rhinitis, they have been reported to improve coexisting *mild* seasonal asthma symptoms and improve pulmonary function (Fig 6).[34] Signaling a new trend, the role of cysteinyl leukotriene modifiers, defined initially in asthma, is now also being investigated in allergic rhinitis.[35]

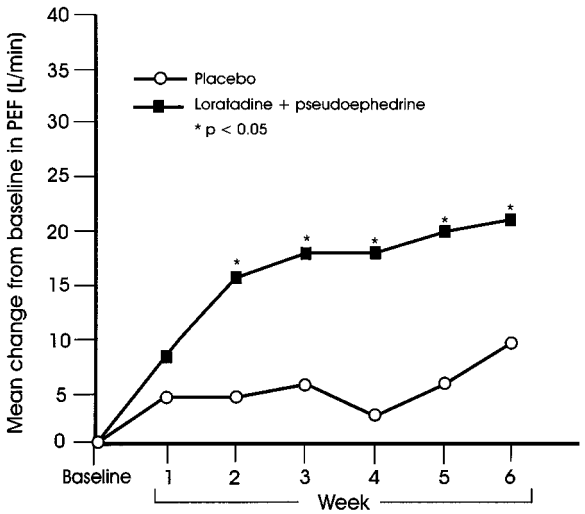


FIG 6. In allergic rhinitis and mild seasonal asthma "usual" rhinitis doses of orally administered H_1-antagonist decrease asthma symptoms as well as rhinitis symptoms. In a 6-week randomized, double-blind, placebo-controlled study of 193 subjects during the fall allergy season, loratadine 5 mg and pseudoephedrine 120 mg twice daily significantly decreased nasal symptoms, asthma symptoms (cough, morning wheeze, dyspnea, and chest tightness), significantly improved morning and evening peak expiratory flows, increased FEV_1, and improved asthma-related quality of life. Morning peak expiratory flow is shown. (Modified from Corren J, Harris AG, Aaronson D, Beaucher W, Berkowitz R, Bronsky E, et al. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. J Allergy Clin Immunol 1997;100:781-8.)

SUMMARY

The new term *allergic rhinobronchitis* accurately describes chronic allergic inflammation throughout the airways of patients with concurrent allergic rhinitis and asthma. Although perhaps an oversimplification, it is introduced with the hope that physicians who never fail to examine the chest will also remember to examine the nose and that those who routinely examine the nose will not neglect the chest. Rhinitis with partial or complete upper airways obstruction may contribute significantly to asthma symptoms, and uncontrolled allergic rhinitis may lead to worsening of coexisting asthma. The key to management of both disorders lies in addressing the common immunopathologic mechanisms and in preventing and relieving chronic allergic inflammation, not only with appropriate pharmacologic treatment but also by recommending allergen avoidance and, in selected patients, specific immunotherapy.

Additional well-controlled objective studies are needed to clarify the therapeutic links between allergic rhinitis and asthma and to elucidate the mechanisms underlying the physiologic and immunopathologic links between the two disorders.

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The number of references in a Rostrum article is limited, and it is therefore possible to highlight only a few relevant human studies.