

Beyond the Nose: The Systemic Inflammatory Effects of Allergic Rhinitis

Allan T. Luskin, MD

Joseph E. Scherger, MD, MPH

Susan M. Pollart, MD

Contrary to common belief, allergic rhinitis is not a trivial illness but a major medical condition that affects the quality of life of tens of millions of individuals in the United States. Although estimates vary, the number of persons affected by allergic rhinitis in the United States ranges from 23.7 to 79.5 million.¹⁻³ The disease can be lifelong and often starts early, with peak incidence in childhood and adolescence. Estimates of physician-diagnosed allergic rhinitis in children range from 9%⁴ to 42%.⁵

Allergic rhinitis can affect more than the nose, with clinical manifestations extending to several body systems, including the eyes (tearing, ocular pruritus, eyelid and conjunctival edema), sinuses (infection with recurrent pressure or congestion-type headache), and central nervous system (fatigue and somnolence). Furthermore, allergic rhinitis is implicated in the development and exacerbation of other common inflammatory illnesses, including asthma, sinusitis, and otitis media. The economic burden of allergic rhinitis is significant and includes the cost of both medications and lost productivity, the latter being estimated at 3.4 million workdays lost annually.⁶ In addition, patient quality of life can be seriously affected by nocturnal sleep loss, daytime fatigue,⁷ and impaired learning^{7,8} and performance.

This article reviews the pathophysiology of allergic rhinitis and current therapeutic approaches to this important inflammatory disease. After assessing frequency and severity of allergic rhinitis symptoms, the primary goal of treatment is to control the disease by relieving symptoms and improving quality of life. Effective management of allergic rhinitis also may reduce the symptoms of associated inflammatory conditions. Thus, by recognizing and properly treating allergic rhinitis, physicians have the potential to dramatically reduce the morbidity associated with this disease.

PATHOPHYSIOLOGY OF ALLERGIC RHINITIS Mechanisms of Inflammation

The systemic nature of allergic rhinitis has become clearer with enhanced understanding of the disease's pathophysiology as an allergic response in the nasal mucosa, which involves mobilization of inflammatory cells and mediators common to the upper and lower airways. Allergic rhinitis begins when airborne allergens land on the nasal mucosa, causing production of allergen-specific immunoglobulin E (IgE). The IgE then attaches to immune cells, causing the patient to be sensitized, and subsequent allergen exposure induces the clinical symptoms of allergy. Allergens initiate allergic rhinitis when inflammatory mediators are released from the sensitized immune cells, including lymphocytes, macrophages, mast cells, basophils, and eosinophils. Allergic inflammation (typically affecting the nose, ears, sinuses, or small airways of the lungs) acts on local structures (smooth muscle, epithelial cells, and nerves) to produce increased sensitivity of the affected tissue to specific allergens.

Among inflammatory cells, eosinophils represent a common thread in upper and lower airway inflammation. Eosinophils have been shown to be elevated in the nasal lavage of allergic rhinitis patients following allergen challenge,⁹ in the sputum of asthma patients,¹⁰ in the sinuses of patients with allergic rhinitis and sinusitis,¹¹ and in the middle ear of patients with otitis media.¹² Furthermore, the severity of symptoms of both allergic rhinitis and asthma has been correlated with

Dr. Luskin is a clinical associate professor, Department of Medicine, University of Wisconsin, Madison, WI. Dr. Scherger is a clinical professor, Department of Family and Preventive Medicine, University of California at San Diego, CA. Dr. Pollart is an associate professor and vice chair, Department of Family Medicine, and director, Generalist Scholars Program, University of Virginia, Charlottesville, VA.

the degree of eosinophilia in the nose⁹ and sputum,¹⁰ respectively. For many patients with perennial and seasonal allergy, ongoing inflammation of the nose is a problem even if the patients are apparently symptom free. This *minimal persistent inflammation* is present during periods of minimal allergen exposure.^{13–15}

The inflammatory mediators released after allergen challenge are common to both the upper and lower airways. These mediators include histamine, cysteinyl leukotrienes (ie, LTC₄, LTD₄, and LTE₄), prostaglandins, kinins, and neuropeptides.¹⁶ In the so-called *early-phase reaction* that occurs minutes after allergen challenge, histamine is released into nasal secretions and produces vasodilation, increased capillary leakage, and mucus secretion.^{17,18} Histamine binds to H₁ receptors, leading to the well-known symptoms of sneezing,^{19,20} pruritus,^{20,21} rhinorrhea,^{20,22} and (to some extent) congestion.^{20,21}

In the so-called *late-phase reaction* that occurs 4 to 5 hours after allergen challenge, newly synthesized cysteinyl leukotrienes and prostaglandins attract more inflammatory cells (eosinophils, basophils, and activated T cells) to the area. These cells, in turn, generate more inflammatory mediators, exacerbating local inflammation.^{16,23} Levels of cysteinyl leukotrienes increase in the nasal fluid of allergic patients.²⁴ The cysteinyl leukotrienes are 5000 times more potent than histamine in inducing nasal response.²² In nasal and bronchial tissues, leukotrienes cause vascular permeability, tissue edema, airway mucus secretion, impaired ciliary clearance, and accumulation of inflammatory cells.^{22,25} In the lower airway, they produce bronchoconstriction.²³ Additionally, the cysteinyl leukotrienes may help eosinophils survive by decreasing their apoptosis, thereby maintaining eosinophilic inflammation.²⁶ These inflammatory cells produce a variety of chemokines and cytokines that produce and augment tissue inflammation and hyperactivity.

Common Associated Inflammatory Diseases

Allergic rhinitis often is associated with other inflammatory diseases.^{27,28} These diseases share common inflammatory mediators with allergic rhinitis, which may explain why treating allergic rhinitis may improve comorbid conditions.

Asthma is diagnosed in 21%²⁹ to 58%³⁰ of patients with allergic rhinitis; conversely, 86%²⁹ to 92%³¹ of patients with asthma are diagnosed with allergic rhinitis. In children, allergic rhinitis can be a risk factor for developing asthma⁵; 22% of those with diagnosed allergic rhinitis also are found to have asthma.⁴ Underlying

asthma may be exacerbated by altered bronchial responsiveness resulting from allergic rhinitis.³² Mouth breathing, which often is caused by nasal obstruction in allergic rhinitis, also can elicit asthma-like symptoms and potentiate lower airway hyperresponsiveness and exercise-induced bronchospasm.³³

Up to 53% of patients with allergic rhinitis have coexistent sinusitis.³⁴ Conversely, 25%³⁵ to 58%³⁶ of patients with sinusitis have allergic rhinitis. In allergic patients, sinusitis can worsen after nasal allergen challenge, as evidenced by radiographic changes in the maxillary sinuses.³⁷

Allergic rhinitis also can be associated with otitis media, especially in children younger than 15 years, in whom otitis media with effusion (OME) represents up to 11.8% of total visits to a physician for any reason (2.7% for the general population).³⁸ Of children with allergic rhinitis, 21% were found to have OME,^{39,40} whereas 50%³⁹ of children diagnosed with chronic OME had concomitant allergic rhinitis. Allergic rhinitis also can be associated with acute or perennial allergic conjunctivitis, leading to tearing, itching, and burning of the eyes.

APPROACH TO MANAGEMENT OF ALLERGIC RHINITIS

Therapeutic Goals

Appropriate management of allergic rhinitis not only improves symptoms of the disease but also concomitantly reduces inflammation and improves comorbid inflammatory conditions. Conversely, poorly controlled allergic rhinitis can contribute to the development or worsening of other diseases and conditions, including acute and chronic sinusitis, recurrence of nasal polyps, otitis media, hearing impairment, abnormal craniofacial development, and sleep apnea.⁴¹

The primary goal of allergic rhinitis management should be control of the disease by relief of symptoms and improvement of quality of life. Successful treatment should result in no complications of allergic rhinitis, including uncontrolled asthma; otitis media; sinusitis; frequent upper respiratory infections; or abnormalities in learning, memory, alertness, performance, multitasking, mood, or behavior. Environmental and social factors should be optimized to allow patients to lead a normal life.

Matching Therapy to Disease Severity

In 2001, a World Health Organization initiative culminated in the publication of the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, which propose a disease classification model on which to base allergic

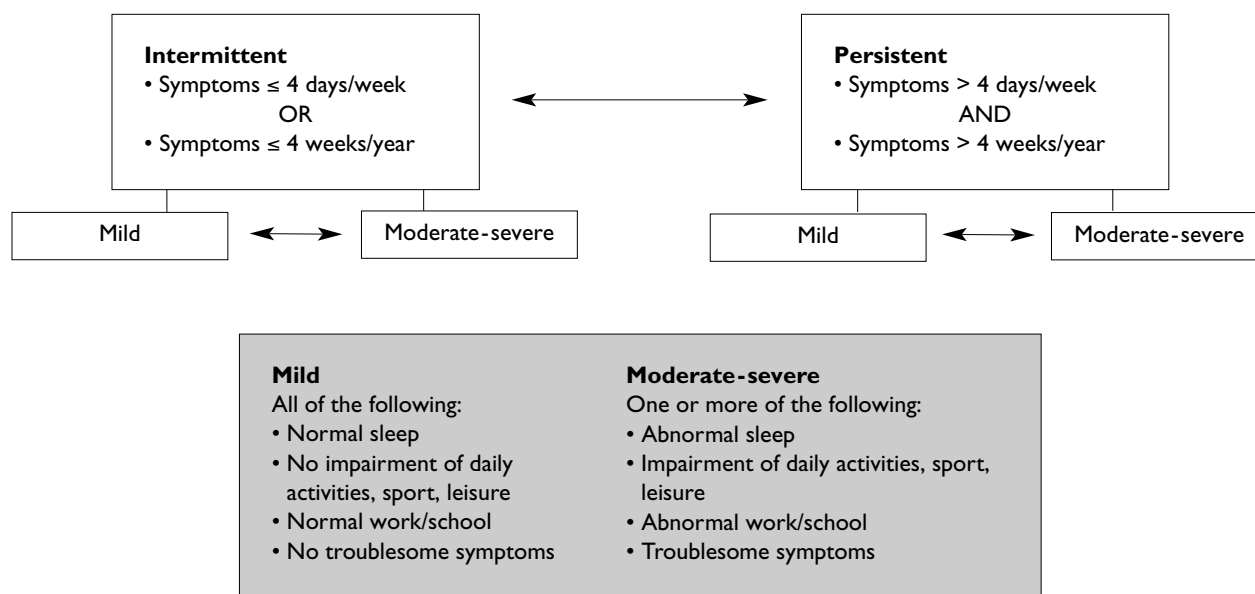


Figure 1. Revised classification of allergic rhinitis, based on frequency and severity of symptoms, as proposed by the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines. The ARIA guidelines describe allergic rhinitis as a complex syndrome involving upper and lower airways, with the confounding issues of seasonal, perennial, or occupation-related occurrence. The ARIA classification model considers allergic rhinitis to be intermittent or persistent in duration and grades the symptoms as either mild or moderate-severe. (Adapted from Bousquet J, van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *Aria Workshop Group; World Health Organization. J Allergy Clin Immunol* 2001;108[5 Suppl]:S147–334.)

rhinitis treatment.⁴² According to this model, allergic rhinitis is divided into 2 subcategories—persistent and intermittent—with symptoms graded by severity and by their effect on patient quality of life (**Figure 1**). Answers to simple questions based on this classification scheme enable physicians to assess the severity of allergic rhinitis in their patients (**Table 1**).⁴² Once allergic rhinitis is classified, treatment is prescribed.

The severity classification may vary. Some patients may have relatively mild perennial symptoms that do not severely disrupt daily activities. During pollen season, however, these patients may experience exacerbation of their symptoms, and their disease then could be classified as moderate-severe persistent.⁴³ Physicians using the ARIA classification scheme establish a starting point for treatment; subsequently, classification may be seen as fluid, with patients moving from one categorization to another depending on exacerbations or disease control. **Figure 2** shows a stepwise approach to the management of allergic rhinitis based on the ARIA classification scheme.⁴³ For efficacy and safety, the ARIA guidelines recommend combining the treatment of upper and lower airway disease.⁴²

TREATMENT MODALITIES

Treatment modalities for allergic rhinitis include allergen avoidance, pharmacotherapy, and immunotherapy. Effective treatment requires patient adherence to a therapeutic regimen. Convenience of use and patient education are critical to improved adherence.

Allergen Avoidance

The first step in the treatment of allergic rhinitis is to help patients recognize offending allergens and, to the extent possible, minimize contact with them. Although not always easily accomplished and therefore not fully effective in controlling symptoms, this step remains a cornerstone of treatment.⁴³

Pharmacotherapy

A variety of medications have proven efficacious for treating allergic rhinitis. When choosing a specific drug, the clinician must consider the age of the patient, potential adverse effects of the medication, and factors that may influence patient adherence (eg, preference for an oral versus a topical agent). Considering all these parameters, the clinician should be able to

Table 1. Patient Questionnaire to Assess Severity of Allergic Rhinitis

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1. In the past 12 months, how many times have symptoms, such as sneezing or runny or blocked nose, occurred?
 - Four or less days a week or 4 or less weeks in the year?
 - More than 4 days a week and more than 4 weeks in the year?
 2. In the past 12 months, have these nose problems been accompanied by sleep disturbance?
 3. In the past 12 months, how much has this nose problem interfered with your daily activities, such as school, work, leisure activities, or sport?
 - Not at all
 - A little
 - A moderate amount
 - A lot
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Adapted from Bousquet J, van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. Aria Workshop Group; World Health Organization. *J Allergy Clin Immunol* 2001;108(5 Suppl): S147–334, with permission from Elsevier Science.

prescribe a therapy that optimizes treatment adherence and, subsequently, disease control.

Intranasal corticosteroids. Topical nasal steroids are the most potent anti-inflammatory medications commercially available for allergic rhinitis treatment.⁴⁴ Three international reports on the management of rhinitis now consider these agents as first-line therapy for adults in moderate-to-severe cases of seasonal and perennial allergic rhinitis.^{45–47} Nasal steroids can suppress many of the stages of the allergic inflammatory process, which helps to explain their potent effect on allergic symptomatology (**Figure 3**). Nasal steroids affect local inflammatory activity in the nose, and oral administration of the equivalent amount of drug produces no benefit.

Because allergic rhinitis symptoms result from mechanisms of priming by allergen and hyperreactivity, it is best to begin intranasal steroid therapy *before* the onset of symptoms. Even if steroids are given after immediate reaction to an allergen, they may prevent inflammation from developing and thus prevent symptomatic response.⁴⁸ Regular prophylactic use effectively reduces nasal blockage, rhinorrhea, sneezing, and nasal itching in adults and children. In seasonal and perennial allergic rhinitis, nasal steroids control nasal symptoms in most patients. Analysis has shown that in rhinitis, intranasal steroids are more effective than oral antihistamines⁴⁹ and intranasal cromolyn.⁵⁰ Furthermore, decreasing nasal

congestion with nasal steroids may improve sleep, reduce daytime fatigue, and increase the quality of life of patients with allergic rhinitis.⁵¹

In asthma patients with rhinitis, nasal steroids reduced the relative risk (RR) for an emergency department (ED) visit to 0.7 (patients prescribed antihistamines had an indeterminate RR), suggesting that treatment of nasal inflammation with nasal steroids significantly protected against ED visits for asthma exacerbations.⁵² In adult patients with seasonal allergic rhinitis and concomitant asthma, treatment with a nasal steroid (beclomethasone or flunisolide) or cromolyn (nasal solution) not only improved allergic rhinitis symptoms during pollen season but also significantly improved symptoms of asthma.⁵⁰

Currently available intranasal steroids are well tolerated and can be used on a long-term basis without atrophy of the mucosa.⁵³ Although systemic absorption may occur following use of nasal or inhaled corticosteroids,^{54,55} the low doses required and the limited systemic drug availability across nasal mucosa put patients receiving only intranasal steroid therapy at very low risk for developing hypothalamic-pituitary-adrenal (HPA) axis suppression.^{56,57} The newer glucocorticoids—fluticasone propionate, budesonide, triamcinolone acetonide, and mometasone furoate—usually show no effect on the HPA axis.^{58–60} In patients already taking inhaled steroids (eg, for treatment of asthma), the addition of a nasal steroid to their therapeutic regimen may lead to increased adverse effects; therefore, caution should be used when prescribing a nasal steroid. If the patient's symptoms are mild or intermittent, an antihistamine or possibly a leukotriene receptor antagonist (LTRA) could be a good choice.⁴²

Antihistamines. Antihistamines have a long history of use in treating allergic diseases. They can be divided into 2 groups: first-generation (sedating) and second-generation (nonsedating). First-generation oral antihistamines (chlorpheniramine, diphenhydramine, promethazine, and triprolidine) have an overall unfavorable risk-benefit ratio because of poor selectivity and sedative and anticholinergic effects. Their impact on the central nervous system can impair learning and driving.⁸ Therefore, if possible, these drugs should no longer be prescribed for the treatment of allergic rhinitis.⁴² One first-generation antihistamine, astemizole, is available for topical use as a nasal spray. Onset of action is rapid, making it useful for treatment on an as-needed basis. However, sedation may occur and combined with bad taste may limit patient acceptance.

Second-generation antihistamines (cetirizine, loratadine, and fexofenadine), introduced over the past

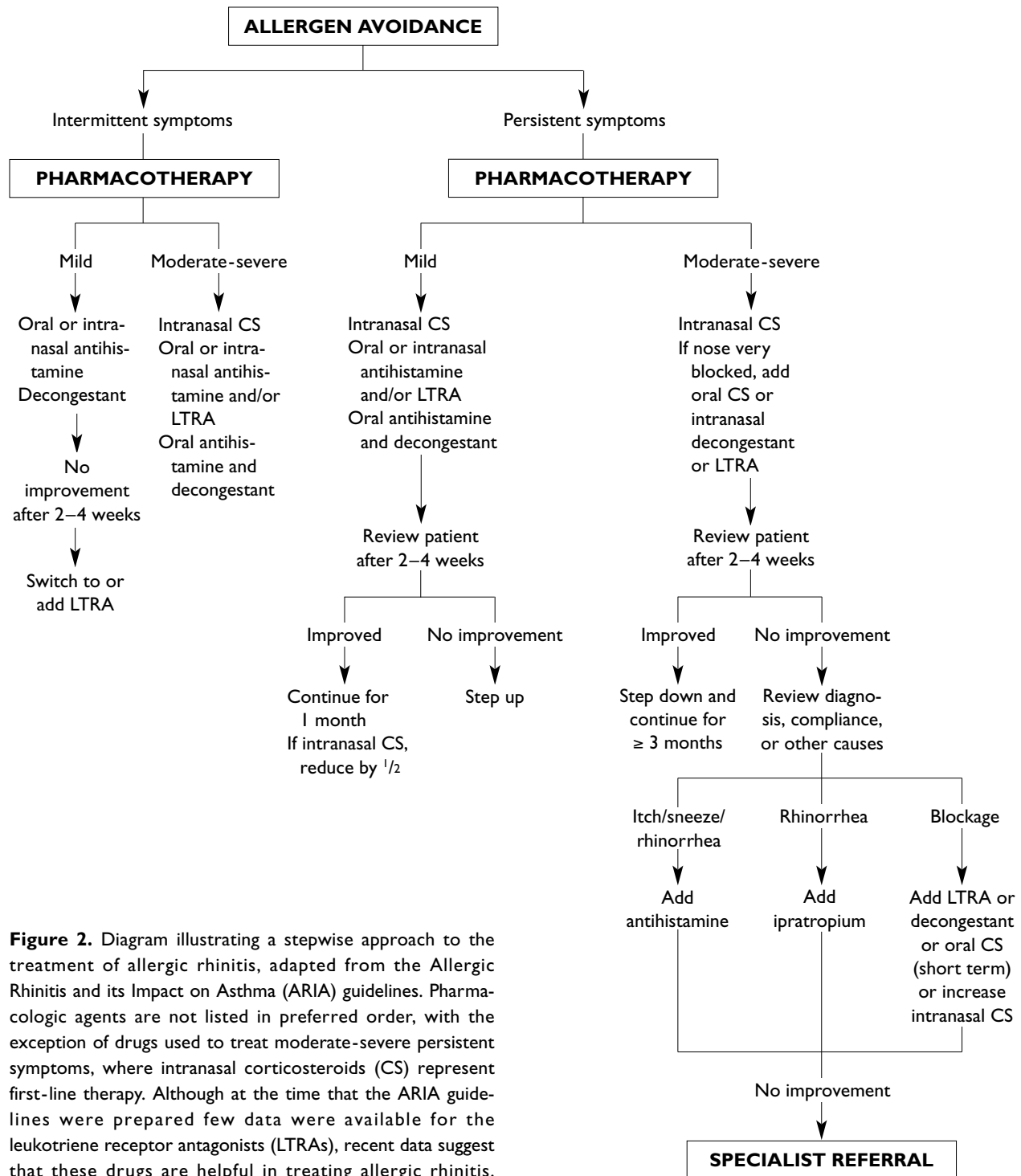


Figure 2. Diagram illustrating a stepwise approach to the treatment of allergic rhinitis, adapted from the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines. Pharmacologic agents are not listed in preferred order, with the exception of drugs used to treat moderate-severe persistent symptoms, where intranasal corticosteroids (CS) represent first-line therapy. Although at the time that the ARIA guidelines were prepared few data were available for the leukotriene receptor antagonists (LTRAs), recent data suggest that these drugs are helpful in treating allergic rhinitis. Therefore, LTRAs are included in this scheme to reflect their potential role in allergic rhinitis therapy. (Adapted from Bousquet J, van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *Aria Workshop Group; World Health Organization. J Allergy Clin Immunol* 2001;108 [5 Suppl]:S147–334, with permission from Elsevier Science.)

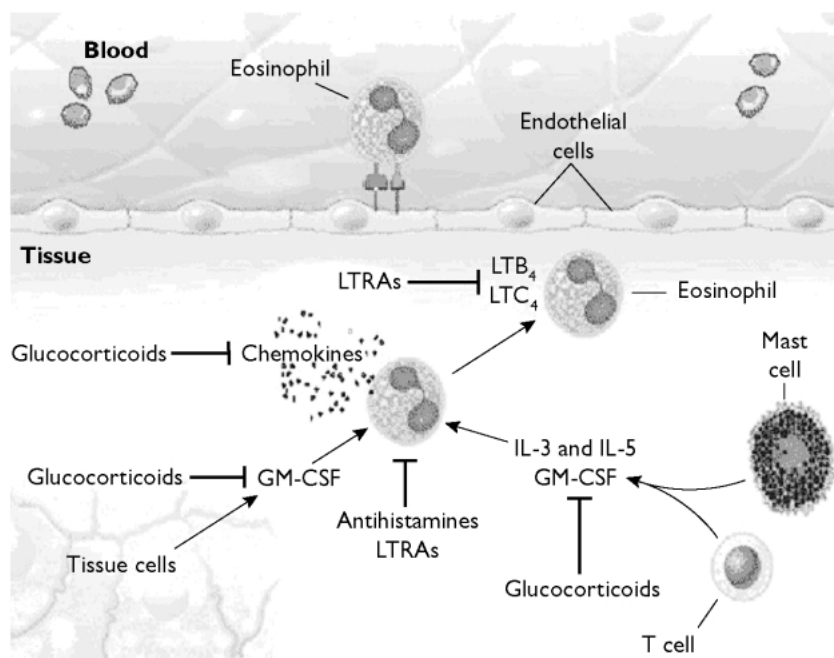


Figure 3. Eosinophilic inflammation, such as observed in allergic rhinitis or asthma, can be treated at various levels using intranasal glucocorticoids, antihistamines, or leukotriene receptor antagonists (LTRAs). The chemoattraction process can be targeted at various steps, including interference with the synthesis or activity of leukotrienes B₄ and C₄ (LTB₄, LTC₄) or inhibition of chemokine production. Glucocorticoids can block the proliferation, survival, and activation of eosinophils by interfering with the generation of eosinophil hematopoietins such as granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3), and interleukin-5 (IL-5). LTRAs also inhibit eosinophil adhesion, migration, and survival. (Adapted with permission from Rothenberg ME. Eosinophilia. *N Engl J Med* 1998;22:1592–600. Copyright © 1998 Massachusetts Medical Society. All rights reserved.)

15 years, are highly selective for the H₁ receptor and offer many improvements over first-generation agents, including higher potency, faster onset and longer duration of action, and minimal sedative effects. (Of the currently available second-generation antihistamines, only cetirizine has significant sedative potential at usual doses.) In addition, they usually can be administered once daily. Second-generation antihistamines are very effective in reducing many nasal symptoms, including itching, sneezing, and rhinorrhea, as well as conjunctivitis. They have less effect on nasal obstruction, however. In the past, antihistamines have not been considered to be anti-inflammatory drugs, but laboratory studies with fexofenadine and cetirizine suggest possible anti-inflammatory effects.^{61,62} More studies are needed to confirm this.

Leukotriene modifiers. The role of cysteinyl leukotrienes as important mediators of nasal allergic reactions suggests that LTRAs may be useful in the treatment of allergic rhinitis, either alone or in combination with antihistamines. The LTRA montelukast was recently approved for treatment of seasonal allergic rhinitis. Montelukast brought significant improvement to allergic rhinitis patients during both spring and fall.^{63,64} Compared with patients receiving placebo, patients treated with montelukast had significantly reduced daytime nasal symptom scores (congestion, rhinorrhea, pruritus, and sneezing) as well as night-

time symptom scores (difficulty going to sleep, nocturnal awakening, and nasal congestion upon awakening).^{63,64}

The rationale for using both an LTRA and an antihistamine to treat allergic diseases is based on the premise that blocking both inflammatory mediators would be more beneficial than blocking only one. Patients with seasonal allergic rhinitis benefited similarly from either a combination of montelukast and the antihistamine cetirizine or the intranasal steroid mometasone, suggesting that the combination of an LTRA and an antihistamine could be as effective as a nasal steroid alone.⁶⁵ Also, in patients with both seasonal allergic rhinitis and asthma, the combination of cetirizine with montelukast was as effective as the combination of inhaled and nasal budesonide,⁶⁶ and these 2 combinations were equally effective in improving asthma.⁶⁷

Decongestants. By their agonist activity at α -adrenergic receptors, decongestants cause vasoconstriction⁶⁸ and, consequently, reduced swelling. Intranasal decongestants are effective therapies for nasal obstruction in allergic rhinitis patients; however, they do not improve rhinorrhea, sneezing, or nasal itching. They generally have short-lasting effects (< 1 hour), although oxymetazoline effects can last up to 8 hours after inhalation.⁶⁹ More than 10 days of use can lead to tachyphylaxis-based rebound of nasal mucosal swelling and possible rhinitis medicamentosa (drug-induced rhinitis).^{70,71}

Oral decongestants are commonly used, particularly pseudoephedrine.^{72–74} These agents typically take effect within 30 minutes and last from 6 hours (regular tablets) to 24 hours (extended-release tablets).⁴² As with intranasal sympathomimetics, oral decongestants improve only nasal congestion and not other allergic rhinitis symptoms. Systemic adverse effects with oral decongestants are common and dose dependent; they include irritability, dizziness, headaches, tremor, insomnia,⁴² tachycardia,⁷⁵ and hypertension.^{76,77} Caution should be taken, therefore, when these drugs are used.

Patient considerations when choosing medication. Although comparative studies confirm the clinical superiority of intranasal steroids over antihistamines, nasal steroids must be taken intranasally and may be most effective if their use is started before symptom onset—both factors that tend to reduce patient adherence. Surveys suggest that most patients favor once-daily oral dosing with antihistamines over nasal steroids. This notion was borne out in a study reviewing prescription refill data over 2 years as a measure of adherence in 1000 patients with at least moderate allergic rhinitis (Figure 4).⁷⁸ Only 15% of patients who were prescribed both an antihistamine and a nasal steroid persisted with both medications; 17% were persistent with the steroid but not the antihistamine, and 68% were persistent with the antihistamine but not the steroid. In a separate group of patients prescribed only intranasal steroid, 55% were persistent. Therefore, patients preferred antihistamines. The percentage of patients persisting with intranasal steroid therapy (55%) decreased if antihistamines also were prescribed (32%).⁷⁸ This study suggests that prescribing patterns may not be maximally effective, and, if patient preferences are not considered, adherence may actually decrease.

Immunotherapy

Allergen-specific immunotherapy. Allergen-specific immunotherapy involves administration of gradually increasing quantities of an allergen vaccine to an allergic subject to ameliorate symptoms from subsequent exposure to the causative allergen. Allergen-induced, IgE-mediated inflammation should be seen as a multi-organ disease, and specific immunotherapy should be based on allergen sensitization rather than on a specific disease.

Specific immunotherapy is more effective for children and young adults than for persons later in life. In adults (mean age 35 years) with severe summer allergic rhinitis, specific immunotherapy significantly improved symptom scores and reduced the need for medication.⁷⁹ By reducing the severity of allergic rhinitis and

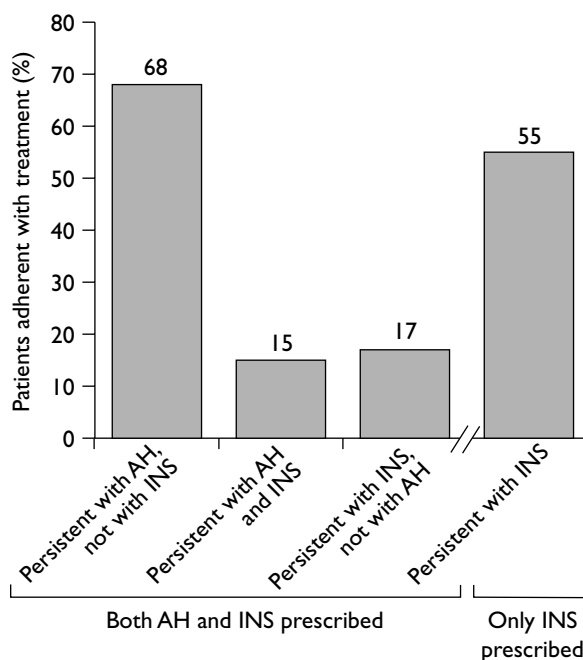


Figure 4. Summary of results from a study of patient adherence with various treatments for moderate allergic rhinitis. The 3 bars on the left represent patients for whom both antihistamines (AH) and intranasal steroids (INS) were prescribed. The bar on the right represents patients in a separate study who were prescribed only intranasal steroids. The percentage of patients persisting with intranasal steroid therapy decreased from 55% to 17% if antihistamines were also prescribed (Data from Luskin AT, Bukstein DA. Compliance with therapy in allergic rhinitis (AR): effect of medication type [abstract]. *Ann Allergy Asthma Immunol* 2000;84:124.)

the need for anti-allergy drugs, immunotherapy can improve patient quality of life⁸⁰ and reduce long-term costs. Using immunotherapy to treat allergic rhinitis in children with concomitant OME has been shown to significantly increase the interval between recurrences of OME compared with untreated children.³⁹ Specific immunotherapy in children also may modify the long-term prognosis of allergic inflammation and disease.

Because of possible anaphylactic reactions, a trained physician who is able to treat systemic reactions should administer the immunotherapy.⁴² The time commitment required to complete a full 3- to 5-year course of specific immunotherapy may represent a major barrier to its acceptance.

Monoclonal antibodies in development. An immunotherapy that is not allergen specific has been developed and is approved for use in patients with asthma but is not yet approved for treatment of allergic

rhinitis. Omalizumab (rhuMab-E25) uses a recombinant humanized monoclonal antibody against human IgE. When administered to patients with allergic rhinitis, omalizumab decreased free IgE levels in serum⁸¹ and significantly reduced symptom scores and drug use.⁸² In allergic asthmatic patients, this monoclonal antibody reduced levels of serum IgE and reduced early- and late-phase reactions following allergen bronchial challenge.⁸³ In patients with moderate-to-severe perennial allergic asthma who were dependent on inhaled or oral corticosteroids or both, omalizumab reduced asthma symptom scores significantly, compared with placebo; more individuals receiving the antibody were able to decrease or discontinue their use of corticosteroids and experienced improved quality of life.⁸⁴

CONCLUSION

A major barrier to appropriate allergic rhinitis management is the widespread misperception that allergic rhinitis is only a trivial nasal disease without broader clinical implications. In reality, allergic rhinitis is an inflammatory disease affecting both the upper and the lower airways. Furthermore, it is implicated in the development and exacerbation of other inflammatory diseases, notably asthma, sinusitis, conjunctivitis, and otitis media, and its effective treatment may reduce the symptoms of these comorbid conditions beyond the nose. Thus, allergic rhinitis is an important disease that must be taken seriously.

Physicians should be able to prescribe an effective therapeutic regimen for allergic rhinitis that optimizes adherence. A number of effective treatment modalities are available, including intranasal steroids, antihistamines, LTRAs, decongestants, and immunotherapy. Because a minimal persistent inflammation is possible in allergic rhinitis, treating even asymptomatic patients may be helpful.

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