Treatment of Allergic Rhinitis

DENISE K. SUR, MD, and STEPHANIE SCANDALE, MD, *David Geffen School of Medicine, University of California, Los Angeles, California*

Allergic rhinitis is a common chronic respiratory illness that affects quality of life, productivity, and other comorbid conditions, including asthma. Treatment should be based on the patient's age and severity of symptoms. Patients should be advised to avoid known allergens and be educated about their condition. Intranasal corticosteroids are the most effective treatment and should be first-line therapy for mild to moderate disease. Moderate to severe disease not responsive to intranasal corticosteroids should be treated with second-line therapies, including antihistamines, decongestants, cromolyn, leukotriene receptor antagonists, and nonpharmacologic therapies (e.g., nasal irrigation). With the exception of cetirizine, second-generation antihistamines are less likely to cause sedation and impair performance. Immunotherapy should be considered in patients with a less than adequate response to usual treatments. Evidence does not support the use of mite-proof impermeable covers, air filtration systems, or delayed exposure to solid foods in infancy. (*Am Fam Physician.* 2010;81(12):1440-1446. Copyright © 2010 American Academy of Family Physicians.)

ILLUSTRATION BY MARK LEFKOWITZ

▶ **Patient information:** A handout on this topic is available at http://familydoctor.org/083.xml.

Allergic rhinitis is an immunoglobulin E–mediated disease, thought to occur after exposure to indoor and outdoor allergens such as dust mites, insects, animal danders, molds, and pollens. Symptoms include rhinorrhea, nasal congestion, obstruction, and pruritus.[1] Optimal treatment includes allergen avoidance, targeted symptom control, immunotherapy, and asthma evaluation, when appropriate.[2] In 2001, Allergic Rhinitis and Its Impact on Asthma guidelines were published in cooperation with the World Health Organization, suggesting that the treatment of allergic rhinitis make use of a combination of patient education, allergen avoidance, pharmacotherapy, and immunotherapy.[3] In contrast with previous guidelines, these recommendations are based on symptom severity and age, rather than the type or frequency of seasonal, perennial, or occupational exposures. *Table 1* lists recommended treatments based on symptoms.

Pharmacotherapy

Pharmacologic options for the treatment of allergic rhinitis include intranasal corticosteroids, oral and topical antihistamines, decongestants, intranasal cromolyn (Nasalcrom), intranasal anticholinergics, and leukotriene receptor antagonists.[4,5] The International Primary Care Respiratory Group, British Society for Allergy and Clinical Immunology, and American Academy of Allergy Asthma and Immunology recommend initiating therapy with an intranasal corticosteroid alone for mild to moderate disease and using second-line therapies for moderate to severe disease.[4-7] Patients with moderate to severe disease not responding to oral or topical treatments should be referred for consideration of immunotherapy.[3,8] *Table 2* gives a summary of pharmacologic treatments for allergic rhinitis.

INTRANASAL CORTICOSTEROIDS

Intranasal corticosteroids are the mainstay of treatment of allergic rhinitis. They act by decreasing the influx of inflammatory cells and inhibiting the release of cytokines, thereby reducing inflammation of the nasal mucosa.[3] Their onset of action is 30 minutes, although peak effect may take several hours

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
The initial treatment of mild to moderate allergic rhinitis should be an intranasal corticosteroid alone, with the use of second-line therapies for moderate to severe disease.	A	4, 5, 7
Compared with first-generation antihistamines, second-generation antihistamines have a better adverse effect profile, including less sedation (with the exception of cetirizine [Zyrtec]).	A	22
The adverse effects and higher cost of intranasal antihistamines, as well as their decreased effectiveness compared with intranasal corticosteroids, limit their use as first- or second-line therapy for allergic rhinitis.	A	28, 29
Although safe for general use, intranasal cromolyn (Nasalcrom) is not considered first-line therapy for allergic rhinitis because of its decreased effectiveness at relieving the symptoms of allergic rhinitis and its inconvenient dosing schedule.	C	1, 3
Nasal saline irrigation is beneficial in treating the symptoms of chronic rhinorrhea and may be used alone or as adjuvant therapy.	B	53
Although dust mite allergies are common, studies have not found any benefit to using mite-proof impermeable mattress and pillow covers.	A	54-56
Interventions without documented effectiveness in the prevention of allergic rhinitis include breastfeeding, delayed exposure to solid foods in infancy, and the use of air filtration systems.	B	57-61

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

to days, with maximum effectiveness usually noted after two to four weeks of use.[9]

Many studies have demonstrated that nasal corticosteroids are more effective than oral and intranasal antihistamines in the treatment of allergic rhinitis.[4,5,10-12] One randomized controlled trial (RCT) looking at quality-of-life measures compared the antihistamine loratadine (Claritin) with the nasal corticosteroid fluticasone (Flonase) in 88 adults over a four-week period.[13] The study's results showed that symptom scores were comparable, but quality-of-life scores were superior in the nasal corticosteroid group.

Although there is no evidence that one intranasal corticosteroid is superior to another, many of the available products have different age indications from the U.S. Food and Drug Administration (FDA). Only budesonide (Rhinocort) carries the FDA pregnancy category B safety rating, and only mometasone (Nasonex) has a delivery device that received recognition from the National Arthritis Foundation for ease of use.[14]

The adverse effects most commonly experienced with the use of intranasal corticosteroids are headache, throat irritation, epistaxis, stinging, burning, and nasal dryness.[3,15] Although the use of intranasal corticosteroids has raised concern for potential systemic adverse effects, including the suppression of the hypothalamic-pituitary axis, the products currently available have not been shown to have such effects.[16] There are a few studies that looked specifically at the effects of intranasal corticosteroids on skeletal growth and adrenal activity. One RCT found the rate of skeletal growth unaffected in children using mometasone for one year.[17] Similarly, a well-designed prospective study did not show any difference in growth in children using nasal

Table 1. Allergic Rhinitis Treatment Based on Symptoms

Treatment type	*Ocular symptoms*	*Nasopharyngeal itching*	*Sneezing*	*Rhinorrhea*
Intranasal corticosteroids	✔	✔	✔	✔
Oral antihistamines	✔	✔	✔	✔
Intranasal antihistamines	—	✔	✔	✔
Decongestants	✔	—	—	✔
Intranasal cromolyn (Nasalcrom)	—	✔	✔	✔
Intranasal anticholinergics	—	—	—	✔
Leukotriene receptor antagonists	✔	—	—	✔
Nasal saline irrigation	—	—	—	✔
Immunotherapy	✔	—	✔	✔

NOTE: *Listed in order of treatment preference.*

Table 2. Summary of Treatments for Allergic Rhinitis

Treatment	*Pregnancy category*	*Minimum age*	*Mechanism and onset of action*	*Adverse effects*
Intranasal corticosteroids				
Beclomethasone (Beconase)	B	Six years	Inhibits the influx of inflammatory cells; onset of action is less than 30 minutes	Bitter aftertaste, burning, epistaxis, headache, nasal dryness, potential risk of systemic absorption, rhinitis medicamentosa, stinging, throat irritation
Budesonide (Rhinocort)	C	Six years		
Ciclesonide (Omnaris)	C	Six years		
Flunisolide	C	Six years		
Fluticasone furoate (Veramyst)	C	Two years		
Fluticasone propionate (Flonase)	C	12 years		
Mometasone (Nasonex)	C	Two years		
Triamcinolone (Nasacort)	C	12 years		
Oral antihistamines				
Cetirizine (Zyrtec)	B	Six months	Blocks H1 receptors; onset of action is 15 to 30 minutes	Dry mouth, sedation at higher than recommended doses
Desloratadine (Clarinex)	C	Six months		
Fexofenadine (Allegra)	C	Six months		
Levocetirizine (Xyzal)	B	12 years		
Loratadine (Claritin)	B	Two years		
Intranasal antihistamines				
Azelastine (Astelin)	C	Five years	Blocks H1 receptors; onset of action is 15 minutes	Bitter aftertaste, epistaxis, headache, nasal irritation, sedation
Olopatadine (Patanase)	C	Six years		
Oral decongestants				
Pseudoephedrine	C	12 years	Vasoconstriction; onset of action is 15 to 30 minutes	Arrhythmias, dizziness, headache, hypertension, insomnia, nervousness, tremor, urinary retention
Intranasal cromolyn				
Cromolyn (Nasalcrom)	B	Two years	Inhibits histamine release; results typically noted in one week, but may take two to four weeks for full effect	Epistaxis, nasal irritation, sneezing
Intranasal anticholinergics				
Ipratropium (Atrovent)	B	Six years	Blocks acetylcholine receptors; onset of action is 15 minutes	Epistaxis, headache, nasal dryness
Leukotriene receptor antagonists				
Montelukast (Singulair)	B	Six months	Blocks leukotriene receptors; onset of action is two hours	Elevated levels of alanine transaminase, aspartate transaminase, and bilirubin

NOTE: *Listed in order of treatment preference.*

corticosteroids for at least three years.[18] However, one randomized trial of 90 children (six to nine years of age) who were treated with beclomethasone (Beconase) or placebo for one year showed suppressed growth rates in the group taking beclomethasone compared with the placebo group.[19] Although nasal fluticasone has been shown to reduce endogenous cortisol excretion in one study, its impact on growth is unknown.[20] Despite the data, all intranasal corticosteroids carry a warning that long-term use may restrict growth in children.

ORAL ANTIHISTAMINES

Histamine is the most studied mediator in early allergic response. It causes smooth muscle constriction, mucus secretion, vascular permeability, and sensory nerve stimulation, resulting in the symptoms of allergic rhinitis.[21]

The first-generation antihistamines include brompheniramine, chlorpheniramine, clemastine, and diphenhydramine (Benadryl). They may cause substantial adverse effects, including sedation, fatigue, and impaired mental status. These adverse effects occur because the older antihistamines are more lipid soluble and more readily cross the blood-brain barrier than second-generation antihistamines. The use of first-generation antihistamines has been associated with poor school performance, impaired driving, and an increase in automobile collisions and work injuries.[22-25] Although one RCT of 63 children eight to 10 years of age did not show that the short-term use of first- or second-generation antihistamines caused drowsiness or impaired school performance, the children in this study were only treated for three days, and the sample size was small.[26]

Compared with first-generation antihistamines, second-generation antihistamines have a better adverse-effect profile and cause less sedation, with the exception of cetirizine (Zyrtec).[21,22] The second-generation oral antihistamines include desloratadine (Clarinex), levocetirizine (Xyzal), fexofenadine (Allegra), and loratadine. Second-generation antihistamines have more complex chemical structures that decrease their movement across the blood-brain barrier, reducing central nervous system adverse effects such as sedation. Although cetirizine is a second-generation antihistamine and a more potent histamine antagonist, it does not have the benefit of decreased sedation. As a group, the second-generation oral antihistamines are thought to stabilize and control some of the nasal and ocular symptoms, but have little effect on nasal congestion.[21]

In general, first- and second-generation antihistamines have been shown to be effective at relieving the histamine-mediated symptoms associated with allergic rhinitis (e.g., sneezing, pruritus, rhinorrhea, ocular symptoms), but are less effective than intranasal corticosteroids at treating nasal congestion. Because their onset of action is typically within 15 to 30 minutes and they are considered safe for children older than six months, antihistamines are useful for many patients with mild symptoms requiring "as needed" treatment.[27]

INTRANASAL ANTIHISTAMINES

Compared with oral antihistamines, intranasal antihistamines offer the advantage of delivering a higher concentration of medication to a specific targeted area, resulting in fewer adverse effects.[3] Currently, azelastine (Astelin; approved for ages five years and older) and olopatadine (Patanase; approved for ages six years and older) are the two FDA-approved intranasal antihistamine preparations for the treatment of allergic rhinitis. As a class, their onset of action occurs within 15 minutes and lasts up to four hours. Adverse effects include a bitter aftertaste, headache, nasal irritation, epistaxis, and sedation. Although intranasal antihistamines are an option in patients whose symptoms did not improve with second-generation oral antihistamines, their use as first- or second-line therapy is limited by their adverse effects and cost compared with second-generation oral antihistamines, and by their decreased effectiveness compared with intranasal corticosteroids.[28,29]

DECONGESTANTS

Oral and topical decongestants improve the nasal congestion associated with allergic rhinitis by acting on adrenergic receptors, which causes vasoconstriction in the nasal mucosa, resulting in decreased inflammation.[3-5] Although the most commonly available decongestants are phenylephrine, oxymetazoline (Afrin), and pseudoephedrine, the abuse potential for pseudoephedrine should be weighed against its benefits.

Common adverse effects that occur with the use of intranasal decongestants are sneezing and nasal dryness. Duration of use for more than three to five days is usually not recommended, because patients may develop rhinitis medicamentosa or have rebound or recurring congestion.[3] However, a study of 35 patients found no rebound when oxymetazoline was used for 10 days.[30] Because oral decongestants may cause headache, elevated blood pressure, tremor, urinary retention, dizziness, tachycardia, and insomnia, patients with underlying cardiovascular conditions, glaucoma, or hyperthyroidism should only use these medications with close monitoring.[3-5] A study of 25 patients with controlled hypertension provides some reassurance about the use of oral decongestants; compared with placebo, this randomized crossover study found minimal effect on blood pressure with pseudoephedrine use.[31]

INTRANASAL CROMOLYN

Intranasal cromolyn is available over the counter and is thought to act by inhibiting the degranulation of mast cells.[1] Although safe for general use, it is not considered first-line therapy for allergic rhinitis because of its decreased effectiveness at relieving symptoms compared with antihistamines or intranasal corticosteroids, and its inconvenient dosing schedule of three or four times daily.[1,3]

INTRANASAL ANTICHOLINERGICS

Ipratropium (Atrovent) has been shown to provide relief only for excessive rhinorrhea. Advantages include that it does not cross the blood-brain barrier and is not systemically absorbed.[1] Adverse effects include dryness of the nasal mucosa, epistaxis, and headache. Compliance is also an issue because it needs to be administered two or three times daily.[1]

LEUKOTRIENE RECEPTOR ANTAGONISTS

Although the leukotriene LTD_4 receptor antagonist montelukast (Singulair) is FDA approved for the treatment of allergic rhinitis, a systematic review of 20 trials involving adults treated with montelukast for allergic rhinitis showed only minimal improvement (which was not clinically relevant) in the symptom of nasal congestion.[32] Another RCT involving 58 adults comparing montelukast with pseudoephedrine for two weeks

showed no difference between the two therapies.[33] In addition, two large, independent meta-analyses concluded that although montelukast is better than placebo, it is not as effective as intranasal corticosteroids or antihistamines and should only be considered as second- or third-line therapy.[32,34]

COMBINATION THERAPY

Although many studies have looked at the combination of an intranasal corticosteroid with an antihistamine or leukotriene receptor antagonist, most have concluded that combination therapy is no more effective than monotherapy with intranasal corticosteroids.[11,35-37] However, one study looking at the combination of fluticasone and azelastine found this treatment combination to be superior to either treatment alone in patients with moderate to severe allergic rhinitis.[38] Therefore, although patients should not have therapy initiated with more than one agent, combination therapy is an option for patients with severe or persistent symptoms.

Immunotherapy

Immunotherapy should be considered for patients with moderate or severe persistent allergic rhinitis that is not responsive to usual treatments.[8] Targeted immunotherapy is the only treatment that changes the natural course of allergic rhinitis, preventing exacerbation.[39] It consists of a small amount of allergen extract given sublingually or subcutaneously over the course of a few years, with maintenance periods typically lasting between three to five years. The greatest risk associated with immunotherapy is anaphylaxis. Although the usefulness of sublingual immunotherapy in adults with allergic rhinitis has been supported by several large trials, studies in children have met with mixed results, and the FDA has yet to approve a commercial product for sublingual use.[8,40-42]

Recombinant DNA technology has also played a role in immunotherapy, allowing for the development of allergen-specific vaccines. In a multicenter RCT involving 134 adults receiving a recombinant birch pollen vaccine for 12 consecutive weeks followed by monthly injections for 15 months, patients noted statistically significant improvements in rhinosinusitis symptoms, medication use, and skin sensitivities when compared with placebo.[43]

Omalizumab (Xolair), an anti-immunoglobulin E antibody, has been shown to be effective in reducing nasal symptoms and improving quality-of-life scores in patients with allergic rhinitis.[44] The main limitations of its current use are its high cost (average wholesale price is $679 to $3,395 per month[45]) and lack of FDA approval for home use.

Nonpharmacologic Therapies

ACUPUNCTURE

Although the precise mechanism by which acupuncture works is unclear, proponents suggest that it releases neurochemicals such as beta-endorphins, enkephalins, and serotonin, which in turn mediate the inflammatory pathways involved in allergic rhinitis. Based on RCTs looking at acupuncture as a treatment for allergic rhinitis in adults and children, there is insufficient evidence to support or refute its use.[46-49]

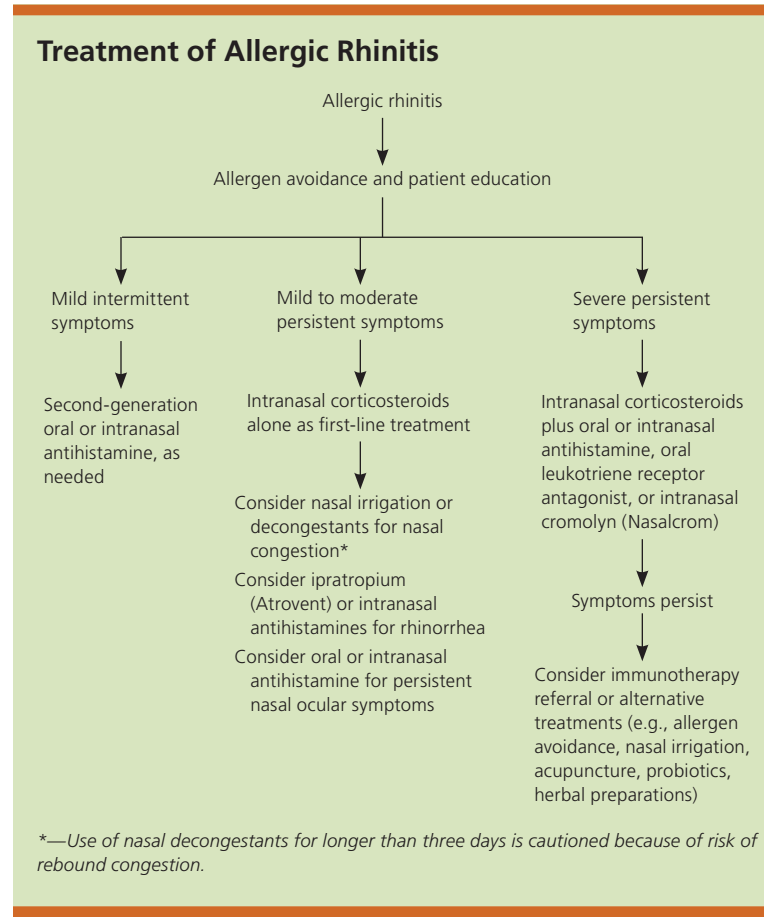

Figure 1. Algorithm for the treatment of allergic rhinitis.

PROBIOTICS

Based on the limited data to date, probiotics cannot be endorsed as a useful alternative therapy for allergic rhinitis. Studies of probiotics gave mixed results and included 12 RCTs and one study looking at prenatal treatment.[50,51]

HERBAL PREPARATIONS

Many herb and plant-extract compounds have been studied with respect to allergic rhinitis treatment, but the effectiveness and safety of these compounds have not been established.[52]

OTHER

Patients with allergic rhinitis should avoid exposure to cigarette smoke, pets, and allergens to which they have a known sensitivity. Nasal irrigation is beneficial in the treatment of chronic rhinorrhea and may be used alone or as adjuvant therapy.[53] Irrigation using a neti pot is superior to saline sprays; it may also be done with a low-pressure squeeze bottle.[53]

Prevention has been a large focus in the study of allergic rhinitis, but few interventions have proven effective. Although dust mite allergies are common, studies have not found any benefit to using mite-proof impermeable mattress and pillow covers.[54-56] Other examples of proposed interventions without documented effectiveness include breastfeeding, delayed exposure to solid foods in infancy, and use of air filtration systems.[57-61] *Figure 1* provides an algorithm for the treatment of allergic rhinitis with pharmacologic and nonpharmacologic therapies.

The Authors

DENISE K. SUR, MD, is clinical professor, vice chair for education, and residency director in the Department of Family Medicine at the David Geffen School of Medicine, University of California, Los Angeles.

STEPHANIE SCANDALE, MD, is an assistant clinical professor in the Department of Family Medicine at the David Geffen School of Medicine.

Address correspondence to Denise K. Sur, MD, UCLA Family Health Center, Department of Family Medicine, 1920 Colorado Ave., Santa Monica, CA 90404 (e-mail: dsur@mednet.ucla.edu). Reprints are not available from the authors.

Author disclosure: Nothing to disclose.

REFERENCES

1. Nelson HS, Rachelefsky GS, Bernick J. *The Allergy Report.* Milwaukee, Wis.: American Academy of Allergy, Asthma & Immunology; 2000.
2. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy.* 2008;63(suppl 86):8-160.
3. Bousquet J, Van Cauwenberge P, Khaltaev N; ARIA Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol.* 2001;108(5 suppl):S147-S334.
4. Price D, Bond C, Bouchard J, et al. International Primary Care Respiratory Group (IPCRG) Guidelines: management of allergic rhinitis. *Prim Care Respir J.* 2006;15(1):58-70.
5. Scadding GK, Durham SR, Mirakian R, et al.; British Society for Allergy and Clinical Immunology. BSACI guidelines for the management of allergic and non-allergic rhinitis. *Clin Exp Allergy.* 2008;38(1):19-42.
6. Plaut M, Valentine MD. Clinical practice. Allergic rhinitis. *N Engl J Med.* 2005;353(18):1934-1944.
7. Wallace DV, Dykewics MS, Bernstein DI, et al. The diagnosis and management of rhinitis: an updated practice parameter [published correction appears in *J Allergy Clin Immunol.* 2008;122(6):1237]. *J Allergy Clin Immunol.* 2008;122(2 suppl):S1-S84.
8. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev.* 2007;(1):CD001936.
9. Derendorf H, Meltzer EO. Molecular and clinical pharmacology of intranasal corticosteroids: clinical and therapeutic implications. *Allergy.* 2008; 63(10):1292-1300.
10. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. *BMJ.* 1998;317(7173):1624-1629.
11. Ratner PH, van Bavel JH, Martin BG, et al. A comparison of the efficacy of fluticasone propionate aqueous nasal spray and loratadine, alone and in combination, for the treatment of seasonal allergic rhinitis. *J Fam Pract.* 1998;47(2):118-125.
12. Yáñez A, Rodrigo GJ. Intranasal corticosteroids versus topical H1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol.* 2002;89(5):479-484.
13. Kaszuba SM, Baroody FM, deTineo M, Haney L, Blair C, Naclerio RM. Superiority of an intranasal corticosteroid compared with an oral antihistamine in the as-needed treatment of seasonal allergic rhinitis. *Arch Intern Med.* 2001;161(21):2581-2587.
14. Waddell AN, Patel SK, Toma AG, Maw AR. Intranasal steroid sprays in the treatment of rhinitis: is one better than another? *J Laryngol Otol.* 2003;117(11):843-845.
15. Demoly P. Safety of intranasal corticosteroids in acute rhinosinusitis. *Am J Otolaryngol.* 2008;29(6):403-413.
16. Lumry WR. A review of the preclinical and clinical data of newer intranasal steroids used in the treatment of allergic rhinitis. *J Allergy Clin Immunol.* 1999;104(4 pt 1):S150-S158.
17. 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.* 2000;105(2):E22.
18. Mansfield LE, Mendoza CP. Medium and long-term growth in children receiving intranasal beclomethasone dipropionate: a clinical experience. *South Med J.* 2002;95(3):334-340.
19. Skoner DP, Rachelefsky GS, Meltzer EO, et al. Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. *Pediatrics.* 2000;105(2):E23.
20. Wilson AM, McFarlane LC, Lipworth BJ. Effects of repeated once daily dosing of three intranasal corticosteroids on basal and dynamic measures of hypothalamic-pituitary-adrenal-axis activity. *J Allergy Clin Immunol.* 1998;101(4 pt 1):470-474.
21. Alexander S. The pharmacology & biochemistry of histamine receptors. August 1996. http://www.nottingham.ac.uk/~mqzwww/histamine.html. Accessed November 19, 2009.
22. Bender BG, Berning S, Dudden R, Milgrom H, Tran ZV. Sedation and performance impairment of diphenhydramine and second-generation antihistamines: a meta-analysis. *J Allergy Clin Immunol.* 2003;111(4):770-776.
23. Verster JC, Volkerts ER. Antihistamines and driving ability: evidence from on-the-road driving studies during normal traffic [published

corrections appear in *Ann Allergy Asthma Immunol.* 2004;92(6):675, and *Ann Allergy Asthma Immunol.* 2005;94(3):409-410]. *Ann Allergy Asthma Immunol.* 2004;92(3):294-303.

24. Robb G, Sultana S, Ameratunga S, Jackson R. A systematic review of epidemiological studies investigating risk factors for work-related road traffic crashes and injuries. *Inj Prev.* 2008;14(1):51-58.
25. Kay GG, Quig ME. Impact of sedating antihistamines on safety and productivity. *Allergy Asthma Proc.* 2001;22(5):281-283.
26. Bender BG, McCormick DR, Milgrom H. Children's school performance is not impaired by short-term administration of diphenhydramine or loratadine. *J Pediatr.* 2001;138(5):656-660.
27. Lipworth BJ, Jackson CM. Safety of inhaled and intranasal corticosteroids: lessons for the new millennium. *Drug Saf.* 2000;23(1):11-33.
28. Corren J, Storms W, Bernstein J, Berger W, Nayak A, Sacks H; Azelastine Cetirizine Trial No. 1 (ACT 1) Study Group. Effectiveness of azelastine nasal spray compared with oral cetirizine in patients with seasonal allergic rhinitis. *Clin Ther.* 2005;27(5):543-553.
29. Berger WE, White MV; Rhinitis Study Group. Efficacy of azelastine nasal spray in patients with an unsatisfactory response to loratadine. *Ann Allergy Asthma Immunol.* 2003;91(2):205-211.
30. Graf P, Enerdal J, Hallén H. Ten days' use of oxymetazoline nasal spray with or without benzalkonium chloride in patients with vasomotor rhinitis. *Arch Otolaryngol Head Neck Surg.* 1999;125(10):1128-1132.
31. Coates ML, Rembold CM, Farr BM. Does pseudoephedrine increase blood pressure in patients with controlled hypertension? *J Fam Pract.* 1995;40(1):22-26.
32. Grainger J, Drake-Lee A. Montelukast in allergic rhinitis: a systematic review and meta-analysis. *Clin Otolaryngol.* 2006;31(5):360-367.
33. Mucha SM, deTineo M, Naclerio RM, Baroody FM. Comparison of montelukast and pseudoephedrine in the treatment of allergic rhinitis. *Arch Otolaryngol Head Neck Surg.* 2006;132(2):164-172.
34. Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med.* 2004;116(5):338-344.
35. Juniper EF, Kline PA, Hargreave FE, Dolovich J. Comparison of beclomethasone dipropionate aqueous nasal spray, astemizole, and the combination in the prophylactic treatment of ragweed pollen-induced rhinoconjunctivitis. *J Allergy Clin Immunol.* 1989;83(3):627-633.
36. Barnes ML, Ward JH, Fardon TC, Lipworth BJ. Effects of levocetirizine as add-on therapy to fluticasone in seasonal allergic rhinitis. *Clin Exp Allergy.* 2006;36(5):676-684.
37. Di Lorenzo G, Pacor ML, Pellitteri ME, et al. Randomized placebo-controlled trial comparing fluticasone aqueous nasal spray in monotherapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic rhinitis [published correction appears in *Clin Exp Allergy.* 2004;34(8):1329]. *Clin Exp Allergy.* 2004;34(2):259-267.
38. Ratner PH, Hampel F, Van Bavel J, et al. Combination therapy with azelastine hydrochloride nasal spray and fluticasone propionate nasal spray in the treatment of patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol.* 2008;100(1):74-81.
39. Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol.* 2006;117(4):802-809.
40. Bousquet J, Khaltaev N. *Global Surveillance, Prevention and Control of Chronic Respiratory Diseases: A Comprehensive Approach.* Geneva: World Health Organization; 2007.
41. Dahl R, Kapp A, Colombo G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol.* 2006;118(2):434-440.
42. Compalati E, Penagos M, Tarantini F, Passalacqua G, Canonica GW. Specific immunotherapy for respiratory allergy: state of the art according to current meta-analyses. *Ann Allergy Asthma Immunol.* 2009;102(1):22-28.
43. Pauli G, Larsen TH, Rak S, et al. Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis [published correction appears in *J Allergy Clin Immunol.* 2009;123(1):166]. *J Allergy Clin Immunol.* 2008;122(5):951-960.
44. Casale TB, Condemi J, LaForce C, et al.; Omalizumab Seasonal Allergic Rhinitis Trial Group. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. *JAMA.* 2001;286(23):2956-2967.
45. *Red Book*. Montvale, N.J.: Medical Economics Data; 2007.
46. Ng DK, Chow PY, Ming SP, et al. A double-blind, randomized, placebo-controlled trial of acupuncture for the treatment of childhood persistent allergic rhinitis. *Pediatrics.* 2004;114(5):1242-1247.
47. Xue CC, English R, Zhang JJ, Da Costa C, Li CG. Effect of acupuncture in the treatment of seasonal allergic rhinitis: a randomized controlled clinical trial. *Am J Chin Med.* 2002;30(1):1-11.
48. Brinkhaus B, Witt CM, Jena S, Liecker B, Wegscheider K, Willich SN. Acupuncture in patients with allergic rhinitis: a pragmatic randomized trial. *Ann Allergy Asthma Immunol.* 2008;101(5):535-543.
49. Roberts J, Huissoon A, Dretzke J, Wang D, Hyde C. A systematic review of the clinical effectiveness of acupuncture for allergic rhinitis. *BMC Complement Altern Med.* 2008;8:13.
50. Kuitunen M, Kukkonen K, Juntunen-Backman K, et al. Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort. *J Allergy Clin Immunol.* 2009;123(2):335-341.
51. Vliagoftis H, Kouranos VD, Betsi GI, Falagas ME. Probiotics for the treatment of allergic rhinitis and asthma: systematic review of randomized controlled trials. *Ann Allergy Asthma Immunol.* 2008;101(6):570-579.
52. Schapowal A; Petasites Study Group. Randomised controlled trial of butterbur and cetirizine for treating seasonal allergic rhinitis. *BMJ.* 2002;324(7330):144-146.
53. Pynnonen MA, Mukerji SS, Kim HM, Adams ME, Terrell JE. Nasal saline for chronic sinonasal symptoms: a randomized controlled trial. *Arch Otolaryngol Head Neck Surg.* 2007;133(11):1115-1120.
54. Koopman LP, van Strien RT, Kerkhof M, et al.; Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study. Placebo-controlled trial of house dust mite-impermeable mattress covers: effect on symptoms in early childhood. *Am J Respir Crit Care Med.* 2002;166(3):307-313.
55. Terreehorst I, Hak E, Oosting AJ, et al. Evaluation of impermeable covers for bedding in patients with allergic rhinitis. *N Engl J Med.* 2003;349(3):237-246.
56. Sheikh A, Hurwitz B, Shehata Y. House dust mite avoidance measures for perennial allergic rhinitis. *Cochrane Database Syst Rev.* 2007;(1):CD001563.
57. Zutavern A, Brockow I, Schaff B, et al.; LISA Study Group. Timing of solid food introduction in relation to eczema, asthma, allergic rhinitis, and food and inhalant sensitization at the age of 6 years: results from the prospective birth cohort study LISA. *Pediatrics.* 2008;121(1):e44-e52.
58. Greer FR, Sicherer SH, Burks AW; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics.* 2008;121(1):183-191.
59. Kramer MS, Matush L, Vanilovich I, et al.; Promotion of Breastfeeding Intervention Trial (PROBIT) Study Group. Effect of prolonged and exclusive breast feeding on risk of allergy and asthma: cluster randomised trial. *BMJ.* 2007;335(7624):815.
60. Kilburn S, Lasserson TJ, McKean M. Pet allergen control measures for allergic asthma in children and adults. *Cochrane Database Syst Rev.* 2003;(1):CD002989.
61. Wood RA, Johnson EF, Van Natta ML, Chen PH, Eggleston PA. A placebo-controlled trial of a HEPA air cleaner in the treatment of cat allergy. *Am J Respir Crit Care Med.* 1998;158(1):115-120.