

Symposium Cont. Progressive Management Strategies in the Treatment of Rhinitis

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ABSTRACT

Although environmental controls and immunotherapy have important roles in the management of rhinitis, pharmacotherapy is the mainstay of most treatment programs. Before effective pharmacotherapy can be instituted, correct diagnosis is required. There are rhinitis subtypes (allergic, nonallergic, or mixed), which influence pharmacologic choices. Correct diagnosis is, for a large part, reliant on collection of a thorough patient history. After correct diagnosis, a progressive management program can be developed. The effectiveness of the treatment program is dependent on accurate identification of the role allergic and nonallergic causes of rhinitis. (Allergy and Asthma Proc 24:163–169, 2003)

A variety of management strategies have been used to treat rhinitis. The guiding principle in promoting a successful outcome is the importance of fitting the therapy to the diagnosis. Many factors must be considered in designing an individualized treatment regimen. Of course, the effectiveness of the medication itself is of prime importance. However, the value of adherence to treatment should not be underestimated. To optimize compliance, the clinician might also consider the potential side effects of the medication, relative cost of the drug(s), patient preference for drug delivery route (oral versus topical), and dosing frequency. Although a comprehensive regimen that includes

several medications combined with saline washes may be optimal, it is also important to consider patient convenience with respect to integrating the regimen into the patient's schedule or combining it with concurrent medication regimens. Patients also sometimes show strong preferences for the delivery route and, initially, may resist nasal delivery routes. These hesitations can be allayed by establishing the use of an intranasal inhaler and providing suggestions to prevent local side effects. Patient education that integrates instruction in the use of the intranasal inhaler and emphasizes the importance of adherence can be of great value. Together, these efforts will help avoid both delays in relief and unnecessary costs.

An additional, but not inconsequential, benefit of prescribing an effective treatment is the possibility of lowering the risk of onset of comorbid disease, including sinusitis and asthma.^{1–5} This management goal can be achieved best by treating the respiratory system as a whole, rather than treating isolated rhinitis symptoms.^{4–7} By asking pertinent questions—Is there evidence of asthma or bronchial hyperresponsiveness? Is the rhinitis triggered by allergens, or are both allergic and nonallergic components present?—the underlying pathophysiology can be addressed.⁸ A key element of the diagnosis is determining whether the patient has allergic, nonallergic, or mixed rhinitis.

Recently, rhinitis management approaches have emphasized preventive measures.⁹ Environmental control of the home or workplace is aimed at removing exposure to relevant allergens in patients with allergic or mixed rhinitis or respiratory irritants in patients with nonallergic or mixed rhinitis, to reduce symptoms.^{9,10} Obviously, avoidance therapy requires identification of rhinitis triggers. Another measure that has been successful in patients with allergic rhinitis is immunotherapy. In fact, some studies have indicated its prophylactic value in preventing multiple sensitizations and impeding the progression from allergic rhinitis to

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Pharmacologic Therapy

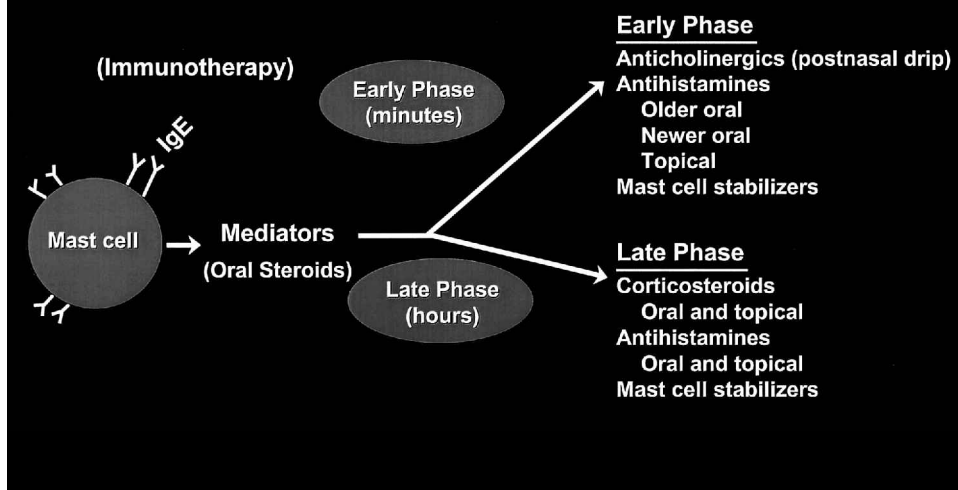


Figure 1. Effects of pharmacologic therapy on pathophysiology of allergic rhinitis.

asthma.^{11–13} However, pharmacotherapy remains the cornerstone of treatment for all types of rhinitis.

BROAD-BASED PHARMACOTHERAPY FOR ALLERGIC RHINITIS

Allergic rhinitis is the quintessential immunoglobulin E (IgE)-mediated reaction, occurring in two phases.¹⁴ Repeated low-dose exposure to certain allergens induces the development of specific IgE antibodies in atopic individuals. On subsequent reexposure to the inhaled allergen, cross-linking of these IgE molecules on the surface of mast cells triggers the release of numerous mediators, including histamine, leukotrienes, prostaglandins, and cytokines.^{15–19} During the early phase reaction, clinical symptoms occur within minutes of allergen exposure, beginning with sneezing and followed by an increase in nasal secretion.^{14,15,20} Within 5 minutes, airflow becomes reduced because of swelling of the nasal mucosa. Most of these early symptoms are caused by the binding of histamine to H₁-receptors on mucous-secreting cells, blood vessels, and nerve endings, which leads to nasal secretion, vasodilation, vascular permeability, and reflex cholinergic stimulation giving rise to enhanced glandular secretion in the nose, itching, and sneezing.^{15,21} These acute symptoms usually abate within 1 hour.

A late-phase reaction occurs in approximately one-half of rhinitis patients, manifesting as the recurrence of symptoms 4–8 hours later. Congestion is the predominant symptom of the late-phase reaction, mediated primarily by histamine, leukotrienes, and cytokines.^{15,20} The late phase also is characterized by an increased sensitivity to the offending aller-

gen and other irritants, referred to as priming, and the presence of chronic inflammation of the nasal mucosa, a direct result of the influx of inflammatory cells, particularly eosinophils and T-helper cells, and the concomitant release of their mediators, especially cytokines.^{15–17}

A wide spectrum of medications is used in the pharmacotherapy of allergic rhinitis, each drug interfering with a different aspect of the underlying pathophysiology (Fig. 1). Because of their competitive antagonism of histamine, antihistamines reduce the early and, to a lesser extent, the late reaction (Table I).^{21,22} Similarly, mast cell stabilizers impede both phases, although anticholinergic agents only partly modify the early phase reaction.²³ Corticosteroids are particularly effective at intervening in the late-phase response and preventing chronic inflammation because of their ability to inhibit the transcription of a variety of regulatory genes involved in inflammation.^{24,25}

Oral antihistamines are considered first-line treatment for seasonal and perennial allergic rhinitis, a broad-based class of drugs that reduce the symptoms of rhinorrhea, sneezing, and itching.⁹ Although antihistamines also exert a partial effect on nasal congestion, their effect is mitigated in part by the impact of leukotrienes and other mediators on nasal congestion. Because of their ability to cross the blood/brain barrier and their lack of specificity, first-generation oral antihistamines are associated with dopaminergic and cholinergic side effects, particularly drowsiness and cognitive impairment.^{9,22} The second-generation oral antihistamines—cetirizine, loratadine, fexofenadine, and desloratadine—represent a marked improvement over the first-gen-

TABLE I

Effectiveness of Pharmacologic Therapy

Pharmacologic Agent	Early Phase	Late Phase	Inflammation	Congestion	Rhinorrhea	Sneezing	Nasal Itch	Ocular Symptoms
Mast cell stabilizers	±	±	±	±	±	±	±	±
Anticholinergics	±	—	—	—	+	—	—	—
Decongestants	±	—	—	+	—	—	—	—
Topical corticosteroids	+	+	+	+	+	+	+	±
First-generation oral antihistamines	+	—	?	—	+	+	+	+
Second-generation oral antihistamines	+	±	±	±	+	+	+	+
Topical antihistamines	+	+	±	+	+	+	+	+

eration agents, owing to their reduced effects on the central nervous system, and receptor specification and long half-life.^{9,26} The benefits of the second-generation antihistamines have been enhanced further by the development of topical antihistamines such as azelastine, the intranasal delivery of which increases local drug concentration and limits systemic distribution. Because of its expanded range of activities, azelastine also relieves congestion and postnasal drip, and nasal hyperreactivity.^{27,28}

Both topical and oral second-generation antihistamines also are endowed with additional anti-inflammatory activities that render them more effective. These include the abilities to inhibit the synthesis and release of mediators, impede chemotaxis by affecting the production of adhesion molecules, inhibit the release of neurokinin, and alter transcription.^{22,28–36} The other distinct advantage of the second-generation antihistamines is their low side effect profile, reduced sedation being particularly critical because rhinitis itself can impair cognition.³⁷ However, even in adults, first-generation antihistamines are associated with an increased risk of automobile accidents and occupational accidents.⁹

An alternative broad-based treatment for certain types of allergic rhinitis are the mast cell stabilizers such as intranasal cromolyn sodium. Although readily available without prescription as Nasalcrom, this product must be administered prophylactically before the start of allergy season or exposure to a specific allergen because it functions by preventing the degranulation and release of mediators from mast cells. Also, for maximal effectiveness, it must be administered several (up to four to six) times throughout the day, which may influence compliance. Cromolyn sodium is most effective when combined with other broad-based therapies in severe cases of seasonal allergic rhinitis. Among the safest rhinitis treatments available, mast cell stabilizers are particularly useful in the pediatric and pregnant patients.⁹

Corticosteroids represent another broad-based treatment that, by virtue of their wide range of anti-inflammatory activities, are the most potent drugs available for treating seasonal and perennial allergic rhinitis. Corticosteroids are considered first-line therapy for moderate-to-severe cases of

rhinitis, effectively relieving most rhinitis symptoms. They accomplish these effects by acting at cellular and molecular levels to prevent the synthesis and release of cytokines; inhibit the IgE-mediated release of basophil- and mast cell-derived mediators; and reduce the recruitment and circulatory levels of proinflammatory cells, including mast cells, basophils, neutrophils, eosinophils, lymphocytes, and monocytes.^{39–45} These cellular effects ultimately diminish the pathophysiological processes that lead to inflammation, including vascular permeability, mucus secretion, and vasodilation.²⁴

Six topical intranasal corticosteroids have been approved in the United States for use in allergic rhinitis: beclomethasone, budesonide, flunisolide, fluticasone, triamcinolone, and mometasone. Short courses of oral steroids may, on rare occasions, be used for severe cases of rhinitis that fail to respond to other treatments. Although the side effect profiles of the intranasal corticosteroids are a marked improvement over those of oral steroids, caution is still required. Local side effects can include nasal irritation and low frequencies of ocular effects, bloody nasal discharge, and septal perforation.⁹ Patients should be monitored continually for the presence of mucosal erosions, the predecessor to septal perforation, and instructed to direct the spray away from the septum. The potentially growth-suppressive effects of intranasal corticosteroids in children also have raised concern, although studies have indicated that fluticasone and mometasone are relatively safe.^{45–48}

SYMPTOMATIC TREATMENT OF RHINITIS

Another management strategy for treating rhinitis is a symptomatic approach. This management strategy bridges the overlap between allergic and nonallergic rhinitis, recognizing that the symptoms of allergic, nonallergic, and mixed rhinitis, while resembling one another, require distinct treatment approaches. As a result, this approach highlights why treatment tailored to the diagnosis is superior to empiric treatment. For example, although congestion often accompanies allergic rhinitis, congestion is the hall-

TABLE II

Algorithms for Symptomatic Management of Congestion and Postnasal Drip

Congestion (or headache)
Vasomotor rhinitis
• Nasal antihistamine/nasal corticosteroid/saline nasal irrigation
Allergic rhinitis
• Oral antihistamine with or without decongestant/nasal corticosteroid
• Consider nasal antihistamine
• Consider oral or nasal decongestant
Postnasal drip (or cough)
Vasomotor rhinitis
• Nasal antihistamine/nasal corticosteroid/saline nasal irrigation
• Oral or nasal decongestant
• Oral or nasal anticholinergics
Allergic rhinitis
• Oral antihistamine/nasal corticosteroid/saline nasal irrigation
• Nasal antihistamine
• Oral or topical anticholinergic agent

mark of nonallergic rhinitis, particularly vasomotor rhinitis.⁴⁹ The congestion of vasomotor rhinitis is best treated with the combined use of a topical antihistamine and an intranasal corticosteroid (Table II). Nasal irrigation with saline washes is also helpful when added to pharmacotherapy. Severe cases of congestion might also require use of an oral decongestant, such as pseudoephedrine. Decongestants are α -adrenergic agonists that relieve nasal congestion by controlling the blood supply to the nasal turbinates, although their vasoconstrictive effects sometimes cause side effects such as insomnia, loss of appetite, hypertension, and nervousness. They should be used cautiously in patients with cardiovascular conditions or hyperthyroidism.⁹ Prolonged treatment with decongestants is restricted to oral agents, because topical decongestants can be used only for periods of up to 1 week, to avoid rebound congestion and rhinitis medicamentosa.⁹ Conversely, the congestion of allergic rhinitis is best treated with the combined use of an oral antihistamine and an intranasal corticosteroid, with or without a decongestant. Addition of a topical antihistamine to this regimen may provide improved relief in allergic rhinitis patients with severe congestion. Headaches often are a sign of congestion and can be managed with the use of an intranasal corticosteroid plus an oral or topical antihistamine for allergic or nonallergic rhinitis, respectively, accompanied by saline nasal irrigation. A topical decongestant may be added to the regimen, if required, for short periods.

A similar treatment rationale is used in the symptomatic management of postnasal drip. The most effective treatment for postnasal drip in vasomotor rhinitis patients is the com-

TABLE III

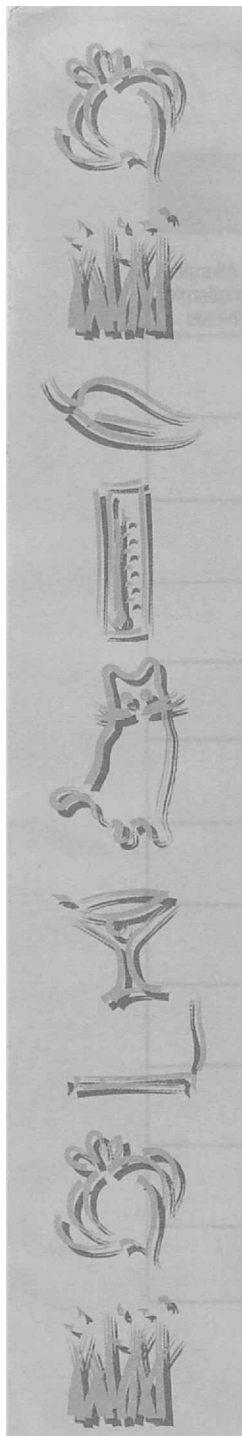
Algorithms for Progressive Management Approaches

Allergic rhinitis
• Oral antihistamine plus nasal corticosteroid
• Oral antihistamine plus nasal corticosteroid plus nasal antihistamine for residual symptoms
• Saline nasal irrigation
Vasomotor rhinitis
• Nasal antihistamine plus nasal corticosteroid
• Nasal antihistamine plus nasal corticosteroid plus oral or nasal decongestant
• Nasal antihistamine plus nasal corticosteroid plus oral or nasal anticholinergic agent
• Saline nasal irrigation
Mixed rhinitis
• Treat for condition thought to be of primary importance
• If vasomotor rhinitis, same as aforementioned
• If allergic rhinitis, same as aforementioned

bined use of a topical antihistamine and an intranasal corticosteroid, together with saline nasal irrigation. A topical or oral anticholinergic agent can provide additional relief. Topical anticholinergics such as ipratropium bromide effectively reduce rhinorrhea but have limited effects on postnasal drip. Ipratropium bromide, available as an aqueous 0.03 or 0.06% solution intranasal spray, diminishes both the severity and the duration of rhinorrhea, with modest effects on congestion.⁵⁰ Side effects are rare. Allergic rhinitis patients with postnasal drip benefit from the combined use of an oral antihistamine and an intranasal corticosteroid, together with saline nasal irrigation, a topical nasal antihistamine, and/or an oral anticholinergic agent. This approach is particularly effective in patients with perennial allergic rhinitis.⁵¹ The presence of cough should be treated similarly to postnasal drip, which often is the cause of the cough. Treatment consists of a topical antihistamine for nonallergic rhinitis or an oral antihistamine for allergic rhinitis, combined with an intranasal corticosteroid, saline nasal irrigation, and an oral or topical anticholinergic.

Symptoms typical of allergic rhinitis—primarily sneezing, nasal itching, and rhinorrhea—benefit most from an intranasal corticosteroid combined with an oral antihistamine, to which a topical antihistamine can be added for additional symptomatic control.

Anosmia or hyposmia is a recalcitrant symptom that often accompanies sinusitis or polypsis. It requires extremely aggressive treatment with high-dose intranasal corticosteroids and saline nasal irrigation, and it may even require oral steroids. For lasting results, the most effective management strategies for anosmia address the underlying cause of the sinusitis or polypsis.



The American Academy of Family Physicians Foundation has favorably reviewed this material through 12/04. Favorable review means that medical information is accurate, but does not imply endorsement of any conclusions presented.

PATIENT RHINITIS SCREEN

This form will help determine the kind of rhinitis you have. Please check the box next to your symptoms.

Date: _____

Patient Name: _____

Patient Age: _____

Age when you first started having symptoms? _____

When do you have symptoms?

What symptoms do you have?

	All year?	Spring	Summer	Fall	Winter
Sneezing					
Stuffy nose/congestion					
Runny nose					
Postnasal drainage					
Itchy eyes/itchy nose					

What medication(s) do you take for your symptoms? _____

Are your symptoms: ☐ completely controlled? ☐ somewhat controlled? ☐ uncontrolled?

Patient: Please check all the things that you think make your symptoms worse:

Allergens	Inhaled/Strong Odor Triggers
Freshly mowed grass	Smoke (tobacco/burning items)
Dead grass	Perfumes/colognes/fragrances
Hay	Cosmetics
Dead leaves	Cleaning products/detergents/soaps
Pollen	Paint fumes or paint products
Trees/tree pollen	Hairspray
Weeds (ragweed)	Outside dust
Molds	Exhaust (cars, trucks, buses)
House dust	Gasoline fumes
Cats/cat hair	
Dogs/dog hair	Weather Change Triggers
Feathers	Windy days
	Cold days
	Damp days
	Humidity/temperature changes
	Ingestant Triggers
	Alcoholic beverages (beer, wine)
	Spicy foods
TOTAL	TOTAL
Consider Allergic Rhinitis if ONLY boxes on this side are checked.	Consider Vasomotor (Nonallergic) Rhinitis* if ONLY boxes on this side are checked.

Consider "Mixed Rhinitis" (or coexisting disease) if boxes on BOTH sides are checked.

* Vasomotor rhinitis is the major type of nonallergic rhinitis. Other types of nonallergic rhinitis include: infectious, hormonal, exercise-, drug-, or reflex-induced etiologies, NARES and ciliary dyskinesia syndromes, and atrophic rhinitis. See guidelines by Dykewicz, et al for complete information (*Ann Allergy Asthma Immunol.* 1998;81:478-518).

Figure 2. Rhinitis screening tool.

PROGRESSIVE MANAGEMENT ALGORITHMS

In an attempt to standardize management of allergic rhinitis, the World Health Organization recently issued new guidelines for treating allergic rhinitis, referred to as Allergic Rhinitis and Its Impact on Asthma, that resemble the progressive treatment approach recommended for asthma.^{52,53} The guidelines propose a stepwise approach to the management of allergic rhinitis based on symptom severity. The Allergic Rhinitis and Its Impact on Asthma guidelines and other successful management strategies for allergic rhinitis suggest the combined use of an oral antihistamine with an intranasal corticosteroid (Table III).^{9,52,53} Residual symptoms can be treated by adding the topical antihistamine azelastine to the regimen. Saline nasal irrigation can provide additional relief.

A progressive approach to treating vasomotor rhinitis would begin with the combined use of the topical antihistamine azelastine and an intranasal corticosteroid. Cases that are more recalcitrant would benefit from adding an oral decongestant to this regimen when congestion is the predominant symptom or an anticholinergic agent when rhinorrhea predominates.

Mixed rhinitis is characterized by the presence of both allergic and nonallergic rhinitis components. Because symptoms arising from the nonallergic component can be the most recalcitrant, initial treatment should take into account the effectiveness of each component of the plan. If vasomotor rhinitis is considered the primary cause, treatment should be targeted primarily at the nonallergic component and would entail the combined use of the topical antihistamine azelastine and an intranasal corticosteroid, plus saline nasal irrigation. Residual symptoms can be treated by first adding an oral antihistamine to this regimen and progressing to an oral or topical anticholinergic agent if rhinorrhea persists.

OPTIMIZING TREATMENT IN THE PRIMARY CARE ARENA

Because optimal treatment requires a correct diagnosis of the rhinitis subtype, primary care practitioners who do not use ancillary testing are at a definite disadvantage. However, given the increasing number of rhinitis patients who are treated by primary care physicians, what can be done to improve the frequency of successful treatment outcomes?

The most important diagnostic tool in distinguishing the type of rhinitis is the patient history. To facilitate diagnosis in the primary care setting, allergists have developed a rhinitis screening tool that can be integrated into the patient history that helps distinguish among allergic, nonallergic, and mixed rhinitis (Fig. 2).⁵⁴ The rhinitis screening tool is a patient questionnaire that gathers information about both the temporal expression of rhinitis symptoms throughout the year and the specific triggers of rhinitis. Patients are asked to select their symptoms from a checklist of total rhinitis

symptoms, state when the symptoms occur, report the age when symptoms began, and then select from two lists of triggers that cause symptom exacerbation. The lists differ with respect to etiology, one containing exclusively allergens and the other containing exclusively nonimmunogenic irritants associated with nonallergic rhinitis. By examining the nature of the triggers, the temporal expression of symptoms, and the age when symptoms began, clinicians are guided to consider the presence of allergic, nonallergic, or mixed rhinitis.

By using the rhinitis screening tool, primary care physicians can benefit from the expertise of allergists in diagnosing the rhinitis subtype without having to perform ancillary tests. The screen identifies information relevant to the diagnosis, and patients are encouraged to participate in this process. This cooperative approach saves time for the practitioner by guiding the patient to observe relevant clinical details. It also allows the clinician to establish a symptom profile for the patient that facilitates the development of a treatment plan.

In conclusion, the frequency of nonallergic rhinitis, and particularly vasomotor rhinitis, is far more common than previously recognized. Its presence in conjunction with allergic rhinitis often complicates the treatment of rhinitis, because oral antihistamines alone do not provide adequate relief. To improve the likelihood of a successful outcome, both the allergic and the nonallergic components must be addressed. Vasomotor rhinitis responds well to combined treatment with a topical antihistamine and an intranasal corticosteroid.

REFERENCES

1. Corren J. Allergic rhinitis and asthma: how important is the link? *J Allergy Clin Immunol* 99:S781-S786, 1997.
2. Leynaert B, Neukirch F, Demoly P, et al. Epidemiologic evidence for asthma and rhinitis comorbidity. *J Allergy Clin Immunol* 106:S201-S205, 2000.
3. Kaliner MA, Osguthorpe JD, Fireman P, et al. Sinusitis: bench to bedside. *J Allergy Clin Immunol* 99:S829-S848, 1997.
4. Rachelefsky GS. National guidelines needed to manage rhinitis and prevent complications. *Ann Allergy Asthma Immunol* 82:296-305, 1999.
5. Slavin RG. Complications of allergic rhinitis: implications for sinusitis and asthma. *J Allergy Clin Immunol* 101:S357-S360, 1998.
6. Grossman J. One airway, one disease. *Chest* 111:11S-16S, 1997.
7. Vinuya RZ. Upper airway disorders and asthma: a syndrome of airway inflammation. *Ann Allergy Asthma Immunol* 88(suppl):8-15, 2002.
8. Ledford D. Nonallergic rhinitis: assessing the damage. Presented at the Presymposium to the Eastern Allergy Meeting, Key Biscayne, FL, May 2, 2002.
9. Dykewicz MS, and Fineman S (Eds). Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on practice parameters in allergy, asthma, and immunology. *Ann Allergy Asthma Immunol* 81:478-518, 1998.
10. Tovey E, and Marks G. Methods and effectiveness of environmental control. *J Allergy Clin Immunol* 103:179-191, 1999.
11. Jacobsen L, Dreborg S, Moller C, et al. Immunotherapy as a preventive treatment. *J Allergy Clin Immunol* 97:232, 1996.
12. Vinuya RZ. Specific allergen immunotherapy for allergic rhinitis and asthma. *Pediatric Ann* 29:425-432, 2000.

13. Des Roches A, Paradis L, Menardo J-L, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitization in children. *J Allergy Clin Immunol* 99:450–453, 1997.
14. Lieberman P. Rhinitis. In *Expert Guide to Allergy and Immunology*. Slavin RG, and Reisman RE (Eds). Philadelphia: American College of Physicians, 21–40, 1997.
15. Naclerio RM, and Baroody F. Understanding the inflammatory processes in upper allergic airway disease and asthma. *J Allergy Clin Immunol* 101:S345–S351, 1998.
16. Wang D, Smitz J, Waterschoot S, et al. An approach to the understanding of the nasal early phase reaction induced by nasal allergen challenge. *Allergy* 52:162–167, 1997.
17. White MV, and Kaliner MA. Mediators of allergic rhinitis. *J Allergy Clin Immunol* 52:162–167, 1992.
18. Baraniuk JN. Pathogenesis of allergic rhinitis. *J Allergy Clin Immunol* 99:S763–S772, 1997.
19. Togias A. Unique mechanistic features of allergic rhinitis. *J Allergy Clin Immunol* 105:S599–S604, 2000.
20. Naclerio RM. Pathophysiology of perennial allergic rhinitis. *Allergy* 52(suppl 36):7–13, 1997.
21. Bachert C. Histamine—a major role in allergy? *Clin Exp Allergy* 28(suppl 6):15–19, 1998.
22. Day J. Pros and cons of the use of antihistamines in managing allergic rhinitis. *J Allergy Clin Immunol* 103:S395–S399, 1999.
23. Meltzer EO. An overview of current pharmacotherapy in perennial rhinitis. *J Allergy Clin Immunol* 103:1097–1110, 1999.
24. Meltzer EO. The pharmacological basis for the treatment of perennial allergic rhinitis and non-allergic rhinitis with topical corticosteroids. *Allergy* 52(suppl 36):33–40, 1997.
25. Kamado AD, and Szeffler SJ. Mechanisms of action of glucocorticoids in asthma and rhinitis. In *Asthma and Rhinitis*. Busse WW, and Holgate ST (Eds). Boston: Blackwell Scientific Publications, 1255–1266, 2000.
26. Slater JW, Zechnich AD, and Haxby DG. Second-generation antihistamines: a comparative review. *Drugs* 57:31–47, 1999.
27. Berger WF, Fineman SM, Lieberman P, et al. Double-blind trials of azelastine nasal spray monotherapy versus combination therapy with loratadine tablets and beclomethasone nasal spray in patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 82:535–541, 1999.
28. McNeely W, and Wiseman LR. Intranasal azelastine: a review of its efficacy in the management of allergic rhinitis. *Drugs* 56:91–114, 1998.
29. Cuss FM. Beyond the histamine receptor: effect of antihistamines on mast cells. *Clin Exp Allergy* 29(suppl 3):54–59, 1999.
30. Miadonna A, Cottini M, Milazzo N, et al. *In vivo* and *ex vivo* inhibitory effects of loratadine on histamine release in patients with allergic rhinitis. *Allergy* 53:1183–1188, 1998.
31. Ciprandi G, Passalacqua G, and Canonica GW. Effects of H1 antihistamines on adhesion molecules: a possible rationale for long-term treatment. *Clin Exp Allergy* 29(suppl 3):49–53, 1999.
32. Canonica GW, and Ciprandi G. Minimal persistent inflammation may be controlled by cetirizine. *Ann Allergy Asthma Immunol* 83:445–448, 1999.
33. Simpson K, and Jarvis B. Fexofenadine: a review of its use in the management of seasonal allergic rhinitis and chronic idiopathic urticaria. *Drugs* 59:310–321, 2000.
34. Markham A, and Wagstaff AJ. Fexofenadine. *Drugs* 55:269–274, 1998.
35. Shichijo M, Inagaki N, Nakai N, et al. The effects of anti-asthma drugs on mediator release from cultured human mast cells. *Clin Exp Allergy* 28:1228–1236, 1998.
36. Lieberman P. Management of allergic rhinitis with a combination antihistamine/anti-inflammatory agent. *J Allergy Clin Immunol* 103: S400–S404, 1999.
37. Vuurman EFPM, van Veggel LMA, Uiterwijk MMC, et al. Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy* 71:121–126, 1993.
38. Pinto YM, van Gelder IC, Heeringa M, et al. QT lengthening and life-threatening arrhythmias associated with fexofenadine. *Lancet* 353:980, 1999.
39. Pauwels R. Mode of action of corticosteroids in asthma and rhinitis. *Clin Allergy* 16:281–288, 1986.
40. Otsuka H, Denburg JA, Befus AD, et al. Effect of beclomethasone dipropionate on nasal metachromatic cell subpopulations. *Clin Allergy* 16:589–595, 1986.
41. Bascom R, Wachs M, Naclerio RM, et al. Basophil influx occurs after nasal antigen challenge: effects of topical corticosteroid pretreatment. *J Allergy Clin Immunol* 81:580–589, 1988.
42. Fahey JV, Guyre PM, and Munck A. Mechanisms of antiinflammatory actions of glucocorticoids. *Adv Inflamm Res* 2:21–51, 1981.
43. Schleimer RP, MacGlashan DW, Schulman ES, et al. Mediators of immediate hypersensitivity: mechanisms of release and modulation by drugs. In *Bronchial Hyperreactivity*. Morley J (Ed). New York: Academic Press, 1982.
44. Sim TC, Hilsmeier KA, Alam R, et al. Effect of topical corticosteroids on the recovery of histamine releasing factors in nasal washings of patients with allergic rhinitis. *Am Rev Respir Dis* 145:1316–1320, 1992.
45. Holm AF, and Fokkens WJ. Topical corticosteroids in allergic rhinitis: effects on nasal inflammatory cells and nasal mucosa. *Clin Exp Allergy* 31:529–535, 2001.
46. Richards DH, and Scadding GK. Inhaled and intranasal steroids: the differences explained in terms of potential for growth effects. *Allergy* 55:S252, 2000.
47. Schenkel EJ, Skoner DP, Bronsky EA, et al. Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray. *Pediatrics* 105:415, 2000.
48. Wolthers OD, and Pedersen S. Short-term growth in children with allergic rhinitis treated with oral antihistamine, depot and intranasal glucocorticosteroids. *Acta Paediatr* 82:635–640, 1993.
49. Kaliner MA. Recognizing and treating the nonallergic rhinitis patient. *Female Patient* 2002.
50. Dockhorn R, Aaronson D, Bronsky E, et al. Ipratropium bromide nasal spray 0.03% and beclomethasone nasal spray alone and in combination for the treatment of rhinorrhea in perennial rhinitis. *Ann Allergy Asthma Immunol* 82:349–359, 1999.
51. Meltzer EO, Orgel HA, Bronsky EA, et al. Ipratropium bromide aqueous nasal spray for patients with perennial allergic rhinitis: a study of its effect on their symptoms, quality of life, and nasal cytology. *J Allergy Clin Immunol* 90:242–249, 1992.
52. Storms WW. Rethinking our approach to allergic rhinitis management. *Ann Allergy Asthma Immunol* 88(suppl):30–35, 2002.
53. Bosquet J, and the ARIA Workshop Group. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 108:S1–S265, 2001.
54. Lieberman PL, Rakel RE, Hedges HH, III, et al. Quantifying the incidence of mixed rhinitis with a new patient screening tool. *Ther Trends* 20:221–232, 2002. □

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