The diagnosis and management of rhinitis: An updated practice parameter

Chief Editors: **Dana V. Wallace, MD, and Mark S. Dykewicz, MD**
Co-Editors: **David I. Bernstein, MD, Joann Blessing-Moore, MD, Linda Cox, MD, David A. Khan, MD, David M. Lang, MD, Richard A. Nicklas, MD, John Oppenheimer, MD, Jay M. Portnoy, MD, Christopher C. Randolph, MD, Diane Schuller, MD, Sheldon L. Spector, MD, and Stephen A. Tilles, MD**

These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology.

The American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing "The diagnosis and Management of Rhinitis: An Updated Practice Parameter." This is a complete and comprehensive document at the current time. The medical environment is a changing environment, and not all recommendations will be appropriate for all patients. Because this document incorporated the efforts of many participants, no single individual, including those who served on the Joint Task Force, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

Published practice parameters of the Joint Task Force on Practice Parameters for Allergy and Immunology include the following:

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl):S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
5. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
6. The diagnosis and management of anaphylaxis. J Allergy Clin Immunol 1998;101(suppl):S465-S528.
7. Algorithm for the diagnosis and management of asthma: a practice parameter update. Ann Allergy 1998;81:415-20.
8. Diagnosis and management of rhinitis: parameter documents of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Ann Allergy 1998; 81(suppl):S463-S518.
9. Parameters for the diagnosis and management of sinusitis. J Allergy Clin Immunol 1998;102(suppl):S107-S144.
10. Stinging insect hypersensitivity: a practice parameter. J Allergy Clin Immunol 1999;103:963-80.
11. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999;83(suppl):S665-S700.
12. Diagnosis and management of urticaria: a practice parameter. Ann Allergy 2000;85(suppl):S521-S544.
13. Allergen immunotherapy: a practice parameter. Ann Allergy 2003;90(suppl):S1-S540.
14. Symptom severity assessment of allergic rhinitis, part I. Ann Allergy 2003;91:105-14.

Disclosure of potential conflict of interest: D. V. Wallace is on the speakers' bureau for Schering-Plough, Aventis, Pfizer, and Merck and is on the advisory board for AstraZeneca. M. S. Dykewicz has consulting arrangements with AstraZeneca, GlaxoSmithKline, McNeil, Medpointe/Meda, Merck, Novartis/Genentech, Schering-Plough, and Teva; has received research support from AstraZeneca, GlaxoSmithKline, Novartis/Genentech, and Schering-Plough; and is on the speakers' bureau for AstraZeneca, GlaxoSmithKline, and Merck. D. I. Bernstein has research contracts with GlaxoSmithKline, AstraZeneca, Schering-Plough, Novartis, and Greer; is on the speakers' bureau for Sanofi and Teva; and is on the advisory panel for Schering-Plough. J. Blessing-Moore has received research support from AstraZeneca and Novartis and is on the speakers' bureau for Schering-Plough, Merck, AstraZeneca, Teva, Novartis-Genentech, and Sepracor. L. Cox has consulting arrangements with Stallergenes, Greer, Novartis/Genentech, Planet Technology, and Schering-Plough and is on the speakers' bureau for Novartis/Genentech and AstraZeneca. D. A. Khan has received research support from AstraZeneca and is on the speakers' bureau for Merck and GlaxoSmithKline. D. M. Lang has consulting arrangements with, has received research support from, and is on the speakers' bureau for GlaxoSmithKline, AstraZeneca, Sanofi-Aventis, Merck, Novartis/Genentech, Venus, Dey, and Schering-Plough. J. Oppenheimer has consulting arrangements with, has received research support from, and is on the speakers' bureau for AstraZeneca, GlaxoSmithKline, Sepracor, Apeiron, Merck, and Schering-Plough. J. M. Portnoy has consulting arrangements with GlaxoSmithKline, Sanofi-Aventis, and Greer; has received research support from Clorox; and is on the speakers' bureau for Merck, Schering-Plough, Sanofi-Aventis, AstraZeneca, and GlaxoSmithKline. S. L. Spector has consulting arrangements with Merck, Novartis, Genentech, Critical Therapeutics, and AstraZeneca; has received research support from Merck, Genentech, Schering-Plough, and AstraZeneca; and is on the speakers' bureau for Merck, Novartis, Genentech, Critical Therapeutics, Schering-Plough, and AstraZeneca. S. A. Tilles has consulting arrangements with GlaxoSmithKline and Schering-Plough and has received research support from Meda, Alcon, and Schering-Plough. F. Baroody has consulting arrangements with GlaxoSmithKline; has received research support from GlaxoSmithKline and Alcon; and is on the speakers' bureau for Merck and GlaxoSmithKline. G. Rachelefsky has consulting arrangements with AstraZeneca, Schering-Plough, Merck, and Medpoint and is on the speakers' bureau for AstraZeneca, Schering-Plough, Merck, Medpoint, and Genentech. R. Settipane has consulting arrangements with GlaxoSmithKline and Alcon; has received research support from Alcon, Medpoint, GlaxoSmithKline, and Schering-Plough; and is on the speakers' bureau for Sanofi-Aventis, UCB, AstraZeneca, GlaxoSmithKline, Alcon, and Genentech. D. Skoner has consulting arrangements with Merck; has received research support from AstraZeneca, Sanofi-Aventis, GlaxoSmithKline, Novartis, Merck, and Greer Laboratories; and is on the speakers' bureau for AstraZeneca, Sanofi-Aventis, GlaxoSmithKline, Merck, Schering-Plough, and Novartis. S. Stoloff has consulting arrangements with GlaxoSmithKline, AstraZeneca, Alcon, Schering-Plough, Novartis, Genentech, Aventis, Teva, and Dey; is on the speakers' bureau for GlaxoSmithKline and AstraZeneca; and has served as an expert witness for GlaxoSmithKline. The other authors have declared that they have no conflict of interest.

Reprint requests: Joint Council of Allergy, Asthma and Immunology, 50 N Brockway St, #3-3, Palatine, IL 60067.

J Allergy Clin Immunol 2008;122:S1-84.
0091-6749/$34.00

doi:10.1016/j.jaci.2008.06.003

15. Disease management of atopic dermatitis: an updated practice parameter. Ann Allergy 2004;93(suppl):S1-S21.
16. Stinging insect hypersensitivity: a practice parameter update. J Allergy Clin Immunol 2004;114;4:869-86.
17. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol 2005;115(suppl): S483-S523.
18. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy 2005;94(suppl):S1-S63.
19. Attaining optimal asthma control: a practice parameter. J Allergy Clin Immunol 2005;116(suppl):S3-S11.
20. The diagnosis and management of sinusitis: a practice parameter update. J Allergy Clin Immunol 2006;116(suppl): S13-S47.
21. Food allergy: a practice parameter. Ann Allergy 2006; 96(suppl):S1-S68.
22. Contact dermatitis: a practice parameter. Ann Allergy 2006; 97(suppl):S1-S37.
23. Allergen immunotherapy: a practice parameter second update. J Allergy Clin Immunol 2007;120(suppl):S25-S85.
24. Allergy diagnostic testing: an updated practice parameter. Ann Allergy 2008;100(suppl):S1-S148.

These parameters are also available on the internet at http://www.jcaai.org.

CONTRIBUTORS

The Joint Task Force has made a concerted effort to acknowledge all contributors to this parameter. If any contributors have been excluded inadvertently, the Task Force will ensure that appropriate recognition of such contributions is made subsequently.

CHIEF EDITOR—JOINT TASK FORCE

Dana V. Wallace, MD
Assistant Clinical Professor
Nova Southeastern University
Davie, Fla

CHIEF EDITOR—PARAMETER WORKGROUP CHAIR

Mark S. Dykewicz, MD
Professor of Internal Medicine
Chief, Section of Allergy and Clinical Immunology, Division of Immunobiology
Director, Allergy and Immunology Fellowship Program
Saint Louis University School of Medicine
St Louis, Mo

TASK FORCE REVIEWERS

David I. Bernstein, MD
Professor of Clinical Medicine and Environmental Health
Division of Allergy/Immunology
University of Cincinnati College of Medicine
Cincinnati, Ohio
I. Leonard Bernstein, MD
Clinical Professor of Medicine and Environmental Health
University of Cincinnati College of Medicine
Cincinnati, Ohio
Joann Blessing-Moore, MD
Clinical Associate Professor of Medicine and Pediatrics
Stanford University Medical Center
Department of Immunology
Palo Alto, Calif
Linda Cox, MD
Assistant Clinical Professor of Medicine
Nova Southeastern University College of Osteopathic Medicine
Davie, Fla
David A. Khan, MD
Associate Professor of Internal Medicine
University of Texas Southwestern Medical Center
Dallas, Tex
David M. Lang, MD
Head, Allergy/Immunology Section
Division of Medicine
Director, Allergy and Immunology Fellowship Training Program
Cleveland Clinic Foundation
Cleveland, Ohio
Richard A. Nicklas, MD
Clinical Professor of Medicine
George Washington Medical Center
Washington, DC
John Oppenheimer, MD
Department of Internal Medicine
New Jersey Medical School
Pulmonary and Allergy Associates
Morristown, NJ
Jay M. Portnoy, MD
Chief, Section of Allergy, Asthma and Immunology
Children's Mercy Hospital
Professor of Pediatrics
University of Missouri–Kansas City School of Medicine
Kansas City, Mo
Christopher C. Randolph, MD
Clinical Professor of Pediatrics
Yale Affiliated Hospitals
Center for Allergy, Asthma, and Immunology
Waterbury, Conn
Diane E. Schuller, MD
Professor of Pediatrics
Pennsylvania State University Milton S. Hershey Medical College
Hershey, Pa
Sheldon L. Spector, MD
Clinical Professor of Medicine
University of California–Los Angeles School of Medicine
Los Angeles, Calif
Stephen A. Tilles, MD
Clinical Assistant Professor of Medicine
University of Washington School of Medicine
Redmond, Wash

ASSIGNED REVIEWERS

Kathleen R. May, MD
Allegany Allergy and Asthma
Cumberland, Md
Travis A. Miller, MD
University of Michigan
Capital Allergy and Respiratory Disease Center
Sacramento, Calif

Howard M. Druce, MD, FAAAAI
Clinical Associate Professor of Medicine
University Hospital
Morris Plains, NJ

PARAMETER WORKGROUP MEMBERS

Faud M. Baroody, MD
Professor of Otolaryngology–Head and Neck Surgery and Pediatrics
Pritzker School of Medicine
University of Chicago
Chicago, Ill
Jonathan A. Bernstein, MD
Professor of Medicine
Division of Immunology/Allergy Section
Department of Internal Medicine
University of Cincinnati College of Medicine
Cincinnati, Ohio
Timothy J. Craig, DO
Professor of Medicine, Pediatrics and Graduate Studies
Pennsylvania State University
Hershey, Pa
John W. Georgitis, MD
LaFayette Clinic
Fayetteville, NC
Ruby Pawankar, MD, PhD
Professor of Medicine
Division of Rhinology and Allergy
Department of Otolaryngology
Nippon Medical School
Tokyo, Japan
Gary S. Rachelefsky, MD
Clinical Professor of Allergy and Immunology
Center for Asthma, Allergy and Respiratory Diseases
University of California–Los Angeles Medical Center
Los Angeles, Calif
Russell A. Settipane, MD
Clinical Associate Professor of Medicine
Brown University Medical School
Providence, RI
David P. Skoner, MD
Professor of Pediatrics
Drexel University College of Medicine
Director, Division of Allergy, Asthma and Immunology
Allegheny General Hospital
Pittsburgh, Pa
Stuart W. Stoloff, MD
Clinical Professor of Family and Community Medicine
University of Nevada School of Medicine
Reno, Nev

Classification of recommendations and evidence
Category of evidence

Ia. Evidence from meta-analysis of randomized controlled trials
Ib. Evidence from at least 1 randomized controlled trial
IIa. Evidence from at least 1 controlled study without randomization
IIb. Evidence from at least 1 other type of quasi-experimental study
III. Evidence from nonexperimental descriptive studies, such as comparative studies
IV. Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

LB Evidence from laboratory-based studies.
NR Not rated.

Strength of Recommendation

A Directly based on category I evidence
B Directly based on category II evidence or extrapolated recommendation from category I evidence
C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence

Diagnosis and management of rhinitis: An updated practice parameter

Note: The Summary Statements that are associated with the sections of the Preface and Exective Summary are Indicated inside the brackets.

PREFACE [SUMMARY STATEMENTS 8, 9, 13]

Rhinitis, as defined for the purposes of this document, is characterized by 1 or more of the following nasal symptoms: congestion, rhinorrhea (anterior and posterior), sneezing, and itching. Rhinitis is usually associated with inflammation, but some forms of rhinitis such as vasomotor rhinitis or atrophic rhinitis are not predominantly inflammatory.

Rhinitis is a significant cause of widespread morbidity, medical treatment costs, reduced work productivity, and lost school days. Although sometimes mistakenly viewed as a trivial disease, symptoms of allergic and nonallergic rhinitis may significantly affect a patient's quality of life and can be associated with conditions such as fatigue, headache, cognitive impairment, and sleep disturbance. Appropriate management of rhinitis may be an important component in effective management of coexisting or complicating respiratory conditions, such as asthma, sinusitis, and sleep apnea. The financial burden to society for allergic rhinitis is substantial. The total direct ($7.3 billion) and indirect costs ($4.28 billion, including loss of productivity) estimated in the United States for 2002 were $11.58 billion.[1]

Allergic rhinitis affects between 10% and 30% of all adults and as many as 40% of children.[2,3-6] In most studies, the ratio of allergic to pure nonallergic rhinitis is 3:1.[2] Preliminary data suggest that 44% to 87% of patients with rhinitis may have mixed rhinitis, a combination of allergic and nonallergic rhinitis.[2,7] Worldwide, the prevalence of allergic rhinitis continues to increase.

The objective of ''Diagnosis and Management of Rhinitis: An Updated Practice Parameter'' is to improve the care of patients by providing the practicing physician with an evidence-based approach by reviewing data in the medical literature and

incorporating this evidence into development of this guideline. While giving an overview of all categories of rhinitis, the parameter will focus on the diagnosis and treatment of allergic rhinitis. Using the 1998 practice parameter on ''Diagnosis and Management of Rhinitis''[8] as the basis, the working draft of this updated rhinitis practice parameter was prepared by a work group chaired by Mark S. Dykewicz, MD, and was revised and edited by the Joint Task Force on Practice Parameters under the leadership of Dana V. Wallace, MD. Preparation of this draft included a review of the recent medical literature using a variety of search engines such as PubMed. Published clinical studies were rated by category of evidence and used to establish the strength of the recommendations, as defined in the preamble to this parameter. The parameter was then reviewed by experts on rhinitis selected by the sponsoring organizations of the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma, and Immunology. Based on this process, this parameter represents an evidence-based document.

Components and organization of this parameter

The ''Diagnosis and Management of Rhinitis: An Updated Practice Parameter'' contains an annotated algorithm that presents the major decision points for the appropriate evaluation and treatment of patients with suspected rhinitis. This is followed by a collation of Summary Statements, which represent key points in the evaluation and management of this condition. Tables that provide clinically useful information in a concise format precede the body of the practice parameter, which provides a referenced narrative discussion of each Summary Statement. The graded references and figures complete the document. The Executive Summary emphasizes the key updates since the 1998 rhinitis parameter (Box).

To obtain the maximum value from this practice parameter in the most time-efficient manner, the clinician should review the Executive Summary, annotated algorithm, Summary Statements, and tables because these are created to provide the key information. The text and graded references provide the foundation on which the Joint Task Force formulated and graded the Summary Statements.

Key updates

The following is a list of key updates discussed in this document:

- Pharmacologic products introduced since publication of the 1998 ''Diagnosis and Management of Rhinitis: Complete Guidelines''
- More defined positioning of agents (eg, leukotriene receptor antagonists) in management based on more recent evidence
- Introduction of *episodic* as a term to describe rhinitis elicited by sporadic exposures to inhalant aeroallergens, and implications for treatment
- Use of certain agents—that is, intranasal corticosteroids—on an as-needed basis
- Emphasis on recognizing comorbidities of allergic rhinitis (AR), such as asthma, sinusitis, and obstructive sleep apnea, and conducting appropriate studies, such as pulmonary function testing and sleep apnea studies
- Evidence on using combination therapy, specifically leukotriene receptor antagonists, with antihistamines
- Need to consider the benefits versus recently raised safety concerns about oral decongestants before their use in children below age 6 years
- Recommendation of considering second-generation antihistamines as safe agents for use during pregnancy
- Use of intranasal corticosteroids for symptoms of allergic conjunctivitis associated with rhinitis
- Consideration of using a Rhinitis Action Plan
- Emerging diagnostic and surgical procedures, such as acoustic rhinometry and radiofrequency volumetric tissue reduction

ABBREVIATIONS

ACE: Angiotensin-converting enzyme
AERD: Aspirin-exacerbated respiratory disease
ARIA: Allergic Rhinitis and its Impact on Asthma
BHR: Bronchial hyperresponsiveness
CF: Cystic fibrosis
CNS: Central nervous system
CSF: Cerebral spinal fluid
CT: Computed tomography
cysLT: Cysteinyl leukotriene
ECP: Eosinophilic cationic protein
FDA: US Food and Drug Administration
HEPA: High-efficiency particulate air
IOC: International Olympic Committee
IOP: Intraocular pressure
LT: Leukotriene
LTRA: Leukotriene receptor antagonist
MRI: Magnetic resonance imaging
NARES: Nonallergic rhinitis with eosinophilia syndrome
NSAID: Nonsteroidal anti-inflammatory drug
OA: Occupational asthma
OME: Otitis media with effusion
OSAS: Obstructive sleep apnea syndrome
OTC: Over-the-counter
PCD: Primary ciliary dyskinesia
PRN: When necessary (from Latin *pro re nata*)
QOL: Quality of life
RFVTR: Radiofrequency volumetric tissue reduction
RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire
RUDS: Reactive upper-airways dysfunction syndrome
SIT: Specific immunotherapy
SPT: Skin prick test
USOC: US Olympic Committee

COLLATION OF SUMMARY STATEMENTS

Definition and classification of rhinitis

1. Rhinitis is characterized by 1 or more of the following symptoms: nasal congestion, rhinorrhea (anterior and posterior), sneezing, and itching. **D**

Differential diagnosis of rhinitis and associated conditions

2. Rhinitis should be classified by etiology as allergic or nonallergic and differentiated from conditions that mimic symptoms of rhinitis. **C**

3. Symptoms of allergic rhinitis may occur only during specific seasons, may be perennial without seasonal exacerbation, may be perennial with seasonal exacerbations, or may occur episodically after specific aeroallergen exposures. **C**
4. *Episodic* allergic rhinitis is a new rhinitis category that denotes allergic nasal symptoms elicited by sporadic exposures to inhalant aeroallergens. **D**
5. The severity of allergic rhinitis ranges from mild and intermittent to seriously debilitating. **D**
6. Although there is no generally accepted method of grading the severity of rhinitis, the clinician may want to consider a graphic rating scale. **D**
7. Mixed rhinitis (combined allergic and nonallergic rhinitis) is noted in approximately 44% to 87% of patients with allergic rhinitis and is more common than either pure allergic rhinitis or nonallergic rhinitis. **C**

Burden and epidemiology of rhinitis

8. Allergic rhinitis affects 30 to 60 million people in the United States annually, including 10% to 30% of adults and as many as 40% of children. **C**
9. Risk factors for allergic rhinitis include (1) family history of atopy, (2) serum IgE >100 IU/mL before age 6 years, (3) higher socioeconomic class, and (4) presence of a positive allergy skin prick test (SPT). **C**
10. The influence of early childhood exposure to infections, animals, and secondary tobacco smoke on the development of atopy and allergic rhinitis is still unknown. **C**
11. Aeroallergen sensitization may occur within the first 2 years of life. **C**
12. The cost of treating allergic rhinitis and indirect costs related to loss of workplace productivity resulting from the disease are substantial. Rhinitis is also a significant cause of lost work and school days. **C**

Allergic rhinitis

Pathogenesis

13. The symptoms of allergic rhinitis result from a complex allergen-driven mucosal inflammation caused by interplay between resident and infiltrating inflammatory cells and a number of vasoactive and proinflammatory mediators, including cytokines. Sensory nerve activation, plasma leakage, and congestion of venous sinusoids also contribute. **C**
14. Allergic rhinitis may be characterized by early-phase and late-phase responses. Each type of response is characterized by sneezing, congestion, and rhinorrhea, but congestion predominates in the late phase. **C**

Seasonal and perennial allergic rhinitis

15. Seasonal allergic rhinitis is caused by an IgE-mediated reaction to seasonal aeroallergens. The length of seasonal exposure to these allergens is dependent on geographic location and climatic conditions. **C**
16. Perennial allergic rhinitis is caused by an IgE-mediated reaction to perennial environmental aeroallergens. These may include dust mites, molds, animal allergens, or certain occupational allergens, as well as pollen in areas where pollen is prevalent perennially. **C**

Associated allergic conjunctivitis

17. Allergic rhinitis is often accompanied by symptoms of allergic conjunctivitis. **C**
18. Many treatments used for allergic rhinitis can benefit associated symptoms of allergic conjunctivitis, and a variety of topical ophthalmic agents is useful for specific treatment of associated ocular symptoms. **A**
19. Intranasal corticosteroids, oral antihistamines, and intranasal antihistamines have similar effectiveness in relieving ocular eye symptoms associated with rhinitis. **A**

Nonallergic rhinitis syndromes

20. Nonallergic rhinitis is characterized by periodic or perennial symptoms of rhinitis that are not a result of IgE-dependent events. Examples of nonallergic rhinitis are infectious rhinitis, vasomotor rhinitis, and the nonallergic rhinitis with eosinophilia syndrome (NARES). **C**

Vasomotor rhinitis

21. Vasomotor rhinitis (idiopathic rhinitis) accounts for a heterogeneous group of patients with chronic nasal symptoms that are not immunologic or infectious in origin and is usually not associated with nasal eosinophilia. **D**

Rhinitis from foods and alcohol

22. Rhinitis may occur after ingestion of foods or alcoholic products. This may be a result of vagally mediated mechanisms, nasal vasodilation, food allergy, and/or other undefined mechanisms. Food allergy is a rare cause of rhinitis without associated gastrointestinal, dermatologic, or systemic manifestations. **B**

Infectious rhinitis

23. Infectious rhinitis and rhinosinusitis may be acute or chronic. Acute infectious rhinitis is usually a result of 1 of a large number of viruses, but secondary bacterial infection with sinus involvement may be a complication. Symptoms of acute infectious rhinosinusitis include nasal congestion, mucopurulent nasal discharge, pain and pressure, headache, olfactory disturbance, postnasal drainage, and cough. **C**
24. Viral infections account for as many as 98% of acute infectious rhinitis and the majority of rhinitis symptoms in the young child. Routine nasopharyngeal cultures when bacterial infections are suspected do not add diagnostic value. **C**

NARES

25. NARES is characterized by nasal eosinophils in patients who have perennial symptoms and occasionally reduced sense of smell. These patients often lack evidence of allergic disease as demonstrated by absence of positive skin tests and/or specific IgE antibodies in the serum. **C**

Occupational rhinitis

26. Occupational rhinitis is rhinitis arising in response to airborne substances in the workplace, which may be mediated by allergic or nonallergic factors, such as laboratory animal

antigen, grain, wood dusts, chemicals, and irritants. It often coexists with occupational asthma (OA). **C**

Hormonal rhinitis

27. Causes of hormonal rhinitis include pregnancy and menstrual cycle–related rhinitis. Pregnancy rhinitis, when present, is associated with significant nasal congestion, starts after the second month of pregnancy, and usually disappears within 2 weeks after delivery. **C**

Drug-induced rhinitis

28. Drug-induced rhinitis may be caused by a number of medications, including angiotensin-converting enzyme (ACE) inhibitors, phosphodiesterase-5–selective inhibitors, phentolamine, α-receptor antagonists, aspirin, and other nonsteroidal anti-inflammatory drugs (NSAIDs). Rhinitis medicamentosa is a syndrome of rebound nasal congestion that follows the overuse of intranasal α-adrenergic decongestants or cocaine. **C**

Atrophic rhinitis

29. Treatment of primary and secondary atrophic rhinitis involves reducing crusting and alleviating the foul odor by continuous nasal hygiene, such as nasal lavage and crust debridement, and the use of topical and/or systemic antibiotics when purulent secretions or an acute infection is present. **C**

Conditions that mimic rhinitis

Nasal polyps

30. Nasal polyps may occur in conjunction with chronic rhinitis or sinusitis and may contribute significantly to the patient's symptoms. Nasal polyps should always be considered in the differential diagnosis of patients who present with invariant nasal congestion and/or anosmia and its sequelae. Allergy as a cause of nasal polyps has not been established, but nasal polyps may occur in conjunction with allergic rhinitis. **C**

Anatomic abnormalities

31. Signs and symptoms suggestive of rhinitis can be produced by other conditions, including nasal septal deviation, tumors, and hypertrophy of the nasal turbinates. **C**
32. In infants and young children, nasal congestion or obstruction can result from structural problems, such as cleft palate and adenoidal hypertrophy, or functional problems, such as laryngopharyngeal reflux. **D**

Cerebral spinal fluid rhinorrhea

33. Refractory clear rhinorrhea may be a result of cerebral spinal fluid (CSF) leak, which is often caused by trauma or recent surgery. **B**

Ciliary dysfunction

34. Ciliary dysfunction can be primary (primary ciliary dyskinesia; PCD) or secondary (eg, viral infection) and may contribute to recurrent rhinitis and sinus infections. **C**

Evaluation and diagnostic studies

History

35. An effective evaluation of the patient with rhinitis often includes the following: a determination of the pattern, chronicity, and seasonality of nasal and related symptoms (or lack thereof); response to medications; presence of coexisting conditions; occupational exposure; and a detailed environmental history and identification of precipitating factors. **D**
36. Evaluation of rhinitis therapy should include assessment of quality of life (QOL). **C**

Physical examination

37. A physical examination of all organ systems potentially affected by allergies with emphasis on the upper respiratory tract should be performed in patients with a history of rhinitis. The nasal examination supports but does not definitely establish the diagnosis of rhinitis. **D**

Testing for specific IgE antibody

Skin testing

38. Determination of specific IgE, preferably by skin testing, is indicated to provide evidence of an allergic basis for the patient's symptoms, to confirm or exclude suspected causes of the patient's symptoms, or to assess the sensitivity to a specific allergen for avoidance measures and/or allergen immunotherapy. **B**
39. Skin tests are the preferred tests for the diagnosis of IgE-mediated sensitivity. The number of skin tests and the allergens selected for skin testing should be determined on the basis of the patient's age, history, environment, and living situation, such as area of the country, occupation, and activities. **D**

In vitro assays for specific IgE

40. The precise sensitivity of specific IgE immunoassays compared with skin prick/puncture tests is approximately 70% to 75%. Immunoassays have similar sensitivity to skin tests in identifying those patients with nasal symptoms elicited after natural or controlled allergen challenge tests. **C**
41. Interpretation of specific IgE immunoassays may be confounded by variables such as potency of allergens bound to solid support systems, cross-reactive proteins and glycoepitopes, specific IgG antibodies in the test serum, and high total IgE. **D**

Special diagnostic techniques

42. In selected cases, special techniques such as fiber optic nasal endoscopy and/or rhinomanometry may be useful in evaluating patients presenting with rhinitis symptoms. These tests may require special expertise for performance and interpretation. Patients with nasal disease require appropriate examination for associated diseases, such as sinusitis and otitis media. **B**
43. Nasal smears for eosinophils are not necessary for routine use in diagnosing allergic rhinitis when the diagnosis is clearly supported by the history, physical examination, and specific IgE diagnostic studies but may be a useful adjunct when the diagnosis of allergic rhinitis is in question. **C**

44. Although the saccharin test for mucociliary clearance has been relied on as a clinical screening test, it cannot be relied on for a definitive diagnosis of mucociliary dysfunction. **C**
45. Nasal biopsy may be indicated when determining whether a lesion is neoplastic or granulomatous or if there is an abnormality in the ultrastructure of cilia. **C**
46. The measurement of total IgE and IgG subclasses for the diagnosis of allergic rhinitis has limited value and should not be routinely performed. **C**
47. The presence of β-2-transferrin in the nasal secretions is a sensitive method of confirming cerebral spinal fluid rhinorrhea. **B**

Special testing considerations in children

48. In children with rhinitis, the use of immune studies, sweat test, sinus computed tomography (CT), and nasal endoscopy may be indicated when they are suspected to have comorbid conditions such as immune deficiency, cystic fibrosis (CF), and chronic sinusitis. **C**

Testing for comorbid conditions

49. A formal evaluation for obstructive sleep apnea may be considered in children and adults presenting with chronic rhinitis and other risk factors associated with sleep-disordered breathing. **C**
50. Pulmonary function tests should be considered in patients with rhinitis to assess the possibility that asthma might be present. **D**

Tests without diagnostic validity

51. There is no evidence that the following procedures have diagnostic validity for allergic rhinitis: cytotoxic tests, provocation-neutralization, electrodermal testing, applied kinesiology, iridology, and hair analysis. **B** (see ''Allergy Diagnostic Testing: An Updated Practice Parameter''[9])

Management of rhinitis

Environmental control measures

52. The most common allergic triggers for rhinitis include pollens, fungi, dust mites, furry animals, and insect emanations. **B**
53. The types of pollen responsible for rhinitis symptoms vary widely with locale, climate, and introduced plantings. **B**
54. Highly pollen-allergic individuals should limit exposure to the outdoors when high pollen counts are present. **B**
55. Fungi are ubiquitous organisms, many of which produce clinically important allergens. **B**
56. Reduction of indoor fungal exposure involves removal of moisture sources, replacement of contamination materials, and the use of dilute bleach solutions on nonporous surfaces. **D**
57. Clinically effective dust mite avoidance requires a combination of humidity control, dust mite covers for bedding, high-efficiency particulate air (HEPA) vacuuming of carpeting, and the use of acaricides. **B**
58. Avoidance is the most effective way to manage animal sensitivity. **D**
59. Cockroaches are a significant cause of nasal allergy, particularly in inner-city populations. **C**
60. The best treatment for rhinitis triggered by irritants, such as tobacco smoke and formaldehyde, is avoidance. **B**

Pharmacologic therapy

Oral antihistamines

61. Second-generation antihistamines are generally preferred over first-generation antihistamines for the treatment of allergic rhinitis. First-generation antihistamines have significant potential to cause sedation, performance impairment, and anticholinergic effects. Although occasionally advantageous (eg, sleep induction when taken at bedtime or a reduction in rhinorrhea), these properties are usually undesirable and are potentially dangerous. Second-generation antihistamines have less or no tendency to cause these effects. **B**
62. Before prescribing or recommending a first-generation antihistamine, the physician should ensure that the patient understands both the potential for adverse effects and the availability of alternative antihistamines with a lower likelihood of adverse effects. **D**
63. There are important differences among the second-generation antihistamines in regard to their sedative properties: fexofenadine, loratadine, and desloratadine do not cause sedation at recommended doses; loratadine and desloratadine may cause sedation at doses exceeding the recommended dose; cetirizine and intranasal azelastine may cause sedation at recommended doses. **A**
64. Among the newer, nonsedating antihistamines, no single agent has been conclusively found to achieve superior overall response rates. **C**

Intranasal antihistamines

65. Intranasal antihistamines may be considered for use as first-line treatment for allergic and nonallergic rhinitis. **A**
66. Intranasal antihistamines are efficacious and equal to or superior to oral second-generation antihistamines for treatment of seasonal allergic rhinitis. **A**
67. Because systemic absorption occurs, currently available intranasal antihistamines have been associated with sedation and can inhibit skin test reactions. **A**
68. Intranasal antihistamines have been associated with a clinically significant effect on nasal congestion. **A**
69. Intranasal antihistamines are generally less effective than intranasal corticosteroids for treatment of allergic rhinitis. **A**

Oral and topical decongestants

70. Oral decongestants, such as pseudoephedrine and phenylephrine, are α-adrenergic agonists that can reduce nasal congestion but can result in side effects such as insomnia, irritability, and palpitations. **A**
71. Oral and topical decongestants agents should be used with caution in older adults and young children, and in patients

of any age who have a history of cardiac arrhythmia, angina pectoris, cerebrovascular disease, hypertension, bladder neck obstruction, glaucoma, or hyperthyroidism. **C**

72. Topical decongestants can be considered for short-term and possibly for intermittent or episodic therapy of nasal congestion, but are inappropriate for regular daily use because of the risk for the development of rhinitis medicamentosa. **C**

Over-the-counter cough and cold medications for young children

73. The efficacy of cold and cough medications for symptomatic treatment of upper respiratory tract infections has not been established for children younger than 6 years. Because of the potential toxicity of these medications, the use of these over-the-counter (OTC) drugs generally should be avoided in all children below 6 years of age. **A**

Intranasal corticosteroids

74. Intranasal corticosteroids are the most effective medication class for controlling symptoms of allergic rhinitis. **A**
75. In most studies, intranasal corticosteroids have been shown to be more effective than the combined use of an antihistamine and leukotriene (LT) antagonist in the treatment of seasonal allergic rhinitis. **A**
76. Intranasal corticosteroids may provide significant relief of symptoms of seasonal allergic rhinitis when used not only on a regular basis but also on an as-needed basis. **B** However, as-needed use may not be as effective as continuous use of intranasal corticosteroids. **D**
77. When comparing the available intranasal corticosteroids, the overall clinical response does not appear to vary significantly between products irrespective of the differences in topical potency, lipid solubility, and binding affinity. **C**
78. Intranasal corticosteroids may be useful in the treatment of some forms of nonallergic rhinitis. **A**
79. Intranasal corticosteroids when given in recommended doses are not generally associated with clinically significant systemic side effects. **A**
80. Although local side effects are typically minimal with the use of intranasal corticosteroids, nasal irritation and bleeding may occur. Nasal septal perforation is rarely reported. **B**

Oral corticosteroids

81. A short course (5-7 days) of oral corticosteroids may be appropriate for the treatment of very severe or intractable nasal symptoms or to treat significant nasal polyposis. However, single administration of parenteral corticosteroids is discouraged and recurrent administration of parenteral corticosteroids is contraindicated because of greater potential for long-term corticosteroid side effects. **D**

Intranasal cromolyn

82. Intranasal cromolyn sodium is effective in some patients for prevention and treatment of allergic rhinitis and is associated with minimal side effects. It is less effective in most patients than corticosteroids and has not been adequately studied in comparison with LT antagonists and antihistamines. **A**

Intranasal anticholinergics

83. Intranasal anticholinergics may effectively reduce rhinorrhea but have no effect on other nasal symptoms. Although side effects are minimal, dryness of the nasal membranes may occur. **A**
84. The concomitant use of ipratropium bromide nasal spray and an intranasal corticosteroid is more effective than administration of either drug alone in the treatment of rhinorrhea without any increased incidence of adverse events. **A**

Oral anti-LT agents

85. Oral anti-LT agents alone, or in combination with antihistamines, have proven to be useful in the treatment of allergic rhinitis. **A**

Omalizumab

86. Omalizumab has demonstrated efficacy in AR; however, it has US Food and Drug Administration (FDA) approval for use only in allergic asthma. **A**

Nasal saline

87. There is evidence that topical saline is beneficial in the treatment of the symptoms of chronic rhinorrhea and rhinosinusitis when used as a sole modality or for adjunctive treatment. **A**

Allergen immunotherapy

88. Allergen immunotherapy is effective for the treatment of allergic rhinitis. **A**
89. Allergen immunotherapy should be considered for patients with allergic rhinitis who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens, and its use depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**
90. Allergen immunotherapy may prevent the development of new allergen sensitizations and reduce the risk for the future development of asthma in patients with allergic rhinitis. **B**

Surgery

91. Although there is no surgical treatment for allergic rhinitis, surgery may be indicated in the management of comorbid conditions, such as nasal obstruction from severe nasal septal deviation or inferior turbinate hypertrophy, adenoidal hypertrophy, or refractory sinusitis and complications thereof. **C**

Management decisions

92. Management and monitoring of rhinitis should be individualized and based on the spectrum, duration, and severity of symptoms; physical examination findings; comorbidities; age of the patient; and patient preferences using both step-up and step-down approaches. **C**

93. Effective allergic rhinitis management requires the development of a physician/patient/family partnership, avoidance of environmental triggers, and the appropriate use of prescribed therapeutic interventions. **C**

Education of patient and caretakers

94. Education is a key element in promoting adherence and optimizing treatment outcomes in allergic rhinitis. **D**

Major comorbid conditions

95. Patients with allergic rhinitis are at increased risk for the development of asthma. **A**
96. Treatment of allergic rhinitis may improve asthma control in patients with coexisting allergic rhinitis and asthma. **B**
97. There is no established cause-and-effect relationship of rhinitis with recurrent otitis media and otitis media with effusion (OME). **C**

Special considerations

Pregnancy

98. When selecting medications for treating rhinitis in pregnancy, the clinician might consider the FDA risk categories that are based largely on animal data and limited human studies. However, it is also beneficial to review human cohort and case-control studies as well as birth registry data before reaching a decision. **C**
99. The most critical time for concern about potential congenital malformation because of medication use is the first trimester, when organogenesis is occurring. **D**
100. A sufficient amount of human observational data has now been accumulated to demonstrate safety for second-generation as well as first-generation antihistamines. **C**
101. Oral decongestants should be avoided during the first trimester. Topical decongestants when used on a short-term basis may have a better safety profile than oral agents for first trimester use. **C**
102. Sodium cromolyn is a safe treatment for allergic rhinitis during pregnancy. **C**
103. Montelukast is a safe treatment for allergic rhinitis during pregnancy. **C**
104. Intranasal corticosteroids may be used in the treatment of nasal symptoms during pregnancy because of their safety and efficacy profile. **C**
105. Immunotherapy for allergic rhinitis may be continued during pregnancy but without dose escalation. **C**

Elderly patients

106. Rhinitis in the elderly may be caused by types of rhinitis common in other age groups but may also be influenced by age-related physiologic changes such as cholinergic hyperactivity, anatomic changes, and medications taken for other medical conditions. **C**

Athletes

107. Athletic performance can be affected by rhinorrhea and chronic or rebound nasal congestion. Rhinitis medication for the competitive athlete must be a US Olympic Committee (USOC) and/or International Olympic Committee (IOC)–approved product and should be one that does not adversely affect performance. **C**

Consultation with an allergist/immunologist

108. Allergist/immunologist care improves patient outcomes; however, consultation/referral services are often underused. **C**
109. Consultation with an allergist/immunologist should be considered for patients with rhinitis who have inadequately controlled symptoms, a reduced QOL and/or ability to function, adverse reactions to medications, a desire to identify the allergens to which they are sensitized and to receive advice on environmental control, or comorbid conditions such as asthma and recurrent sinusitis, or when allergen immunotherapy is a consideration. **C**

EXECUTIVE SUMMARY

Definition of rhinitis [Summary Statement 1]

Rhinitis is characterized by 1 or more of the following symptoms: nasal congestion, rhinorrhea (anterior and posterior), sneezing, and itching. Rhinitis is usually associated with inflammation, but some forms of rhinitis such as vasomotor rhinitis or atrophic rhinitis are not predominantly inflammatory. Rhinitis frequently is accompanied by symptoms involving the eyes, ears, and throat.

Classification and differential diagnosis of rhinitis and associated conditions [Summary Statements 2-7]

Rhinitis is classified as allergic or nonallergic, but not all types of rhinitis can be easily separated into one of these categories. For example, occupational rhinitis has been classified separately from allergic and nonallergic because it may have components of both allergic and nonallergic rhinitis. Conditions that mimic symptoms of rhinitis include nasal polyps, cerebrospinal fluid rhinorrhea, ciliary dyskinesia syndrome, and structural/mechanical factors, such as deviated septum and pharyngonasal reflux (Tables I and II).

There is no generally accepted method of grading rhinitis severity. In an attempt to do this, an international working group (Allergic Rhinitis and its Impact on Asthma [ARIA])[9] has proposed a classification for allergic rhinitis that placed patients into 1 of 4 categories: (1) mild intermittent, (2) mild persistent, (3) moderate/severe intermittent, and (4) moderate/severe persistent.[10] This classification system discarded the terms *seasonal* and *perennial*, emphasizing that an aeroallergen (eg, grass pollen) that occurs seasonally in one region may be detected throughout the year in another geographical area. The ARIA definition of *mild* rhinitis may be a useful comparative reference point for other severity grading schemes; this states that none of the following items is present: sleep disturbance; impairment of daily activities, leisure, and/or sport; impairment of school or work; and symptoms present but not troublesome.[11] This updated parameter supports the concept that *more severe rhinitis* is defined as more symptoms or interference with QOL, because data show that it may not be

TABLE I. Types of rhinitis

I	Allergic rhinitis
A	Seasonal
B	Perennial
C	Episodic
II	Nonallergic rhinitis
A	Vasomotor rhinitis
1	Irritant triggered (eg, chlorine)
2	Cold air
3	Exercise (eg, running)
4	Undetermined or poorly defined triggers
B	Gustatory rhinitis
C	Infectious
1	Acute
2	Chronic
D	NARES
III	Occupational rhinitis
A	Caused by protein and chemical allergens, IgE-mediated
B	Caused by chemical respiratory sensitizers, immune mechanism uncertain
C	Work-aggravated rhinitis
IV	Other rhinitis syndromes
A	Hormonally induced
1	Pregnancy rhinitis
2	Menstrual cycle related
B	Drug-induced
1	Rhinitis medicamentosa
2	Oral contraceptives
3	Antihypertensives and cardiovascular agents
4	Aspirin/NSAIDs
5	Other drugs
C	Atrophic rhinitis
D	Rhinitis associated with inflammatory-immunologic disorders
1	Granulomatous infections
2	Wegener granulomatosis
3	Sarcoidosis
4	Midline granuloma
5	Churg-Strauss
6	Relapsing polychondritis
7	Amyloidosis

TABLE II. Differential diagnosis of rhinitis

	Conditions that may mimic symptoms of rhinitis
A	Nasal polyps
B	Structural/mechanical factors
1	Deviated septum/septal wall anomalies
2	Adenoidal hypertrophy
3	Trauma
4	Foreign bodies
5	Nasal tumors
a	Benign
b	Malignant
6	Choanal atresia
7	Cleft palate
8	Pharyngonasal reflux
9	Acromegaly (excess growth hormone)
C	Cerebrospinal fluid rhinorrhea
D	Ciliary dyskinesia syndrome

possible to separate patients into moderate and severe categories.[12] A modified 7-point visual analog (graphic rating) scale for grading severity of nasal and nonnasal symptoms of allergic rhinitis and the effects of this disorder on the QOL has been developed (but not validated) and published by the Joint Task Force on Practice Parameters and is included, with minor modification, in Figs 1-4.[13]

In this document, the Joint Task Force retains and uses the terms *seasonal* and *perennial* in classifying patients with allergic rhinitis. These traditional descriptive terms are clinically useful and allow for accurate categorization of the vast majority of patients as having seasonal, perennial, or perennial allergic rhinitis with seasonal exacerbations. It has become well recognized that the traditional seasonal/perennial and ARIA schemes define different patient populations.[12] This parameter introduces the term *episodic allergic rhinitis*, denoting allergic nasal symptoms elicited by sporadic exposures to inhalant aeroallergens that are not usually encountered in the patient's indoor or outdoor environment, such as while visiting a farm where there is exposure to horses or while visiting a home with pets when a patient has no pet exposure in their own home or work environments.

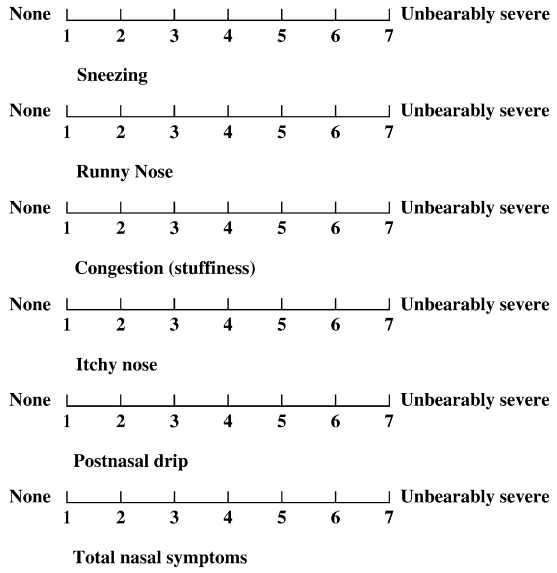


FIG 1. Assessment of nasal symptom severity.

Allergic rhinitis: Risk factors and presentation [Summary Statements 8-17]

Risk factors for allergic rhinitis

Risk factors for allergic rhinitis include (1) family history of atopy, (2) serum IgE >100 IU/mL before age 6 years, (3) higher socioeconomic class, and (4) the presence of a positive allergy SPT.[4,14-16] The influence of early childhood exposure to infections

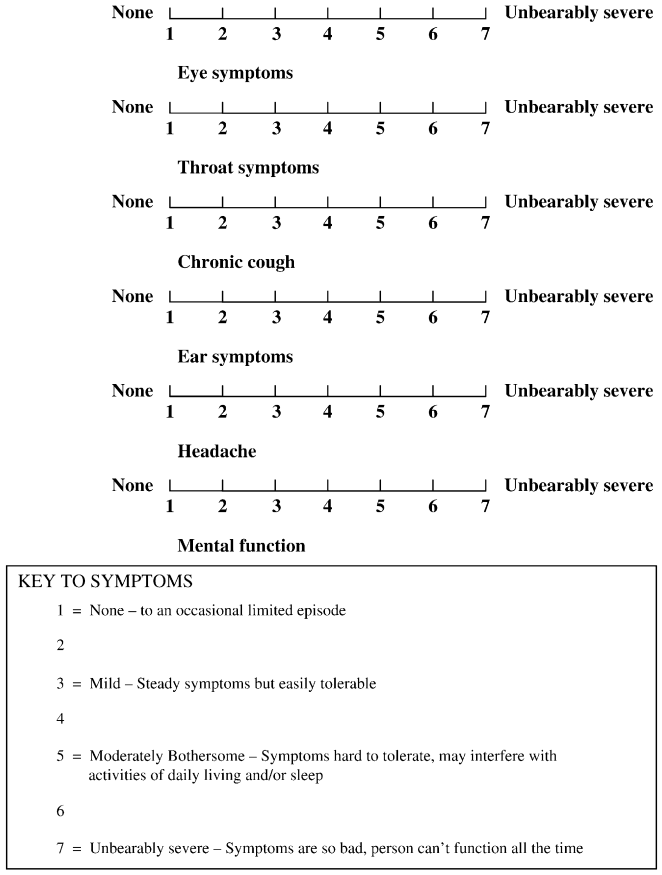


FIG 2. Assessment of non-nasal symptom severity.

(the hygiene hypothesis), animals, and secondary tobacco smoke on the development of atopy and allergic rhinitis is still unknown.[17-24]

Presentation of allergic rhinitis

In childhood, allergic rhinitis is more frequent in boys, but in adults, it is more frequent in women. Children with a bilateral family history of atopy may develop symptoms more frequently and at a younger age than those with a unilateral family history.[6,25] Aeroallergen sensitization rarely begins before 6 months of age[26] but may start between 6 months and 2 years of life.[27] Infants born to atopic families are sensitized to pollen aeroallergens more frequently than to indoor aeroallergens in the first year of life.[27] Seasonal allergic rhinitis symptoms generally do not develop until 2 to 7 years of age.[28-30] Food ingestion rarely causes allergic rhinitis in infants, children, or adults unless there are associated gastrointestinal, dermatologic, or systemic manifestations. The prevalence of seasonal allergic rhinitis is higher in children and adolescents, whereas perennial allergic rhinitis has a higher prevalence in adults.[31]

Early-phase and late-phase responses in allergic rhinitis

As in patients with asthma, early-phase and late-phase responses may be seen in allergic rhinitis. Both the early-phase and late-phase responses in allergic rhinitis are characterized by symptoms of sneezing, rhinorrhea, and nasal congestion. However, nasal congestion is predominantly a late-phase response. Mediators released from eosinophils during the late phase contribute to tissue damage.[32,33] Pretreatment with

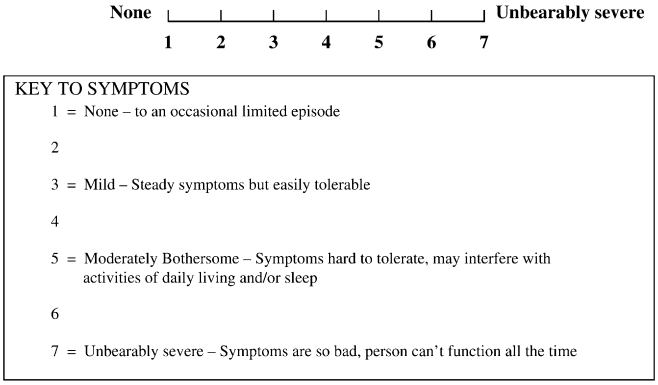
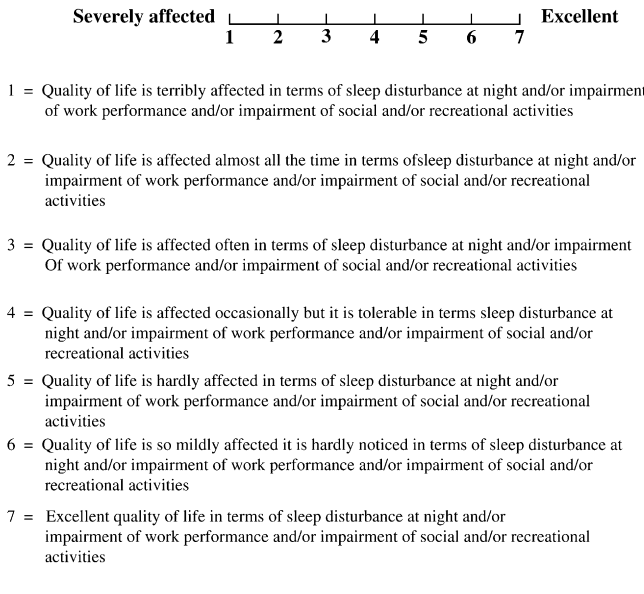


FIG 3. Global assessment of nasal and non-nasal symptom severity.



* This classification lends itself to a numeric scoring including individual scores or combination scores.

FIG 4. Assessment of quality of life.

glucocorticoids effectively reduces eosinophils and the release of cytokines during the late-phase response.[34-36]

When allergen challenges are given repeatedly, the amount of allergen required to induce an immediate response decreases. This *priming* effect is thought to be a result of the release of inflammatory mediators from effector cells during ongoing, prolonged allergen exposure and repeated late-phase responses. Consequently, at the end of a pollen season, symptoms may decline at a slower rate than the pollen count. Therefore, it is important to know the full spectrum of aeroallergens to which the patient responds as well as seasonal variations in symptoms. Initiating anti-inflammatory therapy before pollen season or before any repetitive aeroallergen exposure, as indicated, will modify the late-phase response that is associated with the priming effect.

Allergic conjunctivitis [Summary Statements 17-19]

Oral antihistamines, intranasal antihistamines, oral anti-LT agents, intranasal corticosteroids, and allergen immunotherapy are treatments for allergic rhinitis that have been reported to relieve associated ocular allergy symptoms in controlled trials.[37-52] In systematic reviews of randomized controlled studies, intranasal

corticosteroids compared with oral antihistamines[53,54] and intranasal corticosteroids compared with intranasal antihistamines[46] were not significantly different in relieving eye symptoms.

Use of cold compresses and irrigation with saline solution or artificial tears has been advocated to relieve mild symptoms of allergic conjunctivitis. Topical ophthalmic agents are indicated for specific treatment of itching or symptoms of allergic conjunctivitis. Vasoconstrictors are indicated for relief of ocular redness, although they do not reduce the allergic response. Prolonged use of ocular decongestants may lead to rebound hyperemia, which is often referred to as ''conjunctivitis medicamentosa.''[55] Use limited to 10 days does not appear to induce this condition.[56] The combination of an ocular antihistamine and a vasoconstrictor works better than either agent alone.[57] Mast cell stabilizers, also approved for vernal and atopic keratoconjunctivitis, have a slow onset of action and may require several days of treatment before optimal symptom relief is achieved,[58] making them more suitable for prophylactic or longer-term treatment of chronic ocular allergies than for acute symptom relief. Topical NSAIDs reduce prostaglandin production involved in mediating ocular allergy.[59] Multiple-action agents possess both antihistamine and mast cell stabilizer activities, generally have onset of action within 30 minutes, and are suitable for acute and long-term treatment of allergic conjunctivitis symptoms. Ocular corticosteroids should be reserved for more severe symptoms of allergic conjunctivitis considering that the ocular side effects from their use can threaten vision because of the increased risk of cataract formation, elevated intraocular pressure (IOP), and secondary infections. The modified steroid loteprednol is indicated for the temporary relief of symptoms and signs of seasonal allergic conjunctivitis and has a greatly reduced risk of causing increased IOP compared with many other ocular corticosteroids.[60-64]

Vasomotor rhinitis [Summary Statements 20-22]

Vasomotor rhinitis, a type of nonallergic rhinitis, may be episodic or perennial.[7] The exact pathophysiology of vasomotor rhinitis has never been established, and for this reason, it is often classified as ''idiopathic'' rhinitis.[9] When rhinorrhea is the predominant symptom, there appears to be enhanced cholinergic glandular secretory activity based on the fact that atropinelike agents effectively reduce secretions.[65] Gustatory rhinitis (rhinitis symptoms associated with eating) is a form of nonallergic rhinitis felt to be vagally mediated that may respond to intranasal anticholinergic agents.[66] Patients with predominant nasal congestion may have nociceptive neurons that have heightened sensitivity to stimuli such as temperature change, airborne irritants, foods (especially hot and spicy foods), alcoholic beverages, cold dry air, and exercise.[67-70] Temperature change has also been noted to increase symptoms and the inflammatory nasal response in patients with allergic rhinitis.[71]

Acute infectious rhinitis [Summary Statements 23, 24]

Acute viral upper respiratory infections are the most common predisposing factor for bacterial sinusitis, accounting for 90% to 98% of all episodes of sinusitis in children and adults.[72-76] In uncomplicated cases of viral rhinitis, a 7-day to 10-day observation period for spontaneous resolution of symptoms is recommended before prescribing antibiotics.[77] Acute bacterial rhinosinusitis is usually associated with a viral upper respiratory infection and is characterized by symptoms persisting beyond the usual 7-day to 10-day duration of a viral infection. Careful consideration of the need for antimicrobial use is increasingly important because antibiotic use has been causally related to the development of bacterial drug resistance.[78-82] Furthermore, the administration of antimicrobials increases the carriage of antimicrobial-resistant strains of certain bacterial pathogens, such as *Streptococcus pneumonia,* especially in children.[78,79,83,84] Although it is generally believed that atopic children experience more episodes of acute otitis media and acute sinusitis compared with nonallergic children, this has not been firmly established.[77,85,86] Differentiating allergic rhinitis from infectious rhinosinusitis or adenoiditis may be difficult, especially in children, because the symptoms overlap and even purulent nasal drainage may be present in noninfectious rhinitis.

Acute and chronic sinusitis [Summary Statements 23, 24]

Distinguishing noninfectious perennial rhinitis from acute and chronic sinusitis can be difficult because many symptoms, such as mucosal erythema, increased pharyngeal secretions, olfactory disturbance, cough, nasal congestion, and headache, are found in both types of rhinitis. Although nasal cytology may be useful in differentiating infectious from noninfectious nasal and/or sinus disease, the clinical value, particularly for the diagnosis of allergic rhinitis, is limited by low specificity and sensitivity.[87-91] For example, neutrophils may be present not only in acute and chronic sinusitis but also in conjunction with eosinophils in patients with allergic rhinitis who also have an acute infection process.[92] Cultures of the nasopharynx without visualization in children with rhinitis is of no value because pathogenic bacteria, as part of the normal flora, have been recovered in as many as 92% of asymptomatic healthy children.[93] In adults, endoscopically directed middle meatus cultures have given promising results in diagnosing acute bacterial sinusitis.[94-97]

Nonallergic rhinitis with eosinophilia syndrome [Summary Statement 25]

Patients with NARES have paroxysmal exacerbations of symptoms, including sneezing, profuse watery rhinorrhea, nasal pruritus, nasal congestion, and occasional anosmia. These patients are typically middle-age. The prevalence in the general population is unknown. NARES is characterized by large numbers (inconsistently defined as >5% to >20%) of eosinophils on nasal smear.[98-102] The etiology is unknown. In some patients, NARES may precede the development of nasal polyposis and aspirin sensitivity.[103] Patients with NARES are at increased risk for the development of obstructive sleep apnea.[104]

Occupational rhinitis [Summary Statement 26]

Occupational rhinitis may be triggered by allergic factors, such as laboratory animal antigen and psyllium,[105,106] or irritant factors, such as chemicals, grain dust, and ozone.[107-109] Allergic occupational rhinitis frequently coexists with OA.[110] Irritant exposures elicit neutrophilic inflammation in the nasal mucosa,[107-109] whereas allergic exposures are associated with eosinophils, basophils, eosinophilic cationic protein (ECP), and tryptase in the nasal lavage.[111-113] However, immunologic mechanisms may also be important in the response to chemical sensitizers, such as acid anhydrides, where both neutrophils and eosinophils are increased in nasal lavage fluid of workers with serum specific IgE to the relevant anhydride-human serum albumin (HSA) antigen.[114] The prevalence of occupational rhinitis is essentially 100% among workers with OA who are sensitized to high-molecular-weight proteins, whereas only 50% of those with OA caused by chemicals have been identified with

work-related rhinitis.[110] Atopy and intensity of exposure are risk factors for developing occupational rhinitis.[115] An asymptomatic latency period of exposure lasting weeks to years often precedes work-related symptoms.[105,116] Symptoms are temporally related to exposure at work and often improve away from the workplace. The diagnostic validity of nasal allergen challenge for occupational allergens has not been evaluated.[112,114] Optimal management is avoidance of the occupational trigger, but avoidance of nonoccupational allergens that contribute to the nasal symptoms is also recommended. Chronic pharmacologic therapy as used for allergic and nonallergic rhinitis can be instituted. In general, there is insufficient evidence to support the efficacy of immunotherapy for IgE-dependent occupational rhinitis, and it is inappropriate to use immunotherapy to treat occupational rhinitis caused by low-molecular-weight chemical allergens.[117]

Pregnancy and menstrual cycle rhinitis [Summary Statement 27]

Symptoms of rhinitis during pregnancy and at the time of patients' menstrual cycles have long been considered to be hormonally induced. The most common causes of nasal symptoms during pregnancy are allergic rhinitis, sinusitis, rhinitis medicamentosa, and vasomotor rhinitis. Symptoms of allergic rhinitis increase in 1/3 of pregnant patients,[118] perhaps attributed to nasal vascular pooling caused by vascular dilatation and increased blood volume.[119] A type of rhinitis unique to the pregnant patient is ''vasomotor rhinitis of pregnancy'' or ''pregnancy rhinitis.'' Pregnancy rhinitis had been defined as rhinitis without an infectious, allergic, or medication-related cause that starts before the last 6 weeks of pregnancy (corresponding to 34 weeks gestation), persists until delivery, and resolves completely within 2 weeks after delivery.[120] When pregnancy rhinitis causes snoring, it may even be a factor in the development of pre-eclampsia.[121] Although it is assumed that hormonal changes contribute to this condition, there is no convincing evidence.[120] There may be an association of nasal congestion with ovulation and the rise in serum estrogen during the normal menstrual cycle in some women.[122]

Drug-induced rhinitis [Summary Statement 28]

Drug-induced rhinitis may be caused by ACE inhibitors,[123] α-receptor antagonists used in the treatment of benign prostatic hypertrophy,[124] and phosphodiesterase-5 selective inhibitors used for treatment of erectile dysfunction.[125] There is no direct evidence that the current combined oral contraceptive pills cause nasal symptoms.[126] Aspirin and other NSAIDs may produce rhinorrhea as an isolated symptom or as part of aspirin-exacerbated respiratory disease (AERD), formerly termed ''Samter's triad.''[127,128]

Rhinitis medicamentosa [Summary Statement 28]

Rhinitis medicamentosa may develop after the repetitive and prolonged use of topical α-adrenergic nasal decongestant sprays such as oxymetazoline and phenylephrine. The recreational use of cocaine may result in a rhinitis medicamentosa–like state.[129,130] Benzalkonium chloride in vasoconstrictor spray products, when used for 30 days or more, may augment local pathologic effects.[131,132] Patients may develop rebound congestion, tachyphylaxis, reduced mucociliary clearance because of loss of ciliated epithelial cells,[133] and on rare occasions, nasal septal perforation.[134] The pathophysiology of this condition is not understood. Treatment of rhinitis medicamentosa consists of suspending the use of topical decongestants and administering intranasal corticosteroids to control symptoms while allowing the rebound effects of the nasal decongestant spray to resolve. At times, a short course of oral corticosteroids may be needed to control the patients' symptoms while the effects of the nasal decongestant spray dissipate.[129,135] Once the rhinitis medicamentosa is treated, the patient should be evaluated for an underlying condition, such as allergic rhinitis.

Atrophic rhinitis [Summary Statement 29]

Primary (idiopathic) atrophic rhinitis is a chronic condition characterized by progressive atrophy of the nasal mucosa, nasal crusting, nasal dryness (caused by atrophy of glandular cells), and fetor.[136,137] The nasal cavities appear abnormally wide on examination, and there is absence of identifiable turbinates on sinus CT, referred to as the ''empty nose syndrome.''[138] Secondary atrophic rhinitis is most commonly a result of chronic sinusitis or excessive surgery to the nasal turbinates.[138] Although saline irrigation is the mainstay of treatment, topical or systemic antibiotics are indicated with the appearance of purulent nasal secretions.[139,140]

Conditions that mimic rhinitis

Conditions that mimic rhinitis must be considered in the differential diagnosis of nasal symptoms.

Nasal polyps [Summary Statement 30]

Nasal polyps may coexist with allergic rhinitis; however, allergy as a cause of nasal polyps has not been established. Nasal polyps have a prevalence of 2% to 4%[141-143] and usually occur after age 40 years.[143] Although previous studies showed a 2:1 male to female prevalence of nasal polyps,[142,144,145] a recent large population study showed no sex preference.[143] AERD, previously referred to as the *aspirin triad*, consists of nasal polyps, acetylsalicylic acid intolerance, and asthma, and is recognized in 13% to 40% of patients with nasal polyposis.[146,147] Eosinophils are a consistent finding in nasal polyp tissue. When nasal polyps are associated with asthma, there is hypersecretion of cysteinyl LTs (cysLTs).[148] Oral steroids may be required in severe nasal polyposis to reduce polyp size, improve airflow, and allow for effective topical medication delivery. A short course of oral steroids followed by maintenance use of intranasal corticosteroid administered twice daily should follow.[149,150,151] Subjective improvement has been observed when LT modifiers are administered in addition to intranasal corticosteroids.[152,153] One study demonstrated that after surgery, reoccurrence rates and rescue medication requirements were the same in patients treated postoperatively with montelukast or beclomethasone.[154] In some adult patients with nasal polyps and AERD, aspirin desensitization followed by long-term daily aspirin treatment has successively reduced the need for removal of nasal polyps and systemic corticosteroids.[155-157]

Anatomic abnormalities and cerebral spinal fluid rhinorrhea [Summary Statements 31-33]

Nasal septal deviation and turbinate hypertrophy may lead to postnasal drip or nasal obstruction. Unilateral obstruction, especially when associated with bleeding, hyposmia or anosmia, pain, and otalgia, should alert one to the possibility of a tumor.[158,159] Clear rhinorrhea, even in the absence of trauma or recent surgery, may rarely be a result of a CSF leak.[160] Nasal symptoms, particularly congestion, may be noted in infants and children with pharyngonasal reflux resulting from prematurity, neuromuscular disease, or cleft palate.[161] In infants and children, the most common acquired anatomic cause of nasal obstruction is adenoidal hypertrophy.

TABLE III. Representative generic QOL questionnaires

Questionnaire	Web site for information	Cost for noncommercial use	Reference
Generic QOL adult			
Short Form 36 (Versions 1 and 2)	http://www.rand.org/health/surveys_tools/mos/mos_core_36item_survey.htmll	Free http://www.rand.org/health/surveys_tools/mos/mos_core_36item.html	625-627
SF-12 (Versions 1 and 2)	http://www.medal.org/Visitor/www/active/ch1/ch1.aspx	http://www.qualitymetric.com/products/license/	628
Health Utilities Index Mark 2 and 3 (HUI2 and 3)	http://www.healthutilities.com/hui2.htm http://www.hqlo.com/content/1/1/54	Contact http://www.healthutilities.com/aplcnform.htm	629, 630
Nottingham Health Profile	http://www.cebp.nl/media/m83.pdf	http://www.medal.org/visitor/www/Active/ch1/ch1.07/ch1.07.01.aspx	631-633
Functional Status Questionnaire	http://www.jasonprogram.org/Articles/fun_status_question.pdf	http://www.jasonprogram.org/Articles/fun_status_question.pdf	634
Duke Health Profile	http://www.outcomes-trust.org/instruments.htm More info: george.parkerson@duke.edu	Free single use with permission $155 master http://www.outcomes-trust.org/instruments.htm	635
Generic QOL child			
CHQ PF-50	http://www.qualitymetric.com/products/chq.aspx	http://www.qualitymetric.com/products/license/	636
CHQ PF-28	http://www.epa.state.oh.us/dapc/atu/AppendixA.pdf	http://www.qualitymetric.com/products/license/	637
SF-10	http://www.qualitymetric.com/products/chq.asqx	http://www.qualitymetric.com/products/license/	638
Pediatric Quality of Life Inventory (PedsQL)	http://www.mapi-research.fr/t_03_serv_dist_Cduse_pedsql.htm	Free Single Copy http://www.mapi-research.fr/t_03_serv_dist_ReviewPedsQLGenericsf.htm	639-642
Health Utilities Index Mark 2 and 3 (HUI2 & 3)	http://www.healthutilities.com/hui2.htm http://www.hqlo.com/content/1/1/54	Contact http://www.healthutilities.com/aplcnform.htm	629, 630

Questionnaires have been validated for research groups but not for an individual.

Ciliary dysfunction syndromes [Summary Statement 34]

Ciliary dysfunction syndromes cause ineffective mucociliary clearance and include (1) PCD[162] (also known as immotile-cilia syndrome), a rare genetic disorder, and (2) secondary ciliary dysfunction,[163,164] a more common condition caused by acute or chronic infections, multiple sinus surgeries, or irritant rhinitis. In PCD, the clinical history may include recurrent sinusitis, otitis, rhinitis, chronic cough, nasal polyposis, atypical asthma that is unresponsive to therapy, and bronchiectasis.[165] Approximately 50% of subjects with PCD are affected by situs inversus (Kartagener syndrome). Whereas screening diagnostic tests for mucociliary clearance use saccharine[166] or Teflon (DuPont) tagged particles, definitive diagnosis requires biopsy and examination by electron microscopy.[167-169] After an infection, resolution of secondary ciliary dysfunction and cytopathic epithelial damage may require weeks.[163,164,170-172] An adverse effect of tobacco smoke on mucociliary clearance in the upper airways in healthy smokers has not been established.[173,174]

Evaluation and diagnostic studies in patients with rhinitis

History [Summary Statements 35, 36]

A thorough allergic history remains the best diagnostic tool available. The history will include the patient's chief concerns and symptoms and often includes the pattern, chronicity, seasonality, and triggers of nasal and related symptoms, family history, current medications, response to previous treatment modalities, presence of coexisting conditions, occupational exposure, and a detailed environmental history. Questions relating symptoms to pollen and animal exposure have been shown to have positive predictive value for diagnosing allergic rhinitis.[175] In addition to upper respiratory symptoms, it is important to determine the effect of rhinitis on QOL, including symptoms of fatigue, sleep disturbances, learning and attention problems, and absenteeism and presenteeism (present but with impaired function) at work and/or school.[176-179] The psychological ramifications of untreated allergic rhinitis can lead to low self-esteem, shyness, depression, and anxiety.[180] Recent findings that the sexual QOL is affected by seasonal allergic rhinitis and that appropriate treatment improves the patient's sexual functioning emphasizes that allergic rhinitis is an underappreciated disease with systemic effects.[181] As evidence of the disparities between patients' and physicians' perspectives of allergic rhinitis, the symptom severity and the reduced work, home, and social functioning, as indicators of QOL, are often underrecognized and inadequately treated by the patient's physician.[182]

The effect of rhinitis on QOL has been measured using both generic and disease-specific questionnaires (Tables III and IV). Using generic QOL questionnaires, it has been shown that adults with moderate to severe perennial rhinitis and moderate to severe asthma have equal functional impairment.[183,184] On the other hand, disease-specific QOL questionnaires, including those specific for rhinitis, describe disease-associated problems more accurately and seem to be more responsive to measuring the change with therapeutic interventions. Although both the generic and disease-specific QOL questionnaires are often used in research trials, their sensitivity and precision for use with individual patients have not been determined.[185-190]

Physical examination [Summary Statement 37]

The physical examination (Table V) of all organ systems potentially affected by allergies should be performed in all patients with a history of rhinitis. Emphasis should be on the upper respiratory tract, but the examiner should carefully look for accompanying otitis[191] or eustachian tube dysfunction,[192] chronic sinusitis, nasal polyps, conjunctivitis, asthma,[193] and atopic dermatitis. If the patient is asymptomatic or mildly symptomatic at the time of the physical examination, there may be minimal or no findings even with a history suggestive of rhinitis.

The nasal and oropharyngeal examination may be accomplished with a nasal speculum with appropriate lighting, otoscope

TABLE IV. Representative rhinitis QOL questionnaires

Questionnaire	Web site for information	Cost of noncommercial use	Reference
Rhinitis QOL adult			
RQLQ	http://www.qoltech.co.uk/Rhinocon.htm#rqlq#rqlq	Free request: adultrqlqpack@qoltech.co.uk	643-645
Standardized Rhinoconjunctivitis Quality of Life Questionnaire	http://www.qoltech.co.uk/Rhinocon.htm#rqlqs	Free request: adultrqlqpack@qoltech.co.uk	646
Mini Rhinoconjunctivitis Quality of Life Questionnaire	http://www.qoltech.co.uk/Rhinocon.htm#minirqlq	Free request: adultrqlqpack@qoltech.co.uk	647
Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire	http://www.qoltech.co.uk/Rhinocon.htm#noct	Free request: adultrqlqpack@qoltech.co.uk	648
Rhinitis Quality of Life Questionnaire	http://www.qoltech.co.uk/Rhinocon.htm#rhinqlq	Free request: adultrqlqpack@qoltech.co.uk	649
Rhinitis Symptom Utility Index			650
Rhinitis QOL pediatric and adolescent			
Paediatric Rhinoconjunctivitis Quality of Life Questionnaire	http://www.qoltech.co.uk/PaedRhinocon.htm#prqlq	Free, request: paedrqlqpack@qoltech.co.uk	651
Adolescent Rhinoconjunctivitis Quality of Life Questionnaire	http://www.qoltech.co.uk/PaedRhinocon.htm#arqlq	Free, request: paedrqlqpack@qoltech.co.uk	652

Questionnaires have been validated for research groups but not for an individual.

TABLE V. Physical examination of patient presenting with symptoms compatible with rhinitis

Vital signs including weight and height should be recorded in all patients.
General observations: facial pallor, elongated facies, preferred mouth breathing, and any evidence of systemic disease.
Eyes: Excessive lacrimation, erythema and swelling of the bulbar and/or palpebral conjunctiva, cobblestoning of the tarsal conjunctiva, swelling or dermatitis of outer eyelids, Dennie-Morgan lines, or venous stasis below the lower eyelids (''allergic shiners'').
Nose: Reduced patency of nasal valve; alar collapse; transverse external crease; external deformity such as saddle nose; sepal deviation or perforation, spurs, ulcers, perforation, prominent vessels, or excoriation; nasal turbinate hypertrophy, edema, pallor or erythema, and crusting; discharge (amount, color, consistency), and nasal polyps. The presence of tumors or foreign bodies should be noted.
Ears: Tympanic membrane dullness, erythema, retraction, perforation, reduced or increased mobility, and air-fluid levels.
Oropharynx: Halitosis, dental malocclusion, high arched palate, tonsillar or adenoidal hypertrophy. Observe for malocclusion or high arched palate associated with chronic mouth breathing, tonsillar hypertrophy, cobblestoning of the oropharyngeal wall, pharyngeal postnasal discharge, temporomandibular joint pain or clicking with occlusion, furrowing, coating, or ulceration of tongue or buccal mucosa.
Neck: Lymphadenopathy, thyroid enlargement, or tenderness.
Chest: Signs of asthma. Chest wall deformity or tenderness, abnormal percussion, egophony, audible wheezing, or abnormal or diminished sounds by auscultation.
Abdomen: Tenderness, distension, masses, or enlargement of liver or spleen.
Skin: Rashes, especially eczematous or urticarial (distribution and description), or dermatographism.
Other organ systems when history or general observation indicate these should be included.

Note: This list is not intended to be totally inclusive. Elements of the examination that will assist in the differential diagnosis of rhinitis or that may indicate complications of treatment are included. Documentation of presence or absence of these elements should be considered.

with nasal adapter, indirect mirror, and/or rigid or flexible nasopharyngoscope, based on the expertise of the examiner and/or the assessment needs.[194] If after applying a topical decongestant there is a reduction of turbinate mucosa edema, this may assist in delineating mucosal versus bony hypertrophy and in differentiating severely edematous mucosa from nasal polyps. A pneumatic otoscope is used to assess tympanic membrane mobility. At times, an impedance tympanometer is also needed to assess the tympanic membrane mobility and the presence or absence of fluid, especially in children.

Many typical allergic findings are supportive of but not specific for allergic rhinitis.[195] Mucosal appearance may not distinguish between allergic and nonallergic noninfectious rhinitis or even infectious rhinitis, because hyperemia, for example, may be present with all 3. Likewise, classic ''allergic shiners'' are reported in 38% of nonatopic individuals.[196]

Testing for specific IgE [Summary Statements 38-41]

Determination of specific IgE, preferably by skin testing, is indicated to (1) provide evidence of an allergic basis for the patient's symptoms, (2) confirm suspected causes of the patient's symptoms, or (3) assess the sensitivity to a specific allergen for avoidance measures and/or allergen immunotherapy.[197,198] The number of skin tests and the allergens selected for skin testing should be determined on the basis of the patient's age, history, and environment and living situation, such as area of the country, occupation, and activities.[9] The precise sensitivity of specific IgE immunoassays compared with skin prick/puncture tests can vary with the technique used, from less than 50% to greater than 90%, with the average 70% to 75%.[199-209] Similar sensitivity has been reported when these immunoassays are compared with symptoms induced after natural or controlled challenge—that is, nasal provocation challenge. The simplicity, ease, and rapidity of performance, low cost, and high sensitivity make skin testing preferable to *in vitro* testing for determining the presence of specific IgE antibodies in patients with rhinitis. However, specific IgE immunoassays may be preferable to skin testing in certain clinical situations, such as extensive skin disease, skin test suppressive therapy (for example, antihistamines) that cannot be discontinued, or uncooperative patients, or when the history suggests an unusually high risk of

anaphylaxis from skin testing. Positive results of testing for specific IgE antibody to allergens must be correlated with history and physical findings to assess their clinical significance.[210,211] A positive immediate hypersensitivity skin test in the absence of symptoms has been shown to be a significant risk factor for the later development of seasonal allergic rhinitis.[4,14,15]

Special diagnostic techniques [Summary Statement 42]

Special diagnostic techniques may be useful in selected cases. Fiber optic nasal endoscopy[212,213] may be especially useful when symptoms or physical findings are atypical, complications or other conditions are suspected, or symptoms do not respond adequately to therapy. Although CT and magnetic resonance imaging (MRI) are not indicated in the evaluation of patients with uncomplicated rhinitis, they may be useful with suspected complications or comorbidities such as nasal polyposis and/or concomitant sinusitis.[214,215] MRI provides better imaging of soft tissue than CT, but it is less suited to imaging the bony anatomy. Standard radiographs are generally not indicated because of the availability of preferred procedures, as noted. When available, dynamic video rhinoscopy is more accurate at assessing adenoidal hypertrophy than a lateral nasopharyngeal radiograph.[216]

Rhinomanometry and acoustic rhinometry [Summary Statement 42]

Rhinomanometry, a technique that measures functional obstruction to airflow in the upper airway, may be used (1) to obtain objective assessment of nasal congestion, and may be particularly helpful in occupational rhinitis, or in assessing response to therapeutic interventions; (2) to assess the severity of anatomical abnormalities; or (3) to assist in the evaluation of patients with obstructive sleep apnea.[217] Acoustic rhinometry reflects acoustic signals from structures in the nasal cavity, thereby producing an image that represents variations in the cross-sectional dimensions of the nasal cavity.[218-220] This produces an approximate nasal cavity volume and identifies the distance to the minimal cross-sectional area from the nares. Measurement by acoustic rhinometry has been validated by comparison to CT and MRI.[221] Using this comparison, there is high correlation for the anterior 2/3 of the nasal cavity, but the posterior nasal cavity shows more variance.[222-225] Clinically, acoustic rhinometry may be of value to monitor response and adherence to medical therapy as well as nasal pharyngeal surgical outcome.[226,227] Although nasal congestion does not interfere with acoustic rhinometry, profuse nasal secretions may lead to measurement inaccuracy.[228] Acoustic rhinometry is rapid, safe, and noninvasive; requires minimal patient training and cooperation; and may obviate the need of CT and MRI in some situations, such as when septoplasty and turbinoplasty are considered, as well as for postoperative evaluation.[229,230] Acoustic rhinometry and rhinomanometry have similar reproducibility[231] and compare favorably in challenge studies,[232] but measure nasal obstruction differently and are therefore best viewed as complementary.[233-235]

Nasal provocation testing [Summary Statement 42]

Nasal allergen challenge may be used for confirmation of sensitivity to an allergen. A single allergen dose may be used to measure nasal reactivity, whereas incremental doses of allergen can be used to assess sensitivity.[236] The clinical utility of measuring nasal sensitivity/hyperresponsiveness to histamine and methacholine is limited because of a considerable overlap in the response of patients with allergic and nonallergic rhinitis.[237-240]

Nasal cytology [Summary Statement 43]

Nasal smears for eosinophils are not recommended for routine use in diagnosing allergic rhinitis, but a positive nasal smear (>10% eosinophils)[90] may prompt nasal or conjunctival challenge when there remains a high index of suspicion of allergy in a history-positive, skin test–negative patient.[241] A negative allergen challenge in a patient with >5% eosinophils on nasal smear would support a diagnosis of NARES.[102] If nasal smears are obtained, nasal secretions from both nostrils should be studied.[242] A prominence of neutrophils on nasal smear suggests an infectious process,[92] with nasal neutrophils usually higher in bacterial than viral infections.[243] However, the presence of neutrophils on nasal smear is not diagnostic because as many as 79% of asymptomatic school children have neutrophils in their nasal secretions.[88]

Saccharin test and cilia biopsy [Summary Statements 44, 45]

The saccharin test for nasal mucociliary clearance can be performed in the office but has limited utility as a screening test for ciliary dyskinesis. It cannot be relied on for a definitive diagnosis of primary nasal ciliary dyskinesis but may be useful in diagnosing and following the resolution of secondary nasal ciliary dysfunction.[163-165] For a definitive diagnosis of primary nasal ciliary dyskinesis, a brush biopsy is obtained from the inferior concha and examined by electron microscopy.[244,245] Combining electron microscopy with computer-based image processing algorithms can improve the visualization of ultrastructural defects.[165,169]

Additional laboratory testing [Summary Statements 46-48]

Laboratory studies that may be indicated in some patients with rhinitis include immune function studies and sweat test and/or genetic typing for CF. Total IgE, including cord blood samples, and specific IgG_4 subclasses have limited clinical benefit and should not be routinely performed in patients with rhinitis.[246-254] The presence of β-2-transferrin in the nasal secretions is a sensitive method of confirming CSF rhinorrhea.[255,256]

Sleep apnea study [Summary Statement 49]

Atopy has been associated with habitual snoring in infants.[257] In children, the presence of rhinitis is a strong predictor of habitual snoring.[258] Children who are African American, have upper respiratory disease, and have a family history of sleep apnea are at enhanced risk for sleep-disordered breathing.[259] Thus, formal evaluation for obstructive sleep apnea syndrome (OSAS) may be considered in children as well as adults presenting with chronic rhinitis and other risk factors associated with sleep-disordered breathing.

In snoring adults with rhinitis and sleep apnea symptoms, increased nasal airway resistance has been associated with apnea and hypopnea.[260,261] Intranasal corticosteroids reduce nasal airway resistance and apnea-hypopnea frequency in patients with OSAS and rhinitis and may be of benefit in the treatment of some patients with OSAS.[261]

Studies based on the link between the upper and lower airway (pulmonary function test) [Summary Statement 50]

Rhinitis and asthma are linked by common epidemiologic, physiologic, and pathologic mechanisms, as well as common comorbidities and therapeutic approaches.[262-265] Therefore, it has been suggested that patients with persistent allergic rhinitis be evaluated for asthma.[9] Because allergic rhinitis frequently

coexists with asthma and patients may not recognize symptoms of asthma, pulmonary function tests should be considered in patients with rhinitis. The presence of asthma may not be apparent because such patients (1) may have difficulty in recognizing their symptoms, (2) may not have consistent symptoms throughout the day, (3) may have a physical examination of the respiratory system that appears normal, and (4) may present with symptoms that are atypical (see Major Comorbid Conditions, Summary Statements 95-97).

Diagnostic tests with no validity [Summary Statement 51]

There is no evidence that the following procedures have diagnostic validity for allergic rhinitis: cytotoxic tests, provocation-neutralization, electrodermal testing, applied kinesiology, iridology, and hair analysis (see "Allergy Diagnostic Testing: An Updated Practice Parameter"[9]).

Management of rhinitis

Environmental control measures for allergens [Summary Statement 52]

The success of environmental control measures for rhinitis should be judged by clinical improvement, such as reduction in symptoms and medication scores, and not by a decrease in allergen concentration.[266] Individual host sensitivity to an aeroallergen influences the intensity of symptoms; for example, the pollen counts that causes symptoms may vary on the basis of an individual's degree of sensitivity and may be different for different pollens. Studies have not been consistently able to demonstrate symptom and/or medication reduction with any of the commonly used environmental control measures in patients with rhinitis.

Pollens [Summary Statements 53, 54]

Patients with allergic rhinitis caused by pollens may be exposed to allergen from (1) nonpollen plant fragments, (2) allergenic bioaerosols without intact pollen grains, and (3) even high pollen concentrations of insect-pollinated plants.[267-269] Pollen counts are generally highest on sunny, windy days with low humidity. Because the interplay of different weather factors (eg, wind, temperature, rain, and humidity) is complex, it may not be possible reliably to predict levels of outdoor aeroallergens on the basis of the influence of a single weather factor.[270-272]

Fungi [Summary Statements 55, 56]

Hydrophilic fungi, such as *Fusarium* and *Phoma*, are most abundant during rainy weather,[273] whereas *Alternaria* and *Cladosporium* have elevated levels during dry, windy weather.[274-276] When involved in plant-disturbing activity, such as gardening and lawn mowing, facemasks can reduce exposure to fungi.[277,278] The first step in reduction of indoor fungal exposure consists of eliminating the source of moisture, such as water intrusion, cold surfaces, and elevated humidity. As a second step, dilute bleach solution with detergent denatures fungal allergens and may prevent regrowth with application to nonporous surfaces, whereas porous surfaces must be removed and/or replaced.

Dust mites and cockroaches [Summary Statements 57, 59]

Dust mite exposure can be reduced through measures that kill the mites or degrade and/or prevent their fecal pellets from becoming airborne. This may include HEPA air filtration[279] and vacuum cleaning with a HEPA filter,[280] low humidity,[281] hard surface flooring,[282] hot water laundry,[283] barrier protection on pillows and mattresses,[279,284,285] and the use of acaricides.[279,286-288] The patient should be encouraged to use multiple interventions because an isolated intervention, such as use of dust mite–impermeable bedding, is unlikely to offer clinical benefit.[288] On the other hand, regular dusting and duct cleaning have not been shown to offer significant benefit. Some of these measures are also helpful for animal and insect allergen reduction, but none are as effective as removing the animal and/or insects. Cockroach allergen, a significant cause of nasal allergy in urban populations, is most abundant in the kitchen area. Environmental control of cockroach allergen involves an integrated pest management with the combination of family education—for example, emphasis on food debris removal and sealing of all sources of food and repetitive home cleaning; the use of newer gel or bait pesticides, such as odorless and colorless hydramethylnon and abamectin; and structural elimination of harborages. As with animal dander, it may take more than 6 months of aggressive pest management control to remove residual cockroach allergen.[289,290]

Animals [Summary Statement 58]

Cat and dog allergens have been shown to produce symptoms in sensitized individuals when there is contamination of animal-free homes and schools with passive transport, such as on clothing.[291-294] After cat removal from the home, an average of 20 weeks is required before the allergen concentration reaches levels found in the animal-free home.[295] Confining a cat to an uncarpeted room (other than bedroom) with HEPA filtration may reduce by 90% airborne allergen dissemination to the remainder of the house.[292,296] Some[297-299] but not all[292,296,300] studies have demonstrated reduced airborne cat allergen by washing the animal on a weekly to biweekly basis.

Irritants [Summary Statement 60]

Irritants reported to cause nasal symptoms include tobacco smoke,[301] microbially derived volatile organic compounds from bacteria and fungi, formaldehyde,[302,303] chlorine, and perfume.[304] The symptoms of rhinitis are directly related to the duration of exposure and usually resolve when the irritant is removed. Hyperresponsiveness to irritant triggers such as chlorine is enhanced among patients with seasonal allergic rhinitis during the season when they have symptoms. Formaldehyde, a recognized nasal and ocular irritant, produces symptoms only at concentrations well above those that produce a detectable odor.[305,306]

Pharmacologic therapy

The selection of pharmacotherapy for a patient depends on multiple factors, including the type of rhinitis present (eg, allergic, nonallergic, mixed, episodic), most prominent symptoms, severity, and patient age (Summary Statements 92, 93). Principal medication options are summarized in Table VI. The following sections provide a more expansive discussion of medication options.

Second-generation oral antihistamines [Summary Statements 61-64]

Second-generation antihistamines are generally preferred over first-generation antihistamines for treatment of allergic rhinitis because they have less tendency to cause sedation, performance impairment, and/or anticholinergic adverse effects.[307-311] First-generation antihistamines may produce performance impairment

TABLE VI. Principal medication options for rhinitis (see indicated Summary Statement [SS] discussion for supporting data) (listed in alphabetical order)

Allergic rhinitis: Seasonal allergic rhinitis and perennial allergic rhinitis	
Monotherapy	**Therapeutic considerations**
Oral agents	
Antihistamines, oral (H1 receptor antagonists; SS 61-64)	Continuous use most effective for SAR and PAR, but appropriate for PRN use in episodic AR because of relatively rapid onset of action
	Less effective for nasal congestion than for other nasal symptoms
	Other options, in general, are better choices for more severe AR
	Less effective for AR than INS (SS 74), with similar effectiveness to INS for associated ocular symptoms (SS 19)
	Because generally ineffective for nonallergic rhinitis, other choices are typically better for *mixed* rhinitis
	To avoid sedation (often subjectively unperceived), performance impairment, anticholinergic effects of first-generation antihistamines, second-generation agents generally preferred (SS 61)
	Of second-generation agents, fexofenadine, loratadine, desloratadine without sedation at recommended doses (SS 63)
Corticosteroids, oral (SS 81)	A short course (5-7 days) of oral corticosteroids may be appropriate for very severe nasal symptoms
	Preferred to single or recurrent administration of intramuscular corticosteroids, which should be discouraged (SS 81)
Decongestants, oral (SS 70-72)	Pseudoephedrine reduces nasal congestion (SS 70)
	Side effects include insomnia, irritability, palpitations, hypertension
Leukotriene receptor antagonists (SS 85)	Montelukast approved for SAR and PAR
	No significant difference in efficacy between LTRA and oral antihistamines (with loratadine as usual comparator; SS 85)
	Approved for both rhinitis and asthma; may be considered in patients who have both conditions (SS 85)
	Side effects minimal
Intranasal agents	
Intranasal antihistamines (SS 65-69)	Effective for SAR and PAR (SS 65)
	Have clinically significant rapid onset of action, making them appropriate for PRN use in episodic AR (SS 65-69)
	Effectiveness for AR equal or superior to oral second-generation antihistamines (SS 64), with clinically significant effect on nasal congestion (SS 68)
	Less effective than INS (SS 69) for nasal symptoms
	Appropriate choice for mixed rhinitis, because also approved for vasomotor rhinitis
	Side effects with intranasal azelastine: bitter taste, somnolence (SS 69)
Intranasal anticholinergic (ipratropium; SS 83)	Reduces rhinorrhea but not other symptoms of SAR and PAR
	Appropriate for episodic rhinitis because of rapid onset of action
	Side effects minimal, but dryness of nasal membranes may occur
Intranasal corticosteroids (SS 74-80)	Most effective monotherapy for SAR and PAR (SS 74)
	Effective for all symptoms of SAR and PAR, including nasal congestion
	PRN use (eg, >50% days use) effective for SAR (SS 76)
	May consider for episodic AR
	Usual onset of action is less rapid than oral or intranasal antihistamines, usually occurs within 12 hours, and may start as early as 3 to 4 hours in some patients
	More effective than combination of oral antihistamine and LTRA for SAR and PAR (SS 75)
	Similar effectiveness to oral antihistamines for associated ocular symptoms of AR
	Appropriate choice for mixed rhinitis, because agents in class also effective for some nonallergic rhinitis
	Without significant systemic side effects in adults
	Growth suppression in children with PAR has not been demonstrated when used at recommended doses
	Local side effects minimal, but nasal irritation and bleeding occur, and nasal septal perforation rarely reported (SS 80)
Intranasal cromolyn (SS 82)	For maintenance treatment of AR, onset of action within 4 to 7 days, full benefit may take weeks
	For episodic rhinitis, administration just before allergen exposure protects for 4 to 8 hours against allergic response (SS 82)
	Less effective than nasal corticosteroids, inadequate data for comparison to leukotriene antagonists and antihistamines (SS 82)

TABLE VI. *(Continued)*

Allergic rhinitis: Seasonal allergic rhinitis and perennial allergic rhinitis	
Monotherapy	**Therapeutic considerations**
	Minimal side effects (SS 82)
Intranasal decongestants (SS 71,72)	For short-term and possibly for episodic therapy of nasal congestion, but inappropriate for daily use because of the risk for rhinitis medicamentosa
	May assist in intranasal delivery of other agents when significant nasal mucosal edema present
Combination therapy	**Therapeutic considerations**
Antihistamine, oral with decongestant, oral (SS 63)	More effective relief of nasal congestion than antihistamines alone
Antihistamine, oral with LTRA, oral (SS 85)	May be more effective than monotherapy with antihistamine or LTRA
	Less effective than INS
	An alternative treatment for patients unresponsive to or not compliant with INS
Antihistamine, oral with intranasal antihistamine (SS 65-69)	Combination may be considered, although controlled studies of additive benefit lacking
Antihistamine, oral with intranasal corticosteroids (SS 74-77)	Combination may be considered, although supporting studies limited and many studies unsupportive of additive benefit of adding an antihistamine to an intranasal steroid
Intranasal anticholinergic with intranasal corticosteroid (SS 84)	Concomitant use of ipratropium bromide nasal spray and an intranasal corticosteroid is more effective for rhinorrhea than administration of either drug alone
Intranasal antihistamine with intranasal corticosteroid (SS 65-69)	Combination may be considered based on limited data
	Inadequate data about optimal interval between administration of the 2 sprays
	For mixed rhinitis, there may be significant added benefit to the combination of an intranasal antihistamine with an intranasal corticosteroid
LTRA, oral with intranasal corticosteroid (SS 85)	Subjective additive relief in limited studies, data inadequate

Nonallergic (idiopathic) rhinitis	
Monotherapy	**Therapeutic considerations (for side effects, see AR table)**
Oral agents	
Antihistamines, oral (H1 receptor antagonists; SS 61, 62)	Generally ineffective for nonallergic rhinitis
Decongestants, oral (SS 70, 71)	Pseudoephedrine reduces nasal congestion (SS 70, 71)
Intranasal agents	
Intranasal antihistamines (SS 65-69)	Effective for vasomotor rhinitis
Intranasal anticholinergic (ipratropium; SS 83)	Effective only for rhinorrhea of nonallergic rhinitis syndromes
	Special role for preventing rhinorrhea of gustatory rhinitis
Intranasal corticosteroids (SS 78)	Effective for some forms of nonallergic rhinitis, including vasomotor rhinitis and NARES
Combination therapy	**Inadequate data to provide firm recommendations in nonallergic rhinitis**

AR, Allergic rhinitis; *INS,* intranasal corticosteroids; *PAR,* perennial allergic rhinitis; *SAR,* seasonal allergic rhinitis.

in school[176,312,313] and driving[314-318] that can exist without subjective awareness of sedation;[310] and the use of first-generation antihistamines has been associated with increased automobile and occupational accidents.[314-319] Individual variation exists with respect to development of sedative effects with first-generation antihistamines.[307,309,313] Concomitant use of other central nervous system (CNS)–active substances, such as alcohol and sedatives, may further enhance performance impairment from these antihistamines.[307,309] In part because of prolonged plasma half-life and metabolites (Table VII), these undesirable and potentially dangerous side effects cannot be eliminated by administration of first-generation antihistamines only at bedtime.[320-325] Anticholinergic effects include dryness of mouth and eyes, constipation, inhibition of micturition, and an increased risk for provocation of narrow-angle glaucoma. Increased sensitivity and a greater incidence of pre-existing comorbid conditions, such as prostatic hypertrophy, elevated IOP, and cognitive impairment, place older adults in a high-risk category for the side effects of first-generation antihistamines. The anticholinergic effects of the first-generation antihistamines may explain the reported better control of rhinorrhea compared with the second-generation antihistamines. The overall efficacy of first-generation antihistamines compared with second generation for the management of allergic rhinitis symptoms has not been adequately studied. Second-generation antihistamines differ in their onset of action, sedation properties, skin test suppression, and dosing guidelines (Table VIII). No single agent has been conclusively shown to have superior efficacy.[326,327] Exceeding the recommended dosage may result in increased sedation with many of these products[309,323,328-330] that do not produce sedation at recommended doses. Although antihistamines can be used on an intermittent basis, such as for episodic allergic rhinitis, it has been shown that continuous treatment for seasonal or perennial allergic rhinitis is more effective,[331] primarily because of unavoidable, ongoing allergen exposure.

Intranasal antihistamines [Summary Statements 65-69]

Intranasal antihistamines have demonstrated efficacy that is equal to[332] or superior to[333-335] oral second-generation antihistamines in the treatment of seasonal allergic rhinitis. They are also effective and have been associated with a clinically significant effect on nasal congestion for nonallergic rhinitis[336-338] but

TABLE VII. Oral and intranasal antihistamines

Generic drug	Trade name example	Metabolites if significant (T 1/2 in hours of product or metabolite)	Tmax hours (metabolite)	Skin test suppression mean (max) days	% Sedation/ somnolence or CNS impairment (control)	Dosage forms	Age limit	Adult dose
Second generation								
Acrivastine[d]	Semprex-D	(1.4-3.1)[653]	1.15[654] 1.4[653]	~3, T 1/2 =1.7 h	8[655] 12 (6)[PI]	8 mg	12 y	8 mg qid
Azelastine hydrogen chloride	Astelin nasal	Desmethylazelastine (22)[PI]	2.5[656] .25*[341]	2[656,657]	11.5 (5.4)[PI]	137 mcg/spray	5 y	2 sp/nostril bid
Cetirizine[d]	Zyrtec	None (7-11)[653]	1.0 ± 0.5[656]	3[656]	14 (10)[PI]	5, 10 mg 5 mg/5 mL	6 mo	5-10 mg q d
Desloratadine[d]	Clarinex	3 Hydroxy desloratadine (7.8 ± 4.2)[653]	3.17 (4.76)[658]	~7 (T 1/2 = 21-31 h)	2.1 (1.8)[PI]	5 mg 2.5 mg/ 5 mL	6 mo	5 mg q d
Fexofenadine[d]	Allegra	None (14.4-14.6)[653]	2.6[656]	2[656]	1.3 (.9)[PI]	30, 60, 180 mg 30 mg/5 mL	2 y	180 mg q d or 60 mg bid
Levocetirizine	Xyzal	None (7 ± 1.5)[653]	.9[659] 1.25[PI]	Unknown	6 (2)[PI]	5 mg	6 y	5 mg q d
Loratadine[d]	Claritin	Descarboethoxyloratadine (7.8 ± 4.2)[653]	1.2 ± 0.3[656] (1.5 ± 0.7)[656]	7[656]	8 (6)[PI]	10 mg 5 mg/ 5 mL	2 y	10 mg q d
Olopatadine hydrochloride	Patanase nasal	No major metabolites (8-12)[PI]	.5-1.0[PI]	Unknown	0.9 (0.3)[PI]	665 mcg/spray	12 y	2 sp/nostril bid
First generation								
Brompheniramine	Dimetapp	24.9 ± 9.3[660]	4[661]	>2[660] 4[662]	24 (5)[322]	12 mg		
1 mg/5 mL	2 y	1-2 bid						
Chlorpheniramine[d]	Chlor-Trimeton	Mono and didesmethyl chlorpheniramine (27.9 ± 8.7)[653]	2-6[663] 2.8[653]	3[664] (6[665])	45%[661]	4, 8, 12 mg 2 mg/5 mL	2 y	4 mg qid
Clemastine[d]	Tavist	(21.3 ± 11.6)[666]	4.77 ± 2.26[666]	5[667] (10[667])	14 (1.5)[668]	1.34, 2.68 mg .67 mg/5 mL	6 y	1.34 mg bid to tid
Cyproheptadine	Periactin	(16)[669]	4[670]	9[671] (11[671])	8-50[672]	4 mg 2 mg/ 5 mL	2 y	4 mg tid
Diphenhydramine	Benadryl	Nordiphenhydramine (9.2 ± 2.5)[653]	2.6[673,674] 1.7 ± 1.0[653]	2[664] (5[664])	50%[661]	25, 50 12.5 mg/mL	2 y	25-50 mg qid
Hydroxyzine	Atarax	(20 ± 4.1)[653]	2.1 ± 0.4[653]	5[664] (8[664])	80%[661]	10, 25, 50, 100 mg 10 mg/5 mL	All ages	25 mg qid
Promethazine	Phenergan	Promethazine sulfoxide & N-desmethylpromethazine (9-16)[PI]	4.4[675]	3[664] (5[664])	60-73[676]	12.5, 25, 50 mg 6.25 mg/5 mL	2 y	25 mg qid
Triprolidine	Actifed	(3.2)[PI]	2.0[677]	3[654,660,661,664] (7[7])	10% to 25%			

T 1/2, Half life; *[d]*, available with decongestant; *[PI]*, package insert; *qid*, 4 times a day; *q d*, every day; *bid*, 2 times a day; *tid*, 3 times a day.
*Onset of action, not Tmax.

TABLE VIII. Intranasal corticosteroid sprays

Spray trade name	Generic drug	Type	mcg/ spray	Adult dose	Usual child dose	Age limit (y)	Pregnancy/nursing risk category	Alcohol BKC propylene glycol
Beconase AQ	Beclomethasone, monohydrate	Pump 200 spray	42	1-2 spray nos bid	1-2 sp/nos bid	6	C	Alcohol BKC
Flonase	Fluticasone propionate	Pump 120 spray	50	2 spray nos q d	1-2 sp/nos q d	4	C	Alcohol BKC
Nasarel	Flunisolide	Pump 200 spray	25	2 spray nos bid to tid	2 sp/nos bid	6	C	BKC, propylene glycol
Nasacort AQ	Triamcinolone	Pump 120 spray	55	1-2 spray nos q d	1-2 sp/nos q d	6	C	No alcohol BKC
Nasonex	Mometasone	Pump 120 spray	50	2 spray nos q d	1 sp/nos q d	2	C	No alcohol BKC
Rhinocort AQ	Budesonide	Pump 120 spray	32	1-4 spray/nos q d	1-2 sp/nos q d	6	C	No alcohol No BKC
Veramyst	Fluticasone furoate	Pump 120 spray	50	2 spray/nos q d	1 sp/nos q d	2	C	No alcohol BKC
Omnaris	Ciclesonide	Pump 120 spray	50	2 spray/nos q d	NA	12	C	No alcohol No BKC

nos, Nostril; *bid*, 2 times a day; *q d*, every day; *tid*, 3 times a day; *NA*, not applicable; *BKC*, benzalkonium chloride.

are generally less effective than intranasal corticosteroid for treatment of allergic rhinitis.[46] Combination therapy with intranasal corticosteroids may provide added benefit.[339] The only intranasal antihistamines currently available in the United States, azelastine,[332-338] and olopatadine,[340] have a rapid onset of action.[341] Bitter taste has been reported with both preparations, and sedation may occur[342] (Table VII).

Oral decongestants [Summary Statements 70, 71]

Oral decongestants, such as pseudoephedrine, are effective at relieving nasal congestion in patients with allergic and nonallergic rhinitis but can result in side effects such as insomnia, loss of appetite, irritability, and palpitations.[343] The efficacy of an oral decongestant in combination with an antihistamine in the management of allergic rhinitis has not been adequately documented to increase the efficacy of either drug alone.[344]

Pseudoephedrine is a key ingredient used in making methamphetamine. In an effort to reduce illicit production of methamphetamine, restrictions have been placed on the sale of pseudoephedrine in the United States.[345] This has promoted substitution of phenylephrine for pseudoephedrine in many OTC cold and cough remedies. However, phenylephrine, which appears to be less effective than pseudoephedrine, is extensively metabolized in the gut.[346,347] In fact, the efficacy of phenylephrine as an oral decongestant has not been well established.[345,348,349]

Elevation of blood pressure after taking an oral decongestant is very rarely noted in normotensive patients and only occasionally in patients with controlled hypertension. However, because of variation in patient response, patients receiving oral decongestants should be followed for changes in blood pressure. Concomitant use of caffeine and stimulants, such as medications used for management in attention-deficit/hyperactivity disorder, may be associated with an increase in adverse events.[350] Oral decongestants should be used with caution in patients with rhinitis with certain conditions, such as cerebrovascular or cardiovascular disease, hyperthyroidism, closed-angle glaucoma, and bladder neck obstruction.

Oral decongestants, when used in appropriate doses, are usually very well tolerated in children over 6 years of age. However, use in infants and young children has been associated with agitated psychosis, ataxia, hallucinations, and even death[351-353] (see Summary Statement 73). At times, even at recommended doses these agents may cause increased stimulatory effects resulting in tachyarrhythmias, insomnia, and hyperactivity, especially when combined with other stimulant medications, such as stimulants used in attention deficit hyperactivity disorder management.[354] Therefore, the risks and benefits must be carefully considered before using oral decongestants in children below age 6 years.

Topical decongestants [Summary Statements 71, 72]

Topical decongestants such as phenylephrine or imidazoline derivatives—for example, oxymetazoline and xylometazoline–cause nasal vasoconstriction and decreased nasal edema but have no effect on antigen-provoked nasal response.[355] Xylometazoline was found to have superior efficacy for nasal decongestion compared with intranasal corticosteroids in a 28-day study.[356] However, topical decongestants are not recommended for continuous use because of the potential development of rhinitis medicamentosa.[357] Furthermore, they have no effect on itching, sneezing, or nasal secretion. The development of rhinitis medicamentosa is highly variable; it may develop within 3 days of use[357] or fail to develop after 6 weeks of daily use.[358-360] Topical decongestants can be associated with local stinging or burning, sneezing, and dryness of the nose and throat. Intermittent use of topical decongestants is frequently prescribed; however, the efficacy and safety of this approach have not been formally studied.

OTC cough and cold medications in young children [Summary Statement 73]

Controlled trials have shown that antihistamine-decongestant combination products are not effective for symptoms of upper respiratory tract infections in young children.[361-365] Furthermore, there has been increasing concern over the safety of OTC cough and cold medications in children. An Adverse Event Reporting System review[366] showed that between 1969 and September 2006, there were 54 fatalities associated with 3 reviewed decongestants and 69 fatalities associated with 3 antihistamines found in OTC and prescription preparations. Drug overdose and toxicity were common events reported in these cases.

Currently cough and cold OTC preparations indicate the user should ''consult a physician'' for dosing recommendations below age 2 years for decongestants and below age 6 years for antihistamines. In mid-October 2007, the FDA's Nonprescription Drugs and Pediatric Advisory Committees recommended that the OTC medications used to treat cough and cold no longer be used for children below 6 years of age.[366] The FDA has yet to respond to these recommendations. In contrast, second-generation antihistamines

such as cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine, when used in young children, have been shown to be well tolerated and to have a very good safety profile.[367-374]

Intranasal corticosteroids [Summary Statements 74-80]

Intranasal corticosteroids are the most effective medications for treating allergic rhinitis. In most studies, intranasal corticosteroids are more effective than the combined use of an antihistamine and a LT antagonist.[375-379] The clinical response does not appear to vary significantly between intranasal corticosteroids that are currently available (Table VIII).[53,380-382] The onset of therapeutic effect of intranasal corticosteroid occurs between 3 and 12 hours.[383-385] The as-needed dosing (which equated to 55% to 62% of days) of an intranasal corticosteroid (fluticasone propionate) has been shown to be effective in the treatment of seasonal allergic rhinitis[380,386,387] but may not be as efficacious as continuous use. In 1 study, PRN use of an intranasal corticosteroid (fluticasone propionate) was superior to PRN use of an oral antihistamine (loratadine) for seasonal allergic rhinitis.[380] Intranasal corticosteroids are also effective in the treatment of nonallergic rhinitis, especially NARES[388-390] and vasomotor rhinitis.[389,391,392] Intranasal corticosteroids may also benefit ocular allergy symptoms associated with allergic rhinitis (see Summary Statement 19).

Intranasal corticosteroids when given in recommended doses are not generally associated with clinically significant systemic side effects. Studies in both children and adults have failed to demonstrate any consistent, clinically relevant effect from intranasal corticosteroids on the hypothalamic-pituitary-adrenal (HPA) axis,[393-401] ocular pressure or cataract formation,[393,402-404] or bone density.[405-407] In children, growth effect may be a better indicator of systemic effect than HPA axis suppression. The transient effect on growth suppression that has been demonstrated in children after administration of intranasal corticosteroids is dependent on the specific intranasal corticosteroid, and the dose administered, technique used for measuring growth, time of administration, and concomitant use of oral or inhaled corticosteroid. Studies with intranasal fluticasone propionate, mometasone furoate, and budesonide have shown no effect on growth at recommended doses compared with placebo[408-410] and reference values (at as much as 2 times the recommended doses).[400] Growth suppression from intranasal corticosteroids has been reported only with long-term use of beclomethasone dipropionate that exceeded recommended doses[409] or administration to toddlers.[411]

Local side effects of intranasal corticosteroids such as nasal irritation, bleeding, and nasal septal perforation[412,413] are rare and can be avoided with proper administration technique. The patient should be periodically examined to assure that these side effects are not present. Preparations containing propylene glycol and benzalkonium chloride may result in local irritation or ciliary dysfunction, respectively[414,415] (Table VIII).

Systemic corticosteroids [Summary Statement 81]

Oral corticosteroids, prescribed for a few days, may be required for the treatment of very severe intractable rhinitis or nasal polyposis.[416,417] The use of parenteral and intraturbinate injections of corticosteroids is discouraged.[418-423]

Intranasal cromolyn sodium [Summary Statement 82]

Nasal cromolyn sodium, an inhibitor of mast cell degranulation, is effective in the prevention of symptoms and in the treatment of other types of rhinitis.[424-431] It has a strong safety profile and has a reported onset of action of 4 to 7 days for seasonal or perennial rhinitis. Nasal cromolyn is effective in the treatment of episodic allergic rhinitis—for example, before anticipated allergen exposure, in which case there appears to be a more rapid onset of action.[432-434] Although cromolyn sodium is less effective than intranasal corticosteroids, it has never been adequately studied to determine its effectiveness in comparison with antihistamines or LT antagonists.[435]

Intranasal anticholinergics [Summary Statements 83, 84]

The nasal anticholinergic ipratropium bromide is effective in reducing rhinorrhea caused by allergic rhinitis, nonallergic rhinitis (including cold-induced rhinitis[436] and gustatory rhinitis[66]), and the common cold.[437-447] Ipratropium bromide is only approved (down to the age of 5 years) for the treatment of rhinorrhea, although 1 pediatric study showed modest benefit for controlling nasal congestion.[448] Ipratropium bromide has no adverse effect on physiologic nasal functions (eg, sense of smell, ciliary beat frequency, or mucociliary clearance) and has a low incidence of adverse events, in particular epistasis and nasal dryness.[449] Concomitant use of ipratropium bromide and intranasal corticosteroid or antihistamines has an additive effect in controlling rhinorrhea.[390,442]

LT receptor antagonists [Summary Statement 85]

LT receptor antagonists (LTRAs) are effective in the treatment of seasonal and perennial allergic rhinitis.[450-453] There is no significant difference in efficacy between LTRA and antihistamines (with loratadine as the usual comparator), and their concomitant use may be additive.[40,42,377] However, not all studies with the concomitant administration of an antihistamine and a LTRA have shown an additive effect. Although the concomitant administration of a LTRA and an antihistamine can have an additive effect, in general this approach is less efficacious than administering intranasal corticosteroids as monotherapy.[48,375,377,379] However, such combination therapy may provide an alternative treatment for patients who are unresponsive to or not compliant with intranasal corticosteroids.

Montelukast has an excellent safety profile and has been approved down to 6 months of age. As many as 40% of patients with allergic rhinitis have coexisting asthma. Because montelukast has been improved for both rhinitis and asthma, it may be considered in such patients.[454-456] The combination of montelukast and a second-generation antihistamine may protect against seasonal decrease in lung function in patients with allergic rhinitis.[457]

Omalizumab [Summary Statement 86]

Omalizumab has been shown to have the potential for improvement in nasal and ocular symptoms as well as QOL in 1 study of patients with both seasonal and perennial allergic rhinitis.[458] However, superiority to currently approved rhinitis treatments has not been shown. In addition to the limited data of omalizumab on symptoms of rhinitis, the high cost of omalizumab treatment precludes its use for rhinitis without concomitant asthma to perennial allergens.

Saline [Summary Statement 87]

Although less effective than intranasal corticosteroids and no more effective than other active agents for rhinitis, isotonic and hypertonic saline solutions, used as either single or adjunctive agents, are of modest benefit for reducing symptoms and

TABLE IX. Saline irrigation solutions

First author, year, and reference no.	NaCl (%)	Salt (nonionized)	Water distilled or boiled (warm)	Baking soda	Buffered
Wormald, 2006	.9	1 tsp	500 mL	1 tsp	Yes
Tomooka, 2000[139]	1.6	1/2 tsp	250 mL	None	No
Rombago, 2002[678]	2	1 tsp	480 mL	1/2 tsp	Yes
Brown, 2004[679]	2	1.5	950 mL	None	No
Talbot, 1997[680]	3	2-3 tsp	950 mL	1 tsp	yes
Fellows, 2006[681]	.9	1 tsp	480 mL	None	No

improving the QOL in patients with allergic rhinitis and rhinosinusitis.[459] Various mechanisms, such as improvement in mucus clearance; enhanced ciliary beat activity; removal of antigen, biofilm, or inflammatory mediators; and a protective effect on sinonasal mucosa, have been proposed but not confirmed to explain the reported symptom improvement. The use of topical saline is associated with minimal side effects, such as burning, irritation, and nausea; has low cost; and has overall good patient acceptance.[460,461] The preferred method of delivery, the volume, the concentration—that is, the ratio of isotonic to hypertonic saline[462,463] (Table IX)—and the dose frequency have not been established.

Allergen immunotherapy [Summary Statements 88-90]

Allergen immunotherapy is effective for therapy for allergic rhinitis and can potentially modify the disease.[51,464,465] Unlike pharmacotherapy, the clinical benefits may be sustained years after discontinuation of treatment[466,467] (see allergen immunotherapy practice parameter[50] for more details). Allergen immunotherapy for allergic rhinitis may prevent the development of new allergen sensitization[469-471] and reduce the risk for the future development of asthma in some patients.[472-481] Immunotherapy has been associated with significant improvement in rhinitis symptom and medication scores and QOL measures as well as objective parameters such as nasal provocation challenge.[466,471,479,482-518] Immunotherapy is usually no more costly than pharmacotherapy over the projected course of treatment.[519,520]

Allergen immunotherapy should be considered for patients who have symptoms of allergic rhinitis after natural exposure to allergens and who demonstrate specific IgE antibodies to relevant allergens. There is no specific upper or lower age limitation for allergen immunotherapy. Other factors that justify consideration of immunotherapy include (1) severity and duration of symptoms, (2) responsiveness to other forms of therapy, (3) unacceptable adverse effects of medications, (4) the patient's desire to avoid long-term pharmacotherapy, (5) reduction of the risk of future asthma, and (6) the presence of comorbid conditions, such as sinusitis or asthma. Contraindications include, for example, severe, uncontrolled asthma and significant or unstable cardiovascular disease.[50] There should be a cautious attitude in regard to the concomitant use of β-adrenergic blocking agents and allergen immunotherapy[50,468] because β-adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat (see allergen immunotherapy practice parameter[468]).

Clinical improvement can usually be noted after reaching the patient's maintenance dose. Lack of improvement after 1 year of maintenance treatment should prompt a review of the patient's immunotherapy program and possible discontinuation of immunotherapy. If allergen immunotherapy is effective, treatment may be continued for 3 years or longer. If discontinuation of effective inhalant allergen immunotherapy is considered, there are no specific tests or clinical markers currently available that will distinguish between patients who will or will not remain in long-term clinical remission. Thus, the decision to continue or stop immunotherapy must be individualized. Patients may experience local swelling at the injection site of subcutaneous immunotherapy and, on rare occasions, an anaphylactic reaction to allergen immunotherapy (refer to ''Allergen Immunotherapy: A Practice Parameter Second Update''[50,468] for further information regarding allergen immunotherapy).

Surgery [Summary Statement 91]

Surgery may be indicated for the management of structural/mechanical problems or comorbid conditions of allergic rhinitis, such as nasal polyps and adenoidal hypertrophy.[77,521-523] The most common surgical procedures include (1) septoplasty,[77] (2) reduction of inferior turbinate hypertrophy,[3] (3) adenoidectomy, (4) functional endoscopic sinus surgery, and (5) nasal polypectomy.[524] The reduction of nasal obstruction after surgery not only improves nasal airflow but also allows for better delivery of topical medications.

At times, the nasal congestion of rhinitis may be confused with obstruction created by structural or mechanical problems. A disturbance of normal airflow resistance and turbulent flow pattern creates the perception of nasal obstruction, regardless of the actual size of the air passage.[525] Anterior septal deviation, with or without nasal valve collapse, and anterior inferior turbinate hypertrophy are the major structural components resulting in the symptom of nasal obstruction.[524,526] Whenever there is septal deviation, typically there is compensatory turbinate hypertrophy on the opposite side. Septoplasty is infrequently performed in children because it may have a negative effect on nasal growth, particularly of the nasal dorsum.[527]

Septoplasty,[528] which involves reshaping, repositioning, or recontouring the cartilage, has a high reported success rate[529] and is preferred over submucosal resection, a procedure that involves more extensive resection of cartilage and bone.[529,530] Turbinate hypertrophy reduction surgery may be performed in conjunction with or separate from septoplasty, depending on the surgical assessment.[531,532] The various surgical procedures available (eg, bipolar cautery or radiofrequency ablation)[524,533-535] alleviate the mucosal hypertrophy, the bony hypertrophy (eg, submucosal resection), or a combination of bony and mucosal hypertrophy (eg, powdered turbinoplasty or laser turbinectomy).[536-539] If the patient with rhinitis and coexisting turbinate hypertrophy has been unresponsive to medical therapy, a surgical evaluation can be considered.[540-542]

In children, the indications for adenoidectomy are sleep apnea caused by adenotonsillar hypertrophy, chronic adenoiditis, and

chronic sinusitis.[543] For OME, an adenoidectomy is usually recommended after the first set of tympanostomy tubes extrudes, effusion returns, and a second set of tympanostomy tubes are being considered. An adenoidectomy may also be considered for adenoiditis, postnasal obstruction, or chronic sinusitis.[543] Recent clinical studies recommend a trial of intranasal corticosteroids for adenoidal hypertrophy before surgical intervention.[544-547]

Management decisions [Summary Statements 92, 93]

Management decisions must be individualized and guided by (1) age; (2) frequency, severity, and spectrum of symptoms (eg, predominant congestion versus rhinorrhea); (3) allergen exposure pattern; and (4) comorbidities.[11,548,549] Response to previous treatment, patient and family preferences, compliance with therapy, and cost are additional factors that enter management decisions for the patient with rhinitis.[11,550] Rhinitis medication management frequently will require consideration of a step-up approach, if therapy is inadequate, or a step-down approach, if symptom relief is achieved or maximized with other approaches, such as avoidance measures.[550] Medications may be required only on an intermittent or short-term basis for the treatment of episodic rhinitis. The patient and physician should agree on what therapeutic approach can realistically be instituted. These therapy decisions can be committed to a Rhinitis Action Plan developed jointly with the patient and family (see Fig 5 for sample).

When a patient is compliant with the prescribed medication and yet is not responding to treatment, substitution of another class of medication can be considered. Adding another medication to the patient's treatment regimen will not always improve the patient's symptoms to a degree that outweighs the cost of this approach.[375,450,551]

Appropriate follow-up for patients with rhinitis increases therapeutic success, improves compliance, and identifies complications from rhinitis or its treatment. During each follow-up patient visit, the treatment plan should be reviewed and possibly modified on the basis of physician and patient assessment of how effectively the treatment regimen is, judging from symptom control and improvement in QOL. In large part this will relate to the patient's compliance with the agreed-on therapeutic interventions.

Education of patients and family members or other patient advocates [Summary Statement 94]

Education is a key element in promoting adherence and optimizing treatment outcomes in allergic rhinitis. Education for the patient and family members or other patient advocates begins at the initial encounter and continues at following visits. The education program should emphasize the chronicity of rhinitis as a disease, the realistic outcome of therapy, an understanding of how to implement appropriate environmental changes, appropriate methods of medication administration, medication benefits and possible side effects, the comorbidity of other allergic diseases, and the effect that disease control can make in overall improvement in QOL.[11]

Although it is recognized that education is important for rhinitis, the best delivery method, frequency, and educational setting have yet to be determined. One-on-one allergy treatment educational sessions about rhinitis treatment may not be any more effective than a handout.[552] Reduced use of medication, reduced office visits, or improvement in QOL has not been consistently shown when educational programs are implemented for rhinitis.[553-563] Whatever rhinitis educational delivery method is selected, it is important to review the content of the educational material.[564]

Major comorbid conditions

Asthma [Summary Statements 95, 96]

Patients with allergic rhinitis are at increased risk of developing asthma.[262,565-567] Patients with allergic rhinitis without asthma, especially those sensitized to dust mites, often have nonspecific bronchial hyperresponsiveness (BHR),[568-571] and many patients with seasonal allergic rhinitis experience a seasonal increase in BHR.[572] Conversely, subsegmental bronchial allergen challenge in patients with allergic rhinitis has been shown to result in both bronchial and nasal inflammatory responses.[573] It has been suggested that in patients with moderate to severe allergic rhinitis, especially those with longstanding rhinitis and sensitization to dust mites, a reduced forced expiratory flow at 25% to 75% of forced vital capacity may be a marker of early bronchial pathology.[574-576] Treatment with intranasal corticosteroids has been shown to prevent the seasonal increase in BHR experienced by patients with allergic rhinitis, to reduce existing BHR, and to improve pulmonary function tests.[570,576-578] Allergen immunotherapy for allergic rhinitis may reduce the development of asthma in children and possibly in adults.[473,475-477,579,580] Treatment of allergic rhinitis with intranasal corticosteroids and certain second-generation antihistamines may improve asthma control when both diseases coexist.[581-588]

Recurrent OME [Summary Statement 97]

Recurrent otitis media and OME are frequently associated with allergic rhinitis. Eustachian tube dysfunction remains the most common etiology for otitis media. Mediators released after allergen exposure result in nasal allergic inflammation and contribute to the dysfunction of the eustachian tube by producing eustachian tube edema and inflammation.[543,589,590] Under natural circumstances, the middle ear is not exposed to allergens. However, measurements of elevated ECP,[591] IL-5,[592] and IgA[592] within the middle ear during chronic OME support a localized inflammatory process. Similar cytokine and cellular profiles have been noted concurrently in the middle ear and nasopharynx of atopics.[590] These findings suggest that the ear may be part of the united airway in atopic patients.[590]

Special considerations

Pregnancy [Summary Statements 98-105]

When selecting medications for the pregnant patient, the FDA pregnancy risk categories (Table X) should be considered. However, these are based largely on animal studies with limited human data. Therefore, human cohort and case-control studies as well as birth registry data should be reviewed before making a medication selection. Concern about the potential for congenital malformation because of medication use occurs primarily during the first trimester, when organogenesis is occurring.

First-generation antihistamines have previously been recommended as first-choice agents because of their observed safety and longevity of use.[593] However, in general, their sedative and impaired performance characteristics make them less desirable choices than second-generation antihistamines. The accumulated safety data during pregnancy on the second-generation antihistamines are comparable to those of the first-generation antihistamines (Tables XI and XII). Although there are no reports of increased congenital malformations with the use of fexofenadine during pregnancy and animal studies are negative for

Patient Name
DOB
Phone number
Pharmacy Phone number

Sample Rhinitis Action Plan

Date Completed: _____

Physician Name
Address
Phone number

Signature MD/Physician Extender

These are Your Rhinitis and Allergic Conjunctivitis Medications

Antihistamines

- ❑ Allegra (fexofenadine) ❑ D ____mg tab ❑ Syrup
- ❑ Claritin (loratadine) ❑ D____ mg tab ❑ Syrup
- ❑ Clarinex (desloratadine) ❑ D ___ mg tab ❑ Syrup
- ❑ Xyzal (levocetirizine) ❑ D____mg tab ❑ Syrup
- ❑ Zyrtec (cetirizine) ____ mg tab
- ❑ Benadryl ____ mg tab ❑ Syrup
- ❑ _____ ____ mg tab ❑ Syrup

Nasal Antihistamines

- ❑ Astelin ___ sp./nostril

Combinations

- ❑ _____ _____mg tab ❑ Syrup
- ❑ _____ _____mg tab ❑ Syrup

Nasal Corticosteroids

- ❑ Flonase (fluticasone propionate)
- ❑ Nasacort AQ (triamcinolone acetonide)
- ❑ Nasonex (mometasone)
- ❑ Rhinocort (budesonide)
- ❑ Veramyst (fluticasone furoate)

Leukotriene Modifiers

- ❑ Singulair_____mg tab ❑ Syrup

Mast Cell Inhibitors

- ❑ NasalCrom (cromolyn)

Anti-cholinergics

- ❑Atrovent Nasal (ipratropium) ❑0.03% ❑0.06%

Nasal Saline/moisturizer

- ❑ _____

Oral Decongestants

- ❑ Sudafed ____mg tab ❑ Syrup
- ❑ Phenylephrine

Nasal Decongestants

- ❑ Oxymetazoline (Afrin, Equate, …)
- ❑ Phenylephrine

Eye Drops

- ❑Alamast (pemirolast)
- ❑ Alocril (nedocromil)
- ❑ Crolom (cromolyn)
- ❑ Elestat (epinastine)
- ❑ Emadine (emedastine)
- ❑ Optivar (azelastine)
- ❑ Pataday ❑ Patanol (olopatadine)

Rhinitis Steps	What to do			
Prophylaxis before allergen exposure	❑ NasalCrom	_____ dose(s)	_____ times a day as needed	_____ before exposure
Step 1: Episodic	❑ Decongestant ❑ Nasal ❑ Oral	_____ dose(s)	_____ times a day as needed	❑ AM ❑ PM
	❑ Antihistamine ❑ Oral ❑ Nasal	_____ dose(s)	_____ times a day as needed	❑ AM ❑ PM
	❑ Eye Drops	_____ dose(s)	_____ times a day as needed	❑ AM ❑ PM
	❑ NasalCrom			
	❑ Nasal Corticosteroid			
	❑ Atrovent	_____ dose(s)	_____ times a day as needed	❑ AM ❑ PM
Step 2: Mild (eg: 1 medication)	❑ Nasal Corticosteroid	_____ dose(s)	_____ times a day regularly	❑ AM ❑ PM
	❑ Oral antihistamine ❑ D	_____ dose(s)	_____ times a day regularly	❑ AM ❑ PM
	❑ Nasal antihistamine	_____ dose(s)	_____ times a day regularly	❑ AM ❑ PM
	❑ Singulair	_____ dose(s)	_____ times a day regularly	❑ AM ❑ PM
	❑ Atrovent	_____ dose(s)	_____ times a day regularly	❑ AM ❑ PM
	❑ _____	_____ dose(s)	_____ times a day regularly	❑ AM ❑ PM
Step 3: Mild to Moderate (eg: 2 medications or change to another medication)	❑ Nasal Corticosteroid	_____ dose(s)	_____ times a day regularly	❑ AM ❑ PM
	❑ Oral antihistamine ❑ D	_____ dose(s)	_____ times a day regularly	❑ AM ❑ PM
	❑ Nasal antihistamine	_____ dose(s)	_____ times a day regularly	❑ AM ❑ PM
	❑ Singulair	_____ dose(s)	_____ times a day regularly	❑ AM ❑ PM
	❑ Atrovent	_____ dose(s)	_____ times a day regularly	❑ AM ❑ PM
	❑ _____	_____ dose(s)	_____ times a day regularly	❑ AM ❑ PM
Step 4: Moderate to Severe (eg:2-3 medications and/or change of 1or more medications)	❑ Nasal Corticosteroid	_____ dose(s)	_____ times a day regularly	❑ AM ❑ PM
	❑ Oral antihistamine ❑ D	_____ dose(s)	_____ times a day regularly	❑ AM ❑ PM
	❑ Nasal antihistamine	_____ dose(s)	_____ times a day regularly	❑ AM ❑ PM
	❑ Singulair	_____ dose(s)	_____ times a day regularly	❑ AM ❑ PM
	❑ Atrovent	_____ dose(s)	_____ times a day regularly	❑ AM ❑ PM
	❑ _____	_____ dose(s)	_____ times a day regularly	❑ AM ❑ PM
Step 5: Severe (Oral Corticosteroid)	❑ Orapred 15mg/5mL	_____ mL	_____ times a day regularly for 3-5 days	
	❑ Orapred 15mg ODT	_____ tab(s)	_____ times a day regularly for 3-5 days	
	❑ Prednisone/Medrol ____mg	_____ tab(s)	_____ times a day regularly for 3-5 days	

What to do for Increased Nasal Symptoms

▪ You have a cold ▪It is your allergy season ▪You are exposed to your triggers • **First**, take your step 1 or step 2 medicine

Green Zone	Yellow Zone	Red Zone
Mild Episode	Moderate Episode	Severe Episode
• Complete response to medicine • No Nasal Symptoms	• Fair response to medicine • Mild Nasal Symptoms	• Poor response to reliever medicine • Moderate to severe Nasal Symptoms
Step up 1 level	**Step up 2 levels**	**Step up 3 levels**

Long-Term Management of Nasal Symptoms

Controlled	Fair Control	Not Controlled
• No interference with activities • < 2 days per week sneezing, itching, congestion, eye symptoms	• Mild interference with activities • 2 – 6 days per week sneezing, itching, congestion, eye symptoms	• Severe interference with activities • Daily sneezing, itching, congestion, eye symptoms
Stay at the same step or consider stepping down	Increase treatment by one step	Increase treatment by 2 steps

FIG 5. Sample rhinitis action plan.

teratogenicity, no epidemiologic studies in human pregnancy have been published.[594] Currently, there are also limited data on desloratadine, azelastine, and levocetirizine. Although diphenhydramine is frequently used during pregnancy and has good overall safety data, administration of diphenhydramine has been associated with the development of cleft palate.[595-599] Hydroxyzine should be used cautiously during the first trimester based on animal data.[594]

Oral decongestants should be avoided, if possible, during the first trimester because of conflicting reports of an association of phenylephrine and pseudoephedrine with congenital malformations such as gastroschisis and small intestinal atresia.[594,600] The

TABLE X. FDA pregnancy risk categories

A	Adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.
B	Animal studies have not demonstrated a risk to the fetus, but there are no adequate studies in pregnant women.
	OR
	Animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.
C	Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in human beings/the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
	OR
	There are no animal reproduction studies and no adequate studies in human beings.
D	There is evidence of human fetal risks, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
X	Studies in animals or human beings demonstrate fetal abnormalities, or adverse reaction reports indicate evidence of fetal risk. The risk of use in a pregnant woman clearly outweighs any possible benefit.

risks of such malformations have been reported to be increased by combining a decongestant with acetaminophen or salicylates.[600,601] The safety of intranasal decongestants during pregnancy has not been studied.

Sodium cromolyn and montelukast are both Pregnancy Category B drugs. Sodium cromolyn is a safe treatment for allergic rhinitis in pregnancy with the previously discussed clinical limitations.[599,602-604] Montelukast has reassuring animal reproductive studies and unpublished human safety data. A published observational study including 9 patients on LTRAs (specific agent not identified) demonstrated no adverse events.[605] This drug could be considered if there has been a favorable prepregnancy response.

Intranasal corticosteroids may be used during pregnancy because of their safety and efficacy profile. Clinical and epidemiologic studies on safety in human beings are limited. Although most intranasal corticosteroids are given an FDA Pregnancy Category C rating, gestational risk has not been confirmed in observational human data.[603] A recent meta-analysis concluded that the use of intranasal corticosteroids during pregnancy does not increase the risk of major malformations, preterm delivery, low birth weight, and pregnancy-induced hypertension.[606] The reported safety data on all intranasal corticosteroids have been reassuring, but beclomethasone,[11,602,607-609] budesonide (Pregnancy Category B),[603,610] and fluticasone propionate[227,611] have more accumulated data than triamcinolone,[612,613] mometasone, and flunisolide.[611] Because no substantial difference in efficacy and safety has been shown among the available intranasal corticosteroids, it would be reasonable to continue any of the intranasal corticosteroids that have adequately controlled the patient's symptoms before pregnancy.[609,614] If intranasal corticosteroids are started during pregnancy, intranasal budesonide, which is Pregnancy Category B, largely on the basis of extensive human safety data, may be preferred.[603,610] As with all medication use in pregnancy, intranasal corticosteroids should be administered at the lowest effective dose.

Allergen immunotherapy for allergic rhinitis may be continued during pregnancy if it is effective and not causing significant reactions.[614,615] The immunotherapy doses that the patient receives when she becomes pregnant should not be increased and should be adjusted appropriately during pregnancy if necessary to minimize the chance of inducing a systemic reaction. The benefit/risk considerations do not generally favor starting immunotherapy during pregnancy.[50]

Elderly patients [Summary Statement 106]

Rhinitis in the elderly may be influenced by age-related physiologic changes (eg, cholinergic hyperactivity), anatomic changes, and/or medications taken for other medical conditions. Many of the pathological changes in connective tissue and vasculature associated with aging may predispose to rhinitis symptoms.[616,617] These changes can result in dryness of the mucus membranes and increased nasal congestion in some elderly patients. Intranasal corticosteroids may be safely used for treatment of allergic rhinitis in the elderly because they do not cause any clinical or histological atrophic changes in the nasal mucosa.[618]

Athletes [Summary Statement 107]

Athletes with rhinitis can have their performance affected by rhinorrhea and nasal congestion. Endurance athletes, such as long-distance runners or triathletes, may experience rebound nasal congestion after the initial vasoconstriction that naturally occurs with exercise.[619] Prescription of medication for the competitive athlete should be based on 2 important principles[180]: (1) no medication given to the athlete should be on any list of doping products and should be approved for use by the USOC (www.wada-ama.org) and IOC (1-800-233-0393)[550]; and (2) no medication should adversely affect the athlete's performance.[620] Intranasal corticosteroids and topical decongestants are approved by the USOC, but all oral decongestants are banned. Although antihistamines are approved for use by the USOC, some are banned by the IOC.

Consultation with an allergist/immunologist [Summary Statements 108, 109]

Studies have shown that consultation with an allergist/immunologist improves patient outcomes, including QOL, compliance, and satisfaction,[621-624] by providing education on rhinitis and allergen avoidance. Consultation with an allergist/immunologist should be considered when any of the following are present:

1. The patient has had prolonged manifestations of rhinitis.
2. The patient has complications of rhinitis, such as otitis media, sinusitis, and/or nasal polyposis.
3. The patient has a comorbid condition, such as asthma.
4. The patient has required systemic corticosteroids for the treatment of rhinitis.
5. The patient's symptoms or medication side effects interfere with his/her ability to function, such as causing sleep disturbance or impairing school/work performance.
6. The patient's symptoms significantly decrease QOL, such as a decrease in comfort and well being, sleep disturbance, anosmia, or ageusia.
7. Treatment with medications for rhinitis is ineffective or produces adverse events.
8. The patient has been diagnosed with rhinitis medicamentosa.
9. Allergic/environmental triggers causing the patient's rhinitis symptoms need further identification and clarification.
10. There is a need for more complete education.

TABLE XI. Antihistamines in pregnancy first trimester H1 first-generation antihistamines

H1 antihistamine study drug (FDA pregnancy category)	Reference	Study type	Study group (n)	Control group (n)	Congenital malformations			
					Specific H1%	RR (CI)	All H1%	Control%
Chlorpheniramine (B)	682	Prospective	23	929	Major 0%	NA	4%	3%
Chlorpheniramine (B)	598	Collaborative perinatal project prospective	1070	49,212	8.4%	1.2 (.98, 1.46)		6.4%
Chlorpheniramine (B)	597	Cohort retrospective	257	6252	1.56%	.96 (.36, 2.6)		1.6%
Brompheniramine (C)	598	Collaborative perinatal project prospective	65	50,217	5.4%	2.34 (1.31, 4.17)		6.4%
Brompheniramine (C)	597	Cohort retrospective	172	6337	2.9%	1.84 (.76, 4.46)		1.6%
Brompheniramine (C)	683	Meta-analysis	34	34	2.9%	.5 (.98, 1.26)		1.6%
Triprolidine (C)	597	Cohort retrospective	244	6265	1.2%	.76 (.24, 2.36)		1.6%
Triprolidine (C)	684	Cohort retrospective	384	6452	1.56%	1.36 (.6, 3.11)		1.1%
Clemastine (B)	685	Birth registry	1239	16,967	3.17%	.98 (.72, 1.33)	3.45%	3.24%
Hydroxyzine (C)	598	Collaborative perinatal project prospective	50	50,232	10%	1.57 (.68, 3.62)		6.4%
Triprolidine (C)	686	Prospective double blind	74	34	1.35%	1.4 (.06, 33.51)		0%
Triprolidine (C)	687	Prospective	43	44	13.6%	3.07 (.66, 14.38)		4.5%
Triprolidine (C)	682	Prospective	20	929	5%	1.67	4%	3%
Diphenhydramine (C)	598	Collaborative perinatal project prospective	595	49,687	8%	1.25 (.95, 1.64)		6.9%
Diphenhydramine (C)	595	Drug registry, partly prospective	599	599	3.3%	1.56% (1.25, 1.94)		1.1%
Diphenhydramine (C)	684	Cohort retrospective	361	6476	.27%	.23 (.03, 1.63)		1.2%
Diphenhydramine (C)	597	Cohort retrospective	270	6239	1.5%	.92 (.34, 2.47)		1.6%

NS, Not significant; *RR,* relative risk.

TABLE XII. Antihistamines in pregnancy first trimester H1 second-generation antihistamines live birth data

H1 antihistamine study drug (FDA pregnancy category)	Reference	Study type	Study group (n)	Control group (n)	Congenital malformations				Cardiac	Hypospadias	Spontaneous abortion	
					Specific H1 %	RR (CI)	All H1 %	Control %	Specific H1 %	Specific H1 %	Specific H1 %	Control %
Cetirizine (B)	685	Birth registry	917	403,545	3.95% (NS)	1.22 (.89, 1.69)	3.45%	3.16%	1%	.4%		
Cetirizine (B)	687	Prospective	33	38	Major 0% Minor 6%	1.15 (.17, 7.73)		Major 0% Minor 5%			18% (NS)	2.6%
Loratadine (B)	685	Birth registry	1769	408,545	3.4% (NS)	1.05 (.38, 1.34)	3.45%	3.16%	.5%	.4%		
Loratadine (B)	688	Prospective	140	149	3.5% (NS)	.93 (.48, 1.79)		4%			13% (NS)	8%
Loratadine (B)	682	Prospective	175	844	Major 2.3%	.77 (.27, 2.19)	4%	3%			11%	7.2%
Terfenadine (C)*	685	Birth registry	1162	408,545	3.22% (NS)	.98 (.72, 1.35)	3.45%	3.16%				
Terfenadine (C)*	689	Prospective multicenter	118	118	Major 0%	.57 (.06, 5.39)		2%				
Fexofenadine† (C)	No studies											

NS, Not significant; *RR,* relative risk.
*No longer available.
†The active metabolite of terfenadine.

11. The patient has required multiple and/or costly medications over a prolonged period.
12. Allergy immunotherapy is a treatment consideration.

Consultation with an allergist/immunologist may be indicated in other situations when there is agreement between the patient and the referring physician that such an approach is in the patient's best interests.

ANNOTATIONS

Box 1: Patient presents with symptoms of rhinitis (Fig 6)

Patients with rhinitis can present with symptoms of rhinorrhea, nasal congestion, sneezing, nasal pruritus, postnasal drainage, and/or associated ocular symptoms. These symptoms can occur with both allergic and nonallergic rhinitis. Symptoms of allergic rhinitis may occur only during specific seasons, may be perennial without seasonal exacerbations, may be perennial with seasonal exacerbations, or may occur episodically after specific aeroallergen exposures. Conjunctival symptoms frequently occur in conjunction with allergic rhinitis. Rhinitis symptoms often worsen during complications, such as otitis media and sinusitis, and frequently coexist with symptoms of other comorbid conditions, such as wheezing, cough, and chest tightness caused by asthma. Patients may be initially evaluated either by a generalist, such as a primary care physician, or by a specialist, such as an allergist/immunologist.

The history should include (1) the nature of the presenting symptoms, such as rhinorrhea, nasal congestion, sneezing, and

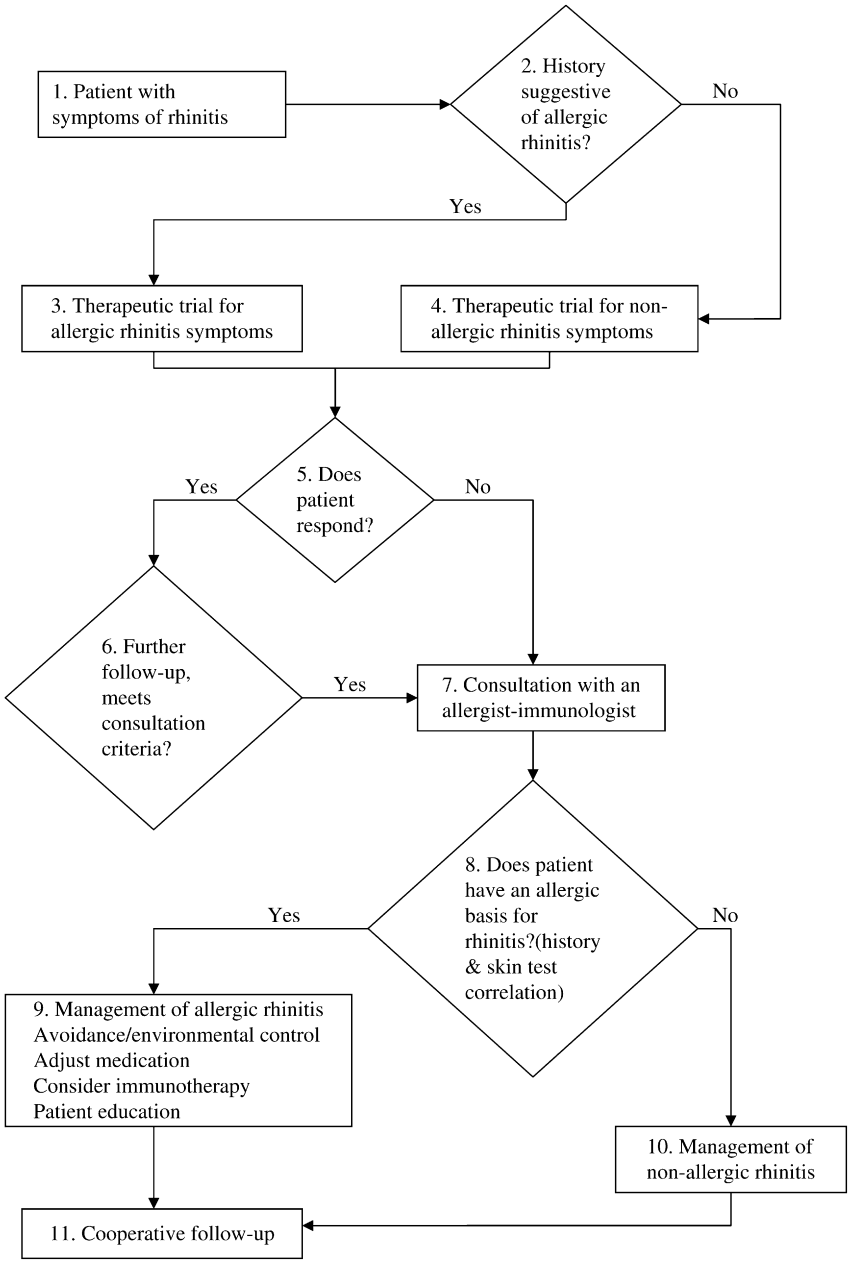


FIG 6. Algorithm.

associated ocular symptoms; (2) length of symptomatology; (3) the current and past medications used for treatment of rhinitis, including duration, effectiveness, and any associated adverse events; (4) current or past medications taken for other medical conditions and the relationship, if any, with rhinitis symptoms; (5) the degree to which the patient's rhinitis symptoms interfere with the patient's QOL; (6) seasonality of nasal and related symptoms (or lack thereof); (7) occupational exposure; (8) a detailed environmental history; (9) identification of precipitating factors; (10) the presence of other medical conditions; (11) presence of symptoms consistent with complications, such as sinusitis or otitis media, or comorbid conditions, such as asthma; (12) family history of allergic rhinitis, asthma, or atopic dermatitis; and (13) personal or family history of chronic sinus problems or infections, as well as diagnoses that may represent allergic symptoms, such as recurrent bronchitis.

When reviewing the allergic history in children, one may inquire about sniffing, snorting, clearing of the throat, chronic gaping mouth, halitosis, cough, dark circles under the eyes, and eye rubbing. The parents may describe the child as having a poor appetite, learning or attention problems, sleep disturbances, malaise, irritability, and a general sense of not feeling well.

The physical examination should focus on examination of the nose but may include evaluation of the ears, eyes, throat, and lungs. Examination of the nose should focus on the appearance of the nasal mucus membranes, the patency of the nasal passageways, unilaterality or bilaterality of findings, causes for anatomical nasal obstruction, and the quality and quantity of the nasal discharge.

Box 2: Is history and examination suggestive of allergic rhinitis?

A diagnosis of allergic rhinitis can be confirmed only on the basis of a history of symptoms after exposure to known allergens, which correlates with specific IgE testing. Nonetheless, the history and physical examination alone is often suggestive of either allergic rhinitis or nonallergic rhinitis. Symptoms of pruritus and sneezing are much more common in allergic than nonallergic rhinitis. Seasonal exacerbations are also suggestive of allergic rhinitis. Patients with allergic rhinitis tend to develop the onset of symptoms earlier in life, typically before the age of 20 years, than those with nonallergic rhinitis. In contrast, isolated postnasal drainage is less likely to be a result of allergic rhinitis. Patients with vasomotor rhinitis may have symptoms triggered by strong odors such as perfume or tobacco smoke. A history of isolated rhinorrhea associated with eating is suggestive of gustatory rhinitis. Patients with chronic and frequent use of topical decongestant sprays may have rhinitis medicamentosa. Symptoms that are primarily unilateral suggest a structural problem, such as a nasal polyp, foreign body, septal deformity, or rarely a tumor. Hyposmia or anosmia are often associated with nasal polyposis but may also occur in other forms of rhinitis.

Many typical allergic findings are supportive of but not specific to allergic rhinitis. Mucosal appearance may not distinguish between allergic and nonallergic rhinitis, because nonallergic rhinitis may also present with mucosal pallor, edema, or hyperemia. However, the physical examination can help identify nasal polyps, foreign bodies, or other structural abnormalities.

Box 3: Therapeutic trial for allergic rhinitis symptoms

Initial treatment of nonsevere rhinitis may include single-agent or combination pharmacologic therapy and avoidance measures.

Oral antihistamines are generally effective in reducing rhinorrhea, sneezing, and itching associated with allergic rhinitis but have little objective effect on nasal congestion. These agents may reduce symptoms of allergic conjunctivitis, which are often associated with allergic rhinitis. Antihistamines have a limited role in treating nonallergic rhinitis syndromes. Although antihistamines can be used on an intermittent basis, such as for episodic allergic rhinitis, it has been shown that continuous treatment for seasonal or perennial allergic rhinitis is more effective,[331] primarily because of unavoidable, ongoing allergen exposure. First-generation antihistamines have significant potential to cause sedation, performance impairment (that may not be subjectively perceived by patients), and/or anticholinergic effects (such as dry mouth and urinary retention). Consequently, second-generation antihistamines, which are associated with less risk or no risk for these side effects, are generally preferred over first-generation antihistamines for the treatment of allergic rhinitis. Intranasal antihistamines may be useful alternatives to oral antihistamines but may cause sedation in some patients and/or may be perceived to have a bitter taste.

Oral anti-LT agents, alone or in combination with antihistamines, have proven to be useful in the treatment of allergic rhinitis. There is no significant difference in efficacy between LTRA and antihistamines (with loratadine as the usual comparator), and their concomitant use may be additive,[40,42,377] but not all studies with the concomitant administration of an antihistamine and a LTRA have shown an additive effect. Although the concomitant administration of a LTRA and an antihistamine can have an additive effect, in general, this approach is less efficacious than administering intranasal corticosteroids.[348,375,377,379]

Oral decongestants, such as pseudoephedrine or phenylephrine, help reduce symptoms of nasal congestion in both allergic and nonallergic rhinitis and are beneficial for use in combination with antihistamines. However, they can cause insomnia, loss of appetite, irritability, and palpitations. Elevation of blood pressure after taking an oral decongestant is very rarely noted in normotensive patients and only occasionally in patients with controlled hypertension. However, based on interindividual variation in response, hypertensive patients should be monitored.

Topical decongestants are appropriate to use on a short-term basis for nasal congestion associated with acute bacterial or viral infections, exacerbations of allergic rhinitis, and eustachian tube dysfunction. Intermittent use of topical decongestants may be considered, but efficacy and safety of this approach have not been formally studied. With regular daily use, some patients may develop rhinitis medicamentosa in 3 days, whereas others may not have evidence of rebound congestion after 4 to 6 weeks of use. Given this variability, it would be prudent to instruct patients of the risk of rhinitis medicamentosa when intranasal decongestants are used more than 3 days.

Intranasal corticosteroids are typically the most effective medication class for controlling sneezing, itching, rhinorrhea, and nasal congestion, the 4 major symptoms of allergic rhinitis. They are particularly useful for treatment of more severe allergic rhinitis and may be useful in some forms of nonallergic rhinitis. Intranasal corticosteroids when given in recommended doses are not generally associated with clinically significant systemic side effects. Although local side effects are minimal, if the patient is carefully instructed in the use of this class of drugs, nasal irritation and bleeding may occur. Patients should be instructed to direct sprays away from the nasal septum. The nasal septum should be periodically examined to assure that there are no mucosal erosions. Although nasal septal perforations are rarely caused by intranasal corticosteroids, mucosal erosions may suggest an increased risk for their subsequent development. In children, intranasal corticosteroids should be used at the lowest effective dose. Intranasal corticosteroids may be considered for initial treatment without a previous trial of antihistamines and/or oral decongestants, and they should always be considered before initiating treatment with systemic corticosteroids for the treatment of rhinitis.

A short course (5-7 days) of oral corticosteroids may be appropriate for the treatment of very severe or intractable rhinitis or nasal polyposis. However, single administration of parenteral corticosteroids is discouraged, and recurrent administration of parenteral corticosteroids is contraindicated because of greater potential for long-term corticosteroid side effects.

Nasal cromolyn is less effective than intranasal corticosteroids. It can reduce symptoms of allergic rhinitis in some patients and is most likely to be effective if initiated before symptoms become severe. For maximum efficacy, nasal cromolyn should be administered 4 times a day.

Intranasal anticholinergics may effectively reduce rhinorrhea but have minimal effects on nasal congestion or other nasal symptoms. The combination of intranasal anticholinergics with either antihistamines or intranasal corticosteroids may provide

increased efficacy over either drug alone without any increased adverse effects.

Empiric avoidance of suspected inciting factors, such as allergens, irritants, and medications, should be implemented, if possible, even in early treatment of rhinitis. In the management of severe seasonal allergic rhinitis, patients should be advised to follow avoidance measures such as staying inside air-conditioned buildings, whenever possible, with windows and doors closed.

Box 4: Therapeutic trial for nonallergic rhinitis symptoms

Many of the medications used to treat allergic rhinitis are also used in the management of nonallergic rhinitis. Intranasal corticosteroids and intranasal antihistamines may relieve both congestion and rhinorrhea associated with vasomotor rhinitis. Intranasal anticholinergics are useful in nonallergic rhinitis with predominant rhinorrhea (eg, gustatory rhinitis). Nonsedating oral antihistamines have not been shown to be effective in nonallergic rhinitis. Oral and intranasal decongestants may be considered in patients with nonallergic rhinitis and nasal congestion with similar precautions as discussed. Avoiding aggravating irritants may be helpful, particularly in patients suspected to have vasomotor rhinitis. For patients with rhinitis medicamentosa, discontinuation of nasal decongestant sprays and treatment with either intranasal or systemic corticosteroids may be necessary. Finally, patients suspected of infectious rhinitis should be treated with supportive measures to relieve ostiomeatal obstruction and judicious use of antibiotics for suspected bacterial sinusitis.

Box 5: Does the patient respond?

In assessing response to therapy, a variety of parameters should be evaluated.

These include nasal symptoms (eg, congestion, itching, and rhinorrhea), physical signs of rhinitis (eg, edema of nasal turbinates), and QOL (eg, affect, ability to sleep, and ability to function effectively at work or school or while driving). In patients who have concomitant conditions that may be aggravated by rhinitis (eg, asthma), an assessment of concomitant conditions should also be made because improved control of rhinitis may be associated with improvement of these conditions. Patients who do not have a good response to treatment should be referred to an allergist/immunologist.

Box 6: Further follow-up, meets consultation criteria?

If the initial treatment of rhinitis is successful, there is still a need for patient follow-up to assure that there is continued control of symptoms, maintenance of improved QOL, lack of impairment of performance at work or school and in other activities, and absence of medication side effects. Consultation with an allergist/immunologist is appropriate when these conditions are not met. Characteristics that should lead to consideration of consultation with an allergist/immunologist include the following:

1. The patient has had prolonged manifestations of rhinitis.
2. The patient has complications of rhinitis, such as otitis media, sinusitis, and/or nasal polyposis.
3. The patient has a comorbid condition, such as asthma and chronic sinusitis.
4. The patient has required a systemic corticosteroid for the treatment of rhinitis.
5. The patient's symptoms or medication side effects interfere with ability to function, such as causing sleep disturbance or impairing school/work performance.
6. The patient's symptoms significantly decrease QOL, such as a decrease in comfort and well being, sleep disturbance, anosmia, or ageusia.
7. Treatment with medications for rhinitis is ineffective or produces adverse events.
8. The patient has been diagnosed with rhinitis medicamentosa.
9. Allergic/environmental triggers causing the patient's rhinitis symptoms need further identification and clarification.
10. There is a need for more complete education.
11. The patient has required multiple and/or costly medications over a prolonged period.
12. Specific allergy immunotherapy is a treatment consideration.

Consultation with an allergist/immunologist may be indicated in other situations when there is agreement between the patient and the referring physician that such an approach is in the patient's best interests.

Box 7: Consultation with an allergist/immunologist

An assessment of rhinitis by a rhinitis specialist requires a detailed history and appropriate physical examination. The history should include all of the components outlined in Box 1 but in more depth. The physical examination should assess the upper airway (nose, oropharynx) and lungs. In addition, rhinoscopy or examination by rigid or flexible rhinolaryngoscopy (endoscope) allows for better visualization of the middle meatus, the posterior septum, the sinus ostia, the nasopharynx, and presence of nasal polyps. Immediate hypersensitivity skin tests or *in vitro* tests for specific IgE to confirm an underlying allergic basis for the patient's symptoms may be necessary. Nasal cytology may be of value. Rarely, other tests may be indicated such as β- transferrin in nasal secretions (for suspected CNS fluid leakage) or tests of nasal ciliary function. Specific tests may also be necessary for coexisting conditions such as asthma (eg, pulmonary function), nasal polyps (eg, rhinoscopy), or sinusitis (eg, CT scan).

A thorough evaluation is the key component to the development of a long-term management plan. Management may include education regarding environmental avoidance and medication compliance, institution of environmental control measures, changes in medication, and allergen immunotherapy.

Box 8: Does patient have an allergic basis for rhinitis?

A diagnosis of allergic rhinitis depends on the history of nasal symptoms after exposure to suspected allergens, which are confirmed with positive skin or *in vitro* tests for specific IgE. Determination of specific IgE, preferably by skin testing, is indicated to provide evidence of an allergic basis for the patient's symptoms, to confirm suspected causes of the patient's symptoms, or to assess the sensitivity to a specific allergen for avoidance measures and/or allergen immunotherapy. The precise sensitivity of specific IgE immunoassays compared with skin prick/puncture tests is approximately 70% to 75%. Skin tests are the preferred tests for the diagnosis of IgE mediated sensitivity. The number of skin tests and the allergens selected for skin testing should be determined on the basis of the patient's age,

history, and environment and living situation—for example, area of the country, occupation, and activities. If there is a poor correlation between allergen exposures and symptoms, patients may have nonallergic rhinitis even if skin tests or *in vitro* tests for specific IgE are positive. For example, a patient with perennial rhinitis with an isolated positive skin test to ragweed would not have ragweed-induced allergic rhinitis as a cause of perennial symptoms and most likely would have nonallergic rhinitis.

A physical examination demonstrating a pale edematous nasal mucosa and the presence of allergic signs (nasal crease, nasal or eye rubbing, dark circles under the eyes) is helpful but does not always differentiate allergic from nonallergic rhinitis. Nasal smears and fiber optic nasal endoscopy are occasionally helpful in making such a differentiation.

Patients who have negative immediate hypersensitivity skin test reactions or negative *in vitro* tests for specific IgE should be considered nonallergic, especially if there is poor correlation between allergen exposure and symptoms.

Box 9: Management of allergic rhinitis

Effective management of allergic rhinitis may require combinations of medications, aggressive avoidance measures, management of coexisting conditions, and/or allergen immunotherapy. Avoidance of triggers of rhinitis, such as allergens, irritants, medications, and occupational factors, is fundamental to the successful management of allergic rhinitis. After triggers are identified, the patient or representative should be educated about avoidance. If it is possible to anticipate the onset of symptoms associated with seasonal exposure to pollen or sporadic exposure to other triggers, early administration of medications (eg, before exposure or the development of symptoms) may lessen the impact of such exposures (see Box 3 annotation for a discussion of appropriate medications).

A short course of oral corticosteroids may be appropriate for the treatment of intractable nasal symptoms (see Box 3 annotation) or severe nasal polyposis. The chronic use of oral or parenteral corticosteroids is inappropriate in allergic rhinitis.

Allergen immunotherapy is effective for treatment of allergic rhinitis and allergic rhinoconjunctivitis. Effective immunotherapy has been associated with significant improvement in symptom and medication scores and QOL measures as well as objective parameters such as nasal provocation challenge, immunologic changes in cell markers, and cytokine profiles. Allergen immunotherapy should be considered for patients with allergic rhinitis who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. The severity and duration of symptoms as well as the impact of the patient's symptoms on QOL should also be considered in assessing the need for specific allergen immunotherapy.

Box 10: Management of nonallergic rhinitis

Nonallergic rhinitis is characterized by sporadic or persistent perennial symptoms of rhinitis that do not result from IgE-mediated immunopathologic events. Examples of nonallergic rhinitis are infectious rhinitis, hormonal rhinitis, vasomotor rhinitis (including gustatory rhinitis), NARES, certain types of occupational rhinitis, and drug-induced rhinitis.

The signs and symptoms suggestive of rhinitis can be produced by anatomic conditions including nasal septal deviation, tumors, adenoidal hypertrophy, and hypertrophy of the nasal turbinates. Examination of the nose should include evaluation of the nasal passageways, secretions, turbinates, septum, and determination of whether nasal polyps are present. In selected cases, fiber optic nasal endoscopy and/or rhinomanometry may be useful. Nasal cytology may aid in differentiating allergic rhinitis and NARES from other forms of rhinitis.

The primary treatments for nonallergic rhinitis syndromes may vary and include (1) avoidance of aggravating irritants that may precipitate symptoms, (2) intranasal corticosteroids, (3) decongestants and exercise to relieve congestion, (4) anticholinergics to relieve rhinorrhea, (5) intranasal corticosteroids and intranasal antihistamines to relieve both congestion and rhinorrhea associated with vasomotor rhinitis, (6) institution of intranasal corticosteroids and discontinuation of nasal decongestant sprays in rhinitis medicamentosa, and (7) antibiotics and supportive measures to relieve ostiomeatal complex obstruction in bacterial rhinosinusitis.

Box 11: Cooperative follow-up

Cooperative follow-up for allergic rhinitis patients includes the patient, family, and health care providers (ie, the primary care physician, allergist/immunologist, and possibly otolaryngologist). Goals include the reduction of symptoms and improvement in the patient's QOL and ability to function. These goals require cooperative management of exacerbations and complications by optimal use of environmental avoidance measures and medications, and in appropriate patients, use of immunotherapy.

Tapering of medications should always be considered to lessen the risk of adverse reactions. Side effects of medications must be carefully looked for during follow-up of patients. Maximizing compliance with medications and environmental controls can be challenging for the patient and physician, especially if the patient is very young or elderly.

Periodic assessment of the patient's QOL is essential. This includes evaluation of time lost from work or other activities, sleep quality, smell and taste, fatigue level, and general well being.

Patient education is a basic part of the follow-up plan for patients with allergic rhinitis. At each visit, it is important to review preventative measures (eg, environmental controls), medication use, and immunotherapy status with the patient. In addition, the presence of comorbid conditions such as sinusitis, asthma, and otitis media should be ascertained.

Effective follow-up requires awareness of the patient's goals, needs, and concerns. Allergen immunotherapy may be appropriate for patients with allergic rhinitis, especially if the patient is not responding to other therapeutic approaches and symptoms are interfering with the patient's ability to function. Follow-up also requires effective interaction between all health care providers as well as interaction with the patient and often the patient's family.

Although there is no surgical treatment for rhinitis, surgery may be indicated in the management of comorbid conditions, such as nasal obstruction from severe nasal septal deviation or inferior turbinate hypertrophy, adenoidal hypertrophy, or refractory sinusitis and complications thereof. Other reasons for referral to an

otolaryngologist include the evaluation of ostiomeatal obstruction, nasal polyp surgery, biopsy of nasal tumors, or other surgical requirements.

SUMMARY STATEMENTS WITH DISCUSSION

Definition

1. Rhinitis is characterized by 1 or more of the following symptoms: nasal congestion, rhinorrhea (anterior and posterior), sneezing, and itching. **D**

Although the term *rhinitis* connotes inflammation, and the majority of rhinitides are associated with inflammation, some forms of rhinitis such as vasomotor rhinitis or atrophic rhinitis may not be associated with inflammation of the nasal mucosa. Rhinitis frequently is accompanied by symptoms involving the eyes, ears, and throat.

Differential diagnosis of rhinitis

2. Rhinitis should be classified by etiology as allergic or nonallergic and differentiated from conditions that mimic symptoms of rhinitis. **C**

Rhinitis is classified as allergic or nonallergic, but not all types of rhinitis can be easily separated into 1 of these categories. For example, occupational rhinitis has been classified separately from allergic and nonallergic because it may have components of both allergic and nonallergic rhinitis. Conditions that mimic symptoms of rhinitis include nasal polyps, cerebrospinal fluid rhinorrhea, ciliary dyskinesia syndrome, and structural/mechanical factors, such as deviated septum and pharyngonasal reflux (see Tables I and II in the Executive Summary).

Classification of allergic rhinitis

3. Symptoms of allergic rhinitis may occur only during specific seasons, may be perennial without seasonal exacerbation, may be perennial with seasonal exacerbations, or may occur episodically after specific aeroallergen exposures. **C**
4. *Episodic* allergic rhinitis is a new rhinitis category that denotes allergic nasal symptoms elicited by sporadic exposures to inhalant aeroallergens. **D**
5. The severity of allergic rhinitis ranges from mild and intermittent to seriously debilitating. **D**
6. Although there is no generally accepted method of grading the severity of rhinitis, the clinician may want to consider a graphic rating scale. **D**

Recently, an international working group released ARIA recommendations and proposed a revised classification for allergic rhinitis that categorized all patients as either intermittent (<4 days per week or <4 weeks) or persistent (>4 days per week and >4 weeks) and classified severity as mild or moderate-severe.[9,10] This system proposes 4 classes, which include (1) mild intermittent, (2) mild persistent, (3) moderate/severe intermittent, and (4) moderate/severe persistent.[10] This classification system discarded the terms *seasonal* and *perennial*, on the basis of several rationales including the observation that an aeroallergen (eg, grass pollen) that occurs seasonally in one region may be detected throughout the year in another geographical area. Demoly et al[690] reported that 44% of patients traditionally classified as having seasonal rhinitis had persistent rhinitis according to the ARIA classification and that 44% with perennial allergic rhinitis were reclassified as intermittent. Thus, the traditional seasonal/perennial and ARIA schemes define different patient populations.

Treatment guidelines based on the ARIA guidelines have not been adequately studied.[12] However, the ARIA definition of *mild rhinitis* may be a useful comparative reference point for other severity grading schemes; this states that none of the following items is present: sleep disturbance; impairment of daily activities, leisure and/or sport; impairment of school or work; and symptoms present but not troublesome.[9] This updated parameter supports the concept that *more severe rhinitis* is defined as more symptoms or interference with QOL, because data show that it may not be possible to separate patients into moderate and severe categories.[12] A nonvalidated modified 7-point visual analog (graphic rating) scale for grading severity of nasal and nonnasal symptoms of allergic rhinitis and the effects of this disorder on the QOL has been developed and published by the Joint Task Force on Practice Parameters and is included, with minor modification, in Figs 1-4.[13]

In this document, the Joint Task Force retains and uses the terms *seasonal* and *perennial* in classifying patients with allergic rhinitis. These traditional descriptive terms are clinically useful and allow for accurate categorization of the vast majority of patients as having seasonal, perennial, or perennial allergic rhinitis with seasonal exacerbations. In addition to seasonal and perennial, *episodic* is used in this practice parameter to denote allergic nasal symptoms elicited by sporadic exposures to inhalant aeroallergens that are not usually encountered in the patient's indoor or outdoor environment. Although the terms *seasonal*, *perennial*, and *episodic* are clinically useful, therapeutic decisions should also be guided by frequency, duration, and severity of symptoms, and by current and previous responsiveness to medications.[13]

Allergic rhinitis

7. Mixed rhinitis (combined allergic and nonallergic rhinitis) is noted in approximately 44% to 87% of patients with allergic rhinitis and is more common than either pure allergic rhinitis or nonallergic rhinitis. **C**
8. Allergic rhinitis affects 30 to 60 million people in the United States annually, including 10% to 30% of adults and as many as 40% of children. **C**
9. Risk factors for allergic rhinitis include (1) family history of atopy, (2) serum IgE >100 IU/mL before age 6 years, (3) higher socioeconomic class, and (4) presence of a positive allergy SPT. **C**
10. The influence of early childhood exposure to infections, animals, and secondary tobacco smoke on the development of atopy and allergic rhinitis is still unknown. **C**
11. Aeroallergen sensitization may occur within the first 2 years of life. **C**
12. The cost of treating allergic rhinitis and indirect costs related to loss of workplace productivity resulting from the disease are substantial. Rhinitis is also a significant cause of lost work and school days. **C**

Rhinitis is reported to be a very frequent disease, although data regarding the true prevalence of rhinitis are difficult to interpret. Most population surveys rely on physician-diagnosed rhinitis for their data, and this may give rise to a much lower reporting of

rhinitis. Some population studies have been performed with questionnaires administered to the subjects, followed in many cases by telephone interviews, to try to make a specific diagnosis of rhinitis. It has been estimated that 25% to 33% of cases of rhinitis are a result of nonallergic rhinitis, and that 44% to 87% of allergic rhinitis has an element of nonallergic rhinitis, referred to as *mixed rhinitis*.[2,7] Several studies may reflect a more accurate prevalence of rhinitis but probably still underreport this disease.[3,14,16,25,691-693] Because skin testing or determination of serum specific IgE is rarely assessed in such large epidemiologic studies, allergic causation is uncertain.

The prevalence of allergic rhinitis in various epidemiologic studies ranges from 3% to 19%.[694] According to the Centers for Disease Control and Prevention, 23.7 million cases of allergic rhinitis were reported in 1996, including 15.9 million cases among persons age 45 years or younger.[695]

Seasonal allergic rhinitis is apparently becoming more common. One study showed that the prevalence of hay fever increased from 4% to 8% in the 10 years from 1971 to 1981.[696] In another study, atopic skin test reactivity increased from 39% to 50% during an 8-year period of evaluation.[697] However, a recent study of Swiss children 5 to 7 years old conducted during the last decade suggests that the increasing prevalence of allergic rhinitis may have plateaued in some countries.[109]

Studies suggest that seasonal allergic rhinitis (hay fever) is found in approximately 10% to 20% of the population.[3-6] However, 1 study of physician-diagnosed allergic rhinitis showed a prevalence of 42% in 6-year-old children.[16] Overall, allergic rhinitis affects 30 to 60 million individuals in the United States annually.[698-700]

In childhood, boys with allergic rhinitis outnumber girls, but the sex ratio becomes approximately equal in adults and may even favor women. Allergic rhinitis develops before age 20 years in 80% of cases. Studies have shown that the frequency of allergic rhinitis increases with age until adulthood and that positive immediate hypersensitivity skin tests are significant risk factors for the development of new symptoms of seasonal allergic rhinitis.[4,14,15] There is a greater chance of a child developing allergic rhinitis if both parents have a history of atopy than if only 1 parent is atopic. Children in families with a bilateral family history of allergy generally develop symptoms before puberty; those with a unilateral family history tend to develop their symptoms later in life or not at all.[6,25]

There tends to be an increased prevalence of allergic rhinitis in nonwhites, in some polluted urban areas, and in individuals with a family history of allergy. Allergic rhinitis is more likely in first-born children. Studies in children in the first years of life have shown that the risk of rhinitis was higher in those youngsters with early introduction of foods or formula, higher serum IgE levels (100 IU/mL before age 6 years), and parental allergic disorders.[16]

Over the past few years, several studies supporting the hygiene hypothesis have suggested that early exposure to viral and bacterial infections, such as day care attendance or more siblings, may reduce the incidence of atopic disease by redirecting the immune system away from the allergic T_H2 pattern to the T_H1 pattern.[17-19] One early explanation proposed that the increased incidence of atopy as explained by the hygiene hypothesis is a result of the reduced production of IL-12 and IFNs by cells of the innate immune system that are normally stimulated by bacterial products via their Toll-like receptors.[20] More recently, the role of reduced activity of regulatory T cells has been emphasized.[20] It is now felt that early infections reinforce the physiological mechanisms of natural dominant tolerance by expanding natural regulatory T cells. It also appears that the proinflammatory ligands of Toll-like receptors on the natural regulatory T cells play a major role in their activation and expansion.[21] However, some recent studies refute the hygiene hypothesis, demonstrating that increased infections in early life increase allergic disease in childhood and do not contribute to any reduction of atopic disease in adults.[22] Animal exposure in early infancy is likewise controversial because some studies have demonstrated that cat exposure in early infancy may reduce atopy and asthma,[23,24] whereas others have shown either no effect[28] or increased allergic disease.[701] Environmental risk factors for rhinitis in early infancy include environmental smoke exposure as well as allergens. Exposure to >20 cigarettes per day has been shown to be associated with an increased risk of developing allergic rhinitis at age 1 year.[28] The effect of tobacco smoke on allergic sensitization at age 1 year and the frequency of upper respiratory infections and ear infections in the young child remain controversial.[28,702] It has been suggested that the month of birth increases the risk of pollen and dust mite sensitization especially in childhood,[703,704] but not all studies agree.[705]

A critical period appears to exist early in infancy in which the genetically programmed individual is at greatest risk of sensitization on exposure to food and aeroallergens.[706] In infancy, food allergies cause primarily gastrointestinal symptoms and atopic dermatitis and rarely induce nasal symptoms.[707] Infants born to atopic families are sensitized to pollen aeroallergens more frequently than to indoor aeroallergens in the first year of life.[27] Although perennial allergic rhinitis (eg, dust mite and animal dander) may be present at a very early age,[28] seasonal allergic rhinitis typically does not develop until the child is 2 to 7 years of age, because 2 seasons of exposure are generally required for sensitization.[29,30] The prevalence of seasonal allergic rhinitis is higher in children and adolescents, whereas perennial allergic rhinitis is higher in adults.[31]

The financial impact on society is tremendous.[708] The severity of allergic rhinitis ranges from mild to seriously debilitating. The direct cost of treating allergic rhinitis and the indirect cost related to loss of workplace productivity resulting from the disease are substantial. The estimated cost of allergic rhinitis based on direct and indirect costs is $2.7 billion for the year 1995, exclusive of costs for associated medical problems such as sinusitis and asthma. The cost to society has continued to increase. Based on pharmacy and medical care expenditure data, the estimated direct medical cost of allergic rhinitis was $7.3 billion for the year 2002, which was primarily incurred by costs of prescriptions and outpatient clinic visits.[695] The total direct cost ($7.3 billion) and indirect cost ($4.28 billion) estimates for allergic rhinitis have been estimated to be $11.58 billion for 2002.[709] This figure included the higher indirect costs associated with increased loss of productivity, which in turn was related to extensive OTC first-generation antihistamine use. Such treatment can cause drowsiness and impair cognitive and motor function.

Rhinitis is also a significant cause of lost school attendance, resulting in more than 2 million absent school days in the United States annually. In children, there is evidence that symptoms of allergic rhinitis can impair cognitive functioning, which can be further impaired by the use of first-generation antihistamines.[176]

13. The symptoms of allergic rhinitis result from a complex allergen-driven mucosal inflammation caused by interplay

between resident and infiltrating inflammatory cells and a number of vasoactive and proinflammatory mediators, including cytokines. Sensory nerve activation, plasma leakage, and congestion of venous sinusoids also contribute. **C**

The nasal mucosa is designed to humidify and clean inspired air. The actions of epithelium, vessels, glands, and nerves are carefully orchestrated to perform these functions.[710] Dysfunction of any of these structures may contribute to the symptoms of allergic and nonallergic rhinitis.

14. Allergic rhinitis may be characterized by early-phase and late-phase responses. Each type of response is characterized by sneezing, congestion, and rhinorrhea, but congestion predominates in the late phase. **C**

Atopic subjects inherit the tendency to produce specific IgE antibodies and T_H2-directed immune responses. Intermittent or continuous exposure to low concentrations of indoor or outdoor aeroallergens over time may result in sensitization, a process initiated by processing of allergens by dendritic cells expressing CD1a and CD11c,[711] in the nasal epithelium mucosa and subsequent presentation of allergenic peptides by MHC II molecules to T-cell receptors on resting $CD4^+$ cells in regional lymph nodes. With appropriate costimulatory signals, allergen-stimulated resting T cells proliferate into T_H2-biased cells that produce IL-3, IL-4, IL-13, IL-5, GM-CSF, and other cytokines. T_H2 cytokines promote B-cell isotype switching and allergen specific IgE production by plasma cells, mast cell proliferation and infiltration of airway mucosa, and eosinophilic infiltration into the nasal mucosa and nasal epithelium.

Early or immediate allergic response

With continued allergen exposure, increasing numbers of IgE-bound mast cells recognize the mucosally deposited allergen and degranulate.[710] Mast cell products include preformed mediators such as histamine, tryptase, chymase, kininogenase, heparin, and other enzymes.[712] Newly formed mediators including prostaglandin D_2[713] and the cysLTs (LTC_4, LTD_4, and LTE_4) are produced by mast cells, eosinophils, basophils, and macrophages and bind to specific receptors in the nose.[714] These mediators produce edema, watery rhinorrhea, and mucosal hypertrophy; stimulate glands to exocytose their mucoglycoconjugates and antimicrobial substances; and dilate arteriole-venule anastomoses to cause sinusoidal filling and occlusion of nasal air passages. The cysLTs also play an active role in recruitment of inflammatory cells.[714] Sensory nerves are stimulated that convey the sensations of nasal itch and congestion and initiate systemic reflexes such as sneezing paroxysms. Within minutes of allergen exposure, there is release of mast cell mediators and induction of the response. This is known as the *early* or *immediate allergic response*. Although most subjects experience sneezing and copious rhinorrhea after allergen exposure, some subjects have sensations of nasal congestion as their predominant symptom. Neuropeptide expression (eg, substance P) has been demonstrated in mucosal nerve fibers of patients with seasonal allergic rhinitis, although the exact roles of sensory neural mediators in the pathogenesis of symptoms of allergic rhinitis are uncertain.[715]

Late-phase response

The mast cells mediators, including cytokines, are thought to play active roles in generating the late-phase response, which is initiated 4 to 8 hours after allergen exposure. LTC_4 increases both during the early-phase and late-phase nasal responses to allergen.[716] In a study evaluating kinetics of mediators and cytokines in nasal secretions after allergen challenge, histamine was increased in nasal secretions during the early-phase and late-phase nasal responses, and IL-1β and IL-4 were significantly elevated during the late-phase response.[712] In another study that examined nasal mucosal late responses after a single nasal grass allergen exposure, T_H2 cytokines including IL-5 and IL-13 were expressed in association with increased numbers of eosinophils.[717]

Local endothelial expression of intercellular adhesion molecule 1, E-selectin, and vascular adhesion molecule 1 have been correlated with increased nasal mucosal eosinophils at 24 hours after nasal allergen provocation, indicating that adhesion molecules are upregulated and facilitate transmigration of activated eosinophils into the nasal mucosa.[718] Chemoattractants, such as IL-5 and eotaxin for eosinophils, as well as chemokines IL-8 and monocyte chemoattractant protein 1 have been detected in nasal secretions during the late-phase response and are thought to enhance infiltration of the superficial lamina propria of the mucosa with neutrophils, eosinophils, and, at later time points, T lymphocytes and macrophages.[716] Eosinophil products such as major basic protein, ECP, hypohalides, LTs, and others are thought to damage the epithelium and other cells, resulting in an inflammatory response that promotes the tissue damage of chronic allergic reactions.[32] Pretreatment with glucocorticoids is effective at reducing eosinophils and the release of cytokines (eg, IL-4, IL-5, and IL-13) during the late-phase response.[34]

Priming response

When allergen challenges are given repeatedly, the amount of allergen required to induce an immediate response decreases.[719-721] This priming effect is thought to be a result of the influx of inflammatory cells during ongoing, prolonged allergen exposure and repeated late-phase responses. The priming effect demonstrates the importance of knowing the full spectrum of aeroallergens to which a patient responds and seasonal variations in allergic symptoms, and provides the rationale to consider initiating effective anti-inflammatory therapies before the pollen season or before other chronic or repetitive aeroallergen exposures.

Seasonal and perennial allergic rhinitis

15. Seasonal allergic rhinitis is caused by an IgE-mediated reaction to seasonal aeroallergens. The length of seasonal exposure to these allergens is dependent on geographic location and climatic conditions. **C**
16. Perennial allergic rhinitis is caused by an IgE-mediated reaction to perennial environmental aeroallergens. These may include dust mites, molds, animal allergens, or certain occupational allergens, as well as pollen in areas where pollen is prevalent perennially. **C**

Symptoms of allergic rhinitis may include paroxysms of sneezing, nasal pruritus and congestion, clear rhinorrhea, and palatal itching. The conjunctiva,[611] eustachian tubes, middle ear, and paranasal sinuses may also be involved.

Allergic rhinitis is associated with ear fullness and popping, itchy throat, and pressure over the cheeks and forehead. Malaise, weakness, and fatigue may also be present. Allergic rhinitis often begins during childhood and may coincide with or precede development of allergic asthma.[722] A positive family history of

atopy is associated with development of allergic rhinitis in childhood.[723]

When not all the typical rhinitis symptoms are expressed, the diagnosis is more difficult to make. Nasal airflow obstruction, a major symptom of seasonal or perennial allergic rhinitis, is associated with nasal eosinophilic inflammation.[89] Distinct temporal patterns of symptom production may aid diagnosis. Symptoms of rhinitis that occur whenever the patient is exposed to a furry pet suggest IgE mediated sensitivity to that pet. Patients who are exquisitely sensitive to animal proteins may develop symptoms of rhinitis and asthma when entering a house or laboratory even though the animal is no longer present. Children who own pets can passively transfer cat allergen on their clothing into schools and may contribute to high levels of ambient cat allergen in classrooms.[724] Seasonal and perennial forms of allergic rhinitis often coexist in the same individual. Symptoms may be chronic and persistent, and patients may present with secondary complaints of mouth-breathing, snoring, or symptoms of sinusitis.[725] Severe allergic rhinitis has been associated with diminished QOL, disordered sleep (in as many as 76% of patients), and impairment in work performance.[10,179,726]

Seasonal allergic rhinitis symptoms typically appear during a defined season in which aeroallergens are abundant in the outdoor air. The length of seasonal exposure to these allergens is dependent on geographic location and climactic conditions.[727,728] Familiarity with the pollinating season of the major trees, grasses, and weeds of the locale makes the syndrome easier to diagnose.[729-731] Certain outdoor mold spores also display seasonal variation, with highest levels in the summer and fall months.[732] Tree (eg, birch, oak, maple, and mountain cedar), grass (eg, timothy and Bermuda), and weed (eg, ragweed) pollens and fungi (eg, *Alternaria*, *Aspergillus*, and *Cladosporium*) are common seasonal allergens.[733] Hyperresponsiveness to irritant triggers such as chlorine is enhanced among patients with seasonal allergic rhinitis.[67,734,735]

In studies of seasonal allergic rhinitis, a correlation between the daily pollen count and overall daily symptom score and medication score has been found.[736] Nasal sensitivity to seasonal pollen allergens increases as the pollen season progresses because of the priming phenomenon.[719] As a consequence of priming, at the end of the pollen season, nasal symptoms may decline more slowly than the pollen counts.[737] Individual host sensitivity to an aeroallergen may influence the intensity of symptoms. The levels of pollen counts that cause symptoms may vary with an individual's degree of sensitivity and with different pollens.[738,739] Indoor allergens responsible for perennial allergic rhinitis are present in the environment throughout the year.[740,741]

Both research and clinical experience support the concept that allergic rhinitis and allergic conjunctivitis may exist in rare patients with negative skin tests and/or *in vitro* tests for specific IgE.[241,742-745] A patient with a compelling history of symptoms after exposure to an allergen can have a positive nasal challenge with that allergen despite negative skin tests and/or *in vitro* tests for specific IgE antibody. Studies have shown that patients with allergic rhinitis symptoms after exposure to house dust have been found to have local inflammation, nasal IgE production, and a positive response to a nasal allergen provocation test with *Dermatophagoides pteronyssinus*, despite having negative skin tests and specific IgE to *D pteronyssinus*.[241,742,743] Further research is needed to determine what allergens are capable of producing this type of reaction, the prevalence of this condition, the mechanism responsible for local allergic antibodies, and the optimal treatment for these patients.

Allergic conjunctivitis

17. Allergic rhinitis is often accompanied by symptoms of allergic conjunctivitis. **C**
18. Many treatments used for allergic rhinitis can benefit associated symptoms of allergic conjunctivitis, and a variety of topical ophthalmic agents is useful for specific treatment of associated ocular symptoms.
19. Intranasal corticosteroids, oral antihistamines, and intranasal antihistamines have similar effectiveness in relieving ocular eye symptoms associated with rhinitis.

Allergic rhinitis is often accompanied by allergic conjunctivitis (a disease complex sometimes referred to as allergic rhinoconjunctivitis) that produces conjunctival injection and chemosis associated with symptoms of itchy eyes and tearing.[43] Estimates of the prevalence and severity of conjunctival symptoms associated with allergic rhinitis vary depending on the aeroallergen, geographic region, and other factors. In 1 seasonal allergic rhinitis study, allergic conjunctivitis symptoms were reported in more than 75% of patients.[746] Sensitivity to pollens is more frequently associated with rhinoconjunctivitis, whereas sensitivity to house dust mites (*D pteronyssinus*, *Dermatophagoides farinae*) is reported to cause less ocular symptoms.[739]

The Joint Task Force is developing a complete Parameter on Diagnosis and Treatment of Allergic Conjunctivitis that will provide more comprehensive discussion than the more limited statements on allergic conjunctivitis in this Rhinitis Parameter. A complete review of the differential diagnosis of conjunctivitis is beyond the scope of this document. Ocular allergy may include seasonal and perennial allergic conjunctivitis discussed here, but also 2 vision-threatening disorders, atopic keratoconjunctivitis (associated with eczematous lesions of the lids and skin) most commonly seen in older adult patients, and vernal keratoconjunctivitis (chronic inflammation of palpebral conjunctiva), seen most commonly seen in the pediatric and adolescent age groups with a male predominance. In seasonal and perennial allergic conjunctivitis associated with allergic rhinitis, both eyes are typically affected, and itching is usually a prominent symptom.[747]

Oral antihistamines, intranasal antihistamines, oral anti-LT agents, intranasal corticosteroids, and allergen immunotherapy are treatments for allergic rhinitis that have been reported to relieve associated ocular allergy symptoms in controlled trials.[37-43,46-54] In systematic reviews of randomized controlled studies, intranasal corticosteroids compared with oral antihistamines[53,54,748] and intranasal corticosteroids compared with intranasal antihistamines[46] were not significantly different in relieving eye symptoms. In placebo-controlled studies of adults, fluticasone furoate nasal spray has been demonstrated to reduce significantly ocular symptoms associated with seasonal allergic rhinitis.[44,45,749]

Use of cold compresses and irrigation with saline solution or artificial tears has been advocated to relieve mild symptoms of allergic conjunctivitis. A variety of topical ophthalmic agents are indicated for specific treatment of itching or symptoms of allergic conjunctivitis. These include medications listed in Table XIII and can be summarized by the following categories.

TABLE XIII. Topical ophthalmic preparations for ocular allergy symptoms

Classification	Drug (trade names)
Vasoconstrictor	Naphazoline (AK-Con, Albalon, Allerest, All-Clear, Antazoline-V, Naphcon, Clear Eyes, Comfort Eye Drops, Degest, Estivin II, Ocu-Zoline, Vasocon, VasoClear)
	Tetrahydrozoline (Visine)
Antihistamine	Emedastine (Emadine)
	Levocabastine (Livostin)
Combination antihistamine/vasoconstrictor	Antazoline (Vasocon-A)
	Pheniramine (Visine-A, Naphcon-A, Opcon-A, Nafazair-A)
Mast cell stabilizer	Cromolyn (Opticrom, Crolom)
	Lodoxamide (Alomide)
	Nedocromil (Alocril)
	Pemirolast (Alamast)
NSAID	Ketorolac (Acular)
Dual action agent (antihistamine and mast cell stabilizer)	Azelastine (Optivar)
	Epinastine (Elestat)
	Ketotifen (Alaway, Zaditor)
	Olopatadine (Pataday, Patanol)
Corticosteroid	Loteprednol etabonate (Alrex)

- Vasoconstrictors are available in OTC preparations and are indicated for relief of ocular redness, although they do not reduce the allergic response. Prolonged use of ocular decongestants may lead to rebound hyperemia or conjunctivitis medicamentosa,[55] although use limited to 10 days does not appear to induce this.[56]
- Antihistamines (H1-receptor antagonists) are available in OTC and prescription ophthalmic preparations and are sometimes combined with a topical vasoconstrictor for acute relief of ocular allergy symptoms. The combination of an antihistamine and a vasoconstrictor works better than either agent alone.[57]
- Mast cell stabilizers have a slow onset of action and may require several days of treatment before optimal symptom relief is achieved,[58] making them more suitable for prophylactic or longer-term treatment of chronic ocular allergies than for acute symptom relief. They are also approved for chronic ocular allergy conditions involving corneal defects including vernal keratoconjunctivitis and atopic keratoconjunctivitis.
- Topical NSAIDs reduce prostaglandin production involved in mediating ocular allergy. Ketorolac is indicated for temporary relief of ocular itching caused by seasonal allergic conjunctivitis.[59]
- Multiple-action agents possess both antihistamine and mast cell stabilizer activities, generally have onset of action within 30 minutes, and are suitable for acute and longer-term treatment of allergic conjunctivitis symptoms.
- Ocular corticosteroids should be reserved for more severe symptoms of allergic conjunctivitis in consideration that ocular side effects from their use can be vision-threatening, and include cataract formation, elevated IOP, and secondary infections. The modified steroid loteprednol is indicated for the temporary relief of symptoms and signs of seasonal allergic conjunctivitis and has a greatly reduced risk of causing increased IOP compared with many other ocular corticosteroids.[60-64]

Oral antihistamines are generally less effective in relieving ocular allergy symptoms than topical ophthalmic agents and have slower onset of action.[750-752] Although comparative efficacy trials of topical ophthalmic agents in real-life settings are generally lacking, studies performed in environmental challenge chambers or using acute ocular allergen challenges have generally demonstrated that dual action ophthalmic agents are more effective in preventing or treating ocular itching than other ocular agents.[753-756] Oral agents have also been associated with excessive drying of the tear film.

Nonallergic rhinitis

20. Nonallergic rhinitis is characterized by periodic or perennial symptoms of rhinitis that are not a result of IgE-dependent events. Examples of nonallergic rhinitis are infectious rhinitis, vasomotor rhinitis, and NARES. **C**

Vasomotor rhinitis

21. Vasomotor rhinitis (idiopathic rhinitis) accounts for a heterogeneous group of patients with chronic nasal symptoms that are not immunologic or infectious in origin and is usually not associated with nasal eosinophilia. **D**

Vasomotor rhinitis is unrelated to allergy, infection, structural lesions, systemic disease, or drug abuse. Although the term *vasomotor* implies increased neural efferent traffic to the blood vessels supplying the nasal mucosa, this has never been proven. Subjects with predominant rhinorrhea (sometimes referred to as *cholinergic rhinitis*) appear to have enhanced cholinergic glandular secretory activity because atropine effectively reduces their secretions.[65] Subjects with predominantly nasal congestion and blockage may have nociceptive neurons that have heightened sensitivity to innocuous stimuli.

The term *vasomotor rhinitis* has been used loosely to describe the condition of patients with perennial rhinitis whose symptoms are intensified by changes in temperature or relative humidity, alcohol, and odors such as bleach, perfume, or solvents. Other triggers include tobacco smoke, dusts, automotive emission fumes, and nonspecific irritant stimuli such as chlorine.[67] Cold dry air and exercise may also trigger symptoms.[68,69,757] The symptoms are variable, consisting mainly of nasal obstruction and increased secretion. Sneezing and pruritus are less common. Although the term *vasomotor* implies increased neural efferent traffic to the blood vessels supplying the nasal mucosa, this has never been proven. A lack of change in nasal compliance after administration of nasal oxymetazoline compared with normal subjects lends support to the hypothesis that vasomotor rhinitis may be attributable to autonomic dysfunction.[758]

Rhinitis from food ingestion

22. Rhinitis may occur after ingestion of foods or alcoholic products. This may be a result of vagally mediated mechanisms, nasal vasodilation, food allergy, and/or other undefined mechanisms. Food allergy is a rare cause of rhinitis without associated gastrointestinal, dermatologic, or systemic manifestations. **B**

Foods can provoke rhinitis symptoms by a variety of different mechanisms.[759,760] Ingested food allergens rarely produce

isolated IgE-mediated rhinitis without involvement of other organ systems. Urticarial rash, facial or lip swelling, or bronchospasm strongly suggest an IgE-mediated reaction.[761] In a large group of children undergoing double-blind, placebo-controlled food challenges, nasal symptoms developed in 70% of the positive challenges.[762,763] In that study, the most common food allergens confirmed in respiratory tract symptoms included egg, cow's milk, peanut, soy, fish, shellfish, and tree nuts. In contrast, rhinitis may occasionally be reported in unusual food allergens—for example, 2 of 43 patients reporting rhinitis with kiwi allergy.[764] In another descriptive study that did not include double-blind, placebo-controlled food challenges, rhinitis or conjunctivitis accounted for 5.7% of the total symptoms reported.[765] In adults, food skin tests may be appropriate in occasional cases if a careful history suggests food-related rhinitis symptoms, particularly if rhinitis symptoms are associated with other systemic symptoms. Although a variety of opinions have been expressed in the literature,[25,759-762,766-770] there are few or no credible data available to justify routine performance of food skin tests in the evaluation of rhinitis in adults. In the evaluation of rhinitis in children, in whom the history may be more difficult to interpret and food allergy is more common, there is greater justification to consider performance of limited food skin testing. Beer, wine, and other alcoholic drinks may produce symptoms by nasal vasodilation. Alcohol-induced hypersensitivity symptoms are also more prevalent in persons with allergic rhinitis and asthma.[70] The syndrome of watery rhinorrhea occurring immediately after ingestion of foods, particularly hot and spicy foods, has been termed *gustatory rhinitis* and is vagally mediated.[66]

Infectious rhinitis

23. Infectious rhinitis and rhinosinusitis may be acute or chronic. Acute infectious rhinitis is usually a result of 1 of a large number of viruses, but secondary bacterial infection with sinus involvement may be a complication. Symptoms of acute infectious rhinosinusitis include nasal congestion, mucopurulent nasal discharge, pain and pressure, headache, olfactory disturbance, postnasal drainage, and cough. **C**

Acute rhinitis is usually associated with a viral upper respiratory infection and frequently presents with rhinorrhea, nasal obstruction, and fever. Initially, viral rhinitis is characterized by clear, watery rhinorrhea that is accompanied by sneezing and nasal obstruction. Edema of the nasal mucosa produces occlusion of the sinus ostia with resulting facial pain or of the eustachian tube with resulting ear fullness. The nasal drainage may become cellular and cloudy due to the presence of organisms, white blood cells, and desquamated epithelium. Responsible viruses include rhinoviruses, respiratory syncytial virus, parainfluenza, influenza, and adenoviruses. Unless there is bacterial superinfection (<2% of the time),[75,76] the condition is self-limiting and usually resolves within 7 to 10 days. Acute bacterial rhinosinusitis may occur *de novo* or may follow viral rhinitis. Nasal obstruction, cloudy drainage, vestibular crusting, and facial pain occur. Not all patients report fever. Bacteria frequently recovered from nasal or sinus cultures include *Streptococcus pneumoniae, Moraxella catarrhalis*, and *Haemophilus influenzae*.[771]

Prominent symptoms reported by patients with chronic rhinosinusitis include nasal congestion, sinus congestion, nasal discharge, headache, fatigue, and change in olfaction.[772] Although nearly 50% of patients diagnosed with chronic rhinosinusitis exhibit no growth on culture, in sinus puncture studies the most frequently isolated organisms are *H influenzae, Staphylococcus aureus,* and *Pseudomonas aeruginosa*.[773] In patients with immunodeficiency, HIV positivity, or AIDS, mycobacterial, fungal, and other opportunistic organisms may be involved.

The symptoms of allergic rhinitis are frequently confused with infectious rhinitis when patients complain of a constant cold. Purulent nasal drainage may be present in either infectious or noninfectious rhinitis. Symptoms persisting longer than 2 weeks should prompt a search for causes other than infection. Foreign body rhinitis should be considered in the differential diagnosis, especially in children. Symptoms may be acute or chronic, unilateral or bilateral, and the nasal discharge may be bloodstained or foul smelling.

Exacerbations of rhinitis symptoms with predominant clear rhinorrhea in patients with a known history of allergic rhinitis may prove to be a diagnostic challenge. The distinction between active infection and allergy should be made. When the history or physical examination is not diagnostic, a nasal smear may be obtained to aid in differentiation. Early in rhinovirus infections, there is an increase in vascular permeability that is likely a result of bradykinin. Later, there may be an increase in glandular secretion, particularly of locally synthesized secretory IgA.[774] Neutrophilic infiltrates may be present in rhinoviral and other viral rhinitis syndromes.

Physical examination findings in both acute and chronic sinusitis may include sinus tenderness on palpation, mucosal erythema, purulent nasal secretions, increased pharyngeal secretions, and periorbital edema. Furthermore, because these symptoms tend to overlap with those of perennial rhinitis, there is a frequent need to perform imaging studies to assist in the differential diagnosis. Nasal cytology may be useful, but the clinical value is limited by low specificity and sensitivity. Although the absence of neutrophils argues against infection, neutrophils may be present in both acute and chronic sinusitis and may be noted alongside eosinophils in allergic rhinitis during acute sinusitis (see ''The Diagnosis and Management of Sinusitis: A Practice Parameter Update''[77] for more detail).

Allergy, mucociliary disturbance, and immune deficiency may predispose certain individuals to the development of more frequent acute[775] or chronic infections. Mucociliary abnormalities may be congenital (eg, PCD, Young syndrome, CF) or secondary to infection.[776,777]

Infectious rhinitis in children

24. Viral infections account for as many as 98% of acute infectious rhinitis and the majority of rhinitis symptoms in the young child. Routine nasopharyngeal cultures when bacterial infections are suspected do not add diagnostic value. **C**

Viral rhinitis, starting in the neonatal period, averages about 3 to 8 episodes per year in children and accounts for the majority of infectious rhinitis.[77,778] The progression from viral rhinitis to secondary bacterial rhinitis occurs in approximately 10% of children and adults.[72-74] These bacterial infections may progress to acute sinusitis and otitis media.[779] Although it is generally accepted that atopic-prone infants and young children compared with their lower-risk cohorts appear to experience more episodes of otitis media and sinusitis,[77] not all research supports this conclusion.[85,86] Primary bacterial rhinitis, although uncommon, may occur in the newborn because of congenital syphilis with

characteristic rhinorrhea followed by ulceration. Primary localized bacterial rhinitis may also occur during β-hemolytic streptococcal infections, particularly when scarlet fever is present (50% prevalence).[93] Secondary bacterial rhinitis with or without sinusitis occurs more frequently in children with antibody, complement, and leukocyte deficiency disorders; hyper-IgE syndrome; structural defects (eg, cleft palate and osteopetrosis); and CF. In CF, *S aureus* and *P aeruginosa* are important pathogens in infectious rhinitis. Children with normal immunity may also develop secondary bacterial rhinitis with *S aureus* infection manifesting as impetigo of the anterior nares with characteristic crusting and irritation. Purulent rhinorrhea, especially if unilateral, persistent, bloody, or malodorous, may suggest an intranasal foreign body.[93] Culturing the nasal pharynx of normal children without visualization is of limited value because pathogenic bacteria within the nasal pharynx have been recovered in as many as 92% of asymptomatic healthy children.[93] However, a recent meta-analysis as well as individual clinical studies have demonstrated that endoscopically directed middle meatus cultures is a highly sensitive and accurate culture method for acute bacterial rhinitis/sinusitis in adults and might be considered in the older child.[94-97]

Differentiating allergic rhinitis from infectious rhinosinusitis or adenoiditis may be difficult especially in children, because the symptoms overlap and even purulent nasal drainage may be present in noninfectious rhinosinusitis. Careful consideration of the need for antimicrobial use is increasingly important because antibiotic use has been causally related to the development of bacterial drug resistance.[78-82] Furthermore, the administration of antimicrobials increases the carriage of antimicrobial-resistant strains of certain bacterial pathogens, such as *S pneumoniae,* especially in children.[78,79,83,84]

NARES

25. NARES is characterized by nasal eosinophils in patients who have perennial symptoms and occasionally reduced sense of smell. These patients often lack evidence of allergic disease as demonstrated by absence of positive skin tests and/or specific IgE antibodies in the serum. **C**

In NARES, individuals experience perennial symptoms of sneezing paroxysms, profuse watery rhinorrhea, nasal pruritus, and occasional loss of smell.[101,780] Patients with NARES are at risk for development of obstructive sleep apnea.[104] They are typically middle-age and have a characteristic perennial course but with paroxysmal episodes. NARES occurs extremely infrequently in childhood and probably accounts for less than 2% of children with nasal eosinophilia.[781] The prevalence of this syndrome in the general population is unknown.

The etiology of the syndrome is obscure but may be an early stage of nasal polyposis and aspirin sensitivity.[103] NARES is characterized by large numbers (inconsistently defined as >5% to >20%) of eosinophils on nasal smear.[98-100,102,782] Similar to findings in patients with allergic rhinitis, mast cells with bound IgE and elevated tryptase have been detected in nasal mucosal biopsies of patients with NARES.[783] Patients commonly lack evidence of allergic disease as determined by skin testing and/or determination of *in vitro* aeroallergen specific IgE assays.

Occupational rhinitis

26. Occupational rhinitis is rhinitis arising in response to airborne substances in the workplace, which may be mediated by allergic or nonallergic factors, such as laboratory animal antigen, grain, wood dusts, chemicals, and irritants. It often coexists with OA. **C**

Occupational rhinitis may be defined as inflammation of the nasal mucosa resulting in nasal symptoms caused by exposures in the workplace. The concept of ''the united airway'' is likely applicable to occupational rhinitis in which the respiratory mucosa forms a continuum from the nose to the lower airways,[784] whereby nasal inflammatory responses triggered by exposure to occupational sensitizers are associated with parallel inflammatory responses in the lower airways.[112] Occupational rhinitis may be caused by direct effects of respiratory irritants or via immunologic mechanisms. Irritant exposures encountered in the workplace to agents such as grain dust constituents (eg, endotoxin), flour dust, fuel oil ash, and ozone elicit neutrophilic inflammation of the nasal mucosa.[107-109] Alternatively, IgE-mediated sensitization and rhinoconjunctival symptoms may result from occupational exposure to protein allergens including flour, laboratory animals (rats, mice, guinea pigs, and so forth), animal products, coffee beans, natural rubber latex, storage mites, mold spores, pollen, psyllium, enzymes, and many other substances.[105,106] In workers with IgE-dependent sensitization to proteins (eg, flour, laboratory animals, and natural rubber latex), eosinophils, basophils, ECP, and tryptase are significantly increased in nasal lavage after nasal allergen challenge.[111-113] Some chemicals such as acid anhydrides, platinum salts, and chloramine may cause IgE-mediated occupational rhinitis.[114,785] After nasal challenge with hexahydrophthalic anhydride, an acid anhydride, increased eosinophils and neutrophils have been identified in nasal lavage fluid.[114] Immunologic mechanisms may be important for other chemical sensitizers (eg, glutaraldehyde and diisocyanates) that cause occupational rhinitis and OA even though specific IgE is not detected consistently.[786,787]

The incidence of occupational rhinitis attributable to specific substances may depend entirely on the nature of industrial exposures encountered in a given geographical region. For example, the relative risk of occupational rhinitis in Finland, which has many agricultural industries, was highest among furriers, bakers, and livestock breeders.[788] The prevalence of occupational rhinitis is essentially 100% among workers with OA who are sensitized to high-molecular-weight protein allergens, whereas only 50% of those with OA caused by chemicals have been identified with work-related rhinitis.[110] The prevalence of work-related rhinoconjunctival symptoms is frequently reported by laboratory animal handlers (24%), although concomitant SPT reactivity to laboratory animal allergens is demonstrated in only a minority (9.6%) of symptomatic workers,[106,789] suggesting that nonallergic factors may also be important. Airborne exposure to endotoxin is commonly detected in animal housing facilities and has been considered as a potential cause of occupational rhinitis, although current evidence is lacking to support effects in animal workers.[789] Occupational rhinitis may precede or accompany the development of OA. Atopy and intensity of exposure are risk factors for developing occupational rhinitis.[115]

Symptoms may occur acutely at work after intermittent exposure or more chronically at work after continuous exposure. Occupational rhinitis should be suspected in patients with nasal symptoms, which are temporally related to exposure at work and often improve away from the workplace. An asymptomatic latency period of exposure lasting weeks to years often precedes

work-related symptoms caused by occupational respiratory sensitizers.[105,116] Skin prick testing may confirm sensitization if appropriate and if suitable reagents are available. Occupational rhinitis has been evaluated with nasal allergen challenge methods that measure prechallenge and postchallenge symptoms scores, nasal lavage cells, and mediators as well as nasal airflow; however, their diagnostic validity has not been evaluated.[112,114]

Irritant-induced rhinitis in an occupational setting, referred to as *reactive upper-airways dysfunction syndrome* (RUDS), is a chronic rhinitis syndrome triggered acutely by high-level exposure to irritants. Chronic RUDS has been reported among fire fighters exposed to complex mixtures of airborne pollutants during the World Trade Center disaster.[790,791] Exposed workers present acutely with nasal burning, hypersecretion of mucus, and nasal congestion.[792] Because there is insufficient information regarding the natural history and diagnosis of RUDS, the condition is poorly defined, and further study is required.

Optimal management of occupational rhinitis is avoidance of the occupational trigger by modifying the workplace, using filtering masks, or removing the patient from the adverse exposure. Pharmacologic therapy as discussed in earlier sections can be instituted, recognizing that chronic use of medication will probably be required. Strategies to prevent or reduce symptoms may include the daily use of intranasal corticosteroids or the administration of antihistamines and/or intranasal cromolyn immediately before allergen exposure. It is also important to institute avoidance measures for nonoccupational (and occupational) allergens that may contribute to rhinitis symptoms. Specific immunotherapy (SIT) is a possible treatment option for IgE-dependent occupational rhinitis to occupational protein allergen. Immunotherapy could be considered when 1 or a few allergens have been linked clinically to disease, avoidance of the triggering allergens is impossible, a commercial allergen extract is available, and efficacy and safety have been demonstrated to the treatment allergens. For example, SIT with pollen extracts may benefit outdoor workers with seasonal allergic rhinitis, and SIT with standardized cat allergen extract may decrease occupational symptoms among sensitized animal workers.[503,793] Trials of subcutaneous SIT have been conducted in workers with natural rubber latex allergy but failed clearly to demonstrate acceptable safety and/or efficacy.[117] Immunotherapy is not appropriate to treat occupational rhinitis caused by low-molecular-weight chemical antigens.

Hormonal-induced rhinitis

27. Causes of hormonal rhinitis include pregnancy and menstrual cycle–related rhinitis. Pregnancy rhinitis, when present, is associated with sigtnificant nasal congestion, starts after the second month of pregnancy, and usually disappears within 2 weeks after delivery. **C**

Rhinitis symptoms are common during pregnancy.[595,596,604,609,614,687,794] The most common causes of nasal symptoms during pregnancy are allergic rhinitis, sinusitis, rhinitis medicamentosa, and vasomotor rhinitis of pregnancy. Allergic rhinitis worsens in approximately 1/3 of pregnant patients.[118] Sinusitis has been reported to be 6 times more common in pregnant than nonpregnant women.[795] Nasal vascular pooling caused by vasodilation and increased blood volume may account for worsening allergic rhinitis and increased sinusitis during pregnancy.[119] The development of a type of rhinitis unique to the pregnant patient is referred to as *vasomotor rhinitis of pregnancy* or *pregnancy rhinitis*. It has been suggested that pregnancy rhinitis be defined as rhinitis without an infectious, allergic, or medication-related cause that starts before the last 6 weeks of pregnancy, persists until delivery, and resolves completely within 2 weeks after delivery.[120] It has been suggested that when pregnancy rhinitis causes snoring, it may even be a factor in the development of pre-eclampsia.[121] Elevated progesterone, estrogen, prolactin, vasoactive intestinal peptide, and/or placental growth hormone levels during pregnancy have been associated with a number of secondary phenomena. They include nasal mucosal swelling caused by vascular pooling of blood and vascular leaking of plasma into the stroma as well as the increase in glandular secretion and nasal vascular smooth muscle relaxation.[120,609,796] However, there is no convincing evidence that any of these hormones contribute directly to pregnancy rhinitis.[120] Pregnancy rhinitis may respond in milder cases to exercise, head of bed elevation, nasal alar dilatation, and saline rinses. Although there is no research on the safety of short-term topical decongestants combined with intranasal corticosteroids in pregnancy, these have been suggested for management of pregnancy rhinitis when the measures discussed are not effective.[120,797]

During the menstrual cycle, nasal congestion has been shown to concur with ovulation and rise in serum estrogens, although additional evidence supporting this relationship is lacking.[122]

Drug-induced rhinitis

28. Drug-induced rhinitis may be caused by a number of medications, including ACE inhibitors, phosphodiesterase-5–selective inhibitors, phentolamine, α-receptor antagonists, aspirin, and other NSAIDs. Rhinitis medicamentosa is a syndrome of rebound nasal congestion that follows the overuse of intranasal α-adrenergic decongestants or cocaine. **C**

Medications may induce symptoms of nasal congestion and/or rhinorrhea. In the past, antihypertensive medications (eg, reserpine and guanethidine) were frequently incriminated, but they are no longer commonly used. Currently, ACE inhibitors[798] and β-blockers[799] occasionally elicit rhinitis symptoms.[123] Rhinitis symptoms are often caused by α-receptor antagonists used in treatment of benign prostatic hypertrophy (eg, prazosin, terazosin).[124] Phosphodiesterase-5–selective inhibitors used for treatment of erectile dysfunction can cause nasal congestion.[125] Phentolamine mesylate, an α-1 and α-2–selective adrenergic receptor antagonist, has been reported to cause rhinitis symptoms in 7.7% of patients treated for erectile dysfunction.[800]

Although oral contraceptives have long been implicated as causes of nasal symptoms, a recent study found no nasal physiologic effects on female patients receiving a modern combined oral contraceptive pill.[126] Aspirin and NSAIDs may produce rhinorrhea as an isolated symptom or as part of a symptom complex of rhinosinusitis, nasal polyposis, and asthma.[127,128]

Prolonged usage of α-adrenergic decongestants may lead to a hypertrophy of the nasal mucosa termed *rhinitis medicamentosa*. The repetitive and prolonged use of topical α-adrenergic nasal decongestant sprays may induce rebound nasal congestion on withdrawal. These agents include OTC products containing oxymetazoline or phenylephrine. Benzalkonium chloride in vasoconstrictor spray products may augment local pathologic effects.[801] Also, patients may develop tachyphylaxis because of the need

for more frequent doses to provide adequate decongestion. The nasal mucosa is often beefy red, appears inflamed, and shows areas of punctate bleeding and scant mucus. There is loss of ciliated epithelial cells leading to reduced mucociliary clearance.[133] Nasal septal perforation is a rare complication.[134] Similar consequences may occur with prolonged use of other vasoconstrictor agents such as cocaine.

Atrophic rhinitis

29. Treatment of primary and secondary atrophic rhinitis involves reducing crusting and alleviating the foul odor by continuous nasal hygiene, such as nasal lavage and crust debridement, and the use of topical and/or systemic antibiotics when purulent secretions or an acute infection is present.

Primary (idiopathic) atrophic rhinitis, more prevalent in developing countries with warm climates,[136,802] is a chronic condition characterized by progressive atrophy of the nasal mucosa, nasal crusting, nasal dryness (caused by atrophy of glandular cells), and fetor.[136,137] The nasal cavities appear abnormally wide on examination, and squamous metaplasia, atrophy of glandular cells, and loss of pseudostratified epithelium have been detected in nasal biopsies.[803] The sinus CT shows the characteristic resorption of underlying bone and the absence of identifiable turbinates, a finding referred to as the ''empty nose syndrome.''[138] The dryness and reduction of nasal mucosal tissue with the resultant resistance to airflow are, paradoxically, perceived by patients as severe nasal congestion. The etiology of primary atrophic rhinitis has not yet been established. *Klebsiella ozaenae* and other bacteria including *S aureus, Proteus mirabilis,* and *Escherichia coli* may be causative, although it is also plausible that these secondarily infect previously damaged nasal mucosa.[138] A genetic association has also been suggested[804] but needs further confirmation.

Primary atrophic rhinitis should be separated from secondary atrophic rhinitis, which develops as a direct result of other primary conditions, such as chronic granulomatous disorders, chronic sinusitis, excessive surgery to the nasal turbinates, trauma, and irradiation.[138] Although secondary atrophic rhinitis may be less severe and progressive, treatment of primary and secondary atrophic rhinitis is aimed at reducing crusting and alleviating the foul odor. There are no controlled trials evaluating therapies for atrophic rhinitis. Although even the published observational data are limited, the mainstay of treatment is continuous nasal hygiene—for instance, intranasal irrigations[139] with saline or sodium bicarbonate solution, and periodic debridement of the crusts, if necessary. As used for recalcitrant rhinitis and sinusitis,[140] adding antibiotics such as mupirocin to the lavage solution has been suggested for purulent secretions. Systemic antibiotics are indicated when an acute infection is present.

Nasal polyps

30. Nasal polyps may occur in conjunction with chronic rhinitis or sinusitis and may contribute significantly to the patient's symptoms. Nasal polyps should always be considered in the differential diagnosis of patients who present with invariant nasal congestion and/or anosmia and its sequelae. Allergy as a cause of nasal polyps has not been established, but nasal polyps may occur in conjunction with allergic rhinitis. **C**

Nasal polyposis is an inflammatory condition of the nasal and sinus mucosa and usually presents as persistent nasal obstruction. Nasal polyps have a prevalence of 2% to 4%[141-143] in the general as well as the allergic population[143] and usually occur after age 40 years.[143] Although previous studies showed a 2:1 male to female prevalence of nasal polyps,[142,144,145] a recent large population study showed no sex preference.[143] Frequently reported symptoms are rhinorrhea (39%), nasal congestion (31%), and anosmia (29%).[805] Chronic nasal polyposis has been associated with reduced QOL and greater risk of sleep disturbances.[806]

Nasal polyps may occur in as many as 50% of children with CF, in immotile cilia syndrome, and in 7% to 15% of adults with asthma.[807-809] Nasal polyps coupled with AERD are rarely noted before the adolescent years. The profile of inflammatory mediators (eg, myeloperoxidase and IL-8) and prominent numbers of neutrophils found in nasal polyps of patients with CF differ from increased eosinophils and associated mediators (eg, IL-5, eotaxin, ECP) detected in adults with non-CF polyps, suggesting that these are different disorders.[803,810] AERD is recognized in 13% of patients with nasal polyposis.[809] In adult patients without CF, the pathogenesis of nasal polyposis is uncertain. Infiltrates of eosinophils, T cells, plasma cells, and mast cells are consistent findings in nasal polyp tissue and may explain why corticosteroids are therapeutically effective.[128] When associated with asthma, patients with nasal polyposis hyperexcrete urinary LTE_4,[148] suggesting that overproduction of cysLTs may play a pathogenetic role. Reduced apoptosis of eosinophils in nasal polyp tissue has been demonstrated, which could enhance tissue inflammation and growth of nasal polyps.[811] Allergy does not appear to predispose to polyp formation. Between 10% and 15% of patients with allergic rhinitis also have nasal polyps.[698] The noses and sinuses of patients with chronic rhinosinusitis and nasal polyps are frequently colonized with fungi (principally *Aspergillus* and *Penicillium*).[812] Allergic fungal sinusitis is a distinct pathologic entity defined by specific IgE for *Aspergillus*, *Bipolaris*, or other mold antigens; chronic sinusitis with nasal polyposis; radiographic sinus opacification and eosinophilic mucin material containing eosinophilic debris; and fungal hyphae in tissue resected from the sinuses.[813,814] Proinflammatory mediators including eosinophilic major basic protein and neutrophil elastase have been identified in allergic mucin.[815] The efficacy of local or systemic antifungal therapy in treating allergic fungal sinusitis has not been established.[812]

The treatment and control of nasal polyps is challenging. Sinus disease and nasal polyps are more difficult to control in patients with asthma and AERD.[809] Intranasal corticosteroids are effective in improving sense of smell and reducing nasal congestion, and effects are optimized with twice-daily versus once-daily dosing.[816] For severe nasal polyposis, a short course of oral prednisone is effective in reducing symptoms and polyp size and improving nasal flow. The beneficial effects are then maintained by subsequent administration of maintenance intranasal corticosteroids.[149,150,151] Subjective improvement in nasal polyp symptoms has been observed in patients administered the LT modifiers montelukast, zafirlukast, and zileuton as add-on therapy to intranasal corticosteroids.[152,153] After sphenoidal ethmoidectomy, recurrence rates and rescue medication requirements in patients treated with montelukast were equivalent to those observed in patients receiving postoperative nasal beclomethasone.[154] In recent years, functional endoscopic sinus surgery has been used extensively for treating rhinosinusitis associated with nasal polyposis. Patients with AERD and nasal polyps have worse outcomes with functional endoscopic sinus surgery

than aspirin-tolerant patients.[817] In patients with nasal polyposis and AERD, aspirin desensitization followed by long-term daily aspirin treatment may be considered. Long-term studies of patients with AERD suggest that maintenance aspirin therapy may reduce nasal symptoms, frequency of sinus infections, requirement for nasal polypectomies, and need for systemic corticosteroids.[155,156] The numbers of nasal mucosal leukocytes expressing cysLT receptors (cysLT1), which are increased in nasal mucosa of patients with AERD, decrease after aspirin desensitization.[157]

Other conditions that may be confused with rhinitis

Anatomic abnormalities

31. Signs and symptoms suggestive of rhinitis can be produced by other conditions, including nasal septal deviation, tumors, and hypertrophy of the nasal turbinates. **C**
32. In infants and young children, nasal congestion or obstruction can result from structural problems, such as cleft palate and adenoidal hypertrophy, or functional problems, such as laryngopharyngeal reflux. **D**

Nasal obstruction may be caused by congenital or acquired anatomic abnormalities, which may mimic symptoms of rhinitis. Reduced airflow through the nasal passages in infants may be a result of congenital choanal atresia. Nasal septal deviation and nasal turbinate or adenoidal hypertrophy many block flow of nasal secretions, leading to rhinorrhea or postnasal drip, as well as causing nasal blockage.

Although comparatively rare, both benign and malignant tumors may cause rhinitis symptoms.[158,159] Lesions generally cause unilateral occlusion of the nasal airway. Rapidly growing nasal malignancies may cause nasal obstruction early in the disease. Lesions arising in the maxillary sinus present with nasal symptoms in the late stages of the disease, usually after the tumor has penetrated the medial wall of the antrum. These tumors may present with bleeding, hyposmia or anosmia, pain, and/or otalgia. Prolonged occupational exposure to chemicals such as nickel and chrome have been associated with carcinoma.[818]

Systemic immunologic and nonimmunologic diseases may affect the nose. These include Wegener granulomatosis, sarcoidosis, relapsing polychondritis, and midline granuloma.[819,820] Patients with uremia develop thinning of the nasal epithelium.[821] At times, the systemic symptoms may be absent or undetected when patients present with nasal complaints. Infections such as tuberculosis, syphilis, leprosy, sporotrichosis, blastomycosis, histoplasmosis, and coccidiomycosis also may cause granulomatous nasal lesions. These are usually ulcerative, and crust formation may lead to nasal obstruction or bleeding. Rhinoscleroma is a rare chronic infectious granulomatous disease caused by *Klebsiella rhinoscleromatis* that presents as a polypoid mass with symptoms of epistaxis and nasal obstruction.[822] Rhinoscleroma is endemic in tropical and subtropical regions of America, Asia, and Africa.

Complete or partial nasal obstruction in the infant below 2 to 6 months of age can lead to fatal airway obstruction, because many neonates are obligate nasal breathers. In the newborn, the nasal passages may contribute to 50% of the total airway resistance.[93,161] Thus, any minor increase of congestion, such as a URI, can create near total obstruction. Although food allergy, such as, milk, is often considered to contribute to nasal symptoms including congestion, 1 large prospective study demonstrated that only .3% of food hypersensitivity in children and adolescents is associated with rhinitis symptoms.[707] Cinematoradiographic findings have implicated a causal relationship of nasal obstruction and sudden infant death syndrome.[823]

The most common acquired anatomic cause of nasal obstruction in infants and children is adenoidal hypertrophy. Enlarged adenoids commonly result in mouth breathing, nasal speech, and snoring. The main indication for adenoidectomy, a common outpatient surgical procedure in children, is sleep apnea caused by adenotonsillar hypertrophy, chronic adenoiditis, and chronic sinusitis. Nasal symptoms, such as congestion, are also common in infants and children with pharyngonasal reflux resulting from prematurity, neuromuscular disease, dysautonomia, velopharyngeal incoordination, or cleft palate.[161] This is a result of inflammation and narrowing of the posterior choanae because of acid inflammation.[161] When gastroesophageal reflux involves the upper esophagus, larynx, and/or pharyngeal area, it is often referred to as *laryngopharyngeal reflux*. Infants with laryngopharyngeal reflux experience frequent choking, apneic spells, recurrent pneumonia (because of concomitant gastroesophageal reflux and/or tracheal aspiration), and aspiration of formula leading to secondary chemical/infectious rhinitis. Although diagnosis of laryngopharyngeal reflux can usually be made with nasopharyngoscopy, milk scintography or a pH probe study may be required in select cases.[161] Thickened feedings, positioning upright after feeding, and the use of histamine-2 receptor antagonists or proton pump inhibitors have become the mainstay of treatment.[161,824] Of some concern is a recent pediatric prospective study showing that therapy with gastric acidity inhibitors, both protein pump inhibitors and H2 blockers, may increase the risk of acute gastroenteritis and community acquired pneumonia,[825] a finding that has also been described in adults.

CSF rhinorrhea

33. Refractory clear rhinorrhea may be a result of CSF leak, which is often caused by trauma or recent surgery. **B**

Cerebral spinal fluid rhinorrhea should be differentiated from the rhinorrhea found in patients with chronic rhinitis. Refractory clear rhinorrhea may be a result of CSF leak even in the absence of trauma or recent surgery, although these remain the most common causes of CSF leak.[160] Benign intracranial hypertension or pseudotumor cerebri, which typically presents in middle-age women with chronic headaches, has been implicated as a cause of spontaneous, nontraumatic CSF rhinorrhea.[826,827] Although detection of glucose historically has been used as an indication for its presence,[828] β-2-transferrin protein is a more sensitive and specific indicator because it is found in cerebral spinal fluid and inner ear perilymph, but not in blood, nasal, or ear secretions.[255,256]

Ciliary dysfunction syndromes

34. Ciliary dysfunction can be primary (PCD) or secondary (eg, viral infection) and may contribute to recurrent rhinitis and sinus infections. **C**

Defective ciliary function in the airway may be described as ciliary immotility (no movement), ciliary dyskinesia (abnormal movement), or ciliary aplasia (absence of cilia). Screening diagnostic techniques for upper airway disease include measures of mucociliary clearance with saccharin or Teflon particles tagged with the short-lived isotope technetium 99. An absence of mucociliary clearance is a sign of immotility, dysmotility, or aplasia that may be congenital or acquired.

Primary ciliary dyskinesia, also known as immotile-cilia syndrome, is a rare genetic defect (1/20,000 to 1/60,000)[162] caused by a genetically, functionally, and ultrastructurally diverse or heterogenous disease involving a defect in ciliary function. Defective epithelial ciliary clearance of secretions from the upper airway compartments including eustachian tubes and sinuses as well as lower airways produces chronic inflammatory injury to these areas.[777,829] Approximately 50% of subjects with PCD are affected by situs inversus (Kartagener syndrome). The majority have an autosomal-recessive form of PCD, but autosomal-dominant and X-linked cases have been reported.

The clinical history is usually that of respiratory disease in the newborn or recurrent upper and lower respiratory disease including recurrent sinusitis, otitis, otosalpingitis, rhinitis, chronic cough, and nasal polyposis. It may also be associated with difficult-to-control asthma and/or cylindrical or saccular bronchiectasis demonstrated on a chest radiograph or chest CT. Additional clinical findings include situs inversus, agenesis of the frontal sinuses, hydrocephalus, heterotaxy, and infertility. Spirometry reveals mild to moderate obstruction with a positive response to a bronchodilator. Any of these clinical findings in combination with a positive family history of diagnosed or probable PCD warrant a full investigation.[165]

Secondary ciliary defects are certainly more common than PCD. Natural as well as experimentally induced viral upper respiratory infections have been associated with prolonged mucociliary clearance as measured by radiolabeled resin beads or dyed saccharin.[163,830] This effect is maximum at 3 days, persists up to 11 days, and is found in a higher proportion of patients with versus without allergy.[163,830] Acute viral infections may also cause cytopathic epithelial damage that may take a number of weeks to resolve.[171,172] Tobacco smoking of 1 or more cigarettes in an *in vitro* frog palate model results in a reduction of mucus clearance and disruption and defoliation of the ciliated epithelium.[831] Although it is often assumed that similar effects occur in human beings, 1 study using saccharin clearance time demonstrated normal mucociliary clearance in healthy smokers, although the average clearance time was longer than in nonsmokers.[173] Likewise, there was no significant difference in mean nasal ciliary beat frequency when comparing healthy smokers with nonsmokers.[173] It has been suggested that tobacco smoking leads to the dysfunction of the normal metachronal waves that drive mucus over nonciliated areas and that prolonged, sustained exposure to cigarettes may produce loss of ciliated epithelium secondary to activation of matrix metalloproteinases.[831] However, even this ciliary dysfunction shows at least partial recovery within 30 minutes of cigarette smoke avoidance in pure air.[174]

Evaluation of rhinitis

History

35. An effective evaluation of the patient with rhinitis often includes the following: a determination of the pattern, chronicity, and seasonality of nasal and related symptoms (or lack thereof), response to medications, presence of coexisting conditions, occupational exposure, and a detailed environmental history and identification of precipitating factors. **D**

An appropriate general medical history and a thorough allergic history are usually the best diagnostic tools available. If a structured allergy history questionnaire[832-834] is used, the physician should review this with the patient during the initial evaluation. When obtaining an allergic history, it is important to ask about chief concerns and symptoms, including the patient's perception of what is causing the allergic symptoms or the patient's self-diagnosis (although this may be misleading) as well as directed questions relating to nasal symptoms. For example, questions relating symptoms to exposure to pollen and animals may have positive predictive value for diagnosing allergic rhinitis.[175] Each complaint or symptom should be separately evaluated for date of onset including (1) related or resolved symptoms from infancy or childhood; (2) frequency (eg, continual or episodic); (3) characteristics (eg, color and tenacity of nasal secretions); (4) pattern (eg, seasonal, perennial, or a combination); (5) severity, both past and present; (6) triggers that precipitate or worsen the complaint, including allergens, irritants, hormonal influences, exercise, eating, medications, and weather changes; (7) timing after exposure to trigger (eg, immediate or delayed onset); (8) association with geographical and environmental (eg, home vs work vs day care) location or relationship with a particular activity or event (eg, dusting or raking leaves); (9) previous medical evaluation and treatment results, including specific pharmacologic success or failure; and (10) severity (an estimate of effect of the allergic symptoms on QOL, including work or school performance and sleep quality). When a likely allergen is identified by history, a directed question regarding willingness to modify the exposure, such as house pet or occupational allergen, can be asked of the patient and family/care givers. In addition, preferences for the treatment of allergic symptom control including delivery method (eg, oral or nasal) of pharmacologic therapy or a long-term treatment approach with allergy immunotherapy may be explored with the patient and/or others involved in this decision.

Each patient concern or symptom should be evaluated and documented. This could include (1) nasal congestion, sneezing, and rhinorrhea; (2) throat symptoms of soreness, dryness, and PND; (3) cough; (4) ocular redness, tearing, and itching; (5) voice changes; (6) snoring; (7) sinus pain or pressure; (8) ear pain, blockage, or reduced hearing; and (9) itching of nose, ears, or throat. Hyposmia and anosmia are most often associated with severe obstructive upper airway disease, frequently caused by the presence of nasal polyps. It may be helpful to question the patient about symptoms of fatigue, irritability, poor quality sleep, absenteeism and presenteeism at work and/or school, and general QOL problems during their symptomatic periods.[176-178]

When reviewing the allergic history in children, one may inquire about sniffing, snorting, clearing of the throat, chronic gaping mouth, halitosis, cough, dark circles under the eyes, and eye rubbing.[835] The parents may describe the child as having a poor appetite, learning or attention problems, sleep disturbances, malaise, irritability, and a general sense of not feeling well.[180] When allergic symptoms are recurrent but nonseasonal, the presenting complaint may be recurrent URIs, because the parent cannot differentiate a URI in a young child attending day care from allergic rhinitis. Further complicating this differentiation is the increased responsiveness of the nasal mucosa to allergens and irritants after a viral URI.[836]

The history for rhinitis generally includes the family history of allergic rhinitis, asthma, atopic dermatitis, chronic sinus problems or infections, diagnoses that may represent allergic symptoms such as recurrent bronchitis, and all major nonallergic medical diagnoses. Although a positive family history makes it more likely that

the patient's nasal symptoms are a result of allergic rhinitis, a negative family history by no means rules out the diagnosis of allergic rhinitis. Important components of the initial interview include the past medical history, previous trauma or surgery to the nose and sinuses, and established allergic and nonallergic medical diagnoses. Response to previous therapeutic interventions, such as pharmacotherapy or surgery, should be discussed. Documentation of all current medications or herbal preparations, physician-prescribed or OTC, is recommended. An environmental survey should be conducted exploring potential sources for indoor and outdoor allergens in the patient's home and the homes of close relatives, friends, and caretakers, as well as school and work settings. Questions relating to the indoor environment will usually include items such as the presence of pets and insects, carpet, curtains, and upholstered furniture; age and composition of mattress, pillows, and bed coverings; and the cleaning methods in use. One should inquire about the air conditioning and heating sources and their customary use patterns. It is also important to determine the presence of active or passive tobacco smoke exposure.

36. Evaluation of rhinitis therapy should include assessment of QOL. **C**

At any age, allergic rhinitis can compromise QOL.[178] In adults, this often manifests as sleep disorders, impairment at work, limitations of activities, or impairment of social functioning. Recent findings that the sexual QOL is affected by seasonal allergic rhinitis and that appropriate treatment brings the patient's sexual functioning back toward normal emphasizes that allergic rhinitis is an underappreciated disease with systemic effects.[181] As evidence of the disparities between patients' and physicians' perspectives of allergic rhinitis, the symptom severity and the reduced work, home, and social functioning, as indicators of QOL, are often underrecognized and inadequately treated by the patient's physician. [182] Understanding the impact of allergic rhinitis on the patient's QOL represents the cornerstone of therapy.

There are definitely some significant consequences of untreated allergic rhinitis in children. Unrecognized or uncontrolled allergic rhinitis can lead to structural complications and permanent disfigurement such as increased facial length, a high arched palate, class II dental malocclusions, and retrognathic maxilla and mandible.[180] Allergic rhinitis that is poorly controlled can result in poor sleep, school absenteeism, learning impairment, inability to integrate with peers, anxiety, and family dysfunction.[177,550] After effective treatment of perennial allergic rhinitis, improvement in school attendance, school work concentration, and sleep can be demonstrated.[448] Furthermore, chronic nasal congestion and secondary sleep apnea and disordered sleep can lead to systemic symptoms of headache, fatigue, irritability, poor growth, and reduced QOL. The psychological ramifications of untreated allergic rhinitis can lead to low self-esteem, shyness, depression, anxiety, and fearfulness.[180]

The effect of rhinitis on QOL has been measured using both generic and disease-specific questionnaires (Tables III and IV). The advantage of using a generic questionnaire is that the burden of rhinitis can be compared with other diseases, such as asthma. In fact, in adults, moderate-to-severe perennial rhinitis and moderate-to-severe asthma have equal functional impairment.[183,184] On the other hand, disease-specific QOL questionnaires describe disease-associated problems more accurately and seem to be more responsive to measuring the change with therapeutic interventions. Adult generic questionnaires include the Sickness Impact Profile, the Duke Health Profile, the Nottingham Health Profile, and the Medical Outcome Survey Short Form 36 (Table III). The Short Form 36 has been used to evaluate the effects of a nonsedating H1-antihistamine on QOL.[837] Generic QOL questionnaires in children, such as the Child Health Questionnaire–Parental Form 50, Pediatric Quality of Life Inventory, and SF-10 (Table III), are used at times for comparing different allergic diseases. Disease-specific rhinitis QOL questionnaires have been adapted to different age groups. For example, when studying rhinitis in children the Juniper Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ),[651] can be used for ages 6 to 12 years and Juniper Adolescent RQLQ[652] for ages 12 to 20 years (Table IV). Although both the generic and disease-specific QOL questionnaires are often used in research trials for the evaluation of a study group, their sensitivity and precision for use with individual patients has been questioned, especially because QOL and clinical measurements may not be fully interchangeable and distortion, masking, or faking can occur.[185,186] For example, there are studies documenting a clear clinical improvement after antihistamines or bronchodilators, but these are not accompanied by detectable changes in the health-related quality of life.[187,188] In contrast, in other studies, the clinical evaluation did not discriminate between 2 different treatments, whereas a difference was noted with QOL assessment.[189,190] Use of generic QOL measurements in individual patients when studied in other areas of medicine has not led to changes in practice style and has not improved patients' health outcomes.[838] While we await the development of a tool that will be valid and useful for following the individual patient, the clinician may find the current QOL questionnaires of benefit in select clinical settings and in clinical trials. The use of a modified visual analog (graphic rating) scale for assessing the severity of allergic rhinitis has been recommended for the clinician when assessing the individual patient for nasal and nonnasal symptom severity, global nasal and nonnasal severity, and QOL assessment of rhinitis severity[13] (see Figs 1-4). We are also starting to see the development of rhinitis instruments, such as the Multiattribute Rhinitis Symptom Utility index,[650] to assist in comparing the cost effectiveness of various medical treatments of rhinitis.

Physical examination

37. A physical examination of all organ systems potentially affected by allergies with emphasis on the upper respiratory tract should be performed in patients with a history of rhinitis. The nasal examination supports but does not definitely establish the diagnosis of rhinitis. **D**

The elements of the physical examination of the patient with rhinitis with emphasis on the nasal passages are described in Table V. The examiner should carefully look for any signs of accompanying otitis,[191] eustachian tube dysfunction,[192] acute or chronic sinusitis, allergic conjunctivitis, asthma,[193] and atopic dermatitis in addition to findings compatible with rhinitis. In children, findings of dental malocclusion, a high-arched palate, and upper lip elevation may suggest early-onset and/or longstanding disease.[839] On the other hand, if the patient is asymptomatic at the time of the physical examination, there may be minimal or no findings even with a history suggestive of rhinitis.

The nasal examination should note the patency of the nasal valve and any alar collapse. If there is improvement in breathing when performing the Cottle maneuver—pulling the patient's cheek laterally to open the nasal valve angle—this may suggest nasal valve pathology. A deviated/deformed nose may suggest previous trauma, whereas a saddle nose deformity may indicate previous trauma, previous surgery, cocaine abuse, or an inflammatory process.

The nasal and nasopharyngeal examination is accomplished with a nasal speculum with appropriate lighting, otoscope with nasal adapter, indirect mirror, and/or rigid or flexible nasopharyngoscope, based on the expertise of the examiner and the assessment needs.[194] The anterior rhinoscopy examination will reveal any caudal septal deformity or inferior turbinate hypertrophy. If there is significant caudal septal deflection, the inferior turbinate on the side opposite the deviation is often enlarged. If after applying a topical decongestant there is a reduction of turbinate mucosal edema, this may assist in delineating mucosal versus bony hypertrophy.

The use of the nasopharyngoscope allows for better visualization of the middle meatus, the posterior septum, the sinus ostia, posterior choanae, the nasopharynx, and the presence of nasal polyps. The presence of mucopurulent material in this region is suggestive of sinusitis. The use of a mirror or the nasopharyngoscope is necessary to complete a posterior rhinoscopy examination. A pneumatic otoscope is used to assess tympanic membrane mobility. At times, the impedance tympanometer is also needed to assess the tympanic membrane mobility and the presence or absence of fluid, especially in children.

Many typical allergic findings are supportive but not specific to allergic rhinitis. Mucosal appearance may not distinguish between allergic and nonallergic rhinitis, because nonallergic rhinitis may also present with mucosal pallor, edema, or hyperemia. The mucosa is usually reddened in acute infections and with overuse of topical decongestant sprays. Occasionally, the mucosa can be hyperemic with allergic rhinitis. Dennie-Morgan lines, often noted in patients with atopic dermatitis, are symmetrical, prominent folds extending from the medial aspect of the lower lid. These are usually present at birth, or appear shortly thereafter, and persist for life. Dennie-Morgan lines (noted in 60% to 80% of atopic children[195]) are very similar to the folds seen in patients with Down syndrome. They may have an ethnic variation and are characteristically but not exclusively present in patients with allergy. Allergic shiners, asymptomatic, symmetrical, blue-grey discolorations of the periorbital skin, are most apparent below the orbit and are attributed to venous stasis. They are reported to occur in as many as 60% of atopic patients and in 38% of nonatopic individuals.[196] Their presence is usually associated with nasal congestion.[196] These do tend to fade with increasing age and are often found in atopic family members.[196]

The quantity and quality of nasal secretions should be noted. With allergic rhinitis, there may be watery mucus on the epithelial surface or on the floor of the nasal passage. With abnormal mucociliary clearance or total nasal obstruction, thick secretions can be seen pooling in the floor of the nose. Unlike the nasal turbinates, with which they are often confused, polyps appear glistening, mobile, and opaque and are insensitive to touch.[840] Nasal polyps may be differentiated from severely edematous mucosa by applying a small amount of a topical vasoconstrictor such as phenylephrine to the mucosa and reexamining the mucosa 5 to 10 minutes later. Nasal polyps will not shrink in size after topical vasoconstrictor has been applied, unlike edematous mucosa.[841] Crusting on an inflamed mucosa may suggest atrophic rhinitis or a systemic disease such as sarcoidosis. The presence of a septal perforation should raise the possibility of intranasal narcotic abuse,[842,843] adverse effects of other topical preparations,[843-845] previous surgery, or systemic granulomatous diseases.

Testing for specific IgE antibody

Skin testing

38. Determination of specific IgE, preferably by skin testing, is indicated to provide evidence of an allergic basis for the patient's symptoms, to confirm or exclude suspected causes of the patient's symptoms, or to assess the sensitivity to a specific allergen for avoidance measures and/or allergen immunotherapy. **B**
39. Skin tests are the preferred tests for the diagnosis of IgE-mediated sensitivity. The number of skin tests and the allergens selected for skin testing should be determined on the basis of the patient's age, history, environment, and living situation, such as area of the country, occupation, and activities. **D**

In vitro assays for specific IgE

40. The precise sensitivity of specific IgE immunoassays compared with skin prick/puncture tests is approximately 70% to 75%. Immunoassays have similar sensitivity to skin tests in identifying those patients with nasal symptoms elicited after natural or controlled allergen challenge tests. **C**
41. Interpretation of specific IgE immunoassays may be confounded by variables such as potency of allergens bound to solid support systems, cross-reactive proteins and glycoepitopes, specific IgG antibodies in the test serum, and high total IgE. **D**

Demonstration of specific IgE antibodies to known allergens by skin testing or *in vitro* tests[197,198] helps determine whether the patient has allergic rhinitis and the specific allergens for avoidance measures and/or allergen immunotherapy. Skin test reactivity alone does not define clinical sensitivity. Skin test positivity must be combined with reported symptoms, increased symptom scores, or physical signs during a known pollen season, controlled laboratory, or environmental exposure unit challenges.[210,211]

A careful history is the most important step toward the diagnosis of allergic disease. Skin testing to allergens is indicated to provide evidence of an allergic basis for the patient's symptoms, to confirm suspected causes of the patient's symptoms, or to assess the sensitivity to a specific allergen. The simplicity, ease, and rapidity of performance, low cost, and high sensitivity make skin tests highly favorable for use in patients with rhinitis.

Quality control measures and proper performance of skin testing are vital to produce accurate and reproducible results. It is important to recognize that there is a variable wheal and flare response with the different devices used for skin testing.[846] The number of skin tests performed may vary depending on the age, potential allergen exposures, and area of the country. It is essential to know which aeroallergens are present locally, are clinically important, and have cross-reactivity with botanically related species to interpret skin tests or *in vitro* tests for specific IgE properly.

In vitro specific-IgE tests (eg, RAST) are an alternative to skin testing. The precise sensitivity of specific IgE immunoassays compared with skin prick/puncture tests has been reported to range from less than 50% to greater than 90%, with the average being around 70% to 75% for most studies.[199-209] Skin tests are therefore the preferred tests for the diagnosis of IgE-mediated sensitivity. Interpretation of specific IgE tests may be confounded by variables such as potency of allergens bound to solid support systems, cross-reactive proteins and glycoepitopes, specific IgG antibodies in the test serum, and high total IgE (see ''Allergy Diagnostic Testing: An Updated Practice Parameter'' for more detail[9]).

Specific IgE immunoassays may be preferable to skin testing under special clinical conditions such as widespread skin disease (ie, severe eczema or dermatographism), skin test suppressive therapy in use, an uncooperative patient, or a history suggesting an unusually high risk of anaphylaxis from skin testing.

Special diagnostic techniques

42. In selected cases, special techniques such as fiber optic nasal endoscopy and/or rhinomanometry may be useful in evaluating patients presenting with rhinitis symptoms. These tests may require special expertise for performance and interpretation. Patients with nasal disease require appropriate examination for associated diseases, such as sinusitis and otitis media. **B**

Although history and routine physical examination are usually sufficient for a diagnosis of allergic rhinitis, special techniques may be useful in selected patients. Furthermore, patients with nonallergic upper airway pathology may initially report symptoms suggestive of rhinitis.

Upper airway endoscopy

Endoscopy may be especially useful for the evaluation of rhinitis when symptoms or physical findings are atypical, complications are noted, therapeutic response is suboptimal, or conditions other than rhinitis are suspected. Without endoscopy, it is not possible to view many of the important recessed structures of the upper airway. Either the rigid or a flexible fiber optic endoscope can be used for this examination.

Upper airway endoscopy (rhinolaryngoscopy) is the most useful diagnostic procedure in an evaluation for anatomic factors causing upper airway symptoms. Endoscopy provides a clear view of the nasal cavity and allows detailed examination of the middle meatus, superior meatus, sphenoethmoidal recess, posterior choanae, and nasopharynx, as well as the structures of the oropharynx and larynx.[212,213] The procedure is usually performed in the office after decongestion and topical anesthesia. Analysis of videotaped fiber optic upper airway endoscopy has also been used as a research technique to measure cross-sectional area of the nasal cavity.[214]

Imaging techniques

The primary goals of radiologic imaging of the upper airway are to provide an accurate reproduction of the regional anatomy and to establish the presence and extent of anatomic disease. This information may assist in planning medical therapy and provide an anatomic guide to facilitate subsequent surgical treatment.[214]

Radiologic imaging techniques, such as plain films, CT, and MRI, have no use in the evaluation of patients with uncomplicated rhinitis. However, imaging may be merited when rhinitis with complications or comorbidities such as nasal polyposis and concomitant sinusitis are present.

CT and MRI

Computerized tomographic scanning and MRI using coronal sections for imaging of sinuses frequently identify turbinate congestion, concha bullosa, nasal polyps, and septal deviation as causes of nasal airway obstruction. Although CT and MRI have been used to validate acoustic rhinometry as a diagnostic technique, they are expensive and may not correlate well with functional obstruction when used for this purpose.

High-resolution CT can demonstrate disease that is not shown on routine x-ray films. It can also delineate pathologic variations and demonstrate anatomic structures inaccessible by physical examination or endoscopy. Because of its superb contrast resolution, CT is an excellent method for examining the complex anatomy of the upper airway, particularly the ostiomeatal complex. The capability of CT to display bone, soft tissue, and air facilitates accurate definition of regional anatomy of the nose and paranasal sinuses. The main indications for the CT are chronic sinusitis not responding to appropriate medical therapy, acute recurrent sinusitis, abnormal diagnostic nasal endoscopic examination, and persistent facial pain.[215]

Magnetic resonance imaging provides better imaging of soft tissue than CT, but it is less suited to imaging the bony anatomy of this region. MRI is useful in the evaluation of upper airway malignancies.[9]

Aerodynamic methods for estimation of nasal airway obstruction

Resistance to airflow through the nose (or conductance, the inverse of resistance) may be measured by rhinomanometry. Rhinomanometry objectively measures functional obstruction to airflow in the upper airway, although the technique has not been fully standardized. Subjective perception of nasal stuffiness may correlate only loosely with measured nasal airway resistance,[235,847,848] and rhinomanometry may be used in the assessment of the severity of symptoms. In addition, rhinomanometry may provide objective information on the results of therapeutic interventions. The objective information obtained from rhinomanometry may be particularly important when it is suspected that occupational exposure results in nasal symptoms, including nasal congestion. Rhinomanometry is not a substitute for careful endoscopy of the nose because significant pathology in the nose can occur with nasal airway resistance values in the normal range.

Rhinomanometry may be used to assess the severity of anatomical abnormalities that are causing airway obstruction in the nose, including nasal valve abnormalities, septal deviation, and polyposis. This application requires measurements before and after a potent intranasal decongestant. Other indications for rhinomanometry include the evaluation of patients with obstructive sleep apnea.[217]

Acoustic rhinometry

Acoustic rhinometry depends on reflection of acoustic signals from structures in the nasal cavity.[218-220] It is currently not a technique used in the routine evaluation of patients with rhinitis. It produces an image that represents variations in the cross-sectional dimensions of the nasal cavity and closely approximates nasal cavity volume and minimal cross-sectional area. It also allows identification of the distance of the minimal cross-sectional area of the nasal cavity from the naris. Changes in nasal geometry measured by acoustic rhinometry during histamine challenge testing have been documented,[849,850] and the results of parallel

determinations by acoustic rhinometry and rhinomanometry are comparable.[850] However, nasal airway resistance cannot be easily computed from the acoustic rhinometry data.

Acoustic rhinometry is a safe, rapid, and noninvasive technique that requires minimal patient cooperation and effort and no patient training.[851] It may be used in the evaluation of infants, children, and adults. It can be performed on a severely congested nose because it does not require nasal flow. Measurements by acoustic rhinometry have been validated by comparison with CT and MRI.[221] Although there is high correlation for the anterior 2/3 of the nasal cavity, the posterior nasal cavity shows more variance.[222-225] Compared with CT and MRI, acoustic rhinometry is more rapid, may be performed at the bedside, and, unlike CT, does not expose the patient to radiation. Acoustic rhinometry and rhinomanometry have similar reproducibility[231] and compare favorably in challenge studies[232] but measure different changes and are best viewed as complementary.[233-235] Clinically, acoustic rhinometry is used to help diagnose rhinitis, evaluate nasal pharyngeal surgical outcome, and monitor response and adherence to medical therapy such as intranasal corticosteroids.[226,227] It is a logical choice for the objective measurement of area and volume in diseases of the nose. A number of factors lead to measurement variation when the procedure is used. Common reasons for measurement inaccuracy are an air leak between the nosepiece and the nose and the presence of nasal secretions.[228] Studies have shown that patient perception of nasal obstruction does not correlate with actual compromised nasal airflow.[235]

Nasal provocation testing

Identification of sensitivity of the nose to a particular aeroallergen usually can be based on a history of symptoms of allergic rhinitis provoked by exposure to the allergen and confirmed by skin testing. Nasal provocation testing with allergen is unnecessary unless criteria that are more stringent are needed to incriminate the suspected allergen. For example, nasal provocation testing with allergen may be required for confirmation of sensitivity to allergens in the workplace. Testing of sensitivity to allergens requires that responses to incremental doses of allergens be assessed.[236] Single-dose allergen provocation measures nasal reactivity to allergens, not sensitivity. Because nasal reactions to instillation of placebo materials may occur, response to diluent must be measured before provocation with allergens.

Nasal sensitivity/hyperresponsiveness to histamine and methacholine has been found in allergic rhinitis[237-239] and vasomotor rhinitis.[240] Although this measurement may be a marker for these diseases, the clinical utility of nasal provocation testing with histamine or methacholine may be limited; there is a considerable overlap between patients with and without allergy in their sensitivity to these agents. However, these provocation tests may be useful during clinical trials to determine the efficacy of drugs and allergen immunotherapy in reducing nasal irritability.

Nasal cytology, ciliary functional studies, and biopsy

43. Nasal smears for eosinophils are not necessary for routine use in diagnosing allergic rhinitis when the diagnosis is clearly supported by the history, physical examination, and specific IgE diagnostic studies but may be a useful adjunct when the diagnosis of allergic rhinitis is in question. **C**
44. Although the saccharin test for mucociliary clearance has been relied on as a clinical screening test, it cannot be relied on for a definitive diagnosis of mucociliary dysfunction. **C**
45. Nasal biopsy may be indicated when determining whether a lesion is neoplastic or granulomatous or if there is an abnormality in the ultrastructure of cilia. **C**

Nasal smears for eosinophils are usually considered elevated when 10% of cells are eosinophils.[90] The presence of eosinophils has been associated with loss of epithelial integrity in patients with both allergic and nonallergic rhinitis.[852] When taking nasal smears, both nostrils should be sampled because the findings from 1 nostril are not reliably representative of the total cell distribution in both nostrils.[242] Samples collected by blowing mucus into transparent wrap contain less cellular material than when a cytology brush, probe or ultrasonic nebulization of hypertonic saline are used, but are adequate for detecting eosinophils and neutrophils.[853-855] Once collected, the nasal secretions are transferred to a slide, fixed, and then treated with Hansel stain, which highlights eosinophil granular contents.[856] Although nasal smears are generally adequate for assessment of nasal eosinophilia, there is some evidence that nasal biopsy for eosinophils is more accurate.[857] Many studies have shown a high correlation of nasal eosinophilia and allergic rhinitis; however, it is questionable how much this benefits the clinician in making the diagnosis of allergic rhinitis.[87-89] In a study of adolescents and adults, adding nasal smears for eosinophils to an expert's clinical evaluation in establishing a diagnosis of allergic rhinitis contributed very little to the final diagnosis and was considered clinically irrelevant.[90] When eosinophils in nasal smears are present, there is only a 71% correlation with SPTs and a 69% correlation with nasal challenge tests, suggesting that routine use of the nasal smear may not be beneficial.[91] In clinical trials, nasal eosinophils have been used to evaluate anti-inflammatory effects of intranasal corticosteroids and may be associated with improved nasal symptom scores.[376,380]

As many as 4.7% of patients with a history very suggestive of allergy will have negative prick tests but a positive nasal challenge and a positive nasal smear for eosinophils,[91] and may have nasal specific IgE,[241] supporting the diagnosis of allergic rhinitis.[91,241] Under special circumstances, when faced with a convincing history, negative SPT, and elevated nasal eosinophils, the clinician may wish to conduct a nasal or conjunctival challenge test. On the other hand, as many as 6% of patients with a similar history suggestive of allergy will have negative prick skin test and nasal challenge but will have nasal eosinophilia, establishing the diagnosis of nonallergic rhinitis with eosinophilia.[91] When both SPTs and nasal smears for eosinophils are negative in patients with rhinitis, a less favorable response to medical therapy can be anticipated.

Additional research is needed to establish whether nasal smears for eosinophils are useful for predicting the onset, course, and progression of allergic disease. In 1 pediatric study, nasal eosinophilia was found to predict prolonged or subsequent allergic rhinitis symptoms.[858] In addition, the nasal eosinophil count has been shown to correlate with the severity of perennial allergic rhinitis in children.[859] Recognizing that many patients with allergic rhinitis have increased airway reactivity and will subsequently develop asthma, the nasal smear for eosinophils may help predict the progression of disease; in adult patients with allergic rhinitis as the only allergic diagnosis, it has been shown that the number of nasal eosinophils correlates with the methacholine response.[89,860]

The absence of eosinophils and the presence of large numbers of polymorphonuclear neutrophils especially when intracellular bacteria are noted suggest an infectious rhinitis or sinuitis.[92] On the

basis of sinus aspirates, the number of polymorphonuclear cells varies with the infecting organism, because *H influenzae* is associated with significantly fewer leukocytes than *Streptococcus pyogenes*.[861] A viral infection is usually associated with fewer polymorphonuclear cells than a bacterial process.[243] However, the mere presence of neutrophilia cannot be diagnostic of an infectious process because as many as 79% of school children and 97% of infants have neutrophils in their nasal secretions.[88]

The saccharin test (with saccharine or a substitute dye marker) may be used by the clinician as a screening test for primary or secondary ciliary dysfunction. The test requires a cooperative subject but is quite noninvasive. The saccharin test involves placement of a 1-mm to 2-mm particle of saccharin on the inferior nasal turbinate 1 cm from the anterior border. The subject then sits with the head bent forward and the test is completed when either the patient tastes the saccharin or the clinician visualizes the presence of the dye marker in the posterior pharynx. If the time is beyond 1 hour or the subject is unable to taste the saccharin or detect the dye, mucociliary clearance is considered impaired. When an abnormal study is obtained, additional studies are required before a firm diagnosis can be established,[166] because the saccharin test has too many false-positives and false-negatives.

Nasal biopsies are used to determine if a suspicious lesion is neoplastic or granulomatous and to evaluate suspected ciliary dysfunction. Biopsies to determine ciliary structure and function can be obtained endoscopically from bronchi or the nasopharynx and by curette or brush from the inferior concha. The cilia can be viewed by video or examined in cross-section by electron microscopy for specific defects or usual ultrastructure.[244,245] Combining electron microscopy with computer-based image processing algorithms can improve the visualization of ultrastructural defects.[165,167-169,862] Depending on the results of the nasal biopsy evaluation of ciliary function, a tracheal biopsy may be required for confirmation of ciliary dyskinesia. Electrophoresis, genetic analysis using a dynein gene probe, and decreased exhaled nitric oxide are additional diagnostic procedures under investigation for the evaluation of ciliary function.[165]

Additional laboratory testing

46. The measurement of total IgE and IgG subclasses for the diagnosis of allergic rhinitis has limited value and should not be routinely performed. **C**
47. The presence of β-2-transferrin in the nasal secretions is a sensitive method of confirming cerebral spinal fluid rhinorrhea. **B**

Measurement of total IgE in cord blood or in children has been proposed as means of predicting the risk of allergic disease; however, recent studies have found that cord blood is not a reliable predictor for atopic disease.[246] The total serum IgE has low sensitivity (43.9%) as well as low positive and negative predictive values when evaluating a patient for allergic rhinitis and therefore is of limited clinical benefit.[247,248]

In recent research, the presence of specific immunoglobulin responses of the IgG subclasses has been suggested to be a risk factor for allergic disease.[863] Furthermore, measurement of nonspecific and specific IgG_4 and/or of other subclasses has been advocated as a diagnostic test for clinical allergy. In general, scientific evidence supporting its use has been controversial and inconclusive.[249-254] The routine measurement of IgG_4 should not be part of the diagnosis evaluation of patients with allergic nasal disease.

Special testing considerations in children

48. In children with rhinitis, the use of immune studies, sweat test, sinus CT, and nasal endoscopy may be indicated when they are suspected to have comorbid conditions such as immune deficiency, CF, and chronic sinusitis. **C**

In children with rhinitis, select tests that may be indicated on an individual basis include quantitative immunoglobulins, complement studies, ciliary functional and morphologic studies (as described in Summary Statements 44, 45), and the sweat test and/or genetic typing for CF when disorders such as immunodeficiency, ciliary dyskinesia, and CF are suspected (see "Allergy Diagnostic Testing: An Updated Practice Parameter"[9] and "Practice Parameter for the Diagnosis and Management of Primary Immunodeficiency"[864]).

There is ongoing controversy on the usefulness of plain sinus radiography in children for the diagnosis of acute bacterial sinusitis.[77,865,866] Although the diagnosis of acute bacterial sinusitis in children can usually be made by clinical assessment, plain radiography may be considered for confirmation in children 6 years and older with persistent symptoms and for all children (regardless of age) with severe or worsening symptoms.[867,868] In children, as in adults, CT scans of the sinuses are more sensitive than plain radiography and should be considered for potential complications of acute bacterial sinusitis, such as orbital or intracranial complications, for patients who fail to improve with appropriate medical therapy, or for the diagnosis of chronic sinusitis.[866,869] A lateral nasopharyngeal radiograph may help to exclude adenoid hypertrophy in children with mouth breathing, snoring, sleep apneic episodes, and nasal obstruction. When available, dynamic video rhinoscopy is more accurate at assessing adenoid hypertrophy and percent airway occlusion than lateral neck radiography.[216] Overnight polysomnography may be necessary to confirm the diagnosis of OSAS, noted in 1% to 3% of children, before surgical removal of enlarged adenoids and tonsils.[870]

Testing for comorbid conditions

49. A formal evaluation for obstructive sleep apnea may be considered in children and adults presenting with chronic rhinitis and other risk factors associated with sleep-disordered breathing.

Atopy has been associated with habitual snoring in infants.[257] In children, the presence of rhinitis is a strong predictor of habitual snoring.[258] Children who are African American, have upper respiratory disease, and have a family history of sleep apnea are at enhanced risk for sleep-disordered breathing.[259] Thus, formal evaluation for OSAS may be considered in children presenting with chronic rhinitis and other risk factors associated with sleep-disordered breathing.

In snoring adults with rhinitis and sleep apnea symptoms, increased nasal airway resistance has been associated with apnea and hypopnea.[260,261] Obstructive sleep apnea episodes determined by polysomnography were more frequent in patients with ragweed allergy during symptomatic periods when nasal resistance was increased than during asymptomatic periods.[871] Intranasal corticosteroids reduce nasal airway resistance and apnea-hypopnea frequency in patients with OSAS and rhinitis and may be of benefit in the management of some patients with OSAS.[261]

50. Pulmonary function tests should be considered in patients with rhinitis to assess the possibility that asthma might be present. **D**

Rhinitis and asthma are linked by common epidemiologic, physiologic, and pathologic mechanisms, as well as common comorbidities and therapeutic approaches, leading to the concept of ''one airway, one disease.''[262-265] This concept has been popularized by a publication of the ARIA workshop group, where it is stated in the introduction, ''…patients with persistent allergic rhinitis should therefore be evaluated for asthma and patients with asthma should be evaluated for rhinitis.''[11] Thus, pulmonary function tests should be considered in patients with rhinitis to assess the possibility that asthma might be present. The presence of asthma may not be apparent because such patients (1) may have difficulty in recognizing their symptoms, (2) may have variable symptoms throughout the day, (3) may have a physical examination of the respiratory system that appears normal, and (4) may present with symptoms that are atypical. Furthermore, the physical examination of the lower respiratory systems may be normal during the medical evaluation of rhinitis.

Unproven tests

51. There is no evidence that the following procedures have diagnostic validity for allergic rhinitis: cytotoxic tests, provocation-neutralization, electrodermal testing, applied kinesiology, iridology, and hair analysis. **B** (see ''Allergy Diagnostic Testing: An Updated Practice Parameter''[9])

Management of rhinitis

Environmental control measures

Environmental triggers for rhinitis can be divided into 2 general categories: allergens and irritants. Ideally, the management of rhinitis includes identification of these triggers when possible and implementation of avoidance measures when practical.

52. The most common allergic triggers for rhinitis include pollens, fungi, dust mites, furry animals, and insect emanations. **B**

Allergens are substances that trigger rhinitis through an IgE-dependent mechanism. The most common allergic triggers for rhinitis include pollens, fungi, dust mites, furry animals, and insect emanations. The ideal way for patients to manage allergic rhinitis is with complete avoidance of all relevant allergens. Because this generally is not possible, patients should be counseled to reduce their exposure to as many relevant allergens as is practical. This may improve their ability to tolerate exposure to unavoidable aeroallergens. With the development of sensitive immunochemical techniques, direct measurement of indoor allergen concentrations to confirm that exposure reduction has occurred is now possible.[293] Even so, the effectiveness of environmental control measures should be judged primarily by clinical parameters such as reduction in patient symptoms and medication scores.[266]

53. The types of pollen responsible for rhinitis symptoms vary widely with locale, climate, and introduced plantings. **B**
54. Highly pollen-allergic individuals should limit exposure to the outdoors when high pollen counts are present. **B**

Pollen that triggers allergic rhinitis principally comes from plants that are wind-pollinated (anemophilous). This includes many trees, grasses, and weeds, although exposure to pollen from insect-pollinated (entomophilous) plants may produce symptoms if sufficient concentrations are encountered.[872] Allergens are quickly eluted from pollen grains on contact with ocular or respiratory mucosa. In addition, similar allergens may be found on fragments derived from other portions of the plant. Pollen allergens, forming an allergenic bio aerosol, can be detected in the outdoor environment even when intact pollen grains are not present.[267-269]

The types of pollen responsible for symptoms vary widely with locale, climate, and introduced plantings.[873,874] In temperate regions of North America, tree pollen generally predominates in early to mid-spring, grasses in late spring and early summer, and weeds from late summer until early fall.[875] The dose of pollen allergen that is able to elicit symptoms depends on the degree of allergic sensitization and on nasal mucosal inflammation that already is present, often referred to as ''priming.''[721,876,877]

Indoor pollen exposure increases when windows are open or attic fans are in use during pollen season. Therefore, to reduce indoor exposure, windows and doors should be kept closed. If air conditioning is used to keep the home or vehicle comfortable, any outdoor vents should remain closed.[878] It may be helpful to take a shower or bath following outdoor activity, thereby reducing indoor pollen contamination. Because pets also can be vectors for pollen intrusion, it may be beneficial to wash furry animals after they have been outdoors. Although it is not practical to remain indoors all of the time, it is helpful to limit outdoor exposure during periods with high pollen counts.[879] For example, because ragweed pollen concentrations tend to peak at noon or in the early afternoon, it may help to plan outdoor activities for the early morning or late evening.[880] Highly sensitive patients whose symptoms are triggered by very low pollen levels may need to limit their outdoor activities.[277] Having such individuals wear a facemask during outdoor activities should be considered.[277] Activities involving extended time outdoors, such as camping trips, may need to be avoided during certain pollen seasons. Because pollen counts tend to be higher on sunny, windy days with low humidity, it may help to limit outdoor activities when those weather conditions are present. In contrast, outdoor activities may be well tolerated after a gentle, sustained rain when pollen counts tend to be low. Because the interplay of different weather factors (eg, wind, temperature, rain, humidity) is complex, it is not reliably possible to predict levels of outdoor aeroallergens on the basis of the influence of a single weather factor.[270-272]

55. Fungi are ubiquitous organisms, many of which produce clinically important allergens. **B**
56. Reduction of indoor fungal exposure involves removal of moisture sources, replacement of contamination materials, and the use of dilute bleach solutions on nonporous surfaces. **D**

Fungi are ubiquitous organisms, many of which produce clinically important allergens.[881-886] They exist in great numbers outdoors but also may contaminate indoor environments. Most fungal allergens are encountered through inhalation of spores, although fragments of hyphae also may be important. Fungi are present in the air throughout the year except during periods of snow cover. In the Northern United States, spore concentrations tend to increase in late spring and again during late summer, whereas in the southern United States, they tend to remain elevated year-round. Most fungi are found in soil and tend to release spores

when the earth is disturbed (eg, during plowing, excavation, and so forth). Outdoor fungi grow on both viable and decaying vegetation and are particularly abundant during harvesting activities in agricultural regions.

Because there is a temporal association between exposure to spores and development of allergic symptoms in sensitive individuals, it is important for patients to be aware of conditions that are associated with elevated spore concentrations.[887] Spore concentrations are strongly influenced by local conditions such as moisture, temperature, wind, rain, and humidity.[274-276] Some fungi require moist conditions for spore release, leading to elevated levels of these spores during rainy weather and with dew formation at night.[273] Such hydrophilic fungi include *Fusarium*, *Phoma*, most ascospores, and basidiospores (mushrooms). Other common allergenic fungi, such as *Alternaria* and *Cladosporium*, are more abundant during dry, windy weather. Rain or high humidity can induce spore release, particularly when the rainy period ends. Thunderstorms have even been associated with spore plumes.[888]

Avoidance of outdoor fungi may require the patient to remain indoors as much as is practical. As with pollen avoidance, air conditioning units, if necessary for comfort, should be used with the outdoor vents closed. Because air conditioning units at home, at work, and in automobiles may become contaminated with fungi, they should be inspected regularly and maintained according to the manufacturer's instructions. Other situations associated with increased fungus exposure include plant-disturbing activities such as mowing, threshing, or raking leaves and proximity to compost, silage, or dry soil. Use of face masks may be helpful for reducing exposure during such outdoor activities.[277,278]

Many factors influence growth of indoor fungi, including the age and construction of the residence; the presence of a basement or crawl space; the type of heating, ventilation, and air conditioning system; and the use of humidifiers. Fungi require oxygen, a source of carbohydrate, and moisture for optimal growth. Moisture becomes available to fungi through entry into the building by intrusion from outside, leakage from pipes, or condensation onto cold surfaces with temperatures that are below the dew point of air. Therefore, environments most likely to become contaminated with fungi include homes with elevated humidity (above 50%), basements with water intrusion, and cold surfaces. Other locations often providing favorable conditions for fungal growth include window moldings, sinks, shower stalls, nonrefrigerated vegetable storage areas, and garbage pails.

Reduction of fungal exposure consists of eliminating the source of moisture. Fungicides may kill or at least retard fungal growth. Products containing a dilute bleach solution with a detergent have been shown to denature fungal allergens and in many cases to prevent regrowth by killing the mycelia. These are effective when used on nonporous surfaces or when contamination is limited to a small area. Applications that treat the surfaces only are unlikely to remediate fungally contaminated porous materials such as wallboard because mycelia can penetrate these surfaces. It may therefore be necessary to remove and replace such materials. Unfortunately, such chemical and physical measures to control indoor fungi will usually fail in the presence of elevated relative humidity and condensation.

Because cool mist humidifiers may be reservoirs for bacteria and fungi, they are best avoided.[889-894] If they are used, they need to be cleaned regularly. Because central humidifiers operate through evaporation, they are less likely to produce particles containing fungi and therefore are preferable. Homes constructed with a crawl space should have a plastic vapor barrier over exposed soil, and foundation vents should be kept open to provide ventilation. Spores also are present in carpeting, bedding, and upholstered furniture and are reduced by the same measures used for dust mite avoidance. Carpeting and upholstered furnishings therefore should be avoided in damp areas or in locations that tend to flood. A dehumidifier should be used and standing water removed as quickly as possible in such locations.

57. Clinically effective dust mite avoidance requires a combination of humidity control, dust mite covers for bedding, HEPA vacuuming of carpeting, and the use of acaricides. **B**

A major source of allergen in house dust is the fecal residue of dust mites belonging to the genus *Dermatophagoides*.[895] A principal food source of dust mites consists of exfoliated human skin cells. Consequently, mites are most abundant in locations where skin cells are shed such as bedding, fabric covered furniture, soft toys, and carpeting.[896,897] In addition to the availability of this food source, the other major factors influencing mite growth are temperature and humidity. To reproduce, dust mites generally require a relative humidity of 50% or greater.[281] Recent changes in home construction and housecleaning methods have created environments conducive to dust mite proliferation. These include enhanced energy efficiency in buildings leading to reduced ventilation and increased humidity, wall-to-wall carpeting, furnished basements, and use of water for laundry that is not hot enough to kill mites.

To reduce mite allergen exposure, humidity should be maintained between 35% and 50%, reservoirs in which they reside should be minimized, and barriers should be created between the mites and the building's occupants. Humidity can be reduced with air conditioning or a dehumidifier and can easily be measured with an inexpensive hygrometer. Common reservoirs to be avoided include upholstered furniture, carpeting, bedding, and stuffed toys. Dust mite fecal pellets easily become airborne when their reservoir is disturbed, although they rapidly settle once the disturbance stops. Ordinary vacuuming and dusting therefore have little effect on mite allergen concentrations because the mites themselves are not removed and the pellets easily pass through low-efficiency vacuum bags, becoming widely dispersed throughout the room.[280] Carpeting therefore is best removed from the bedroom and replaced with smooth finish wood, tile, or vinyl flooring.[282] If this is impractical, one may consider treating carpets with an acaricide (benzyl benzoate) that kills mites.[279,286-288] Carpeting installed over a concrete slab will inevitably become contaminated with both mites and fungi because of condensation and is best avoided if possible. If carpeting is present, vacuum cleaners with HEPA filtration or central vacuums that remove the air to a distant location should be used. Ideally, housecleaning should be performed when the allergic person is not at home, although patients who do their own cleaning may benefit from wearing a face mask.

To create an effective barrier to exposure, mattresses, box springs, and pillows in the patient's bedroom should be encased in zippered, allergen-proof encasings.[279,285] Vinyl encasings are effective, although cloth encasings with semipermeable plastic backing are more comfortable and durable. If a mattress is old, replacement should be considered, but even new hypoallergenic mattresses and pillows should be encased because mite colonization occurs within weeks. Unfortunately, when impermeable

bedding is used as an isolated intervention, it is unlikely to offer clinical benefit.[288] Bedding should be washed in hot water (greater than 130°F) at least every 2 weeks to remove mite allergen and to kill mite ova, although lower temperatures will remove the mite allergen itself.[283] Quilts and comforters should be avoided or covered with an allergen-proof duvet.

Because elimination of mites in upholstered furniture is extremely difficult, plastic, leather or wood furniture is recommended. When upholstered furniture cannot be avoided, a 3% tannic acid solution may be used to denature mite and other allergens on these furnishings. Because this does not kill the mites, the allergen reaccumulates over time, necessitating repeated treatments. Stuffed toys that cannot be washed can be placed in plastic bags and frozen to kill dust mites.

There is increasing evidence that HEPA air filtration is effective for reducing dust mite exposure.[279] On the other hand, duct cleaning has not been demonstrated to be of significant benefit.

58. Avoidance is the most effective way to manage animal sensitivity. **D**

Because of the popularity of indoor pets, allergens from cats, dogs, and other domestic animals are important triggers of allergic rhinitis. All warm-blooded animals, including birds, potentially are capable of sensitizing susceptible patients with allergy. Animal allergens are a significant occupational hazard for workers exposed to mice, rats, guinea pigs, and so forth. Farm workers may develop sensitivities to farm animals. In inner city areas, rodent urine may be an important source of animal allergen. Although furs processed for use in clothing are no longer allergenic, feather products retain significant allergenicity. Because allergen-bearing particles of animal origin are generally quite small and low-density, they remain suspended in air for extended periods and disseminate widely in homes and other facilities. Symptoms of allergic rhinoconjunctivitis may occur within minutes of entering a contaminated area.

The major antigen in cat allergen, Fel d 1, is found on cat skin/dander and in saliva and urine.[898] Cat albumin is also allergenic but is a less frequent cause of sensitivity than Fel d 1. Fel d 1 and albumin are common to all breeds of cats. Cat allergen has been identified in homes and other locations where cats were never present and occasionally may reach concentrations found in homes where cats are kept.[291] This is presumed to be passive contamination from cat allergen borne on clothing. Such contamination may be an unsuspected cause of symptoms in sensitive individuals.[292]

Allergy to dogs appears to be less frequent than cat allergy. The major dog allergen, Can f 1, is found in dog skin/dander and saliva and is present in varying amounts in all breeds tested. Many dog-sensitive patients claim to respond differently to various breeds of dogs or even specific dogs of a single breed. Like cat allergen, Can f 1 has been found in rooms in which dogs were never present, suggesting passive transport on clothing.[291,293,294] Concentrations may be sufficient to elicit symptoms in sensitized patients.

Avoidance is the most effective way to manage animal sensitivity. Patients and their families should be advised to consider removing an animal to reduce exposure. A trial removal of a pet for a few days or even weeks may be of little value or, worse, misleading, because cat allergen can be detected an average of 20 weeks (and in some cases much longer) before reaching concentrations found in homes without cats.[295] Steam cleaning of carpets and upholstered furniture after removal of the animal seems to have little advantage over routine vacuuming with a HEPA filter vacuum system. It also helps to wash the bedding with soap and water.[283] If the patient and/or family decide not to remove the pet, confining the animal to an uncarpeted room (other than the bedroom) containing a HEPA or electrostatic air purifier may reduce airborne allergen in the remainder of the home by 90%.[292,296] In general, measures used to reduce exposure to dust mite work to some extent for cat allergen as well.[285]

Some[297,298] but not all[292,296,300] studies have demonstrated reduced airborne cat allergen by washing the animal on a weekly basis. Frequent bathing of dogs (at least twice a week) similarly has been found to be effective for reducing dog allergen exposure.[299] Litter boxes should be placed in an area separated from the air supply to the rest of the home to avoid dispersal of allergen. If not removed, caged pets (birds, rodents, guinea pigs, and so forth) also should be kept in an uncarpeted area of the home and remote from the patient's bedroom.

59. Cockroaches are a significant cause of nasal allergy, particularly in inner-city populations. **C**

Allergic rhinitis and asthma have been reported after exposure to debris of numerous insects including cockroaches, crickets, caddis flies, houseflies, midges, spider mites, mosquitoes, ladybugs, and moths.[899-906] In endemic areas, such as West Virginia, ladybug is a major allergen causing rhinoconjunctivitis at a prevalence rate of as high as 8%.[904,905] Ladybug skin test sensitization is comparable in frequency and age distribution with cat and cockroach in endemic areas.[904]

Because of their prevalence and indoor living habits, cockroaches are a significant cause of respiratory allergy, especially in inner-city populations. As many as 60% of dust-sensitive patients from urban areas react to cockroach allergens.[903,907] The major cockroach allergens, Bla g I and Bla g II, are found on the insect's body and its feces. Cockroach allergen is most abundant in kitchen floor dust and may reach high levels in poorly maintained homes and apartments. Cockroach elimination requires careful sanitation such as not allowing food to stand open or remain on unwashed dishes, promptly wiping up food spills, and storing garbage in tightly closed containers. Use of roach traps, such as odorless and colorless gel baits containing hydramethylnon or abamectin,[289,290] has been advocated because these permit removal of the allergen-containing bodies of the insects. If the infestation is heavy, repeated applications of insecticide by a professional exterminator or changing homes may be required.

60. The best treatment for rhinitis triggered by irritants, such as tobacco smoke and formaldehyde, is avoidance. **B**

An irritant is defined by the Occupational Health and Safety Administration as ''a noncorrosive chemical which causes a reversible inflammatory effect on living tissue by chemical action at the site of contact.'' A more general definition is that an irritant is a substance that, on immediate, prolonged, or repeated contact with normal living tissue, will induce a local inflammatory reaction.

The amount of inflammation associated with irritants depends on their degree of irritation, the duration of exposure, and the sensitivity of the target organ. The effect of irritants is temporary. Pepper spray, for example, is a severe eye and nose irritant, although it causes no lasting effects. People with asthma tend to be more sensitive to the irritant effects of airborne substances such as perfumes, ozone, and smoke than those with normal lung function. It should be noted that the amount of exposure to a substance

that is capable of causing an irritant reaction often is orders of magnitude less than the amount causing organ toxicity.

Because many substances in buildings are volatile and potentially irritating, it often is difficult to determine the source of a particular inflammatory reaction. To determine whether an irritant is responsible for a symptom, it is necessary to demonstrate that the substance is present in the environment, that exposure is sufficient in magnitude and duration to trigger the observed reaction in the affected individual, and that other substances that could account for the symptoms are not present.

Fungi produce a number of potentially irritating substances. These include microbially derived volatile organic compounds (MVOCs), glucans that are related to endotoxins, and ergosterols. However, the full spectrum of bacterial and fungal irritants has not been fully enumerated. As with other irritants, the health effects of exposure to these substances are directly related to the amount and duration of exposure. Thus, buildings with good ventilation are considered healthier than those in which airborne, potentially respirable irritants can accumulate.

Rhinitis has been attributed to irritants such as tobacco smoke, formaldehyde, perfume and other strong odors, and even newspaper ink. Environmental tobacco smoke is a significant irritant as well as a potentially toxic substance.[301] Because rhinitis symptoms that occur in response to tobacco smoke exposure do not involve IgE, avoidance of passive tobacco smoke is the best treatment. Formaldehyde is known to cause stinging and burning of the eyes and nose, lacrimation, and decreased nasal mucus flow.[302] This appears also to be an irritant effect because even prolonged, high-level formaldehyde exposure rarely results in development of IgE to formaldehyde-protein conjugates, and this does not correlate with clinical symptoms.[303] Because respiratory symptoms generally occur at concentrations well above those at which the odor of formaldehyde is detectable, it is unlikely that formaldehyde would be an unsuspected cause of rhinitis.[305,306] Some patients with rhinitis claim that exposure to perfume and newsprint can elicit symptoms.[304] The mechanism for this is uncertain but is likely to be an irritant reaction also.

Pharmacologic therapy

The selection of pharmacotherapy for a patient depends on multiple factors including the type of rhinitis present (eg, allergic, nonallergic, mixed, episodic), most prominent symptoms, severity, and patient age (Summary Statements 92, 93). Principal medication options are summarized in Table VI. The following sections of the parameter provide detailed discussion of medication options.

Oral antihistamines

61. Second-generation antihistamines are generally preferred over first-generation antihistamines for the treatment of allergic rhinitis. First-generation antihistamines have significant potential to cause sedation, performance impairment, and anticholinergic effects. Although occasionally advantageous (eg, sleep induction when taken at bedtime or a reduction in rhinorrhea), these properties are usually undesirable and are potentially dangerous. Second-generation antihistamines have less or no tendency to cause these effects. **B**
62. Before prescribing or recommending a first-generation antihistamine, the physician should ensure that the patient understands both the potential for adverse effects and the availability of alternative antihistamines with a lower likelihood of adverse effects. **D**

First-generation antihistamines such as diphenhydramine, hydroxyzine, and clemastine are associated with sedative effects—drowsiness and/or performance impairment—in many patients.[307-309] Interindividual variation exists with respect to development of sedative effects with either single-dose or regular use of these agents.[307,309,313] Although patients may deny sedation with first-generation antihistamines, performance impairment can exist without subjective awareness of drowsiness.[310] Although there are conflicting data, first-generation antihistamines have also been associated with impaired learning and school performance in children,[176,312] as well as driving impairment and fatal automobile accidents in adolescents and adults.[313-318] A large epidemiologic study found that drivers responsible for fatal automobile accidents were 1.5 times more likely to be taking first-generation antihistamines than drivers killed but not responsible for accidents.[319] Workers taking first-generation antihistamines may exhibit impaired work performance and productivity; they are more likely to be involved in occupational accidents. Concomitant use of other CNS-active substances, such as alcohol, sedatives, hypnotics, or antidepressant medication, may further enhance performance impairment from antihistamines.[307,309] A recent report found that impaired driving performance associated with hydroxyzine worsened with cellular phone use.[311] Paradoxical CNS stimulation may also occur with use of first-generation antihistamines, particularly in children.[908,909]

In a strategy intended to reduce costs of antihistamine therapy while avoiding daytime drowsiness and performance impairment, administration of a nonsedating second-generation antihistamine (that would otherwise be dosed twice daily) only once daily in the morning, followed by a first-generation (and less costly) antihistamine in the evening, has been advocated. However, first-generation antihistamines dosed only at bedtime can be associated with significant daytime drowsiness, decreased alertness, and performance impairment.[320-325] In part this is because antihistamines and their metabolites have prolonged plasma half-lives, and their end-organ effects persist longer than plasma levels of the parent compound (Table VII). Consequently, an AM/PM dosing regimen, combining a second-generation agent in the AM with a first-generation agent in the PM, is not a preferred strategy for avoiding daytime drowsiness and performance impairment from antihistamine treatment in the management of allergic rhinitis.[910]

Anticholinergic effects can also occur with first-generation antihistamines, including dryness of mouth and eyes, constipation, inhibition of micturition, and an increased risk for provocation of narrow angle glaucoma. Anticholinergic effects may also be desirable in some patients (eg, those with persistent rhinorrhea despite a second-generation antihistamine and a intranasal corticosteroid). However, a topical anticholinergic agent approved for allergic rhinitis without the potential for sedation or performance impairment would generally be preferred over a systemic agent with anticholinergic properties.

Older adults are more sensitive to the psychomotor impairment promoted by first-generation antihistamines,[911] are at increased risk for complications such as fractures and subdural hematomas caused by falls,[912] and are more susceptible to adverse anticholinergic effects. Because of concomitant comorbid conditions (eg, increased IOP, benign prostatic hypertrophy, preexisting cognitive

impairment, and so forth) that may increase the risk associated with regular or even intermittent use, extra caution should be used when considering the use of first-generation antihistamines in older adults.

In comparative studies, the second-generation antihistamines have been associated with less or no tendency for impairment of performance, drowsiness (Table VII), or anticholinergic effects.[307-311] For this reason, the second-generation antihistamines are generally preferred for the treatment of allergic rhinitis. First-generation antihistamines may be prescribed at bedtime when a soporific effect is desired (with the caveat noted that performance impairment can exist the next morning without subjective awareness of drowsiness), and/or it is viewed as advantageous to administer an antihistamine with anticholinergic properties.

63. There are important differences among the second-generation antihistamines in regards to their sedative properties: fexofenadine, loratadine, and desloratadine do not cause sedation at recommended doses; loratadine and desloratadine may cause sedation at doses exceeding the recommended dose; cetirizine and intranasal azelastine may cause sedation at recommended doses. **A**
64. Among the newer, nonsedating antihistamines, no single agent has been conclusively found to achieve superior overall response rates. **C**

The absence of sedative properties among the second-generation agents is not uniform. In multiple studies, the use of fexofenadine, loratadine, and desloratadine when used at recommended doses for the treatment of allergic rhinitis has not been associated with sedative properties compared with placebo.[307,309] Even at higher than FDA-approved doses, fexofenadine has no sedative properties when used for the treatment of allergic rhinitis.[308,913] Loratadine and desloratadine have sedative properties when dosed at higher than recommended doses,[323,328] or at recommended doses in certain individuals. Patients with low body mass for whom a standard dose (based on age) is prescribed may conceivably reach an elevated dosage level (on a milligram per kilogram basis), and thereby develop drowsiness and/or performance impairment.[307,309] Use of cetirizine or intranasal azelastine has been associated with sedative properties compared with placebo[309]; however, in many but not all cases, the effect tends to be milder than that observed with first-generation antihistamines.[307] Nonetheless, patients given these drugs for allergic rhinitis should be cautioned regarding this risk. Cetirizine 10 mg may be associated with mild drowsiness (13.7% for patients $\geq$ age 12 years) compared with placebo (6.3%)[329] but without performance impairment. Development of drowsiness without performance impairment has been observed with both Cetirizine 10 mg (the standard dose)[914] and 20 mg.[330] However, in other studies, the 10 mg or higher dose of Cetirizine, was associated with performance impairment.[307]

Among the newer, nonsedating antihistamines, no single agent has been conclusively shown to have superior efficacy.[326,327] A recent meta-analysis found ebastine (an agent not available in the United States) superior to loratadine for the decrease in mean rhinitis symptom scores in seasonal allergic rhinitis.[915] Several studies have found cetirizine to be superior to loratadine, although in 1 study, the differences were not statistically significant.[915] In a study of patients with seasonal allergic rhinitis who remained symptomatic after treatment with fexofenadine, azelastine significantly improved total nasal symptom score.[335]

The availability of second-generation antihistamines has substantially improved the therapeutic utility of antihistamines, because patients such as older adults who otherwise would avoid antihistamine therapy as a result of sedation or anticholinergic effects can be given antihistamine medications that are favorable for allergic rhinitis management from a risk/benefit standpoint.

Intranasal antihistamines

65. Intranasal antihistamines may be considered for use as first-line treatment for allergic and nonallergic rhinitis. **A**
66. Intranasal antihistamines are efficacious and equal to or superior to oral second-generation antihistamines for treatment of seasonal allergic rhinitis. **A**
67. Because systemic absorption occurs, currently available intranasal antihistamines have been associated with sedation and can inhibit skin test reactions. **A**
68. Intranasal antihistamines have been associated with a clinically significant effect on nasal congestion. **A**
69. Intranasal antihistamines are generally less effective than intranasal corticosteroids for treatment of allergic rhinitis. **A**

Azelastine and olopatadine are the only intranasal antihistamines currently available in the United states, are approved for the treatment of seasonal allergic rhinitis, and have been shown to improve congestion, rhinorrhea, sneezing, and nasal pruritus.[334,335] These agents may be considered as a first-line treatment for allergic rhinitis or as part of combination therapy with intranasal corticosteroids[339] or oral antihistamines. Intranasal azelastine has been demonstrated to be efficacious for nonallergic rhinitis.[916] Several studies have demonstrated that their efficacy for seasonal allergic rhinitis is superior[333-335] or equal to[332] oral second-generation antihistamines. A systematic review of 9 randomized controlled studies comparing intranasal antihistamines with intranasal corticosteroids [46] concluded that intranasal corticosteroids are more effective for controlling symptoms of perennial allergic rhinitis and seasonal allergic rhinitis. For mixed rhinitis, there may be significant benefit to the combination of an intranasal antihistamine with an intranasal corticosteroid.

Astelin (azelastine hydrochloride; Meda Pharmaceuticals, Somerset, NJ)[332-338] is formulated as a 0.1% aqueous solution and Patanase (olopatadine hydrochloride; Alcon Laboratories, Fort Worth, Tex) is formulated as a 0.6% aqueous solution, both in a metered spray delivery device. Recommended dosing is 2 sprays in each nostril twice daily for patients $\geq$12 years of age. Clinically significant onset of action of nasal azelastine has been reported at 15 minutes.[341] The onset of action of nasal olopatadine has been reported at 30 minutes after dosing in an environmental challenge unit. However, head-to-head comparisons of azelastine and olopatadine have not been performed. In clinical trials of nasal azelastine, 19.7% of patients complain of bitter taste, and 11.5% report somnolence.[342] In clinical trials of nasal olopatadine, 12.8% of patients complain of bitter taste, and 0.9% report somnolence.[917] In contrast with oral second-generation antihistamines, intranasal azelastine and olopatadine have been associated with clinically significant reduction in nasal congestion.[336-338,340] Because intranasal antihistamines are absorbed via the gastrointestinal tract, they can suppress skin test response for at least 48 hours in the case of azelastine.[657]

Oral and topical decongestants

70. Oral decongestants, such as pseudoephedrine and phenylephrine, are α-adrenergic agonists that can reduce nasal

congestion but can result in side effects such as insomnia, irritability, and palpitations. **A**

71. Oral and topical decongestants agents should be used with caution in older adults and young children, and in patients of any age who have a history of cardiac arrhythmia, angina pectoris, cerebrovascular disease, hypertension, bladder neck obstruction, glaucoma, or hyperthyroidism. **C**

Oral α-adrenergic agents relieve nasal congestion by acting as vasoconstrictors. These drugs may be useful in the management of allergic rhinitis and nonallergic rhinitis, including relief of nasal congestion caused by upper respiratory infections. The efficacy of an oral decongestant in combination with an antihistamine in the management of allergic rhinitis has not been adequately documented to increase the efficacy of either drug alone.[344]

Adverse effects from oral α-adrenergic agents may include elevated blood pressure, palpitations, loss of appetite, irritability, tremor, and sleep disturbance.[343] Concomitant use of caffeine, which at one time was prescribed by physicians as a decongestant,[350] may be associated with adverse effects that are additive.

Elevation of blood pressure after taking an oral decongestant is generally observed in hypertensive, but not normotensive, individuals. The effect of these agents on blood pressure was examined in 2 meta-analyses of phenylpropanolamine and pseudoephedrine. The meta-analysis of phenylpropanolamine use examined 33 trials reporting 48 treatment arms with 2165 patients[918] and found that exposure to phenylpropanolamine increased systolic blood pressure 5.5 mmHg (95% CI, 3.1-8.0) and diastolic blood pressure 4.1 mmHg (95% CI, 2.2-6.0), with no effect on heart rate. Patients with controlled hypertension were not at greater risk of blood pressure elevation. Eighteen studies included at least 1 treated subject with blood pressure elevation $\geq$140/90 mmHg, an increase in systolic blood pressure $\geq$15 mmHg, or an increase in diastolic blood pressure $\geq$10 mmHg. A meta-analysis that assessed risk for cardiovascular effects with pseudoephedrine[919] found that use of this agent was associated with a small increase in systolic blood pressure (0.99 mmHg; 95% CI, 0.08-1.90) and heart rate (2.83 beats/min; 95% CI, 2.0-3.6), with no effect on diastolic blood pressure (0.63 mmHg; 95% CI, –0.10 to 1.35). Oral decongestants are generally well tolerated by most patients with hypertension. However, based on interindividual variation in response, hypertensive patients should be monitored.

Pseudoephedrine is a key ingredient in making methamphetamine. For this reason, in an effort to reduce illicit production of methamphetamine, restrictions have been placed on the sale of pseudoephedrine in the United States[345] such that pseudoephedrine and pseudoephedrine-containing preparations have been taken off drugstore shelves and are maintained behind the counter.[345] Phenylephrine remains a nonrestricted decongestant because current regulations for pseudoephedrine do not apply to phenylephrine. This has promoted substitution of phenylephrine for pseudoephedrine in many OTC cold and cough remedies. However, phenylephrine is less efficacious compared with pseudoephedrine as an orally administered decongestant because it is extensively metabolized in the gut,[346,347] and its efficacy as an oral decongestant has not been well established.[345,348,349]

Oral α-adrenergic agonists should be used with caution in patients with certain conditions, such as arrhythmias, angina pectoris, coronary artery disease, cerebrovascular disease, and hyperthyroidism.[343] Oral decongestants may also raise IOP and provoke obstructive urinary symptoms; they may need to be avoided in patients with closed-angle glaucoma and bladder neck obstruction. Based on the greater likelihood of comorbid conditions with advancing age, use of oral decongestants may be especially problematic in older adults.[911]

Oral decongestants, when used in appropriate doses, are usually very well tolerated in children over 6 years of age. However, use in infants and young children has been associated with agitated psychosis, ataxia, hallucinations, and even death[351-353] (see Summary Statement 73). At times, even at recommended doses, these agents may cause increased stimulatory effects resulting in tachyarrhythmias, insomnia, and hyperactivity, especially when combined with other stimulant medications, such as stimulants used in attention deficit hyperactivity disorder management.[354] Therefore, the risks and benefits must be carefully considered before using oral decongestants in children below age 6 years.

72. Topical decongestants can be considered for short-term and possibly for intermittent or episodic therapy of nasal congestion, but are inappropriate for regular daily use because of the risk for the development of rhinitis medicamentosa. **C**

Topically applied sympathomimetic decongestant α-adrenergic agonists, are catecholamines, such as phenylephrine, or imidazoline agents, such as oxymetazoline or xylometazoline. These medications cause nasal vasoconstriction and decreased nasal edema but have no effect on antigen provoked nasal response.[355] α-Adrenergic vasoconstrictors reduce nasal obstruction but do not affect itching, sneezing, or nasal secretion. Intranasal decongestants were associated with superior efficacy for nasal decongestion compared with intranasal corticosteroids in a 28-day study.[356] However, topical decongestants are not recommended for long-term treatment because of the concerns of the development of rhinitis medicamentosa.

Although generally well tolerated, topical decongestants may cause local stinging or burning, sneezing, and dryness of the nose and throat. Delivery technique should follow the same general recommendations that apply to intranasal corticosteroids (see Summary Statement 80). Intranasal decongestants usually do not cause systemic sympathomimetic symptoms; however, a variety of cerebrovascular adverse events have been reported, including anterior ischemic optic neuropathy,[920] stroke,[921] branch retinal artery occlusion,[922] and ''thunderclap'' vascular headache.[923,924] Caution for use of decongestants during the first trimester is recommended because fetal heart rate changes with administration during pregnancy[925] have been reported. Topical vasoconstrictors should be used with care below age 1 year because of the narrow margin between the therapeutic and toxic dose, which increases the risk for cardiovascular and CNS side effects.[11]

Topical decongestants are appropriate to use on a short-term basis for nasal congestion associated with acute bacterial or viral infections, exacerbations of allergic rhinitis, and eustachian tube dysfunction. Intermittent use of topical decongestants may be considered, but efficacy and safety of this approach have not been formally studied. Regular use of topical decongestants can lead to rebound nasal congestion with rhinitis medicamentosa.[129] Unfortunately, few prospective studies have critically examined rhinitis medicamentosa. Furthermore, its pathophysiology is not fully understood. Topical decongestants cause vasoconstriction, reduce nasal secretion of mucus, and inhibit nasal ciliary action. Initial relief of nasal congestion can be prompt and dramatic; however, rebound congestion may follow as the vasoconstrictive

action of these agents diminishes. A somewhat paradoxical effect tends to occur with ongoing use; the decongestive action lessens, whereas the sense of nasal obstruction increases. The time of onset of rhinitis medicamentosa with regular use of topical decongestants has not been firmly established. Rebound congestion may occur as soon as the third or fourth day of treatment[357]; however, some studies have shown a lack of rebound congestion with 4 to 6 weeks of intranasal decongestant use.[358-360] The package insert for oxymetazoline nasal—ie, Afrin nasal spray (Schering-Plough, Kenilworth, NJ)—recommends use for no more than 3 days.[926] Because rhinitis medicamentosa may develop at 3 days,[357] it would be prudent to instruct patients of this risk. Longer treatment regimens should be entertained only with caution. First-line treatment of rhinitis medicamentosa consists of suspending topical decongestant use to allow the nasal mucosa to recover. Intranasal corticosteroids and, if necessary, a short course of oral steroids may be used to hasten recovery.[129,135]

OTC cough and cold medications for young children

73. The efficacy of cold and cough medications for symptomatic treatment of upper respiratory tract infections has not been established for children younger than 6 years. Because of the potential toxicity of these medications, the use of these OTC drugs generally should be avoided in all children below 6 years of age.

Differentiating infectious from noninfectious rhinitis can be very difficult both for physicians and for parents of young children. Controlled trials have shown that antihistamine-decongestant combination products are not effective for symptoms of upper respiratory tract infections in young children.[361-365] Furthermore, there has been increasing concern over the safety of OTC cough and cold medications in children. An Adverse Event Reporting System review[366] showed that between 1969 and September 2006, there were 54 fatalities associated with 3 reviewed decongestants found in OTC and prescription preparations (pseudoephedrine, 46; phenylephrine, 4; and ephedrine, 4) for children $\leq$ age 6 years, of whom 43 were below the age of 1 year. During the same reporting period and for the same age group, there were 69 fatalities associated with 3 antihistamines contained in OTC and prescription agents (diphenhydramine, 33; brompheniramine, 9; and chlorpheniramine, 27; with 41 reported below age 2 years). Drug overdose and toxicity were common events reported in these cases. The overdose error resulted from use of multiple cold/cough products, medication errors, accidental exposures, and intentional overdose.

Currently cough and cold OTC preparations indicate users should consult a physician for dosing recommendations below age 2 years for decongestants and below age 6 years for antihistamines. In early October 2007, Wyeth, Novartis, Prestige Brands, and Johnson & Johnson voluntarily removed their cough and cold medications for children under age 2 years from the OTC market. Based on the concerns discussed, in mid-October 2007 the FDA's Nonprescription Drugs and Pediatric Advisory Committees recommended that the OTC medications used to treat cough and cold no longer be used for children below 6 years of age.[366] The FDA has yet to respond to these recommendations. In contrast, second-generation antihistamines such as cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine when used in young children have been shown to be well tolerated and to have a very good safety profile.[367-374]

Intranasal corticosteroids

74. Intranasal corticosteroids are the most effective medication class in controlling symptoms of allergic rhinitis. **A**
75. In most studies, intranasal corticosteroids were shown to be more effective than the combined use of an antihistamine and LT antagonist in the treatment of seasonal allergic rhinitis. **A**
76. Intranasal corticosteroids may provide significant relief of symptoms of seasonal allergic rhinitis when used not only on a regular basis but also when used on an as needed basis. **B**

However, as needed use may not be as effective as continuous use of intranasal corticosteroids. **D**

77. When comparing the available intranasal corticosteroids, the overall clinical response does not appear to vary significantly between products irrespective of the differences in topical potency, lipid solubility, and binding affinity. **C**

The main mechanism by which corticosteroids relieve the symptoms of allergic rhinitis is through their anti-inflammatory activity,[927] although it is possible that they may exert an effect through other mechanisms. The concept of delivering corticosteroids locally to the nasal airways was developed to minimize potential side effects of using systemic corticosteroids. Intranasal corticosteroids are available in various formulations (Table VIII). When comparing the available intranasal corticosteroids, the overall clinical response does not appear to vary significantly between products irrespective of the differences in topical potency, lipid solubility, and binding affinity.[53,380-382]

Intranasal corticosteroids are effective in controlling the 4 major symptoms of allergic rhinitis: sneezing, itching, rhinorrhea, and nasal congestion. In clinical studies, intranasal corticosteroids have been shown to be more effective than nasal cromolyn sodium[435,928] or LTRAs.[929,930] In most studies, intranasal corticosteroids were shown to be more effective than the combined use of an antihistamine and LT antagonist in the treatment of seasonal allergic rhinitis.[375-379] However, for patients who are unresponsive to or noncompliant with intranasal corticosteroids, combination therapy using an antihistamine in combination with an anti-LT or a decongestant may provide a viable alternative. In 2 systematic reviews of randomized controlled studies, intranasal corticosteroids were significantly more effective than oral and intranasal antihistamines in relieving symptoms of sneezing, nasal congestion, discharge, and itching, and were not significantly different for the relief of eye symptoms.[46,54] However, in 1 study included in these reviews, a nasal antihistamine was more efficacious than intranasal corticosteroids. Although the addition of an oral antihistamine to an intranasal corticosteroid generally has not demonstrated greater clinical benefit than intranasal corticosteroid monotherapy in controlled trials,[931,932] in 1 well controlled study of seasonal allergic rhinitis, the addition of cetirizine to intranasal fluticasone propionate led to greater relief of pruritus.[364] In another study, the combination of fluticasone propionate and loratadine was superior to fluticasone propionate alone for some patient-rated symptoms,[931] Likewise, 1 study found that at least 50% of patients need to take both intranasal corticosteroids and oral antihistamines to control symptoms of seasonal allergic rhinitis adequately.[933] A study comparing the effectiveness and safety of intranasal corticosteroids and anticholinergic agents has shown that an intranasal corticosteroid is more effective than an anticholinergic agent for all nasal symptoms except rhinorrhea.[390]

Clinical studies have also shown that intranasal fluticasone propionate can provide significant relief of the symptoms of seasonal allergic rhinitis compared with placebo when used on an as-needed basis (which equated to 55% to 62% usage).[380,386,387] However, this may not be as effective as continuous use. A well controlled trial of intranasal fluticasone propionate compared with loratadine when used on an as-needed basis for seasonal allergic rhinitis demonstrated significantly better scores for the fluticasone-treated patients in activity, sleep, practical, and overall domains.[380] The onset of therapeutic effect of intranasal corticosteroids seems to occur within 12 hours and as early as 3 to 4 hours in some patients for nasal symptoms.[383-385] Because a patent nasal airway is necessary for optimal intranasal delivery of intranasal corticosteroids, use of a nasal decongestant spray may be necessary for several days when intranasal corticosteroids are introduced.

78. Intranasal corticosteroids may be useful in the treatment of some forms of nonallergic rhinitis. **A**

The effectiveness of intranasal corticosteroids has been shown in studies that have involved a large number of patients with nonallergic rhinitis, especially those with NARES.[146,388-390] Intranasal corticosteroids have also been shown to be effective in the treatment of vasomotor rhinitis.[389,391,392]

79. Intranasal corticosteroids when given in recommended doses are not generally associated with clinically significant systemic side effects. **A**

It is unusual for adult patients to develop systemic corticosteroid side effects after administration of intranasal corticosteroids in recommended doses. In children, an effect of intranasal corticosteroids on growth has been demonstrated, as discussed below, although an effect on the HPA axis has not been demonstrated and no reduction in bone density or other systemic effects have been reported.[407]

HPA axis

Studies of corticosteroid preparations at recommended and moderate doses given once daily demonstrate minimal systemic corticosteroid effects on the HPA axis, as assessed by morning cortisol concentrations, cosyntropin stimulation, and 24-hour urinary-free cortisol excretion.[393-397] Studies in children have shown no clinically significant effect of intranasal corticosteroids on the HPA axis.[398-401] However, the effect of intranasal corticosteroids on growth, recognizing the variability in individual patient response, may be a better indicator of systemic effects in children, and can occur without an effect on the HPA axis. Growth suppression is both a sensitive and relatively specific indicator of excessive corticosteroid effect, compared with measures of basal HPA function that are highly sensitive but have limited value as a predictor of a clinically significant effect. Therefore, there may be a disparity between the effect of intranasal corticosteroids on the HPA axis assessment as an indication of systemic effect and their transient effect on growth in children. The transient effect on growth is dependent on the specific intranasal corticosteroid product, dose, techniques for measuring growth, time of administration, and use of concomitant oral or inhaled corticosteroids.

Ocular effects

There have been reports of a possible association between the development of posterior subcapsular cataracts and the use of intranasal or inhaled corticosteroids in older patients,[934] but this association has not been confirmed by other studies with inhaled corticosteroids[935] or studies of intranasal corticosteroids.[402,403] Concomitant use of systemic corticosteroids in some patients receiving intranasal corticosteroids confounds interpretation of these studies. Studies of intranasal corticosteroids in prospective studies of 24 weeks of treatment have not demonstrated the development of lenticular changes consistent with posterior subcapsular cataracts.[393] On the basis of available studies, patients receiving standard doses of intranasal corticosteroids are not at increased risk for the development of glaucoma.[404] As with all potential side effects of intranasal corticosteroids, individual patient variability may allow for the development of ocular effects from intranasal corticosteroids, especially in older patients.

Bone

Studies[405,406] and a review of the literature[407] point toward a negative relationship between total cumulative inhaled corticosteroids and bone marrow density in children and adults with asthma. However, there are limited data examining the effect, and, in particular, the effect after long-term administration of intranasal corticosteroids on bone marrow density. Short-term administration of budesonide, triamcinolone, and mometasone at a dose of 200 mcg/d resulted in no suppression of plasma osteocalcin levels.[936] However, other studies have shown reduced bone mineral density after use of inhaled corticosteroids.[937-939]

Growth

In children, concerns about possible adverse effects on growth raise special considerations. Growth suppression, assessed by stadiometer height measurement, was detected in children with perennial allergic rhinitis treated with intranasal beclomethasone dipropionate for 1 year at twice the usually recommended dose.[409] Similar studies with intranasal fluticasone propionate, mometasone furoate, and budesonide show no effects on growth compared with placebo (at recommended doses)[408-410] and reference values (at as much as 2 times recommended doses),[400] except in toddlers.[411]

80. Although local side effects are typically minimal with the use of intranasal corticosteroids, nasal irritation and bleeding may occur. Nasal septal perforation is rarely reported. **B**

The most common side effects associated with the use of intranasal corticosteroids are a result of local irritation. Burning or stinging is most often associated with the use of propylene glycol-containing solutions.

Nasal bleeding has been seen with intranasal corticosteroids, usually as blown blood-tinged secretions. Nasal septal perforation has rarely been reported with long-term use of intranasal corticosteroids.[412,413] Patients should direct the spray away from the septum to prevent repetitive direct application to the septum. The nasal septum should be periodically examined to assure that there are no mucosal erosions present because these may precede the development of nasal septal perforations.

Nasal biopsies in patients with perennial allergic rhinitis show no evidence of atrophy or other tissue change after 1 to 5 years of therapy.[618,940,941] Evaluation of the histologic and macroscopic appearance of the nasal mucosa after administration of intranasal corticosteroids has shown no deleterious pathological changes from that after placebo or antihistamines.[618,942] *In vitro* and some *in vivo* studies have shown that benzalkonium chloride alone, and in 1 clinical study, a corticosteroid nasal spray containing benzalkonium chloride, can promote ciliary stasis and reduce mucociliary transport.[414,415]

Oral corticosteroids

81. A short course (5-7 days) of oral corticosteroids may be appropriate for the treatment of very severe or intractable nasal symptoms or to treat significant nasal polyposis. However, single administration of parenteral corticosteroids is discouraged and recurrent administration of parenteral corticosteroids is contraindicated because of greater potential for long-term corticosteroid side effects. **D**

Oral corticosteroids should not be administered as therapy for chronic rhinitis, except for rare patients with severe intractable nasal symptoms who are unresponsive to other modalities of treatment. In such patients, especially those with polyposis, a short course of short acting oral corticosteroids, such as prednisone or methylprednisolone, may be appropriate.[416,417] Because of the variability of patient response, as reflected in data from studies addressing adrenal response to oral corticosteroids, the potential for adrenal suppression should be considered in any patient who receives oral corticosteroids.

Parenteral corticosteroid administration is not recommended because of the greater potential for long-term corticosteroid side effects, in particular prolonged adrenal suppression as well as local muscle atrophy and fat necrosis.[418-420] Recurrent parenteral corticosteroid administration in the treatment of rhinitis is contraindicated.

Intraturbinate injection of corticosteroids is sometimes used by otolaryngologists for the treatment of inferior turbinate hypertrophy. Side effects are usually minor, but permanent vision loss because of cavernous vein thrombosis has been reported in 0.006% of patients.[421-423] Nasal and oral corticosteroids are safer alternatives.

Intranasal cromolyn

82. Intranasal cromolyn sodium is effective in some patients for prevention and treatment of allergic rhinitis and is associated with minimal side effects. It is less effective in most patients than corticosteroids and has not been adequately studied in comparison with LT antagonists and antihistamines. **A**

A 4% pump spray solution of cromolyn sodium, United States Pharmacopeia, is available for topical intranasal treatment of seasonal and perennial allergic rhinitis. The main benefit is a strong safety profile. When used to treat symptoms of seasonal allergic rhinitis, cromolyn should be started as early in an allergy season as possible. An effect is normally noted within 4 to 7 days of initiation. However, severe or perennial cases may require 2 weeks or more for maximum effect. Patients who are highly symptomatic may require the addition of an antihistamine-decongestant combination during the first few days of cromolyn treatment. Because a patent nasal airway is a prerequisite, a decongestant may be necessary for a few days. Thereafter, the treatment is continued at whatever maintenance dose is effective for the remainder of the expected season or period of exposure.

Cromolyn sodium has been shown to inhibit the degranulation of sensitized mast cells, thereby preventing the release of mediators of the allergic response and of inflammation. Thus, it prevents the allergic event rather than alleviates symptoms once the reaction has begun.[424-429] Nasal cromolyn is effective in the treatment of episodic rhinitis, such as before anticipated allergen exposure, where there appears to be a more rapid onset of action.[432-434] The protective effect of cromolyn against nasal antigen challenge persists for 4 to 8 hours after insufflation,[943] making it an ideal preventative treatment to consider with predictable exposures such as veterinarians.[944]

In controlled treatment studies, cromolyn was superior to placebo. A randomized, double-blind, placebo-controlled study in children 2 to 5 years of age demonstrated that cromolyn sodium provided relief of symptoms of allergic rhinitis.[945] In addition, the effectiveness of cromolyn sodium in allergic rhinitis was demonstrated among self-selected patients in a nonprescription setting.[946] However, cromolyn was generally less effective than intranasal corticosteroids and has not been adequately studied in comparison with LT antagonists and antihistamines.[435]

Side effects are usually mild and local, including sneezing and nasal stinging or burning. Nasal septal perforations and nasal crusting have not been reported with the use of nasal cromolyn sodium. Because of its excellent safety profile, including a lack of significant drug interaction, cromolyn should be considered in very young children and pregnancy.[602,605] Patient selection is critical, and published review articles describe its limited role in treating and preventing allergic rhinitis symptoms.[947]

There is no evidence that intranasal cromolyn will benefit patients with (1) vasomotor rhinitis, (2) NARES, or (3) nasal polyposis.[430,431]

Intranasal anticholinergics

83. Intranasal anticholinergics may effectively reduce rhinorrhea but have no effect on other nasal symptoms. Although side effects are minimal, dryness of the nasal membranes may occur. **A**
84. The concomitant use of ipratropium bromide nasal spray and an intranasal corticosteroid is more effective than administration of either drug alone in the treatment of rhinorrhea without any increased incidence of adverse events. **A**

Increased cholinergic hyperreactivity has been documented in patients without and with allergy as well as in patients with recent upper respiratory tract infections.[710,948-950] A significant proportion of histamine-induced and antigen-induced secretion appears to be cholinergically mediated.[951,952] In addition to increased glandular secretion, parasympathetic stimulation causes some vasodilation, particularly sinusoidal engorgement, which may contribute to nasal congestion. Ipratropium bromide and glycopyrrolate are quaternary structured ammonium muscarinic receptor antagonists that are poorly absorbed across biological membranes. Ipratropium bromide is poorly absorbed into the systemic circulation from the nasal mucosa.[953]

Ipratropium bromide has been the most extensively studied intranasal anticholinergic agent. Ipratropium bromide exerts its effect locally on the nasal mucosa, resulting in a reduction of systemic anticholinergic effects (eg, neurologic, ophthalmic, cardiovascular, and gastrointestinal effects) that are seen with tertiary anticholinergic amines. Controlled clinical trials have demonstrated that a quaternary agent such as intranasal ipratropium bromide does not alter physiologic nasal functions (eg, sense of smell, ciliary beat frequency, mucociliary clearance, or the air conditioning capacity of the nose).[449] Atrovent (ipratropium bromide; Boehringer-Ingelheim, Ridgefield, Conn) nasal spray 0.03% has been approved for use in patients 6 years of age and older on the basis of its effectiveness in treating rhinorrhea caused by perennial allergic and nonallergic rhinitis in adults and children.[437-442] The 0.06% concentration has been approved for patients 5 years of age and older for rhinorrhea associated with the

common cold. Ipratropium bromide is approved only for the treatment of rhinorrhea, although 1 pediatric study showed modest benefit for controlling nasal congestion.[448] It has been shown that the concomitant use of ipratropium bromide nasal spray and antihistamines may provide increased efficacy over either drug alone without any increase in adverse events.[442] The combined use of ipratropium bromide nasal spray 0.03% and a intranasal corticosteroid is also more effective than administration of either drug alone in the treatment of rhinorrhea without any increased incidence of adverse events.[390] The effectiveness and safety of ipratropium bromide nasal spray 0.03% have also been demonstrated in cold-induced rhinitis (eg, skiers),[436] and it is useful in reducing rhinorrhea associated with eating (gustatory rhinitis).[66] Ipratropium bromide nasal spray 0.06% is effective for rhinorrhea produced by the common cold, in part because of parasympathetic stimulation.[443-447]

The most frequently reported adverse events in studies evaluating ipratropium bromide nasal spray 0.03% (as reported in the product information) were mild transient episodes of epistaxis (9%) compared with 5% after use of saline vehicle and nasal dryness (5%) compared with 1% after use of saline vehicle. In addition, the safety of the 0.06% concentration has been demonstrated in children with upper respiratory infections.[954]

Oral anti-LT agents

85. Oral anti-LT agents alone or in combination with antihistamines have proven to be useful in the treatment of allergic rhinitis. **A**

Leukotriene receptor antagonist produce statistically significant improvement in nasal symptoms and standardized rhinoconjunctivitis QOL scores compared with placebo in a number of studies for seasonal allergic rhinitis,[450-452] and for perennial allergic rhinitis as well.[453] The onset of action occurs by the second day of daily treatment.[49] There is no significant difference in efficacy between LTRA and antihistamines (with loratadine as the usual comparator).[40,42,377] Likewise, compared with pseudoephedrine, montelukast shows similar reduction in all symptoms of allergic rhinitis except the symptom of nasal congestion, for which pseudoephedrine is more effective.[955] Unlike antihistamines, LTRA do not significantly suppress skin tests.[956,957] LTRA are less effective than intranasal corticosteroids.[375,958] The combination of an antihistamine and LTRAs is superior to either therapy when given alone. Intranasal corticosteroids are either equal to[378,379] or superior[48,375] to the combination of an antihistamine and an LTRA. These differences may in part be a result of which antihistamine is used in the combination therapy. Combination therapy with an antihistamine and an anti-LT agent or decongestant may provide alternative treatment for patients who are unresponsive to or not compliant with intranasal corticosteroids, or for whom intranasal corticosteroids are contraindicated.

Montelukast is a safe and effective treatment for the management of allergic rhinitis in children. It is approved for perennial allergic rhinitis in children as young as 6 months and for seasonal allergic rhinitis in children as young as 2 years. Other LTRAs may also be efficacious but have not been adequately studied. Combination of montelukast and a second-generation antihistamine may show added benefit for allergic rhinitis and provide better protection against seasonal decrease in lung function.[457] Recognizing that as many as 40% of patients with allergic rhinitis have coexisting asthma, montelukast may be considered when treatment can benefit the combined upper and lower airway.[454-456] In children with mild persistent asthma and coexisting allergic rhinitis, montelukast has been recommended for monotherapy.[454] The use of LTRA for combined upper and lower airway allergic diseases as either a monotherapy or combined therapy is particularly attractive when treating a child whose parents are steroid-phobic.

Omalizumab

86. Omalizumab has demonstrated efficacy in AR; however, it has FDA approval for use only in allergic asthma. **A**

Although not approved for the use in allergic rhinitis, omalizumab has demonstrated efficacy in this illness. Humanized mAb (omalizumab) has demonstrated efficacy in attenuating bronchial responses to inhaled aeroallergen challenges,[959] and in allergic asthma,[960,961] through a reduction of circulating IgE. Patients with seasonal and perennial allergic rhinitis had significant reduction of both nasal and ocular symptoms and improved QOL[458] after the use of omalizumab. Omalizumab, however, has not demonstrated superiority to currently approved treatments for rhinitis. Thus, when one considers the cost of this treatment, it precludes its use for the treatment of allergic rhinitis in the absence of asthma. Unlike conventional allergen immunotherapy, which may improve the long-term course of allergic rhinitis even after it is discontinued, there is no evidence that omalizumab improves the natural course of allergic rhinitis after its discontinuation.

Saline

87. There is evidence that topical saline is beneficial in the treatment of the symptoms of chronic rhinorrhea and rhinosinusitis when used as a sole modality or for adjunctive treatment.

Topical saline is commonly used as a treatment for rhinitis and rhinosinusitis in both children and adults. Although less effective than intranasal corticosteroids and no more effective than other active agents for rhinitis, isotonic and hypertonic saline solutions, used as either single or adjunctive agents, are of modest benefit for reducing symptoms and improving the QOL in patients with allergic rhinitis and rhinosinusitis.[459] In one 4-week study, the use of saline as a wetting agent for perennial rhinitis demonstrated reduced sneezing and nasal stuffiness, reduced nasal blockage (measured by peak flow), and a reduction in eosinophils (nasal biopsy).[962] Overall, there is no difference in symptom or radiologic scores when comparing isotonic with hypertonic saline.[462,463] Various mechanisms, such as improvement in mucus clearance; enhanced ciliary beat activity; removal of antigen, biofilm, or inflammatory mediators; and a protective role on sinonasal mucosa, have been proposed but not confirmed to explain the reported symptom improvement. Although it has been shown that hypertonic saline solutions improve mucociliary clearance,[462,680] this may not be the explanation for the clinical improvement obtained from saline irrigation.

The use of topical saline is associated with minimal side effects such as burning, irritation, and nausea; has low cost; and has overall good patient acceptance.[460,461] The preferred method of delivery—nose spray, bottle, pump, irrigation, or nebulizer; the volume; and the dose frequency have not been established. Frequently used homemade formulas for isotonic and hypertonic saline are listed in Table IX.

Allergen immunotherapy

88. Allergen immunotherapy is effective for the treatment of allergic rhinitis. **A**
89. Allergen immunotherapy should be considered for patients with allergic rhinitis who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens, and its use depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **(A)**
90. Allergen immunotherapy may prevent the development of new allergen sensitizations and reduce the risk for the future development of asthma in patients with allergic rhinitis. **B**

Multiple randomized, prospective, single-blind or double-blind, placebo-controlled studies demonstrate effectiveness of specific allergen immunotherapy in the treatment of allergic rhinitis.[51,464,465] Allergen immunotherapy is the only treatment intervention that that has been shown to modify the natural history of allergic rhinitis.[50,466] Unlike pharmacotherapy, the clinical benefits may be sustained years after discontinuation of treatment.[466,467] Allergen immunotherapy for allergic rhinitis may prevent the development of new allergen sensitizations[469-471] and reduce the risk for the future development of asthma in patients with allergic rhinitis.[472-481] The expected response to allergen immunotherapy is allergen-specific and depends on proper identification and selection of allergens on the basis of the patient's history, exposure, and diagnostic test results. Allergen immunotherapy is effective in both adults and children.[471,479,482-485] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollen,[466,486-492] fungi,[493-497] animal allergens,[498-505] dust mite,[506-517] and cockroach.[518]

Allergen immunotherapy should be considered for patients who have symptoms of allergic rhinitis or rhinoconjunctivitis after natural exposure to allergens and who demonstrate specific IgE antibodies to relevant allergens. The severity, lack of response to or side effects from other interventions, and duration of symptoms should all be considered when assessing the need for specific allergen immunotherapy. Likewise, the patient's desire to avoid long-term pharmacotherapy and to seek treatment that can potentially modify allergic disease are additional factors to be considered when reaching a decision to initiate allergen immunotherapy. Coexisting medical conditions, such as asthma and sinusitis, should also be considered in evaluation of a patient who may be a candidate for allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed with a combined aggressive regimen of allergen avoidance and pharmacotherapy, but these patients may also benefit from allergen immunotherapy providing their asthma is stable when the allergen immunotherapy injection is administered.[50,468] Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.[519,520]

The risks of allergen immunotherapy include common local reactions, swelling and induration at the injection site, and in rare instances, life-threatening and fatal reactions.[963] The estimated allergen immunotherapy fatality rate was 1 per 2.5 million injections (average of 3.4 deaths per year) according to a recent AAAAI survey of physician members,[964] similar to 2 previous surveys of AAAAI physician members.[965,966] Identified risk factors for anaphylaxis after allergen immunotherapy include symptomatic asthma, injections administered from a new vial, β-blockers, a high degree of skin test reactivity, and injections given during times of symptom exacerbations.[967]

Contraindications for allergen immunotherapy include patients with medical conditions that would reduce their ability to survive allergen immunotherapy systemic allergic reactions or the resultant treatment.[50] Examples include severe asthma uncontrolled by pharmacotherapy and significant cardiovascular disease.

Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose.[494,503,968,969] If clinical improvement is not apparent after 1 year of maintenance therapy, possible reasons for lack of efficacy should be evaluated, and discontinuation of treatment should be considered if none are found. If allergen immunotherapy is effective, treatment may be continued for longer than 3 years depending on the patient's ongoing response to treatment. Currently there are no specific tests or clinical markers that will distinguish between patients who will relapse and those who will remain in long-term clinical remission after discontinuing effective inhalant allergen immunotherapy, and the decision to continue or stop immunotherapy must be individualized (refer to ''Allergen Immunotherapy: A Practice Parameter Second Update''[50] for further information regarding allergen immunotherapy).

Surgical approaches for comorbid conditions.

91. Although there is no surgical treatment for allergic rhinitis, surgery may be indicated in the management of comorbid conditions, such as nasal obstruction from severe nasal septal deviation or inferior turbinate hypertrophy, adenoidal hypertrophy, or refractory sinusitis and complications thereof. **C**

A variety of anatomical variants can lead to persistent nasal obstruction that may amplify the congestion and turbinate hypertrophy secondary to allergic inflammation. Surgery may play a beneficial role in the management of conditions associated with rhinitis—for example, mechanical nasal obstruction caused by anatomical variants such as septal deviation or concha bullosa,[77] refractory sinusitis with or without nasal polyposis,[524] and inferior turbinate hypertrophy, mucosal or bony, refractory to maximal medical treatment.[3] Surgery to reduce nasal obstruction may improve the nasal airflow and allows for more effective delivery of topical medications.

Patients with rhinitis who develop acute bacterial sinusitis will usually require antibiotics. However, even with appropriate treatment, a small percentage of patients will develop complications such as periorbital edema, meningitis, brain abscess, cavernous sinus thrombosis, or subperiosteal abscess with the risk of permanent vision loss or even death.[77,521-523] These patients may require surgical intervention. Patients with chronic sinusitis with or without nasal polyps may also require surgical intervention (see ''The Diagnosis and Management of Sinusitis: A Practice Parameter Update''[77]).

The nasal airway creates more than half of the total respiratory resistance to the lungs. Within the nose the internal nasal valve, the narrowest portion found in the anterior nose, is responsible for more than 2/3 of the airflow resistance produced by the nose.[970] As air passes through the nasal vault in a laminar flow pattern, there is an increase in its speed and pressure. Expanding into the nasal valve cavity, a turbulent flow pattern is created as the air is exposed to a large surface area for conditioning. Any time the turbulent airflow pattern is disturbed, it is perceived as nasal

obstruction, whether the passage is either too narrow or too wide.[525] The septal valve involves the space between the anterior tip of the inferior turbinate and the septum and is the area most commonly associated with the subjective perception of obstruction. A small anterior deviation of the septum is much more significant that a larger posterior deviation. Anterior septal deviation, with or without nasal valve collapse, and anterior inferior turbinate hypertrophy are thus the major structural components resulting in the symptom of nasal obstruction.

Correction of nasal septal deviation is one of the most common surgical procedures completed. The nasal septum is off-center in approximately 80% of the general population and appears deviated by CT in as many as 56%.[971] It has been estimated that in patients with nasal obstruction, a clinically significant deviated nasal septum is present in 26%.[526] Trauma, intrauterine, during birth, or postnatally, is the most common etiology of a deviated septum, and the degree of trauma required for clinically significant deviation is inversely related to the patient's age. Furthermore, the obstruction becomes more pronounced over time with cartilaginous overgrowth on the dominant side. The type of deviation varies, with the most common classifications septal tilt (40%), C-shaped anteroposterior deviation (32%), and S-shaped anteroposterior (9%).[972] Typically there is also unilateral compensatory turbinate hypertrophy on the side opposite the deviation, which may even be bilateral with an S-shaped deviation. The surgical procedures for correction of a deviated septum usually used are submucosal resection and septoplasty. Submucosal resection involves more extensive resection of cartilage and bone, is less tissue-sparing, and has a higher incidence of septal perforation complications.[530] Septoplasty, currently the preferred procedure, reshapes, repositions, or recontours the cartilage, with as many as 77% of patients achieving subjective improvement.[529] The exact techniques, such as scoring, morselization, or removal of cartilage, with manual or powdered instrumentation,[973] and/or the use of cartilage grafts will depend on the type and severity of the septal deviation. Endoscopic septoplasty is replacing traditional septoplasty in many clinical settings.[528] Inferior turbinate reduction surgery, as described below, is often performed concurrently with septoplasty, although some studies fail to show any long-term benefit.[531,532] Because long-term results from septoplasty are not always satisfactory—for example, there may be recurrence of deviation or a disturbed nasal cycle—the surgeon must make a careful preoperative assessment and attempt to differentiate between physiological and pathological septal deviation and consider all factors that may be contributing to nasal obstruction.[974]

Allergic rhinitis and nonallergic rhinitis cause swelling of the nasal mucosa, most notably of the inferior turbinates. It has been estimated that as much as 20% of the population has chronic nasal obstruction caused by turbinate hypertrophy.[524] Medical treatment may not be successful in shrinking the nasal mucosa and alleviating the symptoms of chronic nasal obstruction. At times, unrelated nasal surgery, such as cosmetic rhinoplasty, may inadvertently lead to increased nasal obstruction by reducing the nasal valve or changing the airflow pattern.[538,539] To select the most appropriate surgical procedure for long-term outcome, the surgeon must assess the contribution of turbinate mucosal hypertrophy versus the position and degree of bony hypertrophy. The degree of shrinkage with a topical decongestant may assist in delineating mucosal from bony hypertrophy and predict success of certain procedures, such as radiofrequency volumetric tissue reduction (RFVTR).[975]

Multiple surgical procedures on the inferior turbinate have been described, and all are considered to have some beneficial effects. The goal of these techniques is to reduce the size of the inferior turbinate outright, or to diminish its ability to swell and block the nasal passages. The various surgical procedures address the mucosal hypertrophy, the bony hypertrophy, or a combination of bony and mucosal hypertrophy. Mucosal hypertrophy reduction focuses either on the surface mucosa (eg, electrocautery and laser vaporization) or intramurally (eg, bipolar cautery or radiofrequency ablation), with intentional submucosal tissue injury resulting in tissue loss and subsequent scarring thereby leading to a reduced bulk of the inferior turbinate, while preserving the surface mucosa. Bony hypertrophy is addressed with submucosal resection, which tends to spare submucosa and mucosa. In contrast, partial turbinectomy and turbinoplasty procedures remove bone, submucosa, and mucosa. Lateral outfracture, a procedure of repositioning the turbinate laterally by fracturing the turbinate bone, does not reduce either mucosal or bony hypertrophy and has reduced surgical complications but may give only temporary results.

When bony hypertrophy is present, the surgeon has several techniques from which to choose. Turbinectomy involves fracturing the turbinate bone and then snipping off the bone, submucosa, and mucosa. Turbinoplasty involves fracture, followed by mucosal incision and removal of a wedge of conchal bone with attached inferior and lateral soft tissue. The posterior turbinate tip is also excised. The mucosal flap is then used to form a neoturbinate. Compared with partial turbinectomy, turbinoplasty spares more mucosal surface and has less chance of bleeding and postoperative crusting. Submucosal resection preserves the most mucosa but is more technically difficult and does not address the posterior inferior turbinate.[524] Powered microdebrider-assisted inferior turbinoplasty,[536] a relatively new procedure, can be conducted in the office setting under local anesthesia. After a small incision in the anterior inferior turbinate tip, the powered blade/suction device is introduced, and the bone and submucosa are crushed and removed by suction, thereby preserving the turbinate mucosa.[537] It is associated with no significant bleeding or crusting. It is felt to be superior to both submucosal cauterization and submucosal resection.[538,539] Laser turbinectomy may use the carbon dioxide, neodymium-doped yttrium aluminum garnet, or diode lasers. The tissue is vaporized in areas, leaving islands of intact mucosa. This can be performed under local anesthesia, minimal bleeding is noted, and there is no need for packing. Postoperative crusting may be noted. Any of these procedures may offer a beneficial effect of symptom improvement and increased nasal airflow in patients with allergic rhinitis and coexisting turbinate hypertrophy that has been unresponsive to medical therapy.[540-542]

Electrocautery can be either linear mucosal or submucosal using a unipolar or bipolar electrode inducing fibrosis and wound contracture with resultant volume reduction. Surgical bleeding is minimal; however, mucosal edema and crusting are usually noted for 1 week postoperatively. Cryosurgery results in the formation of intracellular ice crystals causing cell membrane destruction, blood vessel thrombosis, tissue ischemia, and resultant tissue destruction. This procedure can also be completed in the clinic setting under local anesthesia and has minimal bleeding but has

prolonged healing over 6 weeks as the necrotic tissue sloughs and may not have long-term benefit. Argon plasma coagulation uses high-frequency electrocoagulation without tissue contact because the electric current is conducted via ionized argon gas. This produces tissue desiccation but preserves the mucosa and has shown promising 1-year results.[533]

Radiofrequency ablation (RFVTR), a relatively new technique conducted under local anesthesia, creates ionic agitation in the tissue, inducing submucosal necrosis and fibrosis and reduced blood flow to the turbinate. Resultant wound contraction causes volume reduction of the inferior turbinate without damage to the overlying mucosa and preserves mucociliary clearance.[524] There is minimal bleeding and postoperative crusting, there is no requirement for packing, and repeat surgery may be completed if necessary.[534] In 1 small prospective study of patients with allergy not responding to medical treatment, RFVTR reduced nasal obstruction for as long as 6 months.[524,535]

Adenoidectomy in children (average age, 7 years[976]) continues to be 1 of the 10 most frequently performed surgical procedures, with more than 196,000 adenoidectomies performed annually in the United States.[976] In children, the indications for adenoidectomy are sleep apnea caused by adenotonsillar hypertrophy, chronic adenoiditis, and chronic sinusitis.[543] For OME, an adenoidectomy is usually recommended after the first set of tympanostomy tubes extrudes, effusion returns, and a second set of tympanostomy tubes are being considered. An adenoidectomy may also be considered for coexisting adenoiditis, postnasal obstruction, or chronic sinusitis.[543] Recent clinical studies recommend a trial intranasal corticosteroids for adenoidal hypertrophy before surgical intervention.[544-547] Septoplasty is infrequently performed in children because it may have a negative effect on nasal growth, particularly of the nasal dorsum.[527]

Important considerations in management

92. Management and monitoring of rhinitis should be individualized and based on the spectrum, duration, and severity of symptoms; physical examination findings; comorbidities; age of the patient; and patient preferences using both step-up and step-down approaches. **C**
93. Effective allergic rhinitis management requires the development of a physician/patient/family partnership, avoidance of environmental triggers, and the appropriate use of prescribed therapeutic interventions. C

The approach to rhinitis management must be individualized, considering such variable factors as the patient's age as well as the frequency, severity, and spectrum of presenting symptoms, the degree of impairment of QOL, the specific allergens to which the individual is sensitized, the response to previous medications, the presence of comorbid conditions, and the costs.[548] An individualized approach begins with the history, which will reveal the pattern, seasonal or perennial; the frequency, severity, and spectrum of presenting symptoms; the response to and compliance with previous medications; indoor and/or outdoor allergen exposures; and the presence of comorbid conditions such as allergic conjunctivitis and asthma. Symptoms confined to a defined season allow the formulation of a prophylactic regimen consisting of the initiation of medication before the onset of that season.[977] In contrast, perennial symptoms may require daily and, frequently, year-round therapy. The more days per year that therapy is required, the more medication safety and ease of use become prime factors to consider in individualizing therapy. The approach to treatment may also need to be modified for individuals who have perennial symptoms with seasonal exacerbations. Episodic rhinitis may be approached by administering certain medications appropriate as prophylaxis before anticipated acute allergen exposure (eg, nasal cromolyn, oral or intranasal antihistamines) and/or medications suitable for as-needed use in response to symptoms or scheduled shorter-term use (Table VI). Although antihistamines can be used on an intermittent basis, such as for episodic allergic rhinitis, it has been shown that continuous treatment for seasonal or perennial allergic rhinitis is more effective,[331] primarily because of unavoidable, ongoing allergen exposure.

The physical examination will assist in assessing severity of disease as well as the presence of comorbid conditions. For example, the presence of a polyp in a patient may result in modification of the diagnostic tests requested—for example, CF testing in a child—as well as the therapy recommended—for example, oral or high dose intranasal corticosteroids and possibly surgical resection in the adult.

The age of the patient becomes important in developing the individual evaluation and treatment plan. The spectrum of allergens tested as well as the choice of a medical regimen must be modified by the age of the individual. Medical choices are most heavily influenced by the extremes of age as in the infant or young child and the elderly. After allergy testing, the physician should design environmental control measures to target the specific allergens identified for the patient. Environmental controls will frequently also need to target nonallergen, irritant triggers such as tobacco smoke, strong odors, and extremes in temperature and humidity. Individuals who respond poorly to environmental control measures and optimal medical management should be considered for allergen immunotherapy.

The treatment plan should be developed jointly with the patient and family. Ideally it will take into account not only the patient's school or work schedule for medication administration, but also the patient's medication preferences such as liquid versus pill versus spray; realistic goals for environmental modification; and a plan to encourage compliance, such as use of a planning calendar or check-off list.[11] For example, programs tailored for the school-age child highlighting the importance of pleasant taste and ease of use of medications for this age group have resulted in increased adherence to the prescribed medications.[550]

Evidence-based guidelines for the treatment of rhinitis have recommended selection of appropriate medications on the basis of the severity and frequency of the patient's symptoms.[175] In addition, the therapy of rhinitis should involve a step-up approach (when therapy is inadequate) or step-down approach (after symptoms relief is achieved or maximized). As indicated, selection of the pharmacologic agent for treatment (eg, intranasal corticosteroids or second-generation antihistamines) must be individualized on the basis of the patient's age, symptoms, tolerability of route of administration, overall clinical condition, comorbidities,[11] and concomitant medication. This requires a careful benefit/risk assessment in each individual patient.[549] See Table VI for a summary of medication classes and their properties that lend themselves to different types of rhinitis and administration strategies.

Intranasal corticosteroids and second-generation antihistamines (with or without decongestants) have been shown to be safe and effective for most patients. LT antagonists and nasal

cromolyn may also be appropriate in some patients. In regard to nasal congestion, intranasal corticosteroids have been shown consistently to be effective,[54,978,979] whereas oral second-generation antihistamines have not,[980-984] often requiring the addition of an oral decongestant. Decongestant nasal sprays may significantly decrease nasal congestion and if used for short periods or intermittently may not produce rebound nasal congestion. Because most patients have multiple symptoms, the use of a single medication designed primarily for a specific symptom, such as a decongestant for nasal congestion, is usually not necessary. One exception is the use of anticholinergic nasal sprays for patients who have rhinorrhea without other nasal symptoms.

Whatever medication is first selected to treat a patient with rhinitis, addition or substitution of another class of medication should be considered if the first medication does not sufficiently control the patient's symptoms. This may be particularly relevant if there is a need to control other nonnasal symptoms, such as ocular or lower respiratory symptoms, which may also require an additional therapeutic agent. The use of combination therapy for rhinitis, on the other hand, has not always been shown to provide a major therapeutic advantage that outweighs the cost of this approach.[375,450,551] Administration of most medications for a period of 2 to 4 weeks is usually long enough to determine efficacy.

If patient compliance with a therapy was poor in the past or an adverse event was experienced, an alternative medical regimen should be designed with that in mind. Some patients and parents harbor fears of medication side effects, and these should be addressed on an individual basis through education to optimize medication adherence. Individuals vary in their ability to learn to use new devices, so the approach to education often needs to be tailored to the individual.

After initiation of therapy, appropriate follow-up for patients with rhinitis is recommended. This optimizes the likelihood that a patient will benefit from the broad array of therapeutic approaches available and that possible complications from rhinitis or its treatment are identified and addressed. At each follow-up patient visit, the physician should assess symptom control, QOL, and compliance, and evaluate whether current therapy should be maintained, stepped up, or stepped down. Patient and family education should be an integral part of each patient encounter.

Education of patients and family members or other patient advocates

94. Education is a key element in promoting adherence and optimizing treatment outcomes in allergic rhinitis. **D**

Education of the patient and family members or other patient advocates encompasses knowledge of and sensitivity to the cultural, socioeconomic, and demographic characteristics of the patient. To provide for optimal compliance, a trusting partnership of the physician and office staff with the patient and patient's family is needed. Education for the patient and family members begins at the initial encounter and continues at ensuing visits. The education program should emphasize the chronicity of rhinitis as a disease; the realistic outcome of therapy; an understanding of how to implement appropriate environmental change; appropriate methods of medication administration, medication benefits, and possible side effects; the comorbidity of other allergic diseases, such as asthma, sinusitis, and otitis media; and the effect that disease control can make in overall improvement in QOL.[11] In some studies, rhinitis education has been shown to result in enhanced compliance with rhinitis treatment and follow-up care, reduced concomitant asthma symptoms, and reduced use of short-acting β-agonists.[985] Physician-delivered educational programs have also resulted in a decrease in prescribed medications, an increase in the implementation of preventative measures, and improvement in the patient-physician partnership.[986] When allergy immunotherapy is recommended, an emphasis on education is needed to increase patients' knowledge about immunotherapy before and during aeroallergen immunotherapy, to increase compliance and safety, and to aid in the ultimate success of this therapeutic modality.[987]

Although there is general agreement that education is important, the best delivery method, frequency, and educational setting are still not established. The published research on success of rhinitis educational efforts is very limited, and what is published does not always demonstrate a positive result. Contrary to expectations, 1-on-1 allergy treatment educational sessions may not increase knowledge any more than a simple handout.[552] In fact, it is difficult to demonstrate reduced use of medication, reduced office visits, or improvement in QOL when educational programs are implemented for rhinitis or asthma. In recent asthma surveys, for example, nonadherence (at times intentional) to daily controller therapy was related not to lack of information but to a desire for the patient to have active control over use of medications, often using medications on a PRN basis.[553-555] When one reviews asthma educational programs, the newer, more innovative methods, such as videos, computer, and web-based programs, have not demonstrated any measurable advantage over in-office educational discussions, which may increase asthma knowledge and reduce symptoms but which do not show any reduction in acute care visits or rescue inhaler use.[556-563]

Whatever rhinitis educational delivery method is selected, it is important to review the content of the material. Although a large number of commercially prepared brochures and leaflets are available on allergic rhinitis, these are of variable quality and are often outdated, may project a biased treatment perspective, usually have poor readability scores, may contain factual inaccuracies, and are written predominantly for adults.[564]

Patient education is essential to provide the best care for the patient with rhinitis. Additional research to determine the best methods for education delivery is urgently needed to attain this goal.

Major comorbid conditions

95. Patients with allergic rhinitis are at increased risk for the development of asthma. **A**
96. Treatment of allergic rhinitis may improve asthma control in patients with coexisting allergic rhinitis and asthma. **B**
97. There is no established cause-and-effect relationship of rhinitis with recurrent otitis media and OME. **C**

The upper and lower airways are closely related with respect to rhinitis and asthma. Although allergic rhinitis and asthma frequently coexist, patients presenting with allergic rhinitis are at an increased risk for the development of asthma.[262,565-567] There is also evidence of interaction between the upper and lower airways. Patients with allergic rhinitis without asthma, especially those sensitized to dust mites, often have nonspecific BHR,[568-571] and many patients with seasonal allergic rhinitis experience a seasonal increase in BHR.[572] Nasal allergen provocation has been shown to result in temporary increases in BHR,[988] lower

airway adhesion molecules,[718] and lower airway eosinophilic inflammation.[718,988] Conversely, subsegmental bronchial allergen challenge in patients with allergic rhinitis has been shown to result in both bronchial and nasal inflammatory responses.[573] It has been suggested that in patients with moderate to severe allergic rhinitis, especially those with longstanding rhinitis and sensitization to dust mites, a reduced forced expiratory flow at 25% to 75% of forced vital capacity may be a marker of early bronchial impairment.[574-576]

There is clinical evidence that treatment of rhinitis can improve the status of coexisting asthma. Treatment with intranasal corticosteroids has been shown to prevent the seasonal increase in BHR experienced by patients with allergic rhinitis,[577,578] to reduce existing BHR,[570] to improve pulmonary function tests,[576] to diminish asthma symptoms,[435] and to reduce exhaled nitric oxide[989] and hydrogen peroxide.[989]

Treatment of allergic rhinitis with intranasal corticosteroids and certain second-generation antihistamines may improve asthma control when both diseases coexist.[581-588]

Given the convincing relationship between allergic rhinitis and asthma and the beneficial effects of treating rhinitis in patients who have asthma, it is also imperative that physicians who treat patients with asthma also consider aggressive treatment of coexisting rhinitis.

Allergen specific subcutaneous immunotherapy has been associated with a reduction in nonspecific bronchial hyperresponsiveness in patients with perennial allergic rhinitis.[990] Several controlled studies have also reported a reduction in the incidence of asthma in pediatric patients with allergic rhinitis treated with subcutaneous immunotherapy,[476,477,579] and this effect appears to be sustained at least 2 years after discontinuing immunotherapy.[473] One study reported a similar effect in adult patients.[475] Likewise, sublingual immunotherapy for allergic rhinitis, although not yet FDA-approved, may reduce the development of asthma in children.[580]

There has been ongoing discussion of the linkage of rhinitis, especially allergic rhinitis, and recurrent acute otitis media and OME, but there are no controlled studies to show a definite causal relationship. The American Academy of Pediatrics has not recommended any specific allergic rhinitis management for OME.[543] Furthermore, the American Academy of Pediatrics concludes that the use of antihistamines and decongestants are ineffective for OME and are not recommended for treatment. Rhinitis and otitis are both common childhood diseases, making the casual association with viruses, bacteria, and allergens difficult to establish at times. Eustachian tube dysfunction remains the most common etiology for otitis media. However, the same allergic mediators released after allergen exposure resulting in nasal allergic inflammation may contribute to the dysfunction of the eustachian tube by contributing to eustachian tube edema and inflammation.[543,589,590] Although under natural circumstances the middle ear is not exposed to allergens, measurements of elevated ECP,[591] IL-5,[592] and IgA[592] within the middle ear support a localized inflammatory process during chronic OME. Similar cytokine and cellular profiles (↑ Eosinophils, ↑ T lymphocytes, ↑ IL-4 mRNA, ↓ neutrophils, and ↓ IFN-γ mRNA) have been noted concurrently in the middle ear and adenoid tissue of atopics,[590] thus suggesting that the ear may be part of the united airway. Prospective studies examining the effect of allergy immunotherapy or food elimination on the natural course of OME are lacking.

Special considerations

Treatment of rhinitis during pregnancy

98. When selecting medications for treating rhinitis in pregnancy, the clinician might consider the FDA risk categories that are based largely on animal data and limited human studies. However, it is also beneficial to review human cohort and case-control studies as well as birth registry data before reaching a decision. (C)

The FDA pregnancy risk categories A, B, C, D, and X (Table X) were developed to guide the physician in choosing medications for which the benefit versus risk ratio can be weighed in an informed manner. Most medications fall into B or C categories, based predominantly on animal studies, because there are limited human studies available. It is therefore useful to consider, in addition to the FDA risk category, the exposed lives as reported in birth registry as well as case-control and cohort studies when comparing the available medications and developing a treatment plan. The following medication-related Summary Statements use this combined approach.

99. The most critical time for concern about potential congenital malformation because of medication use is the first trimester, when organogenesis is occurring. **D**
100. A sufficient amount of human observational data has now been accumulated to demonstrate safety for second-generation as well as first-generation antihistamines. **C**

First-generation antihistamines, such as chlorpheniramine, have previously been recommended as first-choice agents because of their observed safety and longevity of use.[593] However, their undesirable sedative qualities and possible effect on performance may make them less desirable choices. The safety of second-generation antihistamines used during the first trimester of pregnancy has now been confirmed through large birth registries, case-control studies, and cohort studies (Table XII). The available human data for first trimester use of antihistamines are summarized for first-generation and second-generation antihistamines in Tables XI and XII, respectively. The available safety data, efficacy, and patient preference will all influence the final drug selection. Both first-generation and second-generation antihistamines in general have excellent safety records and do not show a significant increase in congenital malformations when used during the first trimester. However, caution is still advised for a few antihistamines. Although diphenhydramine is often used by pregnant patients and recent studies have not detected any increased risk for congenital malformations, there is still some concern over a case-control study suggesting an association with cleft palate that has yet to be sufficiently refuted.[595-599] Hydroxyzine should be used cautiously during the first trimester based on animal data.[594] Although there are no reports of increased congenital malformations with the use of fexofenadine during pregnancy and animal studies are negative for teratogenicity, no epidemiologic studies in human pregnancy have been published.[594] Currently there are also limited data on desloratadine, azelastine, and levocetirizine. The only ophthalmic antihistamine for which epidemiologic studies have been conducted is pheniramine, and there was no reported increase in congenital malformations.[594]

101. Oral decongestants should be avoided during the first trimester. Topical decongestants when used on a short-term basis may have a better safety profile than oral agents for first trimester use. **C**

There have been conflicting reports of the association of phenylephrine and pseudoephedrine with increased congenital malformations such as gastroschisis and small intestinal atresia.[594,600] The risks of such malformations were increased by combining a decongestant with acetaminophen or salicylates.[600,601] Because of these findings, it is generally recommended that oral decongestants be avoided during the first trimester of pregnancy. Likewise, the data on the safety of topical intranasal decongestants during pregnancy have not been studied.

102. Sodium cromolyn is a safe treatment for allergic rhinitis during pregnancy. **C**

For allergic rhinitis during pregnancy, nasal sodium cromolyn, a Pregnancy Category B drug, may be considered for use in view of its topical application and reassuring gestational human and animal data.[599,602-604] Unfortunately the need for frequent 4 times a day dosing and reduced relative efficacy compared with other agents limits its acceptance by patients.

103. Montelukast is a safe treatment for allergic rhinitis during pregnancy. (C)

Reassuring animal reproductive studies and unpublished human safety data have given montelukast a Pregnancy Category B classification. A published observational study including 9 patients on LTRAs (specific agent not identified) demonstrated no adverse events.[605] Montelukast has been recommended for use in pregnancy for asthma management only when there has been a uniquely favorable prepregnancy response.[614] The same guidelines would be reasonable for the use of montelukast for rhinitis in pregnancy management until additional information on efficacy and safety becomes available.

104. Intranasal corticosteroids may be used in the treatment of nasal symptoms during pregnancy because of their safety and efficacy profile. **C**

Clinical and epidemiologic studies on the safety of intranasal corticosteroids for rhinitis in pregnancy are limited. Although animal gestational studies have shown risk for all inhaled corticosteroids, this does not appear to apply directly to human beings based up observational data.[603] Pharmacologic studies show a much lower systemic exposure after intranasal than (orally) inhaled corticosteroids. It is reasonable, therefore, to extrapolate the safety profile of inhaled corticosteroids to intranasal corticosteroids. A recent meta-analysis concluded that the use of orally inhaled corticosteroids during pregnancy does not increase the risks of major malformations, preterm delivery, low birth weight, and pregnancy-induced hypertension.[606] Inhaled or intranasal corticosteroid use in pregnancy has demonstrated no convincing evidence of congenital defects using beclomethasone,[11,602,607-609] budesonide,[603,610] or fluticasone propionate.[227,611] Reported safety data on triamcinolone,[612,613] mometasone, and flunisolide[611] are extremely limited. No substantial difference in efficacy and safety has been shown among the available intranasal corticosteroids. Thus it would be reasonable to continue any of the intranasal corticosteroids that have adequately controlled the patient's symptoms before pregnancy.[609,614] If intranasal corticosteroids are begun during pregnancy, intranasal budesonide, which is in Pregnancy Category B largely on the basis of extensive human safety data, may be preferred.[603,610] The decision which intranasal corticosteroid to prescribe often requires a discussion of the benefits and risks with the patient. Intranasal corticosteroids may also be used to allow discontinuation of topical decongestants in patients with rhinitis medicamentosa. As with all medication use in pregnancy, intranasal corticosteroids should be tapered to the lowest effective dose.

105. Immunotherapy for allergic rhinitis may be continued during pregnancy but without dose escalation. **C**

Specific allergy immunotherapy for allergic rhinitis may be continued during pregnancy if it is providing benefit without causing systemic reactions.[614,615] The immunotherapy doses that the patient receives when she becomes pregnant should not be increased and should be adjusted appropriately during pregnancy if necessary to minimize the chance of inducing a systemic reaction. However, benefit/risk considerations do not generally favor starting immunotherapy during pregnancy. [50,615]

Rhinitis in the elderly

106. Rhinitis in the elderly may be caused by types of rhinitis common in other age groups but may also be influenced by age-related physiologic changes such as cholinergic hyperactivity, anatomic changes, and medications taken for other medical conditions. **C**

As the US elderly population rapidly increases (41% growth rate for those over 65 years vs 11% for general population), treatment of the elderly with rhinitis will likewise become a major part of the rhinitis practice.[991] Many of the pathological changes in connective tissue and vasculature associated with aging may predispose to rhinitis complaints.[616,617] These include atrophy of the collagen fibers and mucosal glands, loss of dermal elastic fibers, fragmentation and weakening of septal cartilage, and a reduced blood flow to nasal tissues.[138,992,993] These changes can result in drying and increased nasal congestion in some elderly patients. Furthermore, these aging effects often magnify or complicate other causes of rhinitis, such as allergic causes. Nasal steroids, however, may be safely used for treatment of allergic rhinitis, because they do not cause any clinical or histologic atrophic changes in the nasal mucosa.[618]

Rhinitis in the elderly may also be a result of cholinergic hyperreactivity, associated with profuse watery rhinorrhea, which may be aggravated after eating (gustatory rhinitis), α-adrenergic hyperactivity (eg, congestion associated with therapy for hypertension or benign prostatic hypertrophy), or chronic sinusitis. The watery rhinorrhea syndrome frequently responds to intranasal ipratropium bromide.[994] However, ipratropium bromide should be used with caution with pre-existing glaucoma or prostatic hypertrophy.

Elderly patients more commonly have more pronounced clear rhinorrhea from cholinergic hyperactivity associated with the aging process. Medications taken for unrelated medical problems may also cause or contribute to rhinitis in this age group. Selection of medications for rhinitis treatment should take into account that elderly patients may be more susceptible to adverse effects of some of these medications.

Rhinitis in the athlete

107. Athletic performance can be affected by rhinorrhea and chronic or rebound nasal congestion. Rhinitis medication for the competitive athlete must be a USOC and/or IOC–approved product and should be one that does not adversely affect performance. **C**

Rhinitis affects a high proportion of all athletes. In fact, the majority of all individuals, allergic and nonallergic, report nasal symptoms, especially rhinorrhea, with both outdoor (56%) and indoor (61%) exercise, but this rate is higher in patients with allergic rhinitis (72% and 70%, respectively).[69] Furthermore this exercise-induced rhinitis adversely affects athletic performance in athletes with allergy (53%) and without allergy (28%).[69] Among elite athletes, endurance athletes report a higher frequency of physician-diagnosed allergic rhinitis and use of antiallergic medications.[995] Nasal congestion can contribute to sleep dysfunction, leading to daytime fatigue and decreased performance.[996] In normal exercise situations, nasal vasoconstriction and decreased nasal resistance develop and persist for about 1 hour. Athletes, especially long-distance runners, cyclists, or triathletes, may experience a rebound nasal congestion after the initial improvement in nasal patency, which may affect peak performance.[619]

Prescription of medication for the competitive athlete should be based on 2 important principles:[180] no medication given to the athlete should be on any list of doping products and should be approved for use by the USOC and IOC,[550] and no medication should adversely affect the athlete's performance.[620]

The USOC generally observes the IOC list of banned and allowed drugs. Before a competitive athlete takes any medication prior to competition, it should be determined whether it is allowed (www.wada-ama.org). The USOC has a toll-free hotline (1-800-233-0393) to answer any questions a physician or athlete may have. Athletes and their physicians should be aware that all intranasal corticosteroids are allowed but that all decongestants are banned with the exception of topical (nasal or ophthalmologic) phenylephrine and imidazole preparations (ie, oxymetazoline and tetrahydrozoline).

Antihistamines are allowed by the USOC but may be banned by the international federation of certain sports. An adverse influence on physical performance may occur in the athlete with rhinitis treated with first-generation antihistamines, which may have undesirable sedative and anticholinergic effects. After consideration of these issues, the optimal therapy for the athlete with symptomatic allergic rhinitis consists of aggressive allergen avoidance frequently in combination with a second-generation H1-antihistamines and/or intranasal corticosteroids. Intranasal cromolyn may be useful 30 minutes before commencing a competition likely to be associated with high allergen exposure. Immunotherapy may provide help for those athletes with allergic rhinitis not responding adequately to avoidance and medication.

Allergist/immunologist consultation and referral guidelines

108. Allergist/immunologist care improves patient outcomes; however, consultation/referral services are often underused. **C**
109. Consultation with an allergist/immunologist should be considered for patients with rhinitis who have inadequately controlled symptoms, a reduced QOL and/or ability to function, adverse reactions to medications, a desire to identify the allergens to which they are sensitized and to receive advice on environmental control, or comorbid conditions such as asthma and recurrent sinusitis, or when allergen immunotherapy is a consideration. **C**

Allergist/immunologist care for rhinitis is associated with improved QOL, compliance, and satisfaction with care.[621] Patients with rhinitis under the care of primary care physicians often desire more education about their disease.[622] Allergists/immunologists have familiarity with the wide variety of aeroallergens and have the expertise to provide avoidance education.[623,624] They provide expertise in the interpretation of the clinical history and diagnostic studies pertaining to upper and lower airway conditions.[623,624] Allergen immunotherapy, as offered by allergists/immunologists, effectively treats allergic rhinitis with clinical benefits that may be sustained for years after discontinuation of treatment.[51,466,467,997]

It is recognized that whereas some patients may benefit from ongoing allergist/immunologist treatment, others may require only 1 or a few consultation visits, and/or cotreatment with the primary care physician with periodic follow-up care.

There are a variety of circumstances in which the special expertise and training of an allergist/immunologist may offer benefits to a patient with rhinitis. A detailed listing of reasons for consultation with an allergist/immunologist that may be provided as a guide for primary care physicians is detailed in Box 6.

The following outline provides the allergist/immunologist with a referral guideline and associated rationale and level of evidence that is based on recently published consultation and referral guidelines.[998]

Referral guidelines[8,11,50,468]

1. Patients with rhinitis with prolonged and severe disease with
   a. Comorbid conditions
      i. Asthma
      ii. Recurrent sinusitis
      iii. Nasal polyps
   b. Symptoms interfere with
      i. QOL
      ii. Ability to function
   c. Medications are
      i. Ineffective
      ii. Associated with adverse reactions
      iii. Unacceptable for chronic use by patient choice, such as cost or concern with long-term side effects

2. Patients with allergic rhinitis, children, and possibly adults, being considered for allergy immunotherapy as a means of preventing the progression of allergic disease

Referral rationale and evidence level

1. Direct evidence
   - Allergist/immunologist care for rhinitis is associated with improved QOL, compliance, and satisfaction with care.[621]
2. Diagnostic evidence
   - Allergists/immunologists are highly trained to interpret the clinical history and allergy diagnostic test results in upper and lower airways conditions.[624]
3. Indirect evidence
   - Avoidance: Allergists/immunologists have knowledge of aeroallergen exposures in the patient's environment and have the expertise to provide avoidance education.[624]
   - Immunotherapy: Allergy immunotherapy can be highly effective in controlling symptoms of rhinitis and may provide lasting benefit after immunotherapy is discontinued.[466,967]

- Immunotherapy: Allergy immunotherapy has been shown to reduce development of new sensitizations and asthma in children with allergic rhinitis.[476]
- Pharmacologic treatment: Allergists/immunologists are experts in the management of nasal polyps and treatment of complications of sinusitis.[8,624]

REFERENCES

1. Schoenwetter WF, Dupclay L Jr, Appajosyula S, Botteman MF, Pashos CL. Economic impact and quality-of-life burden of allergic rhinitis. Curr Med Res Opin 2004;20:305-17. **IV**
2. Settipane RA. Rhinitis: a dose of epidemiological reality. Allergy Asthma Proc 2003;24:147-54. **IV**
3. Druce H. Allergic and nonallergic rhinitis. In: Middleton E, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, editors. Allergy principles and practice. 5th ed. St Louis: Mosby-Year Book; 1998. p. 1005-16. **IV**
4. Settipane RJ, Hagy GW, Settipane GA. Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students. Allergy Proc 1994;15:21-5. **III**
5. Varjonen E, Kalimo K, Lammintausta K, Terho P. Prevalence of atopic disorders among adolescents in Turku, Finland. Allergy 1992;47:243-8. **III**
6. Smith JM. A five-year prospective survey of rural children with asthma and hay fever. J Allergy 1971;47:23-30. **III**
7. Settipane RA, Charnock DR. Epidemiology of rhinitis: allergic and nonallergic. Clin Allergy Immunol 2007;19:23-34. **IV**
8. Dykewicz MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma, and Immunology. Ann Allergy Asthma Immunol 1998;81:478-518. **IV**
9. Bernstein L, Li J, Bernstein D, Hamilton R, Spector S, Tan R, et al. Allergy diagnostic testing: an updated practice parameter. Ann Allergy 2008;100:S1-148. **IV**
10. Bousquet J, Neukirch F, Bousquet PJ, Gehano P, Klossek JM, Le Gal M, et al. Severity and impairment of allergic rhinitis in patients consulting in primary care. J Allergy Clin Immunol 2006;117:158-62. **III**
11. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001;108:S147-334. **IV**
12. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. Allergy 2005;60:350-3. **III**
13. Spector SL, Nicklas RA, Chapman JA, Bernstein IL, Berger WE, Blessing-Moore J, et al. Symptom severity assessment of allergic rhinitis, part 1. Ann Allergy Asthma Immunol 2003;91:105-14. **IV**
14. Hagy GW, Settipane GA. Prognosis of positive allergy skin tests in an asymptomatic population: a three year follow-up of college students. J Allergy Clin Immunol 1971;48:200-11. **III**
15. Tang RB, Tsai LC, Hwang HM, Hwang B, Wu KG, Hung MW. The prevalence of allergic disease and IgE antibodies to house dust mite in schoolchildren in Taiwan. Clin Exp Allergy 1990;20:33-8. **III**
16. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. Pediatrics 1994; 94:895-901. **III**
17. Hagerhed-Engman L, Bornehag CG, Sundell J, Aberg N. Day-care attendance and increased risk for respiratory and allergic symptoms in preschool age. Allergy 2006;61:447-53. **III**
18. Karmaus W, Botezan C. Does a higher number of siblings protect against the development of allergy and asthma? a review. J Epidemiol Community Health 2002; 56:209-17. **III**
19. Loza MJ, Peters SP, Penn RB. Atopy, asthma, and experimental approaches based on the linear model of T cell maturation. Clin Exp Allergy 2005;35:8-17. **IV**
20. Romagnani S. The increased prevalence of allergy and the hygiene hypothesis: missing immune deviation, reduced immune suppression, or both? Immunology 2004;112:352-63. **IV**
21. Demengeot J, Zelenay S, Moraes-Fontes MF, Caramalho I, Coutinho A. Regulatory T cells in microbial infection. Springer Semin Immunopathol 2006;28:41-50. **IV**
22. Balemans WA, Rovers MM, Schilder AG, Sanders EA, Kimpen JL, Zielhuis GA, et al. Recurrent childhood upper respiratory tract infections do not reduce the risk of adult atopic disease. Clin Exp Allergy 2006;36:198-203. **III**
23. Hesselmar B, Aberg N, Aberg B, Eriksson B, Bjorksten B. Does early exposure to cat or dog protect against later allergy development? Clin Exp Allergy 1999;29: 611-7. **IIb**
24. Frosh AC, Sandhu G, Joyce R, Strachan DP. Prevalence of rhinitis, pillow type and past and present ownership of furred pets. Clin Exp Allergy 1999;29: 457-60. **III**
25. Fougard T. Allergy and allergy-like symptoms in 1,050 medical students. Allergy 1991;46:20-6. **III**
26. Hill LW. Certain aspects of allergy in children: a critical review of the recent literature. N Engl J Med 1961;265:1194-200. **IV**
27. LeMasters GK, Wilson K, Levin L, Biagini J, Ryan P, Lockey JE, et al. High prevalence of aeroallergen sensitization among infants of atopic parents. J Pediatr 2006;149:505-11. **IIa**
28. Biagini JM, LeMasters GK, Ryan PH, Levin L, Reponen T, Bernstein DI, et al. Environmental risk factors of rhinitis in early infancy. Pediatr Allergy Immunol 2006;17:278-84. **III**
29. Fireman P. Therapeutic approaches to allergic rhinitis: treating the child. J Allergy Clin Immunol 2000;105:S616-21. **IV**
30. Kulig M, Klettke U, Wahn V, Forster J, Bauer CP, Wahn U. Development of seasonal allergic rhinitis during the first 7 years of life. J Allergy Clin Immunol 2000; 106:832-9. **III**
31. Jessen M, Malm L. Definition, prevalence and development of nasal obstruction. Allergy 1997;52:3-6. **IV**
32. Gelfand EW. Inflammatory mediators in allergic rhinitis. J Allergy Clin Immunol 2004;114:S135-8. **IV**
33. Pearlman DS. Pathophysiology of the inflammatory response. 1999;104:S132–S137. **IV**
34. Bascom R, Pipkorn U, Lichtenstein LM, Naclerio RM. The influx of inflammatory cells into nasal washings during the late response to antigen challenge: effect of systemic steroid pretreatment. Am Rev Respir Dis 1988;138:406-12. **IIa**
35. Otsuka H, Denburg JA, Befus AD, Hitch D, Lapp P, Rajan RS, et al. Effect of beclomethasone dipropionate on nasal metachromatic cell sub-populations. Clin Allergy 1986;16:589-95. **III**
36. Pipkorn U, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman PS, Naclerio RM. Inhibition of mediator release in allergic rhinitis by pretreatment with topical glucocorticosteroids. N Engl J Med 1987;316:1506-10. **Ib**
37. Schoeneich M, Pecoud AR. Effect of cetirizine in a conjunctival provocation test with allergens. Clin Exp Allergy 1990;20:171-4. **Ib**
38. Bronsky EA, Falliers CJ, Kaiser HB, Ahlbrandt R, Mason JM. Effectiveness and safety of fexofenadine, a new nonsedating H1-receptor antagonist, in the treatment of fall allergies. Allergy Asthma Proc 1998;19:135-41. **Ib**
39. Ciprandi G, Buscaglia S, Pesce GP, Marchesi E, Canonica GW. Protective effect of loratadine on specific conjunctival provocation test. Int Arch Allergy Appl Immunol 1991;96:344-7. **Ib**
40. van Adelsberg J, Philip G, Pedinoff AJ, Meltzer EO, Ratner PH, Menten J, et al. Montelukast improves symptoms of seasonal allergic rhinitis over a 4-week treatment period. Allergy 2003;58:1268-76. **Ib**
41. Van Adelsberg J, Philip G, LaForce CF, Weinstein SF, Menten J, Malice MP, et al. Randomized controlled trial evaluating the clinical benefit of montelukast for treating spring seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2003;90:214-22. **Ib**
42. Philip G, Malmstrom K, Hampel FC, Weinstein SF, LaForce CF, Ratner PH, et al. Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. Clin Exp Allergy 2002;32: 1020-8. **Ib**
43. Bielory L. Differential diagnoses of conjunctivitis for clinical allergist-immunologists. Ann Allergy Asthma Immunol 2007;98:105-14; quiz 14-7, 52. **IV**
44. Kaiser HB, Naclerio RM, Given J, Toler TN, Ellsworth A, Philpot EE. Fluticasone furoate nasal spray: a single treatment option for the symptoms of seasonal allergic rhinitis. J Allergy Clin Immunol 2007;119:1430-7. **Ib**
45. Martin BG, Ratner PH, Hampel FC, Andrews CP, Toler T, Wu W, et al. Optimal dose selection of fluticasone furoate nasal spray for the treatment of seasonal allergic rhinitis in adults and adolescents. Allergy Asthma Proc 2007;28: 216-25. **Ib**
46. Yanez 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;89:479-84. **Ia**
47. DeWester J, Philpot EE, Westlund RE, Cook CK, Rickard KA. The efficacy of intranasal fluticasone propionate in the relief of ocular symptoms associated with seasonal allergic rhinitis. Allergy Asthma Proc 2003;24:331-7. **Ia**
48. Rodrigo GJ, Yanez A. The role of antileukotriene therapy in seasonal allergic rhinitis: a systematic review of randomized trials. Ann Allergy Asthma Immunol 2006;96:779-86. **Ia**
49. Weinstein SF, Philip G, Hampel FC Jr, Malice MP, Swern AS, Dass SB, et al. Onset of efficacy of montelukast in seasonal allergic rhinitis. Allergy Asthma Proc 2005;26:41-6. **Ia**
50. Cox L, Li J, Nelson HS, Lockey R. Allergen immunotherapy: a practice parameter second update. J Allergy Clin Immunol 2007;120:S25-85. **IV**

51. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database Syst Rev 2007:CD001936. **Ia**
52. Bielory L, Mongia A. Current opinion of immunotherapy for ocular allergy. Curr Opin Allergy Clin Immunol 2002;2:447-52. **IV**
53. Nielsen LP, Dahl R. Comparison of intranasal corticosteroids and antihistamines in allergic rhinitis: a review of randomized, controlled trials. Am J Respir Med 2003;2:55-65. **III**
54. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. BMJ 1998;317:1624-9. **Ia**
55. Spector SL, Raizman MB. Conjunctivitis medicamentosa. J Allergy Clin Immunol 1994;94:134-6. **III**
56. Abelson MB, Butrus SI, Weston JH, Rosner B. Tolerance and absence of rebound vasodilation following topical ocular decongestant usage. Ophthalmology 1984; 91:1364-7. **III**
57. Abelson MB, Paradis A, George MA, Smith LM, Maguire L, Burns R. Effects of Vasocon-A in the allergen challenge model of acute allergic conjunctivitis. Arch Ophthalmol 1990;108:520-4. **Ib**
58. Nizami RM. Treatment of ragweed allergic conjunctivitis with 2% cromolyn solution in unit doses. Ann Allergy 1981;47:5-7. **Ib**
59. Ballas Z, Blumenthal M, Tinkelman DG, Kriz R, Rupp G. Clinical evaluation of ketorolac tromethamine 0.5% ophthalmic solution for the treatment of seasonal allergic conjunctivitis. Surv Ophthalmol 1993;38(suppl):141-8. **Ib**
60. Abelson M, Howes J, George M. The conjunctival provocation test model of ocular allergy: utility for assessment of an ocular corticosteroid, loteprednol etabonate. J Ocul Pharmacol Ther 1998;14:533-42. **Ib**
61. Shulman DG, Lothringer LL, Rubin JM, Briggs RB, Howes J, Novack GD, et al. A randomized, double-masked, placebo-controlled parallel study of loteprednol etabonate 0.2% in patients with seasonal allergic conjunctivitis. Ophthalmology 1999;106:362-9. **Ib**
62. Howes JF. Loteprednol etabonate: a review of ophthalmic clinical studies. Pharmazie 2000;55:178-83. **IV**
63. Dell SJ, Lowry GM, Northcutt JA, Howes J, Novack GD, Hart K. A randomized, double-masked, placebo-controlled parallel study of 0.2% loteprednol etabonate in patients with seasonal allergic conjunctivitis. J Allergy Clin Immunol 1998; 102:251-5. **Ib**
64. Dell SJ, Shulman DG, Lowry GM, Howes J. A controlled evaluation of the efficacy and safety of loteprednol etabonate in the prophylactic treatment of seasonal allergic conjunctivitis. Loteprednol Allergic Conjunctivitis Study Group. Am J Ophthalmol 1997;123:791-7. **Ib**
65. Stjarne P, Lundblad L, Lundberg JM, Anggard A. Capsaicin and nicotine-sensitive afferent neurones and nasal secretion in healthy human volunteers and in patients with vasomotor rhinitis. Br J Pharmacol 1989;96:693-701. **IIb**
66. Raphael G, Raphael MH, Kaliner M. Gustatory rhinitis: a syndrome of food-induced rhinorrhea. J Allergy Clin Immunol 1989;83:110-5. **IIa**
67. Shusterman D, Balmes J, Murphy MA, Tai CF, Baraniuk J. Chlorine inhalation produces nasal airflow limitation in allergic rhinitic subjects without evidence of neuropeptide release. Neuropeptides 2004;38:351-8. **IIa**
68. Cruz AA, Naclerio RM, Proud D, Togias A. Epithelial shedding is associated with nasal reactions to cold, dry air. J Allergy Clin Immunol 2006;117:1351-8. **IIb**
69. Silvers WS, Poole JA. Exercise-induced rhinitis: a common disorder that adversely affects allergic and nonallergic athletes. Ann Allergy Asthma Immunol 2006;96:334-40. **III**
70. Linneberg A, Berg ND, Gonzalez-Quintela A, Vidal C, Elberling J. Prevalence of self-reported hypersensitivity symptoms following intake of alcoholic drinks. Clin Exp Allergy 2008;38:145-51. **III**
71. Graudenz GS, Landgraf RG, Jancar S, Tribess A, Fonseca SG, Fae KC, et al. The role of allergic rhinitis in nasal responses to sudden temperature changes. J Allergy Clin Immunol 2006;118:1126-32. **III**
72. Wald ER. Clinical features, evaluation, and diagnosis of acute bacterial sinusitis in children. In: Rose B, editor. UpToDate. Wellesley (MA): UpToDate; 2007. **III**
73. Wald ER, Guerra N, Byers C. Upper respiratory tract infections in young children: duration of and frequency of complications. Pediatrics 1991;87:129-33. **IIa**
74. Fendrick AM, Saint S, Brook I, Jacobs MR, Pelton S, Sethi S. Diagnosis and treatment of upper respiratory tract infections in the primary care setting. Clin Ther 2001;23:1683-706. **IV**
75. Gwaltney JM. Acute sinusitis and rhinosinusitis in adults. In: UpToDate. Rose BD, ed. Waltham, MA; 2008. **IV**
76. Gwaltney JM Jr. Acute community-acquired sinusitis. Clin Infect Dis 1996;23: 1209-23. **IV**
77. Slavin RG, Spector SL, Bernstein IL, Kaliner MA, Kennedy DW, Virant FS, et al. The diagnosis and management of sinusitis: a practice parameter update. J Allergy Clin Immunol 2005;116:S13-47. **IV**
78. Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngol Head Neck Surg 2000;123:5-31. **IV**
79. Nissinen A, Gronroos P, Huovinen P, Herva E, Katila ML, Klaukka T, et al. Development of beta-lactamase-mediated resistance to penicillin in middle-ear isolates of Moraxella catarrhalis in Finnish children, 1978-1993. Clin Infect Dis 1995;21:1193-6. **III**
80. Arason VA, Kristinsson KG, Sigurdsson JA, Stefansdottir G, Molstad S, Gudmundsson S. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? cross sectional prevalence study. BMJ 1996;313: 387-91. **III**
81. Seppala H, Klaukka T, Vuopio-Varkila J, Muotiala A, Helenius H, Lager K, et al. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. N Engl J Med 1997;337:441-6. **III**
82. Seppala H, Klaukka T, Lehtonen R, Nenonen E, Huovinen P. Outpatient use of erythromycin: link to increased erythromycin resistance in group A streptococci. Clin Infect Dis 1995;21:1378-85. **III**
83. Dagan R, Leibovitz E, Greenberg D, Yagupsky P, Fliss DM, Leiberman A. Dynamics of pneumococcal nasopharyngeal colonization during the first days of antibiotic treatment in pediatric patients. Pediatr Infect Dis J 1998;17: 880-5. **IIb**
84. Ekdahl K, Ahlinder I, Hansson HB, Melander E, Molstad S, Soderstrom M, et al. Duration of nasopharyngeal carriage of penicillin-resistant Streptococcus pneumoniae: experiences from the South Swedish Pneumococcal Intervention Project. Clin Infect Dis 1997;25:1113-7. **IIb**
85. Iwens P, Clement PA. [Sinusitis in atopic children]. Acta Otorhinolaryngol Belg 1994;48:383-6. **III**
86. Kvaerner KJ, Tambs K, Harris JR, Mair IW, Magnus P. Otitis media: relationship to tonsillitis, sinusitis and atopic diseases. Int J Pediatr Otorhinolaryngol 1996;35: 127-41. **III**
87. Malmberg H, Holopainen E. Nasal smear as a screening test for immediate-type nasal allergy. Allergy 1979;34:331-7. **III**
88. Malmberg H. Symptoms of chronic and allergic rhinitis and occurrence of nasal secretion granulocytes in university students, school children and infants. Allergy 1979;34:389-94. **III**
89. Ciprandi G, Vizzaccaro A, Cirillo I, Tosca M, Massolo A, Passalacqua G. Nasal eosinophils display the best correlation with symptoms, pulmonary function and inflammation in allergic rhinitis. Int Arch Allergy Immunol 2005;136:266-72. **III**
90. Crobach M, Hermans J, Kaptein A, Ridderikhoff J, Mulder J. Nasal smear eosinophilia for the diagnosis of allergic rhinitis and eosinophilic non-allergic rhinitis. Scand J Prim Health Care 1996;14:116-21. **III**
91. Romero JN, Scadding G. Eosinophilia in nasal secretions compared to skin prick test and nasal challenge test in the diagnosis of nasal allergy. Rhinology 1992;30: 169-75. **III**
92. Bogaerts PA, Clement PA. The diagnostic value of a cytogram in rhinopathology. Rhinology 1981;19:203-8. **III**
93. Zeiger RS. Allergic and nonallergic rhinitis: classification and pathogenesis, part II: non-allergic rhinitis. Am J Rhinology 1989;3:113-39. **IV**
94. Benninger MS, Payne SC, Ferguson BJ, Hadley JA, Ahmad N. Endoscopically directed middle meatal cultures versus maxillary sinus taps in acute bacterial maxillary rhinosinusitis: a meta-analysis. Otolaryngol Head Neck Surg 2006;134:3-9. **III**
95. Vogan JC, Bolger WE, Keyes AS. Endoscopically guided sinonasal cultures: a direct comparison with maxillary sinus aspirate cultures. Otolaryngol Head Neck Surg 2000;122:370-3. **III**
96. Benninger MS, Appelbaum PC, Denneny JC, Osguthorpe DJ, Stankiewicz JA. Maxillary sinus puncture and culture in the diagnosis of acute rhinosinusitis: the case for pursuing alternative culture methods. Otolaryngol Head Neck Surg 2002;127:7-12. **III**
97. Gold SM, Tami TA. Role of middle meatus aspiration culture in the diagnosis of chronic sinusitis. Laryngoscope 1997;107:1586-9. **III**
98. Ellis A, Keith P. Nonallergic rhinitis with eosinophilia syndrome. Curr Allergy Asthma Rep 2006;6:215-20. **IV**
99. Schiavino D, Nucera E, Milani A, Della Corte AM, D'Ambrosio C, Pagliari G, et al. Nasal lavage cytometry in the diagnosis of nonallergic rhinitis with eosinophilia syndrome (NARES). Allergy Asthma Proc 1997;18:363-6. **III**
100. Kirshna M, Mauroleon G, Holgate S. Essentials in allergy. UK: Informa Health Care; 2001. **IV**
101. Jacobs RL, Freedman PM, Boswell RN. Nonallergic rhinitis with eosinophilia (NARES syndrome): clinical and immunologic presentation. J Allergy Clin Immunol 1981;67:253-62. **III**

102. Settipane GA, Klein DE. Non allergic rhinitis: demography of eosinophils in nasal smear, blood total eosinophil counts and IgE levels. N Engl Reg Allergy Proc 1985;6:363-6. **III**
103. Moneret-Vautrin DA, Hsieh V, Wayoff M, Guyot JL, Mouton C, Maria Y. Nonallergic rhinitis with eosinophilia syndrome a precursor of the triad: nasal polyposis, intrinsic asthma, and intolerance to aspirin. Ann Allergy 1990;64: 513-8. **III**
104. Kramer MF, de la Chaux R, Fintelmann R, Rasp G. NARES: a risk factor for obstructive sleep apnea? Am J Otolaryngol 2004;25:173-7. **IIb**
105. Archambault S, Malo JL, Infante-Rivard C, Ghezzo H, Gautrin D. Incidence of sensitization, symptoms, and probable occupational rhinoconjunctivitis and asthma in apprentices starting exposure to latex. J Allergy Clin Immunol 2001; 107:921-3. **III**
106. Rodier F, Gautrin D, Ghezzo H, Malo JL. Incidence of occupational rhinoconjunctivitis and risk factors in animal-health apprentices. J Allergy Clin Immunol 2003;112:1105-11. **III**
107. Clapp WD, Thorne PS, Frees KL, Zhang X, Lux CR, Schwartz DA. The effects of inhalation of grain dust extract and endotoxin on upper and lower airways. Chest 1993;104:825-30. **III**
108. Graham D, Henderson F, House D. Neutrophil influx measured in nasal lavages of humans exposed to ozone. Arch Environ Health 1988;43:228-33. **IIb**
109. Grize L, Gassner M, Wuthrich B, Bringolf-Isler B, Takken-Sahli K, Sennhauser FH, et al. Trends in prevalence of asthma, allergic rhinitis and atopic dermatitis in 5-7-year old Swiss children from 1992 to 2001. Allergy 2006;61: 556-62. **III**
110. Boulet LP, Laviolette M, Turcotte H, Cartier A, Dugas M, Malo JL, et al. Bronchial subepithelial fibrosis correlates with airway responsiveness to methacholine. Chest 1997;112:45-52. **III**
111. Krakowiak A, Ruta U, Gorski P, Kowalska S, Palczynski C. Nasal lavage fluid examination and rhinomanometry in the diagnostics of occupational airway allergy to laboratory animals. Int J Occup Med Environ Health 2003;16:125-32. **IIb**
112. Gorski P, Krakowiak A, Ruta U. Nasal and bronchial responses to flour-inhalation in subjects with occupationally induced allergy affecting the airway. Int Arch Occup Environ Health 2000;73:488-97. **III**
113. Palczynski C, Walusiak J, Ruta U, Gorski P. Nasal provocation test in the diagnosis of natural rubber latex allergy. Allergy 2000;55:34-41. **IIa**
114. Nielsen J, Welinder H, Ottosson H, Bensryd I, Venge P, Skerfving S. Nasal challenge shows pathogenetic relevance of specific IgE serum antibodies for nasal symptoms caused by hexahydrophthalic anhydride. Clin Exp Allergy 1994;24: 440-9. **IIb**
115. Gautrin D, Ghezzo H, Infante-Rivard C, Malo JL. Host determinants for the development of allergy in apprentices exposed to laboratory animals. Eur Respir J 2002;19:96-103. **III**
116. Bernstein JA, Bernstein DI, Craig TJ, Stauder T, Lummus Z, Bernstein IL. A cross-sectional survey of sensitization to Aspergillus oryzae-derived lactase in pharmaceutical workers. J Allergy Clin Immunol 1999;103:1153-7. **III**
117. Sastre J, Fernandez-Nieto M, Rico P, Martin S, Barber D, Cuesta J, et al. Specific immunotherapy with a standardized latex extract in allergic workers: a double-blind, placebo-controlled study. J Allergy Clin Immunol 2003;111: 985-94. **Ib**
118. Schatz M, Zeiger RS. Diagnosis and management of rhinitis during pregnancy. Allergy Proc 1988;9:545-54. **IV**
119. Toppozada H, Michaels L, Toppozada M, El-Ghazzawi I, Talaat M, Elwany S. The human respiratory nasal mucosa in pregnancy: an electron microscopic and histochemical study. J Laryngol Otol 1982;96:613-26. **LB**
120. Ellegard E, Karlsson G. Nasal congestion during pregnancy. Clin Otolaryngol Allied Sci 1999;24:307-11. **III**
121. Ellegard EK. Pregnancy rhinitis. Immunol Allergy Clin North Am 2006;26: 119-35. **IV**
122. Philpott CM, El-Alami M, Murty GE. The effect of the steroid sex hormones on the nasal airway during the normal menstrual cycle. Clin Otolaryngol Allied Sci 2004;29:138-42. **III**
123. Materson BJ. Adverse effects of angiotensin-converting enzyme inhibitors in antihypertensive therapy with focus on quinapril. Am J Cardiol 1992;69:46C-53C. **III**
124. Plosker GL, Goa KL. Terazosin: a pharmacoeconomic evaluation of its use in benign prostatic hyperplasia. Pharmacoeconomics 1997;11:184-97. **Ib**
125. Vitezic D, Pelcic JM. Erectile dysfunction: oral pharmacotherapy options. Int J Clin Pharmacol Ther 2002;40:393-403. **III**
126. Wolstenholme CR, Philpott CM, Oloto EJ, Murty GE. Does the use of the combined oral contraceptive pill cause changes in the nasal physiology in young women? Am J Rhinol 2006;20:238-40. **IIb**
127. Bavbek S, Dursun AB, Dursun E, Eryilmaz A, Misirligil Z. Safety of meloxicam in aspirin-hypersensitive patients with asthma and/or nasal polyps: a challenge-proven study. Int Arch Allergy Immunol 2007;142:64-9. **IIb**
128. Ediger D, Sin BA, Heper A, Anadolu Y, Misirligil Z. Airway inflammation in nasal polyposis: immunopathological aspects of relation to asthma. Clin Exp Allergy 2005;35:319-26. **IIb**
129. Ramey JT, Bailen E, Lockey RF. Rhinitis medicamentosa. J Investig Allergol Clin Immunol 2006;16:148-55. **IV**
130. Warner EA. Cocaine abuse. Ann Intern Med 1993;119:226-35. **IV**
131. Graf P, Hallen H. Effect on the nasal mucosa of long-term treatment with oxymetazoline, benzalkonium chloride, and placebo nasal sprays. Laryngoscope 1996; 106:605-9. **Ib**
132. Hallen H, Graf P. Benzalkonium chloride in nasal decongestive sprays has a long-lasting adverse effect on the nasal mucosa of healthy volunteers. Clin Exp Allergy 1995;25:401-5. **Ib**
133. Knipping S, Holzhausen HJ, Goetze G, Riederer A, Bloching MB. Rhinitis medicamentosa: electron microscopic changes of human nasal mucosa. Otolaryngol Head Neck Surg 2007;136:57-61. **III**
134. Keyserling HF, Grimme JD, Camacho DL, Castillo M. Nasal septal perforation secondary to rhinitis medicamentosa. Ear Nose Throat J 2006;85(376): 8-9. **IV**
135. Lekas MD. Rhinitis during pregnancy and rhinitis medicamentosa. Otolaryngol Head Neck Surg 1992;107:845-8; discussion 9. **IV**
136. Zohar Y, Talmi YP, Strauss M, Finkelstein Y, Shvilli Y. Ozena revisited. J Otolaryngol 1990;19:345-9. **IV**
137. Bunnag C, Jareoncharsri P, Tansuriyawong P, Bhothisuwan W, Chantarakul N. Characteristics of atrophic rhinitis in Thai patients at the Siriraj Hospital. Rhinology 1999;37:125-30. **III**
138. Moore EJ, Kern EB. Atrophic rhinitis: a review of 242 cases. Am J Rhinol 2001; 15:355-61. **III**
139. Tomooka LT, Murphy C, Davidson TM. Clinical study and literature review of nasal irrigation. Laryngoscope 2000;110:1189-93. **IIa**
140. Leonard DW, Bolger WE. Topical antibiotic therapy for recalcitrant sinusitis. Laryngoscope 1999;109:668-70. **III**
141. Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. Int J Epidemiol 1999;28:717-22. **III**
142. Johansson L, Akerlund A, Holmberg K, Melen I, Bende M. Prevalence of nasal polyps in adults: the Skovde population-based study. Ann Otol Rhinol Laryngol 2003;112:625-9. **III**
143. Klossek JM, Neukirch F, Pribil C, Jankowski R, Serrano E, Chanal I, et al. Prevalence of nasal polyposis in France: a cross-sectional, case-control study. Allergy 2005;60:233-7. **IIa**
144. Collins MM, Pang YT, Loughran S, Wilson JA. Environmental risk factors and gender in nasal polyposis. Clin Otolaryngol Allied Sci 2002;27:314-7. **III**
145. Larsen K, Tos M. The estimated incidence of symptomatic nasal polyps. Acta Otolaryngol 2002;122:179-82. **III**
146. Meltzer EO, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. J Allergy Clin Immunol 2004;114:155-212. **IV**
147. Hamilos DL. Nasal polyps as immunoreactive tissue. Allergy Asthma Proc 1996; 17:293-6. **IV**
148. Higashi N, Taniguchi M, Mita H, Kawagishi Y, Ishii T, Higashi A, et al. Clinical features of asthmatic patients with increased urinary leukotriene E4 excretion (hyperleukotrienuria): involvement of chronic hyperplastic rhinosinusitis with nasal polyposis. J Allergy Clin Immunol 2004;113:277-83. **IIb**
149. Alobid I, Benitez P, Pujols L, Maldonado M, Bernal-Sprekelsen M, Morello A, et al. Severe nasal polyposis and its impact on quality of life: the effect of a short course of oral steroids followed by long-term intranasal steroid treatment. Rhinology 2006;44:8-13. **Ib**
150. Hissaria P, Smith W, Wormald PJ, Taylor J, Vadas M, Gillis D, et al. Short course of systemic corticosteroids in sinonasal polyposis: a double-blind, randomized, placebo-controlled trial with evaluation of outcome measures. J Allergy Clin Immunol 2006;118:128-33. **Ib**
151. Martinez-Anton A, Debolos C, Garrido M, Roca-Ferrer J, Barranco C, Alobid I, et al. Mucin genes have different expression patterns in healthy and diseased upper airway mucosa. Clin Exp Allergy 2006;36:448-57. **LB**
152. Ragab S, Parikh A, Darby YC, Scadding GK. An open audit of montelukast, a leukotriene receptor antagonist, in nasal polyposis associated with asthma. Clin Exp Allergy 2001;31:1385-91. **III**
153. Parnes SM, Chuma AV. Acute effects of antileukotrienes on sinonasal polyposis and sinusitis. Ear Nose Throat J 2000;79:18-20, 24-5. III
154. Mostafa BE, Abdel Hay H, Mohammed HE, Yamani M. Role of leukotriene inhibitors in the postoperative management of nasal polyps. ORL J Otorhinolaryngol Relat Spec 2005;67:148-53. **Ib**
155. Stevenson DD, Hankammer MA, Mathison DA, Christiansen SC, Simon RA. Aspirin desensitization treatment of aspirin-sensitive patients with

rhinosinusitis-asthma: long-term outcomes. J Allergy Clin Immunol 1996;98: 751-8. **III**

156. Berges-Gimeno MP, Simon RA, Stevenson DD. Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. J Allergy Clin Immunol 2003;111:180-6. **IIa**
157. Sousa AR, Parikh A, Scadding G, Corrigan CJ, Lee TH. Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. N Engl J Med 2002;347:1493-9. **IIb**
158. Baumgartner BJ, Ladd T, Esquivel C. Low-grade adenocarcinoma of the nasal cavity–an unusual presentation: case report and review of the literature. Ear Nose Throat J 2007;86:97-100. **IV**
159. Komisar A. Nasal obstruction due to benign and malignant neoplasms. Otolaryngol Clin North Am 1989;22:351-65. **IV**
160. Dunn CJ, Alaani A, Johnson AP. Study on spontaneous cerebrospinal fluid rhinorrhoea: its aetiology and management. J Laryngol Otol 2005;119: 12-5. **III**
161. Olnes SQ, Schwartz RH, Bahadori RS. Consultation with the specialist: diagnosis and management of the newborn and young infant who have nasal obstruction. Pediatr Rev 2000;21:416-20. **IV**
162. Van's Gravesande KS, Omran H. Primary ciliary dyskinesia: clinical presentation, diagnosis and genetics. Ann Med 2005;37:439-49. **IV**
163. Alho OP. Nasal airflow, mucociliary clearance, and sinus functioning during viral colds: effects of allergic rhinitis and susceptibility to recurrent sinusitis. Am J Rhinol 2004;18:349-55. **III**
164. Sasaki Y, Togo Y, Wagner HN Jr, Hornick RB, Schwartz AR, Proctor DF. Mucociliary function during experimentally induced rhinovirus infection in man. Ann Otol Rhinol Laryngol 1973;82:203-11.
165. Afzelius B, Berstrom S. Primary ciliary dyskinesia (immotile cilia syndrome). In: Uptodate. Rose BD, editor. Waltham, MA; 2007. **IV**
166. Canciani M, Barlocco EG, Mastella G, de Santi MM, Gardi C, Lungarella G. The saccharin method for testing mucociliary function in patients suspected of having primary ciliary dyskinesia. Pediatr Pulmonol 1988;5:210-4. **III**
167. Afzelius B. Immotile cilia syndrome (primary ciliary dyskinesia) including Kartagener syndrome. In: Scriver C, Sly W, editors. The metabolic and molecular bases of inherited disease. New York: McGraw-Hill, Inc; 1995. **IV**
168. Jorissen M, Willems T, Van der Schueren B, Verbeken E, De Boeck K. Ultrastructural expression of primary ciliary dyskinesia after ciliogenesis in culture. Acta Otorhinolaryngol Belg 2000;54:343-56. **III**
169. Escudier E, Couprie M, Duriez B, Roudot-Thoraval F, Millepied MC, Pruliere-Escabasse V, et al. Computer-assisted analysis helps detect inner dynein arm abnormalities. Am J Respir Crit Care Med 2002;166:1257-62. **III**
170. Alho OP. Nasal airflow, mucociliary clearance, and sinus functioning during viral colds: effects of allergic rhinitis and susceptibility to recurrent sinusitis. Am J Rhinol 2004;18:349-55.
171. Carson JL, Collier AM, Hu SS. Acquired ciliary defects in nasal epithelium of children with acute viral upper respiratory infections. N Engl J Med 1985;312: 463-8. **III**
172. Rautiainen M, Nuutinen J, Kiukaanniemi H, Collan Y. Ultrastructural changes in human nasal cilia caused by the common cold and recovery of ciliated epithelium. Ann Otol Rhinol Laryngol 1992;101:982-7. **III**
173. Stanley PJ, Wilson R, Greenstone MA, MacWilliam L, Cole PJ. Effect of cigarette smoking on nasal mucociliary clearance and ciliary beat frequency. Thorax 1986; 41:519-23. **III**
174. Hee J, Guillerm R. Discussion on smoke and mucociliary transport. Eur J Respir Dis Suppl 1985;139:86-8. **LB**
175. Gendo K, Larson EB. Evidence-based diagnostic strategies for evaluating suspected allergic rhinitis. Ann Intern Med 2004;140:278-89. **IV**
176. Vuurman EF, van Veggel LM, Uiterwijk MM, Leutner D, O'Hanlon JF. Seasonal allergic rhinitis and antihistamine effects on children's learning. Ann Allergy 1993;71:121-6. **IIb**
177. Meltzer EO. Quality of life in adults and children with allergic rhinitis. J Allergy Clin Immunol 2001;108:S45-53. **IV**
178. Thompson AK, Juniper E, Meltzer EO. Quality of life in patients with allergic rhinitis. Ann Allergy Asthma Immunol 2000;85:338-47; quiz 47-8. **IV**
179. Green RJ, Davis G, Price D. Concerns of patients with allergic rhinitis: the Allergic Rhinitis Care Programme in South Africa. Prim Care Respir J 2007;16: 299-303. **III**
180. Berger WE. Allergic rhinitis in children: diagnosis and management strategies. Paediatr Drugs 2004;6:233-50. **IV**
181. Kirmaz C, Aydemir O, Bayrak P, Yuksel H, Ozenturk O, Degirmenci S. Sexual dysfunction in patients with allergic rhinoconjunctivitis. Ann Allergy Asthma Immunol 2005;95:525-9. **III**
182. Meltzer EO. Allergic rhinitis: the impact of discordant perspectives of patient and physician on treatment decisions. Clin Ther 2007;29:1428-40. **IV**
183. Bousquet J, Bullinger M, Fayol C, Marquis P, Valentin B, Burtin B. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. J Allergy Clin Immunol 1994;94: 182-8. **III**
184. Bousquet J, Knani J, Dhivert H, Richard A, Chicoye A, Ware JE Jr, et al. Quality of life in asthma, I: internal consistency and validity of the SF-36 questionnaire. Am J Respir Crit Care Med 1994;149:371-5. **III**
185. McHorney CA, Tarlov AR. Individual-patient monitoring in clinical practice: are available health status surveys adequate? Qual Life Res 1995;4:293-307. **III**
186. van Wijk R. Assessment of quality of life: advantages and pitfalls. Clin Exp Allergy Rev 2005;5:32-5. **IV**
187. Van Cauwenberge P, Juniper EF. Comparison of the efficacy, safety and quality of life provided by fexofenadine hydrochloride 120 mg, loratadine 10 mg and placebo administered once daily for the treatment of seasonal allergic rhinitis. Clin Exp Allergy 2000;30:891-9. **Ib**
188. van der Molen T, Sears MR, de Graaff CS, Postma DS, Meyboom-de Jong B. Quality of life during formoterol treatment: comparison between asthma-specific and generic questionnaires. Canadian and the Dutch Formoterol Investigators. Eur Respir J 1998;12:30-4. **Ib**
189. Juniper EF, Price DB, Stampone PA, Creemers JP, Mol SJ, Fireman P. Clinically important improvements in asthma-specific quality of life, but no difference in conventional clinical indexes in patients changed from conventional beclomethasone dipropionate to approximately half the dose of extrafine beclomethasone dipropionate. Chest 2002;121:1824-32. **Ib**
190. Ciprandi G, Canonica WG, Grosclaude M, Ostinelli J, Brazzola GG, Bousquet J. Effects of budesonide and fluticasone propionate in a placebo-controlled study on symptoms and quality of life in seasonal allergic rhinitis. Allergy 2002;57:586-91. **Ib**
191. Badhwar AK, Druce HM. Allergic rhinitis. Med Clin North Am 1992;76:789-803. **IV**
192. Skoner DP, Doyle WJ, Chamovitz AH, Fireman P. Eustachian tube obstruction after intranasal challenge with house dust mite. Arch Otolaryngol Head Neck Surg 1986;112:840-2. **IIb**
193. Noble SL, Forbes RC, Woodbridge HB. Allergic rhinitis. Am Fam Physician 1995;51:837-46. **IV**
194. Rohr A, Hassner A, Saxon A. Rhinopharyngoscopy for the evaluation of allergic-immunologic disorders. Ann Allergy 1983;50:380-4. **V**
195. Beltrani VS. The clinical spectrum of atopic dermatitis. J Allergy Clin Immunol 1999;104:S87-98. **V**
196. Beltrani VS. Atopic dermatitis. Dermatol Online J 2003;9(1):**IV**
197. Hamilton RG, Adkinson NF Jr. Clinical laboratory assessment of IgE-dependent hypersensitivity. J Allergy Clin Immunol 2003;111:S687-701. **IV**
198. Dolen W. Skin testing. Immunol Allergy Clin North Am 2001;21:273-9. **IV**
199. Miadonna A, Leggieri E, Tedeschi A, Zanussi C. Clinical significance of specific IgE determination on nasal secretion. Clin Allergy 1983;13:155-64. **III**
200. Petersson G, Dreborg S, Ingestad R. Clinical history, skin prick test and RAST in the diagnosis of birch and timothy pollinosis. Allergy 1986;41:398-407. **III**
201. Adinoff AD, Rosloniec DM, McCall LL, Nelson HS. A comparison of six epicutaneous devices in the performance of immediate hypersensitivity skin testing. J Allergy Clin Immunol 1989;84:168-74. **III**
202. Perera MG, Bernstein IL, Michael JG, Johansson SG. Predictability of the radioallergosorbent test (RAST) in ragweed pollenosis. Am Rev Respir Dis 1975;111: 605-10. **IIb**
203. Purohit A, Laffer S, Metz-Favre C, Verot A, Kricek F, Valenta R, et al. Poor association between allergen-specific serum immunoglobulin E levels, skin sensitivity and basophil degranulation: a study with recombinant birch pollen allergen Bet v 1 and an immunoglobulin E detection system measuring immunoglobulin E capable of binding to Fc epsilon RI. Clin Exp Allergy 2005;35:186-92. **III**
204. Bryant DH, Burns MW, Lazarus L. The correlation between skin tests, bronchial provocation tests and the serum level of IgE specific for common allergens in patients with asthma. Clin Allergy 1975;5:145-57. **III**
205. Pauli G, Bessot JC, Thierry R, Lamensans A. Correlation between skin tests, inhalation tests and specific IgE in a study of 120 subjects allergic to house dust and Dermatophagoides pteronyssinus. Clin Allergy 1977;7:337-45. **III**
206. Bousquet J, Lebel B, Dhivert H, Bataille Y, Martinot B, Michel FB. Nasal challenge with pollen grains, skin-prick tests and specific IgE in patients with grass pollen allergy. Clin Allergy 1987;17:529-36. **III**
207. Norman PS, Lichtenstein LM, Ishizaka K. Diagnostic tests in ragweed hay fever: a comparison of direct skin tests, IgE antibody measurements, and basophil histamine release. J Allergy Clin Immunol 1973;52:210-24. **III**
208. Witteman AM, Stapel SO, Perdok GJ, Sjamsoedin DH, Jansen HM, Aalberse RC, et al. The relationship between RAST and skin test results in patients with asthma or rhinitis: a quantitative study with purified major allergens. J Allergy Clin Immunol 1996;97:16-25. **III**

209. Niederberger V, Stubner P, Spitzauer S, Kraft D, Valenta R, Ehrenberger K, et al. Skin test results but not serology reflect immediate type respiratory sensitivity: a study performed with recombinant allergen molecules. J Invest Dermatol 2001; 117:848-51. **III**
210. Jacinto CM, Nelson RP, Bucholtz GA, Fernandez-Caldas E, Trudeau WL, Lockey RF. Nasal and bronchial provocation challenges with bayberry (Myrica cerifera) pollen extract. J Allergy Clin Immunol 1992;90:312-8. **IIb**
211. Day JH, Briscoe MP, Rafeiro E, Hewlett D Jr, Chapman D, Kramer B. Randomized double-blind comparison of cetirizine and fexofenadine after pollen challenge in the Environmental Exposure Unit: duration of effect in subjects with seasonal allergic rhinitis. Allergy Asthma Proc 2004;25:59-68. **IIa**
212. Stafford CT. The clinician's view of sinusitis. Otolaryngol Head Neck Surg 1990; 103:870-5. **IV**
213. Dolen WK, Selner JC. Endoscopy of the upper airway. In: Middleton E, Reed CE, Ellis E, editors. Middleton's Allergy: Principles and Practice. St Louis: Mosby-Year Book; 1998. p. 1017-23. **IV**
214. Zinreich SJ. Radiologic diagnosis of the nasal cavity and paranasal sinuses. In: Druce HM, editor. Sinusitis: pathophysiology and treatment. New York: Marcel Dekker; 1994. **IV**
215. Bingham B, Shankar L, Hawke M. Pitfalls in computed tomography of the paranasal sinuses. J Otolaryngol 1991;20:414-8. **III**
216. Mlynarek A, Tewfik MA, Hagr A, Manoukian JJ, Schloss MD, Tewfik TL, et al. Lateral neck radiography versus direct video rhinoscopy in assessing adenoid size. J Otolaryngol 2004;33:360-5. **III**
217. Anch AM, Remmers JE, Bunce H 3rd. Supraglottic airway resistance in normal subjects and patients with occlusive sleep apnea. J Appl Physiol 1982;53: 1158-63. **IIb**
218. Grymer LF, Hilberg O, Pedersen OF, Rasmussen TR. Acoustic rhinometry: values from adults with subjective normal nasal patency. Rhinology 1991;29: 35-47. **III**
219. Fisher EW, Lund VJ, Scadding GK. Acoustic rhinometry in rhinological practice: discussion paper. J R Soc Med 1994;87:411-3. **IV**
220. Pedersen OF, Berkowitz R, Yamagiwa M, Hilberg O. Nasal cavity dimensions in the newborn measured by acoustic reflections. Laryngoscope 1994;104:1023-8. **III**
221. Grymer LF, Hilberg O, Elbrond O, Pedersen OF. Acoustic rhinometry: evaluation of the nasal cavity with septal deviations, before and after septoplasty. Laryngoscope 1989;99:1180-7. **III**
222. Hilberg O, Jensen FT, Pedersen OF. Nasal airway geometry: comparison between acoustic reflections and magnetic resonance scanning. J Appl Physiol 1993;75: 2811-9. **III**
223. Dastidar P, Heinonen T, Numminen J, Rautiainen M, Laasonen E. Semi-automatic segmentation of computed tomographic images in volumetric estimation of nasal airway. Eur Arch Otorhinolaryngol 1999;256:192-8. **III**
224. Dastidar P, Numminen J, Heinonen T, Ryymin P, Rautiainen M, Laasonen E. Nasal airway volumetric measurement using segmented HRCT images and acoustic rhinometry. Am J Rhinol 1999;13:97-103. **III**
225. Gilain L, Coste A, Ricolfi F, Dahan E, Marliac D, Peynegre R, et al. Nasal cavity geometry measured by acoustic rhinometry and computed tomography. Arch Otolaryngol Head Neck Surg 1997;123:401-5. **III**
226. Parikh A, Scadding GK, Darby Y, Baker RC. Topical corticosteroids in chronic rhinosinusitis: a randomized, double-blind, placebo-controlled trial using fluticasone propionate aqueous nasal spray. Rhinology 2001;39:75-9. **Ib**
227. Ellegard EK, Hellgren M, Karlsson NG. Fluticasone propionate aqueous nasal spray in pregnancy rhinitis. Clin Otolaryngol Allied Sci 2001;26: 394-400. **Ib**
228. Hamilton JW, McRae RD, Jones AS. The magnitude of random errors in acoustic rhinometry and re-interpretation of the acoustic profile. Clin Otolaryngol Allied Sci 1997;22:408-13. **III**
229. Hillberg O, Jackson AC, Swift DL, Pedersen OF. Acoustic rhinometry: evaluation of nasal cavity geometry by acoustic reflection. J Appl Physiol 1989;66:295-303. **III**
230. Hilberg O. Objective measurement of nasal airway dimensions using acoustic rhinometry: methodological and clinical aspects. Allergy 2002;57(suppl 70): 5-39. **IV**
231. Tai CF, Ho KY, Hasegawa M. Evaluating the sensation of nasal obstruction with acoustic rhinometry and rhinomanometry. Kaohsiung J Med Sci 1998;14:548-53. **III**
232. Austin CE, Foreman JC. Acoustic rhinometry compared with posterior rhinomanometry in the measurement of histamine- and bradykinin-induced changes in nasal airway patency. Br J Clin Pharmacol 1994;37:33-7. **Ib**
233. Kesavanathan J, Swift DL, Fitzgerald TK, Permutt T, Bascom R. Evaluation of acoustic rhinometry and posterior rhinomanometry as tools for inhalation challenge studies. J Toxicol Environ Health 1996;48:295-307. **III**
234. Krotov A. [The current methodological approaches in assessing nasal breathing function]. Vestn Otorinolaringol 1998;4:51-2. **IV**
235. Roithmann R, Cole P, Chapnik J, Barreto SM, Szalai JP, Zamel N. Acoustic rhinometry, rhinomanometry, and the sensation of nasal patency: a correlative study. J Otolaryngol 1994;23:454-8. **IIb**
236. Schumacher MJ, Pain MC. Nasal challenge testing in grass pollen hay fever. J Allergy Clin Immunol 1979;64:202-8. **IIb**
237. Birchall MA, Phillips I, Fuller RW, Pride NB. Intranasal histamine challenge in normality and allergic rhinitis. Otolaryngol Head Neck Surg 1993;109:450-6. **IIb**
238. Majchel AM, Proud D, Freidhoff L, Creticos PS, Norman PS, Naclerio RM. The nasal response to histamine challenge: effect of the pollen season and immunotherapy. J Allergy Clin Immunol 1992;90:85-91. **IIb**
239. Hilberg O, Grymer LF, Pedersen OF. Nasal histamine challenge in nonallergic and allergic subjects evaluated by acoustic rhinometry. Allergy 1995;50:166-73. **IIb**
240. Hallen H, Juto JE. Correlation between subjective and objective assessment of nasal hyperreactivity. ORL J Otorhinolaryngol Relat Spec 1994;56:51-4. **IIb**
241. Rondon C, Romero JJ, Lopez S, Antunez C, Martin-Casanez E, Torres MJ, et al. Local IgE production and positive nasal provocation test in patients with persistent nonallergic rhinitis. J Allergy Clin Immunol 2007;119:899-905. **LB**
242. Kaufman HS, Rosen I, Shaposhnikov N, Wai M. Nasal eosinophilia. Ann Allergy 1982;49:270-1. **III**
243. Slavin RG. Allergic rhinitis, conjunctivitis, and sinusitis: sinusitis. ACP Medicine Online: WebMD Inc., 2006. Available at: www.medscape.com/viewarticle/534991. Accessed December 2006. **IV**
244. Afzelius BA. The immotile-cilia syndrome: a microtubule-associated defect. CRC Crit Rev Biochem 1985;19:63-87. **IV**
245. Stannard W, Rutman A, Wallis C, O'Callaghan C. Central microtubular agenesis causing primary ciliary dyskinesia. Am J Respir Crit Care Med 2004;169:634-7. **III**
246. Ownby DR. Clinical significance of IgE. In: Middleton E Jr, Reed C, editors. Allergy: Principles and Practice. St Louis: Mosby Year Book; 1993. p. 1059-76. **V**
247. Tschopp JM, Sistek D, Schindler C, Leuenberger P, Perruchoud AP, Wuthrich B, et al. Current allergic asthma and rhinitis: diagnostic efficiency of three commonly used atopic markers (IgE, skin prick tests, and Phadiatop): results from 8329 randomized adults from the SAPALDIA Study. Swiss Study on Air Pollution and Lung Diseases in Adults. Allergy 1998;53:608-13. **IIb**
248. Banuelos Arias Adel C, Montano Velazquez BB, Campillo Navarrete MR, Mojica Martinez MD, Ayala Balboa JC, Silva Vera RI, et al. [Skin tests, serum specific IgE and total IgE in the diagnosis of patients with perennial allergic rhinitis]. Rev Alerg Mex 2003;50:147-53. **III**
249. Gwynn CM, Ingram J, Almousawi T, Stanworth DR. Bronchial provocation tests in atopic patients with allergen-specific IgG4 antibodies. Lancet 1982;1:254-6. **III**
250. Lee TH, Durham SR, Merrett J, Merrett TG, Kay AB. Allergen-specific IgG-4 in bronchial asthma. Lancet 1982;2:1048-9. **IV**
251. Homburger HA, Mauer K, Sachs MI, O'Connell EJ, Jacob GL, Caron J. Serum IgG4 concentrations and allergen-specific IgG4 antibodies compared in adults and children with asthma and nonallergic subjects. J Allergy Clin Immunol 1986;77:427-34. **III**
252. Stanworth DR. Immunochemical aspects of human IgG4. Clin Rev Allergy 1983; 1:183-95. **IV**
253. Perelmutter L. IgG4 and the immune system. Clin Rev Allergy 1983;1:267-87.
254. AAAI. Measurement of specific and nonspecific IgG4 levels as diagnostic and prognostic tests for clinical allergy. AAAI Board of Directors. J Allergy Clin Immunol 1995;95:652-4. **IV**
255. Skedros DG, Cass SP, Hirsch BE, Kelly RH. Beta-2 transferrin assay in clinical management of cerebral spinal fluid and perilymphatic fluid leaks. J Otolaryngol 1993;22:341-4. **III**
256. Nandapalan V, Watson ID, Swift AC. Beta-2-transferrin and cerebrospinal fluid rhinorrhoea. Clin Otolaryngol Allied Sci 1996;21:259-64. **III**
257. Kalra M, Lemasters G, Bernstein D, Wilson K, Levin L, Cohen A, et al. Atopy as a risk factor for habitual snoring at age 1 year. Chest 2006;129:942-6. **III**
258. Chng SY, Goh DY, Wang XS, Tan TN, Ong NB. Snoring and atopic disease: a strong association. Pediatr Pulmonol 2004;38:210-6. **III**
259. Redline S, Tishler PV, Schluchter M, Aylor J, Clark K, Graham G. Risk factors for sleep-disordered breathing in children: associations with obesity, race, and respiratory problems. Am J Respir Crit Care Med 1999;159:1527-32. **III**
260. Kramer MF, de la Chaux R, Fintelmann R, Rasp G. NARES: a risk factor for obstructive sleep apnea? Am J Otolaryngol 2004;25:173-7. **III**
261. Kiely JL, Nolan P, McNicholas WT. Intranasal corticosteroid therapy for obstructive sleep apnoea in patients with co-existing rhinitis. Thorax 2004;59:50-5. **Ib**
262. Spector SL. Overview of comorbid associations of allergic rhinitis. J Allergy Clin Immunol 1997;99:S773-80. **IV**
263. Grossman J. One airway, one disease. Chest 1997;111:11S-6S. **IV**

264. Rowe-Jones JM. The link between the nose and lung, perennial rhinitis and asthma: is it the same disease? Allergy 1997;52:20-8. **IV**
265. Vignola AM, Chanez P, Godard P, Bousquet J. Relationships between rhinitis and asthma. Allergy 1998;53:833-9. **IV**
266. Platts-Mills TA, Thomas WR, Aalberse RC, Vervloet D, Champman MD. Dust mite allergens and asthma: report of a second international workshop. J Allergy Clin Immunol 1992;89:1046-60. **IV**
267. Moreno-Grau S, Elvira-Rendueles B, Moreno J, Garcia-Sanchez A, Vergara N, Asturias JA, et al. Correlation between Olea europaea and Parietaria judaica pollen counts and quantification of their major allergens Ole e 1 and Par j 1-Par j 2. Ann Allergy Asthma Immunol 2006;96:858-64. **LB**
268. Schappi GF, Taylor PE, Pain MC, Cameron PA, Dent AW, Staff IA, et al. Concentrations of major grass group 5 allergens in pollen grains and atmospheric particles: implications for hay fever and allergic asthma sufferers sensitized to grass pollen allergens. Clin Exp Allergy 1999;29:633-41. **III**
269. Habenicht HA, Burge HA, Muilenberg ML, Solomon WR. Allergen carriage by atmospheric aerosol, II: ragweed-pollen determinants in submicronic atmospheric fractions. J Allergy Clin Immunol 1984;74:64-7. **LB**
270. Pehkonen E, Rantio-Lehtimaki A. Variations in airborne pollen antigenic particles caused by meteorologic factors. Allergy 1994;49:472-7. **LB**
271. Jones AM, Harrison RM. The effects of meteorological factors on atmospheric bioaerosol concentrations: a review. Sci Total Environ 2004;326:151-80. **LB**
272. Makra L, Juhasz M, Borsos E, Beczi R. Meteorological variables connected with airborne ragweed pollen in Southern Hungary. Int J Biometeorol 2004;49:37-47. **LB**
273. Troutt C, Levetin E. Correlation of spring spore concentrations and meteorological conditions in Tulsa, Oklahoma. Int J Biometeorol 2001;45:64-74. **LB**
274. Damialis A, Gioulekas D, Lazopoulou C, Balafoutis C, Vokou D. Transport of airborne pollen into the city of Thessaloniki: the effects of wind direction, speed and persistence. Int J Biometeorol 2005;49:139-45. **LB**
275. Rodriguez-Rajo FJ, Iglesias I, Jato V. Variation assessment of airborne Alternaria and Cladosporium spores at different bioclimatical conditions. Mycol Res 2005; 109:497-507. **LB**
276. Peternel R, Culig J, Hrga I. Atmospheric concentrations of Cladosporium spp. and Alternaria spp. spores in Zagreb (Croatia) and effects of some meteorological factors. Ann Agric Environ Med 2004;11:303-7. **LB**
277. Gotoh M, Okubo K, Okuda M. Inhibitory effects of facemasks and eyeglasses on invasion of pollen particles in the nose and eye: a clinical study. Rhinology 2005; 43:266-70. **III**
278. Kusaka H, Ogasawara H, Munakata M, Tanimura K, Ukita H, Denzumi N, et al. Two-year follow up on the protective value of dust masks against farmer's lung disease. Intern Med 1993;32:106-11. **IIb**
279. Sheikh A, Hurwitz B. House dust mite avoidance measures for perennial allergic rhinitis. Cochrane Database Syst Rev 2001:CD001563. **Ia**
280. Nelson HS, Hirsch SR, Ohman JL Jr, Platts-Mills TA, Reed CE, Solomon WR. Recommendations for the use of residential air-cleaning devices in the treatment of allergic respiratory diseases. J Allergy Clin Immunol 1988;82: 661-9. **III**
281. Burr ML, Dean BV, Merrett TG, Neale E, St Leger AS, Verrier-Jones ER. Effects of anti-mite measures on children with mite-sensitive asthma: a controlled trial. Thorax 1980;35:506-12. **Ib**
282. Munir AK, Einarsson R, Dreborg SK. Vacuum cleaning decreases the levels of mite allergens in house dust. Pediatr Allergy Immunol 1993;4:136-43. **LB**
283. Tovey ER, Taylor DJ, Mitakakis TZ, De Lucca SD. Effectiveness of laundry washing agents and conditions in the removal of cat and dust mite allergen from bedding dust. J Allergy Clin Immunol 2001;108:369-74. **LB**
284. Miller J, Naccara L, Satinover S, Platts-Mills T. Nonwoven in contrast to woven mattress encasings accumulate mite and cat allergen. J Allergy Clin Immunol 2007;120:977-9. **III**
285. Carswell F, Oliver J, Weeks J. Do mite avoidance measures affect mite and cat airborne allergens? Clin Exp Allergy 1999;29:193-200. **LB**
286. Hayden ML, Rose G, Diduch KB, Domson P, Chapman MD, Heymann PW, et al. Benzyl benzoate moist powder: investigation of acaricidal [correction of acarical] activity in cultures and reduction of dust mite allergens in carpets. J Allergy Clin Immunol 1992;89:536-45. **LB**
287. Woodfolk JA, Hayden ML, Couture N, Platts-Mills TA. Chemical treatment of carpets to reduce allergen: comparison of the effects of tannic acid and other treatments on proteins derived from dust mites and cats. J Allergy Clin Immunol 1995; 96:325-33. **LB**
288. Sheikh A, Hurwitz B, Shehata Y. House dust mite avoidance measures for perennial allergic rhinitis. Cochrane Database Syst Rev 2007:CD001563. **IV**
289. Arbes SJ Jr, Sever M, Archer J, Long EH, Gore JC, Schal C, et al. Abatement of cockroach allergen (Bla g 1) in low-income, urban housing: a randomized controlled trial. J Allergy Clin Immunol 2003;112:339-45. **IIa**
290. Sever ML, Arbes SJ Jr, Gore JC, Santangelo RG, Vaughn B, Mitchell H, et al. Cockroach allergen reduction by cockroach control alone in low-income urban homes: a randomized control trial. J Allergy Clin Immunol 2007;120:849-55. **Ib**
291. Munir AK, Einarsson R, Schou C, Dreborg SK. Allergens in school dust, I: the amount of the major cat (Fel d I) and dog (Can f I) allergens in dust from Swedish schools is high enough to probably cause perennial symptoms in most children with asthma who are sensitized to cat and dog. J Allergy Clin Immunol 1993; 91:1067-74. **III**
292. de Blay F, Chapman MD, Platts-Mills TA. Airborne cat allergen (Fel d I): environmental control with the cat in situ. Am Rev Respir Dis 1991;143: 1334-9. **LB**
293. Wood RA, Eggleston PA, Lind P, Ingemann L, Schwartz B, Graveson S, et al. Antigenic analysis of household dust samples. Am Rev Respir Dis 1988;137: 358-63. **LB**
294. Liccardi G, Russo M, Barber D, Carreira J, D'Amato M, D'Amato G. Washing the clothes of cat owners is a simple method to prevent cat allergen dispersal. J Allergy Clin Immunol 1998;102:143-4. **LB**
295. Wood RA, Chapman MD, Adkinson NF Jr, Eggleston PA. The effect of cat removal on allergen content in household-dust samples. J Allergy Clin Immunol 1989;83:730-4. **LB**
296. Munir AK, Einarsson R, Dreborg SK. Indirect contact with pets can confound the effect of cleaning procedures for reduction of animal allergen levels in house dust. Pediatr Allergy Immunol 1994;5:32-9. **III**
297. Moira CY, Ferguson A, Dimich-Ward H, Watson W, Manfreda J, Becker A. Effectiveness of and compliance to intervention measures in reducing house dust and cat allergen levels. Ann Allergy Asthma Immunol 2002;88:52-8. **LB**
298. Avner DB, Perzanowski MS, Platts-Mills TA, Woodfolk JA. Evaluation of different techniques for washing cats: quantitation of allergen removed from the cat and the effect on airborne Fel d 1. J Allergy Clin Immunol 1997;100:307-12. **LB**
299. Hodson T, Custovic A, Simpson A, Chapman M, Woodcock A, Green R. Washing the dog reduces dog allergen levels, but the dog needs to be washed twice a week. J Allergy Clin Immunol 1999;103:581-5. **LB**
300. Klucka CV, Ownby DR, Green J, Zoratti E. Cat shedding of Fel d I is not reduced by washings, Allerpet-C spray, or acepromazine. J Allergy Clin Immunol 1995; 95:1164-71. **LB**
301. Bascom R, Kulle T, Kagey-Sobotka A, Proud D. Upper respiratory tract environmental tobacco smoke sensitivity. Am Rev Respir Dis 1991;143:1304-11. **IIb**
302. Bardana EJ Jr, Montanaro A. Formaldehyde: an analysis of its respiratory, cutaneous, and immunologic effects. Ann Allergy 1991;66:441-52. **Ib**
303. Dykewicz MS, Patterson R, Cugell DW, Harris KE, Wu AF. Serum IgE and IgG to formaldehyde-human serum albumin: lack of relation to gaseous formaldehyde exposure and symptoms. J Allergy Clin Immunol 1991;87:48-57. **III**
304. Theander C, Bende M. Nasal hyperreactivity to newspapers. Clin Exp Allergy 1989;19:57-8. **III**
305. Arts JH, Rennen MA, de Heer C. Inhaled formaldehyde: evaluation of sensory irritation in relation to carcinogenicity. Regul Toxicol Pharmacol 2006;44:144-60. **III**
306. Berglund B, Nordin S. Detectability and perceived intensity for formaldehyde in smokers and non-smokers. Chemical Senses 1992;17:291-306. **III**
307. Shamsi Z, Hindmarch I. Sedation and antihistamines: a review of inter-drug differences using proportional impairment ratios. Hum Psychopharmacol 2000;15: S3-30. **IV**
308. Hindmarch I. Psychometric aspects of antihistamines. Allergy 1995;50:48-54. **IV**
309. Casale TB, Blaiss MS, Gelfand E, Gilmore T, Harvey PD, Hindmarch I, et al. First do no harm: managing antihistamine impairment in patients with allergic rhinitis. J Allergy Clin Immunol 2003;111:S835-42. **IV**
310. Weiler JM, Bloomfield JR, Woodworth GG, Grant AR, Layton TA, Brown TL, et al. Effects of fexofenadine, diphenhydramine, and alcohol on driving performance: a randomized, placebo-controlled trial in the Iowa driving simulator. Ann Intern Med 2000;132:354-63. **Ib**
311. Tashiro M, Horikawa E, Mochizuki H, Sakurada Y, Kato M, Inokuchi T, et al. Effects of fexofenadine and hydroxyzine on brake reaction time during car-driving with cellular phone use. Hum Psychopharmacol 2005;20:501-9. **Ib**
312. Simons FE, Reggin JD, Roberts JR, Simons KJ. Benefit/risk ratio of the antihistamines (H1-receptor antagonists) terfenadine and chlorpheniramine in children. J Pediatr 1994;124:979-83. **IIa**
313. 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;111:770-6. **Ia**
314. O'Hanlon JF, Ramaekers JG. Antihistamine effects on actual driving performance in a standard test: a summary of Dutch experience, 1989-94. Allergy 1995;50: 234-42. **IIa**
315. O'Hanlon JF. Alcohol, drugs and traffic safety. In: Institute for Drugs, Safety and Behavior. Maastrict, The Netherlands: Ryksuniersitet Limberg; 1998. p. 10-2. **IV**

316. Ramaekers JG, Uiterwijk MM, O'Hanlon JF. Effects of loratadine and cetirizine on actual driving and psychometric test performance, and EEG during driving. Eur J Clin Pharmacol 1992;42:363-9. **IIa**
317. Ray WA, Thapa PB, Shorr RI. Medications and the older driver. Clin Geriatr Med 1993;9:413-38. **IV**
318. Cimbura G, Lucas DM, Bennett RC, Warren RA, Simpson HM. Incidence and toxicological aspects of drugs detected in 484 fatally injured drivers and pedestrians in Ontario. J Forensic Sci 1982;27:855-67. **LB**
319. Warren RSH, Hilchie J. Drugs detected in fatally injured drivers inthe province of Ontario. In: Goldberg L, editor. Alcohol, drugs and safety. Stockholm: Almquist and Wiksell; 1981. p. 203-17. **IV**
320. Hindmarch I, Parrott AC. A repeated dose comparison of the side effects of five antihistamines on objective assessments of psychomotor performance, central nervous system arousal and subjective appraisals of sleep and early morning behaviour. Arzneimittelforschung 1978;28:483-6. **III**
321. Goetz DW, Jacobson JM, Apaliski SJ, Repperger DW, Martin ME. Objective antihistamine side effects are mitigated by evening dosing of hydroxyzine. Ann Allergy 1991;67:448-54. **Ib**
322. Klein GL, Littlejohn T 3rd, Lockhart EA, Furey SA. Brompheniramine, terfenadine, and placebo in allergic rhinitis. Ann Allergy Asthma Immunol 1996;77:365-70. **Ib**
323. Mason J, Reynolds R. The systemic safety of fexofenadine HCl. Clin Exp Allergy 1999;29(suppl):163-70. **IV**
324. Alford C, Rombaut N, Jones J, Foley S, Idzikowskit C, Hindmarch I. Acute effects of hydroxyzine on nocturnal sleep and sleep tendency the following day: a C-EEG study. Hum Psychopharmacol 1992;7:25-35. **III**
325. Kay G, Plotkin K, Quig MB, al E. Sedating effects of AM/PM antihistamine dosing with evening chlorpheniramine and morning terfenadine. Am J Managed Care 1997;3:1843-8. **IV**
326. Slater JW, Zechnich AD, Haxby DG. Second-generation antihistamines: a comparative review. Drugs 1999;57:31-47. **III**
327. Meltzer EO. Evaluation of the optimal oral antihistamine for patients with allergic rhinitis. Mayo Clin Proc 2005;80:1170-6. **III**
328. Bradley CM, Nicholson AN. Studies on the central effects of the H1-antagonist, loratadine. Eur J Clin Pharmacol 1987;32:419-21. **III**
329. Zyrtec (cetirizine hydrochloride). 2006. Available at: http://www.pfizer.com/pfizer/download/uspi_zyrtec.pdf. Accessed July 3, 2008. **IV**
330. Gengo FM, Gabos C, Mechtler L. Quantitative effects of cetirizine and diphenhydramine on mental performance measured using an automobile driving simulator. Ann Allergy 1990;64:520-6. **Ib**
331. Ciprandi G, Passalacqua G, Mincarini M, Ricca V, Canonica GW. Continuous versus on demand treatment with cetirizine for allergic rhinitis. Ann Allergy Asthma Immunol 1997;79:507-11. **Ib**
332. Berger W, Hampel F Jr, Bernstein J, Shah S, Sacks H, Meltzer EO. Impact of azelastine nasal spray on symptoms and quality of life compared with cetirizine oral tablets in patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2006;97:375-81. **Ib**
333. Corren J, Storms W, Bernstein J, Berger W, Nayak A, Sacks H. Effectiveness of azelastine nasal spray compared with oral cetirizine in patients with seasonal allergic rhinitis. Clin Ther 2005;27:543-53. **Ib**
334. Horak F, Zieglmayer UP, Zieglmayer R, Kavina A, Marschall K, Munzel U, et al. Azelastine nasal spray and desloratadine tablets in pollen-induced seasonal allergic rhinitis: a pharmacodynamic study of onset of action and efficacy. Curr Med Res Opin 2006;22:151-7. **Ib**
335. LaForce CF, Corren J, Wheeler WJ, Berger WE. Efficacy of azelastine nasal spray in seasonal allergic rhinitis patients who remain symptomatic after treatment with fexofenadine. Ann Allergy Asthma Immunol 2004;93:154-9. **Ib**
336. Newson-Smith G, Powell M, Baehre M, Garnham SP, MacMahon MT. A placebo controlled study comparing the efficacy of intranasal azelastine and beclomethasone in the treatment of seasonal allergic rhinitis. Eur Arch Otorhinolaryngol 1997;254:236-41. **Ib**
337. Ratner PH, Findlay SR, Hampel F Jr, van Bavel J, Widlitz MD, Freitag JJ. A double-blind, controlled trial to assess the safety and efficacy of azelastine nasal spray in seasonal allergic rhinitis. J Allergy Clin Immunol 1994;94:818-25. **Ib**
338. LaForce C, Dockhorn RJ, Prenner BM, Chu TJ, Kraemer MJ, Widlitz MD, et al. Safety and efficacy of azelastine nasal spray (Astelin NS) for seasonal allergic rhinitis: a 4-week comparative multicenter trial. Ann Allergy Asthma Immunol 1996; 76:181-8. **Ib**
339. Ratner P, Hampel F, Van Bavel J, Amar NJ, Daftary P, Wheeler W, et al. Combination therapy with azelastine hydrochloride nasal spray is more effective than either agent alone in the treatment of patients with seasonal allergic rhinitis. Ann Allergy 2008;100:74-81. **Ib**
340. Patel D, Garadi R, Brubaker M, Conroy JP, Kaji Y, Crenshaw K, et al. Onset and duration of action of nasal sprays in seasonal allergic rhinitis patients: olopatadine hydrochloride versus mometasone furoate monohydrate. Allergy Asthma Proc 2007;28:592-9. **Ib**
341. Patel P, Wilson D, D'Andrea C, Sacks H. Onset of action of azelastine nasal spray compared to mometasone nasal spray and placebo in patients with seasonal allergic rhinitis (SAR). J Allergy Clin Immunol 2007;119:S144. **Ib**
342. Astelin (azelastine hydrochloride). 2007. Available at: http://www.astelin.com/Astelin.Public/AstelinPi.pdf. Accessed July 3, 2008. **IV**
343. Greiner AN, Meltzer EO. Pharmacologic rationale for treating allergic and nonallergic rhinitis. J Allergy Clin Immunol 2006;118:985-98. **IV**
344. Falliers CJ, Redding MA. Controlled comparison of anew antihistamine-decongestant combination to its individual components. Ann Allergy 1980;45:75-80. **Ib**
345. Eccles R. Substitution of phenylephrine for pseudoephedrine as a nasal decongeststant: an illogical way to control methamphetamine abuse. Br J Clin Pharmacol 2007;63:10-4. **IV**
346. Kanfer I, Dowse R, Vuma V. Pharmacokinetics of oral decongestants. Pharmacotherapy 1993;13:116S-28S; discussion 43S-46S. **IV**
347. Hengstmann JH, Goronzy J. Pharmacokinetics of 3H-phenylephrine in man. Eur J Clin Pharmacol 1982;21:335-41. **III**
348. Bickerman HA. Physiologic and pharmacologic studies on nasal airway resistance (Rn). Presented at a conference sponsored by the Scientific Development Committee of the Proprietary Association. Washington, D.C.; December 8, 1971. **IV**
349. McLaurin JW, Shipman WF, Rosedale R Jr. Oral decongestants: a double blind comparison study of the effectiveness of four sympathomimetic drugs: objective and subjective. Laryngoscope 1961;71:54-67. **IIa**
350. Downey R. This is your brain on Frappacino. Seattle Weekly 2004. Available at: http://www.alternet.org/story/19622. Accessed July 3, 2008. **IV**
351. Roberge RJ, Hirani KH, Rowland PL 3rd, Berkeley R, Krenzelok EP. Dextromethorphan- and pseudoephedrine-induced agitated psychosis and ataxia: case report. J Emerg Med 1999;17:285-8. **III**
352. Marinetti L, Lehman L, Casto B, Harshbarger K, Kubiczek P, Davis J. Over-the-counter cold medications-postmortem findings in infants and the relationship to cause of death. J Anal Toxicol 2005;29:738-43. **III**
353. Sauder KL, Brady WJ Jr, Hennes H. Visual hallucinations in a toddler: accidental ingestion of a sympathomimetic over-the-counter nasal decongestant. Am J Emerg Med 1997;15:521-6. **III**
354. Pentel P. Toxicity of over-the-counter stimulants. JAMA 1984;252:1898-903. **IV**
355. Togias A, Naclerio RM, Proud D, Baumgarten C, Peters S, Creticos PS, et al. Mediator release during nasal provocation: a model to investigate the pathophysiology of rhinitis. Am J Med 1985;79:26-33. **III**
356. Barnes ML, Biallosterski BT, Gray RD, Fardon TC, Lipworth BJ. Decongestant effects of nasal xylometazoline and mometasone furoate in persistent allergic rhinitis. Rhinology 2005;43:291-5. **Ib**
357. Morris S, Eccles R, Martez SJ, Riker DK, Witek TJ. An evaluation of nasal response following different treatment regimes of oxymetazoline with reference to rebound congestion. Am J Rhinol 1997;11:109-15. **Ib**
358. Yoo JK, Seikaly H, Calhoun KH. Extended use of topical nasal decongestants. Laryngoscope 1997;107:40-3. **IIb**
359. Petruson B. Treatment with xylometazoline (Otrivin) nosedrops over a six-week period. Rhinology 1981;19:167-72. **IIb**
360. Watanabe H, Foo TH, Djazaeri B, Duncombe P, Mackay IS, Durham SR. Oxymetazoline nasal spray three times daily for four weeks in normal subjects is not associated with rebound congestion or tachyphylaxis. Rhinology 2003;41: 167-74. **Ib**
361. Hutton N, Wilson MH, Mellits ED, Baumgardner R, Wissow LS, Bonuccelli C, et al. Effectiveness of an antihistamine-decongestant combination for young children with the common cold: a randomized, controlled clinical trial. J Pediatr 1991; 118:125-30. **Ib**
362. Taylor JA, Novack AH, Almquist JR, Rogers JE. Efficacy of cough suppressants in children. J Pediatr 1993;122:799-802. **Ib**
363. Clemens CJ, Taylor JA, Almquist JR, Quinn HC, Mehta A, Naylor GS. Is an antihistamine-decongestant combination effective in temporarily relieving symptoms of the common cold in preschool children? J Pediatr 1997;130: 463-6. **Ib**
364. Schroeder K, Fahey T. Should we advise parents to administer over the counter cough medicines for acute cough? systematic review of randomised controlled trials. Arch Dis Child 2002;86:170-5. **IV**
365. Smith MB, Feldman W. Over-the-counter cold medications: a critical review of clinical trials between 1950 and 1991. JAMA 1993;269:2258-63. **IV**
366. FDA OoN-PP. Nonprescription Drug Advisory Committee Meeting, Cold, Cough, Allergy, Bronchodilator, Antiasthmatic Drug Products for Over-the-Counter Human Use. 2007. Available at: http://www.fda.gov/OHRMS/DOCKETS/98fr/E7-16169.htm. Accessed July 3, 2008. **IV**

367. Milgrom H, Kittner B, Lanier R, Hampel FC. Safety and tolerability of fexofenadine for the treatment of allergic rhinitis in children 2 to 5 years old. Ann Allergy Asthma Immunol 2007;99:358-63. **Ib**
368. Simons FE. Safety of levocetirizine treatment in young atopic children: an 18-month study. Pediatr Allergy Immunol 2007;18:535-42. **Ib**
369. Simons FE, Silas P, Portnoy JM, Catuogno J, Chapman D, Olufade AO, et al. Safety of cetirizine in infants 6 to 11 months of age: a randomized, double-blind, placebo-controlled study. J Allergy Clin Immunol 2003;111:1244-8. **Ib**
370. Diepgen TL. Long-term treatment with cetirizine of infants with atopic dermatitis: a multi-country, double-blind, randomized, placebo-controlled trial (the ETAC trial) over 18 months. Pediatr Allergy Immunol 2002;13:278-86. **Ib**
371. Simons FE. Prospective, long-term safety evaluation of the H1-receptor antagonist cetirizine in very young children with atopic dermatitis. ETAC Study Group. Early Treatment of the Atopic Child. J Allergy Clin Immunol 1999;104:433-40. **Ib**
372. Bloom M, Staudinger H, Herron J. Safety of desloratadine syrup in children. Curr Med Res Opin 2004;20:1959-65. **Ib**
373. Yang YH, Lin YT, Lu MY, Tsai MJ, Chiang BL. A double-blind, placebo-controlled, and randomized study of loratadine (Clarityne) syrup for the treatment of allergic rhinitis in children aged 3 to 12 years. Asian Pac J Allergy Immunol 2001;19:171-5. **Ib**
374. Lutsky BN, Klose P, Melon J, Menardo JL, Molkhou P, Ronchetti R, et al. A comparative study of the efficacy and safety of loratadine syrup and terfenadine suspension in the treatment of 3- to 6-year-old children with seasonal allergic rhinitis. Clin Ther 1993;15:855-65. **Ib**
375. Pullerits T, Praks L, Ristioja V, Lotvall J. Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 2002;109:949-55. **Ib**
376. Di Lorenzo G, Pacor ML, Pellitteri ME, Morici G, Di Gregoli A, Lo Bianco C, et al. Randomized placebo-controlled trial comparing fluticasone aqueous nasal spray in mono-therapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic rhinitis. Clin Exp Allergy 2004;34:259-67. **Ib**
377. Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. Am J Med 2004;116:338-44. **Ia**
378. Wilson AM, Orr LC, Sims EJ, Dempsey OJ, Lipworth BJ. Antiasthmatic effects of mediator blockade versus topical corticosteroids in allergic rhinitis and asthma. Am J Respir Crit Care Med 2000;162:1297-301. **Ib**
379. Wilson AM, Orr LC, Sims EJ, Lipworth BJ. Effects of monotherapy with intranasal corticosteroid or combined oral histamine and leukotriene receptor antagonists in seasonal allergic rhinitis. Clin Exp Allergy 2001;31:61-8. **Ib**
380. 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;161:2581-7. **Ib**
381. Corren J. Intranasal corticosteroids for allergic rhinitis: how do different agents compare? J Allergy Clin Immunol 1999;104:S144-9. **III**
382. LaForce C. Use of nasal steroids in managing allergic rhinitis. J Allergy Clin Immunol 1999;103:S388-94. **III**
383. Meltzer EO, Rickard KA, Westlund RE, Cook CK. Onset of therapeutic effect of fluticasone propionate aqueous nasal spray. Ann Allergy Asthma Immunol 2001;86:286-91. **Ia**
384. Day JH, Briscoe MP, Rafeiro E, Ellis AK, Pettersson E, Akerlund A. Onset of action of intranasal budesonide (Rhinocort aqua) in seasonal allergic rhinitis studied in a controlled exposure model. J Allergy Clin Immunol 2000;105:489-94. **Ib**
385. Berkowitz RB, Bernstein DI, LaForce C, Pedinoff AJ, Rooklin AR, Damaraju CR, et al. Onset of action of mometasone furoate nasal spray (NASONEX) in seasonal allergic rhinitis. Allergy 1999;54:64-9. **Ib**
386. Jen A, Baroody F, de Tineo M, Haney L, Blair C, Naclerio R. As-needed use of fluticasone propionate nasal spray reduces symptoms of seasonal allergic rhinitis. J Allergy Clin Immunol 2000;105:732-8. **Ib**
387. Dykewicz MS, Kaiser HB, Nathan RA, Goode-Sellers S, Cook CK, Witham LA, et al. Fluticasone propionate aqueous nasal spray improves nasal symptoms of seasonal allergic rhinitis when used as needed (prn). Ann Allergy Asthma Immunol 2003;91:44-8. **Ib**
388. Banov CH, Woehler TR, LaForce CF, Pearlman DS, Blumenthal MN, Morgan WF, et al. Once daily intranasal fluticasone propionate is effective for perennial allergic rhinitis. Ann Allergy 1994;73:240-6. **Ib**
389. Wight RG, Jones AS, Beckingham E, Andersson B, Ek L. A double blind comparison of intranasal budesonide 400 micrograms and 800 micrograms in perennial rhinitis. Clin Otolaryngol Allied Sci 1992;17:354-8. **Ib**
390. Dockhorn R, Aaronson D, Bronsky E, Chervinsky P, Cohen R, Ehtessabian R, 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 1999;82:349-59. **Ib**
391. Clissold SP, Heel RC. Budesonide: a preliminary review of its pharmacodynamic properties and therapeutic efficacy in asthma and rhinitis. Drugs 1984;28:485-518. **IV**
392. Pipkorn U, Berge T. Long-term treatment with budesonide in vasomotor rhinitis. Acta Otolaryngol 1983;95:167-71. **Ib**
393. Van As A, Bronsky EA, Dockhorn RJ, Grossman J, Lumry W, Meltzer EO, et al. Once daily fluticasone propionate is as effective for perennial allergic rhinitis as twice daily beclomethasone diproprionate. J Allergy Clin Immunol 1993;91:1146-54. **Ib**
394. Wihl JA, Andersson KE, Johansson SA. Systemic effects of two nasally administered glucocorticosteroids. Allergy 1997;52:620-6. **Ib**
395. Brannan MD, Herron JM, Reidenberg P, Affrime MB. Lack of hypothalamic-pituitary-adrenal axis suppression with once-daily or twice-daily beclomethasone dipropionate aqueous nasal spray administered to patients with allergic rhinitis. Clin Ther 1995;17:637-47. **Ib**
396. Vargas R, Dockhorn RJ, Findlay SR, Korenblat PE, Field EA, Kral KM. Effect of fluticasone propionate aqueous nasal spray versus oral prednisone on the hypothalamic-pituitary-adrenal axis. J Allergy Clin Immunol 1998;102:191-7. **Ib**
397. Howland WC 3rd, Dockhorn R, Gillman S, Gross GN, Hille D, Simpson B, et al. A comparison of effects of triamcinolone acetonide aqueous nasal spray, oral prednisone, and placebo on adrenocortical function in male patients with allergic rhinitis. J Allergy Clin Immunol 1996;98:32-8. **Ib**
398. Nayak AS, Ellis MH, Gross GN, Mendelson LM, Schenkel EJ, Lanier BQ, et al. The effects of triamcinolone acetonide aqueous nasal spray on adrenocortical function in children with allergic rhinitis. J Allergy Clin Immunol 1998;101:157-62. **Ib**
399. Galant SP, Melamed IR, Nayak AS, Blake KV, Prillaman BA, Reed KD, et al. Lack of effect of fluticasone propionate aqueous nasal spray on the hypothalamic-pituitary-adrenal axis in 2- and 3-year-old patients. Pediatrics 2003;112:96-100. **Ib**
400. Moller C, Ahlstrom H, Henricson KA, Malmqvist LA, Akerlund A, Hildebrand H. Safety of nasal budesonide in the long-term treatment of children with perennial rhinitis. Clin Exp Allergy 2003;33:816-22. **IIb**
401. Boner AL. Effects of intranasal corticosteroids on the hypothalamic-pituitary-adrenal axis in children. J Allergy Clin Immunol 2001;108:S32-9. **IV**
402. Ozturk F, Yuceturk AV, Kurt E, Unlu HH, Ilker SS. Evaluation of intraocular pressure and cataract formation following the long-term use of nasal corticosteroids. Ear Nose Throat J 1998;77:846-8, 50-1. **IIb**
403. Ernst P, Baltzan M, Deschenes J, Suissa S. Low-dose inhaled and nasal corticosteroid use and the risk of cataracts. Eur Respir J 2006;27:1168-74. **IIa**
404. Garbe E, LeLorier J, Boivin JF, Suissa S. Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. JAMA 1997;277:722-7. **IIa**
405. Herrala J, Puolijoki H, Impivaara O, Liippo K, Tala E, Nieminen MM. Bone mineral density in asthmatic women on high-dose inhaled beclomethasone dipropionate. Bone 1994;15:621-3. **IIa**
406. McEvoy CE, Ensrud KE, Bender E, Genant HK, Yu W, Griffith JM, et al. Association between corticosteroid use and vertebral fractures in older men with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:704-9. **III**
407. Leone FT, Fish JE, Szefler SJ, West SL. Systematic review of the evidence regarding potential complications of inhaled corticosteroid use in asthma: collaboration of American College of Chest Physicians, American Academy of Allergy, Asthma, and Immunology, and American College of Allergy, Asthma, and Immunology. Chest 2003;124:2329-40. **Ib**
408. Allen DB, Meltzer EO, Lemanske RF Jr, Philpot EE, Faris MA, Kral KM, et al. No growth suppression in children treated with the maximum recommended dose of fluticasone propionate aqueous nasal spray for one year. Allergy Asthma Proc 2002;23:407-13. **Ib**
409. Schenkel EJ, Skoner DP, Bronsky EA, Miller SD, Pearlman DS, Rooklin A, 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:E22. **Ib**
410. Gradman J, Caldwell MF, Wolthers OD. A 2-week, crossover study to investigate the effect of fluticasone furoate nasal spray on short-term growth in children with allergic rhinitis. Clin Ther 2007;29:1738-47. **Ib**
411. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. N Engl J Med 2006;354:1985-97. **Ib**

412. Schoezel EP, Menzel ML. Nasal sprays and perforation of the nasal septum. JAMA 1985;253:2046. **IV**
413. Cervin A, Andersson M. Intranasal steroids and septum perforation: an overlooked complication? a description of the course of events and a discussion of the causes. Rhinology 1998;36:128-32. **III**
414. Bernstein IL. Is the use of benzalkonium chloride as a preservative for nasal formulations a safety concern? a cautionary note based on compromised mucociliary transport. J Allergy Clin Immunol 2000;105:39-44. **IV**
415. Naclerio RM, Baroody FM, Bidani N, De Tineo M, Penney BC. A comparison of nasal clearance after treatment of perennial allergic rhinitis with budesonide and mometasone. Otolaryngol Head Neck Surg 2003;128:220-7. **Ib**
416. Van Cauwenberge P, Van Hoecke H, Vandenbulcke L, Van Zele T, Bachert C. Glucocorticosteroids in allergic inflammation: clinical benefits in allergic rhinitis, rhinosinusitis, and otitis media. Immunol Allergy Clin North Am 2005;25: 489-509. **Ib**
417. Joos GF, Brusselle GG, Van Hoecke H, Van Cauwenberge P, Bousquet J, Pauwels RA. Positioning of glucocorticosteroids in asthma and allergic rhinitis guidelines (versus other therapies). Immunol Allergy Clin North Am 2005;25:597-612, vii-viii. **IV**
418. Iglesias P, Gonzalez J, Diez JJ. Acute and persistent iatrogenic Cushing's syndrome after a single dose of triamcinolone acetonide. J Endocrinol Invest 2005; 28:1019-23. **IV**
419. Jacobs MB. Local subcutaneous atrophy after corticosteroid injection. Postgrad Med 1986;80:159-60. **IV**
420. Dyment PG. Local atrophy following triamcinolone injection. Pediatrics 1970;46: 136-7. **III**
421. Saunders WH. Surgery of the inferior nasal turbinates. Ann Otol Rhinol Laryngol 1982;91:445-7. **IV**
422. Gill BS. Intraturbinate use of steroids in nasal allergy. J Laryngol Otol 1966;80: 506-10. **IV**
423. Martin PA, Church CA, Petti GH Jr, Hedayi R. Visual loss after intraturbinate steroid injection. Otolaryngol Head Neck Surg 2003;128:280-1. **III**
424. Altounyan RE. Review of clinical activity and mode of action of sodium cromoglycate. Clin Allergy 1980;10(suppl):481-9. **IV**
425. Kay AB, Walsh GM, Moqbel R, MacDonald AJ, Nagakura T, Carroll MP, et al. Disodium cromoglycate inhibits activation of human inflammatory cells in vitro. J Allergy Clin Immunol 1987;80:1-8. **IIb**
426. Cox JS, Beach JE, Blair AM, Clarke AJ, King J, Lee TB, et al. Disodium cromoglycate (Intal). Adv Drug Res 1970;5:115-96. **IV**
427. Fisons C. Cromolyn sodium: clinical considerations. Princeton (NJ): Excerpta Medica; 1987. p. 5-6. **IV**
428. Orie NG, Booij-Noord H, Pelikan Z. Protective effect of disodium cromoglycate on nasal and bronchial reactions after allergen challenge. In: Proceedings of the Symposium on Disodium Cromoglycate in Allergic Airway Disease. London: Butterworths; 1970. p. 33-44. **IV**
429. Pelikan Z, Snoek WJ, Booij-Noord H, Orie NG, de Vries K. Protective effect of disodium cromoglycate on the allergen provocation of the nasal mucosa. Ann Allergy 1970;28:548-53. **IIb**
430. Nelson BL, Jacobs RL. Response of nonallergic rhinitis with eosinophilia (NARES) syndrome to 4% cromoly sodium nasal solution. J Allergy Clin Immunol 1982;70:125-8. **IIa**
431. Donovan R, Kapadia R. The effect of disodium cromoglycate on nasal polyp symptoms. J Laryngol Otol 1972;86:731-9. **IIb**
432. Birchall MA, Henderson JC, Studham JM, Pride NB, Fuller RW. The effect of topical sodium cromoglycate on intranasal histamine challenge in allergic rhinitis. Clin Otolaryngol Allied Sci 1994;19:521-5. **Ib**
433. Pelikan Z, Pelikan-Filipek M. The effects of disodium cromoglycate and beclomethasone dipropionate on the immediate response of the nasal mucosa to allergen challenge. Ann Allergy 1982;49:283-92. **III**
434. Handelman NI, Friday GA, Schwartz HJ, Kuhn FS, Lindsay DE, Koors PG, et al. Cromolyn sodium nasal solution in the prophylactic treatment of pollen-induced seasonal allergic rhinitis. J Allergy Clin Immunol 1977;59:237-42. **Ib**
435. Welsh PW, Stricker WE, Chu CP, Naessens JM, Reese ME, Reed CE, et al. Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. Mayo Clin Proc 1987;62:125-34. **Ib**
436. Bonadonna P, Senna G, Zanon P, Cocco G, Dorizzi R, Gani F, et al. Cold-induced rhinitis in skiers: clinical aspects and treatment with ipratropium bromide nasal spray: a randomized controlled trial. Am J Rhinol 2001;15:297-301. **Ib**
437. Meltzer EO. Intranasal anticholinergic therapy of rhinorrhea. J Allergy Clin Immunol 1992;90:1055-64. **IV**
438. Meltzer EO, Orgel HA, Bronsky EA, Findlay SR, Georgitis JW, Grossman J, 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 1992;90:242-9. **Ib**
439. Druce HM, Spector SL, Fireman P, Kaiser H, Meltzer EO, Boggs P, et al. Double-blind study of intranasal ipratropium bromide in nonallergic perennial rhinitis. Ann Allergy 1992;69:53-60. **Ib**
440. Bronsky EA, Druce H, Findlay SR, Hampel FC, Kaiser H, Ratner P, et al. A clinical trial of ipratropium bromide nasal spray in patients with perennial nonallergic rhinitis. J Allergy Clin Immunol 1995;95:1117-22. **Ib**
441. Georgitis JW, Banov C, Boggs PB, Dockhorn R, Grossman J, Tinkelman D, et al. Ipratropium bromide nasal spray in non-allergic rhinitis: efficacy, nasal cytological response and patient evaluation on quality of life. Clin Exp Allergy 1994;24: 1049-55. **Ib**
442. Grossman J, Banov C, Boggs P, Bronsky EA, Dockhorn RJ, Druce H, et al. Use of ipratropium bromide nasal spray in chronic treatment of nonallergic perennial rhinitis, alone and in combination with other perennial rhinitis medications. J Allergy Clin Immunol 1995;95:1123-7. **Ib**
443. Borum P, Olsen L, Winther B, Mygind N. Ipratropium nasal spray: a new treatment for rhinorrhea in the common cold. Am Rev Respir Dis 1981;123: 418-20. **Ib**
444. Gaffey MJ, Hayden FG, Boyd JC, Gwaltney JM Jr. Ipratropium bromide treatment of experimental rhinovirus infection. Antimicrob Agents Chemother 1988; 32:1644-7. **Ib**
445. Dockhorn R, Grossman J, Posner M, Zinny M, Tinkleman D. A double-blind, placebo-controlled study of the safety and efficacy of ipratropium bromide nasal spray versus placebo in patients with the common cold. J Allergy Clin Immunol 1992;90:1076-82. **Ib**
446. Diamond L, Dockhorn RJ, Grossman J, Kisicki JC, Posner M, Zinny MA, et al. A dose-response study of the efficacy and safety of ipratropium bromide nasal spray in the treatment of the common cold. J Allergy Clin Immunol 1995;95:1139-46. **Ib**
447. Hayden FG, Diamond L, Wood PB, Korts DC, Wecker MT. Effectiveness and safety of intranasal ipratropium bromide in common colds: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1996;125: 89-97. **IV**
448. Milgrom H, Biondi R, Georgitis JW, Meltzer EO, Munk ZM, Drda K, et al. Comparison of ipratropium bromide 0.03% with beclomethasone dipropionate in the treatment of perennial rhinitis in children. Ann Allergy Asthma Immunol 1999; 83:105-11. **Ib**
449. Ohi M, Sakakura Y, Murai S, Miyoshi Y. Effect of ipratropium bromide on nasal mucociliary transport. Rhinology 1984;22:241-6. **IIa**
450. Meltzer EO, Malmstrom K, Lu S, Prenner BM, Wei LX, Weinstein SF, et al. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. J Allergy Clin Immunol 2000;105: 917-22. **Ib**
451. Chervinsky P, Philip G, Malice MP, Bardelas J, Nayak A, Marchal JL, et al. Montelukast for treating fall allergic rhinitis: effect of pollen exposure in 3 studies. Ann Allergy Asthma Immunol 2004;92:367-73. **Ib**
452. Meltzer EO, Philip G, Weinstein SF, LaForce CF, Malice MP, Dass SB, et al. Montelukast effectively treats the nighttime impact of seasonal allergic rhinitis. Am J Rhinol 2005;19:591-8. **Ib**
453. Patel P, Philip G, Yang W, Call R, Horak F, LaForce C, et al. Randomized, double-blind, placebo-controlled study of montelukast for treating perennial allergic rhinitis. Ann Allergy Asthma Immunol 2005;95:551-7. **Ib**
454. Polos PG. Montelukast is an effective monotherapy for mild asthma and for asthma with co-morbid allergic rhinitis. Prim Care Respir J 2006;15:310-1. **IV**
455. Price DB, Swern A, Tozzi CA, Philip G, Polos P. Effect of montelukast on lung function in asthma patients with allergic rhinitis: analysis from the COMPACT trial. Allergy 2006;61:737-42. **III**
456. Ngamphaiboon J. Montelukast in general pediatric practices. J Med Assoc Thai 2005;88(suppl 4):S348-51. **IV**
457. Keskin O, Alyamac E, Tuncer A, Dogan C, Adalioglu G, Sekerel BE. Do the leukotriene receptor antagonists work in children with grass pollen-induced allergic rhinitis? Pediatr Allergy Immunol 2006;17:259-68. **IIa**
458. Casale TB, Bernstein IL, Busse WW, LaForce CF, Tinkelman DG, Stoltz RR, et al. Use of an anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. J Allergy Clin Immunol 1997;100:110-21. **Ib**
459. Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. Cochrane Database Syst Rev 2007: CD006394. **IV**
460. Heatley DG, McConnell KE, Kille TL, Leverson GE. Nasal irrigation for the alleviation of sinonasal symptoms. Otolaryngol Head Neck Surg 2001;125: 44-8. **Ib**
461. Rabago D, Barrett B, Marchand L, Maberry R, Mundt M. Qualitative aspects of nasal irrigation use by patients with chronic sinus disease in a multimethod study. Ann Fam Med 2006;4:295-301. **III**

462. Bachmann G, Hommel G, Michel O. Effect of irrigation of the nose with isotonic salt solution on adult patients with chronic paranasal sinus disease. Eur Arch Otorhinolaryngol 2000;257:537-41. **Ib**
463. Shoseyov D, Bibi H, Shai P, Shoseyov N, Shazberg G, Hurvitz H. Treatment with hypertonic saline versus normal saline nasal wash of pediatric chronic sinusitis. J Allergy Clin Immunol 1998;101:602-5. **Ib**
464. Ross Rn NH, Finegold I. Effectiveness of specific immunotherapy in the treatment of Hymenoptera venom hypersensitivity: a meta-analysis. Clin Ther 2000;22: 351-8. **Ia**
465. Didier A, Malling HJ, Worm M, Horak F, Jager S, Montagut A, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. J Allergy Clin Immunol 2007;120: 1338-45. **Ib**
466. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999;341:468-75. **Ib**
467. Mosbech H, Osterballe O. Does the effect of immunotherapy last after termination of treatment? follow-up study in patients with grass pollen rhinitis. Allergy 1988; 43:523-9. **Ib**
468. Pifferi M, Baldini G. Benefits of immunotherapy with a standardized Dermatophagoides pteronyssinus extract in asthmatic children: a three-year prospective study. Allergy 2002;57:785-90. **Ib**
469. Purello-D'Ambrosio F, Gangemi S, Merendino RA, Isola S, Puccinelli P, Parmiani S, et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not: a retrospective study. Clin Exp Allergy 2001;31:1295-302. **III**
470. Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy: a six-year follow-up study. Clin Exp Allergy 2001;31:1392-7. **III**
471. Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract, VI: specific immunotherapy prevents the onset of new sensitizations in children. J Allergy Clin Immunol 1997;99:450-3. **III**
472. Jacobsen L. Preventive aspects of immunotherapy: prevention for children at risk of developing asthma. Ann Allergy Asthma Immunol 2001;87:43-6. **IV**
473. Niggemann B, Jacobsen L, Dreborg S, Ferdousi HA, Halken S, Host A, et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. Allergy 2006;61:855-9. **Ib**
474. Polosa R, Al-Delaimy WK, Russo C, Piccillo G, Sarva M. Greater risk of incident asthma cases in adults with allergic rhinitis and effect of allergen immunotherapy: a retrospective cohort study. Respir Res 2005;6:153. **III**
475. Polosa R, Li Gotti F, Mangano G, Paolino G, Mastruzzo C, Vancheri C, et al. Effect of immunotherapy on asthma progression, BHR and sputum eosinophils in allergic rhinitis. Allergy 2004;59:1224-8. **Ib**
476. Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109:251-6. **Ib**
477. Jacobsen L, Nuchel Petersen B, Wihl JA, Lowenstein H, Ipsen H. Immunotherapy with partially purified and standardized tree pollen extracts, IV: results from long-term (6-year) follow-up. Allergy 1997;52:914-20. **III**
478. Eng PA, Reinhold M, Gnehm HP. Long-term efficacy of preseasonal grass pollen immunotherapy in children. Allergy 2002;57:306-12. **IIa**
479. Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children: a 14-year study. Pediatrics 1968;42:793-802. **Ib**
480. Eng PA, Borer-Reinhold M, Heijnen IAFM, Gnehm HPE. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. Allergy 2006;61:198-201. **IIa**
481. Marogna M, Falagiani P, Bruno M, Massolo A, Riva G. The allergic march in pollinosis: natural history and therapeutic implications. Int Arch Allergy Immunol 2004;135:336-42. **III**
482. Cantani A, Arcese G, Lucenti P, Gagliesi D, Bartolucci M. A three-year prospective study of specific immunotherapy to inhalant allergens: evidence of safety and efficacy in 300 children with allergic asthma. J Investig Allergol Clin Immunol 1997;7:90-7. **IIa**
483. Cantani A, Micera M. Is specific immunotherapy safe and effective in children? Eur Rev Med Pharmacol Sci 2000;4:139-43. **IV**
484. Ohashi Y, Nakai Y, Tanaka A, Kakinoki Y, Washio Y, Kato A, et al. Serologic study of the working mechanisms of immunotherapy for children with perennial allergic rhinitis. Arch Otolaryngol Head Neck Surg 1998;124:1337-46. **III**
485. Portnoy JM. Immunotherapy for allergic diseases. Clin Rev Allergy Immunol 2001;21:241-59. **IV**
486. Ariano R, Kroon AM, Augeri G, Canonica GW, Passalacqua G. Long-term treatment with allergoid immunotherapy with Parietaria: clinical and immunologic effects in a randomized, controlled trial. Allergy 1999;54:313-9. **Ib**
487. Bousquet J, Becker WM, Hejjaoui A, Chanal I, Lebel B, Dhivert H, et al. Differences in clinical and immunologic reactivity of patients allergic to grass pollens and to multiple-pollen species, II: efficacy of a double-blind, placebo-controlled, specific immunotherapy with standardized extracts. J Allergy Clin Immunol 1991; 88:43-53. **IIb**
488. Bousquet J, Frank E, Soussana M, Hejjaoui A, Maasch HJ, Michel FB. Double-blind, placebo-controlled immunotherapy with a high-molecular-weight, formalinized allergoid in grass pollen allergy. Int Arch Allergy Appl Immunol 1987;82: 550-2. **Ib**
489. Creticos PS, Marsh DG, Proud D, Kagey-Sobotka A, Adkinson NF Jr, Friedhoff L, et al. Responses to ragweed-pollen nasal challenge before and after immunotherapy. J Allergy Clin Immunol 1989;84:197-205. **Ib**
490. Creticos PS, Reed CE, Norman PS, Khoury J, Adkinson NF Jr, Buncher CR, et al. Ragweed immunotherapy in adult asthma. N Engl J Med 1996;334: 501-6. **Ib**
491. Dolz I, Martinez-Cocera C, Bartolome JM, Cimarra M. A double-blind, placebo-controlled study of immunotherapy with grass-pollen extract Alutard SQ during a 3-year period with initial rush immunotherapy. Allergy 1996;51:489-500. **Ib**
492. Lowell FC, Franklin W. A double-blind study of the effectiveness and specificity of injecton therapy in ragweed hay fever. N Engl J Med 1965;273:675-9. **Ib**
493. Malling HJ, Djurup R. Diagnosis and immunotherapy of mould allergy, VII: IgG subclass response and relation to the clinical efficacy of immunotherapy with Cladosporium. Allergy 1988;43:60-70. **Ib**
494. Horst M, Hejjaoui A, Horst V, Michel FB, Bousquet J. Double-blind, placebo-controlled rush immunotherapy with a standardized Alternaria extract. J Allergy Clin Immunol 1990;85:460-72. **III**
495. Malling HJ. Diagnosis and immunotherapy of mould allergy, IV: relation between asthma symptoms, spore counts and diagnostic tests. Allergy 1986;41:342-50. **IIa**
496. Karlsson R, Agrell B, Dreborg S, Foucard T, Kjellman NI, Koivikko A, et al. A double-blind, multicenter immunotherapy trial in children, using a purified and standardized Cladosporium herbarum preparation, II: in vitro results. Allergy 1986;41:141-50. **Ib**
497. Dreborg S, Agrell B, Foucard T, Kjellman NI, Koivikko A, Nilsson S. A double-blind, multicenter immunotherapy trial in children, using a purified and standardized Cladosporium herbarum preparation, I: clinical results. Allergy 1986;41: 131-40. **Ib**
498. Ewbank PA, Murray J, Sanders K, Curran-Everett D, Dreskin S, Nelson HS. A double-blind, placebo-controlled immunotherapy dose-response study with standardized cat extract. J Allergy Clin Immunol 2003;111:155-61. **Ib**
499. Alvarez-Cuesta E, Cuesta-Herranz J, Puyana-Ruiz J, Cuesta-Herranz C, Blanco-Quiros A. Monoclonal antibody-standardized cat extract immunotherapy: risk-benefit effects from a double-blind placebo study. J Allergy Clin Immunol 1994;93:556-66. **Ib**
500. Haugaard L, Dahl R. Immunotherapy in patients allergic to cat and dog dander, I: clinical results. Allergy 1992;47:249-54. **IIa**
501. Hedlin G, Graff-Lonnevig V, Heilborn H, Lilja G, Norrlind K, Pegelow K, et al. Immunotherapy with cat- and dog-dander extracts, V: effects of 3 years of treatment. J Allergy Clin Immunol 1991;87:955-64. **IIa**
502. Ohman JL Jr, Findlay SR, Leitermann KM. Immunotherapy in cat-induced asthma: double-blind trial with evaluation of in vivo and in vitro responses. J Allergy Clin Immunol 1984;74:230-9. **Ib**
503. Varney VA, Edwards J, Tabbah K, Brewster H, Mavroleon G, Frew AJ. Clinical efficacy of specific immunotherapy to cat dander: a double-blind placebo-controlled trial. Clin Exp Allergy 1997;27:860-7. **Ib**
504. Nanda A, O'Connor M, Anand M, Dreskin SC, Zhang L, Hines B, et al. Dose dependence and time course of the immunologic response to administration of standardized cat allergen extract. J Allergy Clin Immunol 2004;114:1339-44. **Ib**
505. Lent AM, Harbeck R, Strand M, Sills M, Schmidt K, Efaw B, et al. Immunologic response to administration of standardized dog allergen extract at differing doses. J Allergy Clin Immunol 2006;118:1249-56. **Ib**
506. Maestrelli P, Zanolla L, Pozzan M, Fabbri LM. Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite. J Allergy Clin Immunol 2004;113:643-9. **Ib**
507. Tabar AI, Echechipia S, Garcia BE, Olagibel JM, Lizaso MT, Gomez B, et al. Double-blind comparative study of cluster and conventional immunotherapy schedules with Dermatophagoides pteronyssinus. J Allergy Clin Immunol 2005; 116:109-18. **Ib**
508. Pichler CE, Marquardsen A, Sparholt S, Lowenstein H, Bircher A, Bischof M, et al. Specific immunotherapy with Dermatophagoides pteronyssinus and D. farinae results in decreased bronchial hyperreactivity. Allergy 1997;52:274-83. **IIb**
509. Aas K. Hyposensitization in house dust allergy asthma: a double-blind controlled study with evaluation of the effect on bronchial sensitivity to house dust. Acta Paediatr Scand 1971;60:264-8. **Ib**

510. Bonno M, Fujisawa T, Iguchi K, Uchida Y, Kamiya H, Komada Y, et al. Mite-specific induction of interleukin-2 receptor on T lymphocytes from children with mite-sensitive asthma: modified immune response with immunotherapy. J Allergy Clin Immunol 1996;97:680-8. **IIa**
511. Bousquet J, Calvayrac P, Guerin B, Hejjaoui A, Dhivert H, Hewitt B, et al. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract, I: in vivo and in vitro parameters after a short course of treatment. J Allergy Clin Immunol 1985;76:734-44. **IIa**
512. Bousquet J, Hejjaoui A, Clauzel AM, Guerin B, Dhivert H, Skassa-Brociek W, et al. Specific immunotherapy with a standardized Dermatophagoides pteronyssinus extract, II: prediction of efficacy of immunotherapy. J Allergy Clin Immunol 1988;82:971-7. **III**
513. Haugaard L, Dahl R, Jacobsen L. A controlled dose-response study of immunotherapy with standardized, partially purified extract of house dust mite: clinical efficacy and side effects. J Allergy Clin Immunol 1993;91:709-22. **Ib**
514. McHugh SM, Lavelle B, Kemeny DM, Patel S, Ewan PW. A placebo-controlled trial of immunotherapy with two extracts of Dermatophagoides pteronyssinus in allergic rhinitis, comparing clinical outcome with changes in antigen-specific IgE, IgG, and IgG subclasses. J Allergy Clin Immunol 1990;86:521-31. **Ib**
515. Olsen OT, Larsen KR, Jacobsan L, Svendsen UG. A 1-year, placebo-controlled, double-blind house-dust-mite immunotherapy study in asthmatic adults. Allergy 1997;52:853-9. **Ib**
516. Pauli G, Bessot JC, Bigot H, Delaume G, Hordle DA, Hirth C, et al. Clinical and immunologic evaluation of tyrosine-adsorbed Dermatophagoides pteronyssinus extract: a double-blind placebo-controlled trial. J Allergy Clin Immunol 1984; 74:524-35. **Ib**
517. Wang H, Lin X, Hao C, Zhang C, Sun B, Zheng J, et al. A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients. Allergy 2006;61:191-7. **Ib**
518. Kang BC, Johnson J, Morgan C, Chang JL. The role of immunotherapy in cockroach asthma. J Asthma 1988;25:205-18. **IIa**
519. Bernstein JA. Pharmacoeconomic considerations for allergen immunotherapy. Clin Allergy Immunol 2004;18:151-64. **III**
520. Omnes LF, Bousquet J, Scheinmann P, Neukirch F, Jasso-Mosqueda G, Chicoye A, et al. Pharmacoeconomic assessment of specific immunotherapy versus current symptomatic treatment for allergic rhinitis and asthma in France. Allerg Immunol (Paris) 2007;39:148-56. **III**
521. Mekhitarian Neto L, Pignatari S, Mitsuda S, Fava AS, Stamm A. Acute sinusitis in children: a retrospective study of orbital complications. Rev Bras Otorrinolaringol (Engl Ed) 2007;73:75-9. **III**
522. Stoll D, Klossek JM, Barbaza MO. [Prospective study of 43 severe complications of acute rhinosinusitis]. Rev Laryngol Otol Rhinol (Bord) 2006;127: 195-201. **III**
523. Cabrera CE, Deutsch ES, Eppes S, Lawless S, Cook S, O'Reilly RC, et al. Increased incidence of head and neck abscesses in children. Otolaryngol Head Neck Surg 2007;136:176-81. **III**
524. Cavaliere M, Mottola G, Iemma M. Comparison of the effectiveness and safety of radiofrequency turbinoplasty and traditional surgical technique in treatment of inferior turbinate hypertrophy. Otolaryngol Head Neck Surg 2005;133:972-8. **IIb**
525. Kimmelman CP. The problem of nasal obstruction. Otolaryngol Clin North Am 1989;22:253-64. **IV**
526. Vainio-Mattila J. Correlations of nasal symptoms and signs in random sampling study. Acta Otolaryngol Suppl 1974;318:1-48. **III**
527. Bejar I, Farkas LG, Messner AH, Crysdale WS. Nasal growth after external septoplasty in children. 1996;122:816-21. **III**
528. Hwang PH, McLaughlin RB, Lanza DC, Kennedy DW. Endoscopic septoplasty: indications, technique, and results. Otolaryngol Head Neck Surg 1999;120: 678-82. **III**
529. Haraldsson PO, Nordemar H, Anggard A. Long-term results after septal surgery: submucous resection versus septoplasty. ORL J Otorhinolaryngol Relat Spec 1987;49:218-22. **III**
530. Bateman ND, Woolford TJ. Informed consent for septal surgery: the evidence-base. J Laryngol Otol 2003;117:186-9. **IV**
531. Illi S, von Mutius E, Lau S, Niggemann B, Gruber C, Wahn U. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. Lancet 2006;368:763-70. **IIa**
532. Illum P. Septoplasty and compensatory inferior turbinate hypertrophy: long-term results after randomized turbinoplasty. Eur Arch Otorhinolaryngol 1997; 254(suppl 1):S89-92. **Ib**
533. Fukazawa K, Ogasawara H, Tomofuji S, Fujii M, Sakagami M. Argon plasma surgery for the inferior turbinate of patients with perennial nasal allergy. Laryngoscope 2001;111:147-52. **III**
534. Kezirian EJ, Powell NB, Riley RW, Hester JE. Incidence of complications in radiofrequency treatment of the upper airway. Laryngoscope 2005;115:1298-304. **III**
535. Nease CJ, Krempl GA. Radiofrequency treatment of turbinate hypertrophy: a randomized, blinded, placebo-controlled clinical trial. Otolaryngol Head Neck Surg 2004;130:291-9. **Ib**
536. Chang CW, Ries WR. Surgical treatment of the inferior turbinate: new techniques. Curr Opin Otolaryngol Head Neck Surg 2004;12:53-7. **IV**
537. Friedman M, Tanyeri H, Lim J, Landsberg R, Caldarelli D. A safe, alternative technique for inferior turbinate reduction. Laryngoscope 1999;109:1834-7. **III**
538. Joniau S, Wong I, Rajapaksa S, Carney SA, Wormald PJ. Long-term comparison between submucosal cauterization and powered reduction of the inferior turbinates. Laryngoscope 2006;116:1612-6. **Ib**
539. Chen YL, Liu CM, Huang HM. Comparison of microdebrider-assisted inferior turbinoplasty and submucosal resection for children with hypertrophic inferior turbinates. Int J Pediatr Otorhinolaryngol 2007;71:921-7. **IIb**
540. Mori S, Fujieda S, Igarashi M, Fan GK, Saito H. Submucous turbinectomy decreases not only nasal stiffness but also sneezing and rhinorrhea in patients with perennial allergic rhinitis. Clin Exp Allergy 1999;29:1542-8. **IIb**
541. Mori S, Fujieda S, Yamada T, Kimura Y, Takahashi N, Saito H. Long-term effect of submucous turbinectomy in patients with perennial allergic rhinitis. Laryngoscope 2002;112:865-9. **III**
542. Inouye T, Tanabe T, Nakanoboh M, Ogura M. Laser surgery for allergic and hypertrophic rhinitis. Ann Otol Rhinol Laryngol Suppl 1999;180:3-19. **III**
543. American Academy of Family Physicians; American Academy of Otolaryngology-Head and Neck Surgery; American Academy of Pediatrics Subcommittee on Otitis Media with Effusion. Otitis media with effusion. Pediatrics 2004;113: 1412-29. **IV**
544. Berlucchi M, Salsi D, Valetti L, Parrinello G, Nicolai P. The role of mometasone furoate aqueous nasal spray in the treatment of adenoidal hypertrophy in the pediatric age group: preliminary results of a prospective, randomized study. Pediatrics 2007;119:e1392-7. **Ib**
545. Demain JG, Goetz DW. Pediatric adenoidal hypertrophy and nasal airway obstruction: reduction with aqueous nasal beclomethasone. Pediatrics 1995;95: 355-64. **Ib**
546. Criscuoli G, D'Amora S, Ripa G, Cinquegrana G, Mansi N, Impagliazzo N, et al. Frequency of surgery among children who have adenotonsillar hypertrophy and improve after treatment with nasal beclomethasone. Pediatrics 2003;111:e236-8. **Ib**
547. Cengel S, Akyol MU. The role of topical nasal steroids in the treatment of children with otitis media with effusion and/or adenoid hypertrophy. Int J Pediatr Otorhinolaryngol 2006;70:639-45. **Ib**
548. Prenner BM, Schenkel E. Allergic rhinitis: treatment based on patient profiles. Am J Med 2006;119:230-7. **IV**
549. Carlsen KH, Kramer J, Fagertun HE, Larsen S. Loratadine and terfenadine in perennial allergic rhinitis: treatment of nonresponders to the one drug with the other drug. Allergy 1993;48:431-6. **Ib**
550. Blaiss M. Current concepts and therapeutic strategies for allergic rhinitis in school-age children. Clin Ther 2004;26:1876-89. **IV**
551. Nayak AS, Philip G, Lu S, Malice MP, Reiss TF. Efficacy and tolerability of montelukast alone or in combination with loratadine in seasonal allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial performed in the fall. Ann Allergy Asthma Immunol 2002;88:592-600. **Ib**
552. Rathkopf MM, Quinn JM, Proffer DL, Napoli DC. Patient knowledge of immunotherapy before and after an educational intervention: a comparison of 2 methods. Ann Allergy Asthma Immunol 2004;93:147-53. **Ib**
553. Bender BG, Long A, Parasuraman B, Tran ZV. Factors influencing patient decisions about the use of asthma controller medication. Ann Allergy Asthma Immunol 2007;98:322-8. **III**
554. Wroe AL. Intentional and unintentional nonadherence: a study of decision making. J Behav Med 2002;25:355-72. **III**
555. Lowry KP, Dudley TK, Oddone EZ, Bosworth HB. Intentional and unintentional nonadherence to antihypertensive medication. Ann Pharmacother 2005;39: 1198-203. **III**
556. Huss K, Winkelstein M, Nanda J, Naumann PL, Sloand ED, Huss RW. Computer game for inner-city children does not improve asthma outcomes. J Pediatr Health Care 2003;17:72-8. **Ib**
557. Sundberg R, Tunsater A, Palmqvist M, Ellbjar S, Lowhagen O, Toren K. A randomized controlled study of a computerized limited education program among young adults with asthma. Respir Med 2005;99:321-8. **Ib**
558. Guendelman S, Meade K, Benson M, Chen YQ, Samuels S. Improving asthma outcomes and self-management behaviors of inner-city children: a randomized trial of the Health Buddy interactive device and an asthma diary. Arch Pediatr Adolesc Med 2002;156:114-20. **Ib**

559. Homer C, Susskind O, Alpert HR, Owusu M, Schneider L, Rappaport LA, et al. An evaluation of an innovative multimedia educational software program for asthma management: report of a randomized, controlled trial. Pediatrics 2000;106:210-5. **Ib**
560. Bartholomew LK, Gold RS, Parcel GS, Czyzewski DI, Sockrider MM, Fernandez M, et al. Watch, discover, think, and act: evaluation of computer-assisted instruction to improve asthma self-management in inner-city children. Patient Educ Couns 2000;39:269-80. **Ib**
561. Rubin DH, Leventhal JM, Sadock RT, Letovsky E, Schottland P, Clemente I, et al. Educational intervention by computer in childhood asthma: a randomized clinical trial testing the use of a new teaching intervention in childhood asthma. Pediatrics 1986;77:1-10. **Ib**
562. Chan DS CCea. Internet-based home monitoring and education of children with asthma is comparable to ideal office-based care: results of a 1-year asthma in-home monitoring trial. Pediatrics 2007;119:569–78. **Ib**
563. Krishna S, Francisco BD, Balas EA, Konig P, Graff GR, Madsen RW. Internet-enabled interactive multimedia asthma education program: a randomized trial. Pediatrics 2003;111:503-10. **Ib**
564. White P, Smith H, Webley F, Frew A. A survey of the quality of information leaflets on hayfever available from general practices and community pharmacies. Clin Exp Allergy 2004;34:1438-43. **III**
565. Leynaert B, Neukirch C, Kony S, Guenegou A, Bousquet J, Aubier M, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. J Allergy Clin Immunol 2004;113:86-93. **III**
566. Bugiani M, Carosso A, Migliore E, Piccioni P, Corsico A, Olivieri M, et al. Allergic rhinitis and asthma comorbidity in a survey of young adults in Italy. Allergy 2005;60:165-70. **III**
567. Burgess JA, Walters EH, Byrnes GB, Matheson MC, Jenkins MA, Wharton CL, et al. Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study. J Allergy Clin Immunol 2007;120:863-9. **III**
568. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca M, Passalacqua G, Pallestrini E, et al. Seasonal and perennial allergic rhinitis: is this classification adherent to real life? Allergy 2005;60:882-7. **III**
569. Choi SH, Yoo Y, Yu J, Rhee CS, Min YG, Koh YY. Bronchial hyperresponsiveness in young children with allergic rhinitis and its risk factors. Allergy 2007;62: 1051-6. **IIa**
570. Shaaban R, Zureik M, Soussan D, Anto JM, Heinrich J, Janson C, et al. Allergic rhinitis and onset of bronchial hyperresponsiveness: a population-based study. Am J Respir Crit Care Med 2007;176:659-66. **III**
571. Marogna M, Massolo A, Berra D, Zanon P, Chiodini E, Canonica GW, et al. The type of sensitizing allergen can affect the evolution of respiratory allergy. Allergy 2006;61:1209-15. **Ib**
572. Ciprandi G, Cirillo I, Tosca MA, Vizzaccaro A. Bronchial hyperreactivity and spirometric impairment in patients with seasonal allergic rhinitis. Respir Med 2004; 98:826-31. **III**
573. Braunstahl GJ, Kleinjan A, Overbeek SE, Prins JB, Hoogsteden HC, Fokkens WJ. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. Am J Respir Crit Care Med 2000;161:2051-7. **IIa**
574. Ciprandi G, Cirillo I, Klersy C, Marseglia GL, Vizzaccaro A, Pallestrini E, et al. Role of FEF25-75 as an early marker of bronchial impairment in patients with seasonal allergic rhinitis. Am J Rhinol 2006;20:641-7. **III**
575. Ciprandi G, Cirillo I, Pistorio A. Impact of allergic rhinitis on asthma: effects on spirometric parameters. Allergy 2008;63:255-60. **III**
576. Kessel A, Halloun H, Bamberger E, Kugelman A, Toubi E. Abnormal spirometry in children with persistent allergic rhinitis due to mite sensitization: the benefit of nasal corticosteroids. Pediatr Allergy Immunol 2008;19:61-6. **IIa**
577. Foresi A, Pelucchi A, Gherson G, Mastropasqua B, Chiapparino A, Testi R. Once daily intranasal fluticasone propionate (200 micrograms) reduces nasal symptoms and inflammation but also attenuates the increase in bronchial responsiveness during the pollen season in allergic rhinitis. J Allergy Clin Immunol 1996;98:274-82. **Ib**
578. Corren J, Adinoff AD, Irvin CG. Changes in bronchial responsiveness following nasal provocation with allergen. J Allergy Clin Immunol 1992;89:611-8. **Ib**
579. Des Roches A, Paradis L, Knani J, Hejjaoui A, Dhivert H, Chanez P, et al. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract, V: duration of the efficacy of immunotherapy after its cessation. Allergy 1996;51:430-3. **III**
580. Novembre E, Galli E, Landi F, Caffarelli C, Pifferi M, De Marco E, et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. J Allergy Clin Immunol 2004;114:851-7. **Ib**
581. Corren J, Harris AG, Aaronson D, Beaucher W, Berkowitz R, Bronsky E, et al. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. J Allergy Clin Immunol 1997; 100:781-8. **Ib**
582. Wood-Baker R, Holgate ST. The comparative actions and adverse effect profile of single doses of H1-receptor antihistamines in the airways and skin of subjects with asthma. J Allergy Clin Immunol 1993;91:1005-14. **IIa**
583. Brik A, Tashkin DP, Gong H Jr, Dauphinee B, Lee E. Effect of cetirizine, a new histamine H1 antagonist, on airway dynamics and responsiveness to inhaled histamine in mild asthma. J Allergy Clin Immunol 1987;80:51-6. **Ib**
584. Rafferty P, Beasley R, Holgate ST. The contribution of histamine to immediate bronchoconstriction provoked by inhaled allergen and adenosine 5' monophosphate in atopic asthma. Am Rev Respir Dis 1987;136:369-73. **IIa**
585. Hamid M, Rafferty P, Holgate ST. The inhibitory effect of terfenadine and flurbiprofen on early and late-phase bronchoconstriction following allergen challenge in atopic asthma. Clin Exp Allergy 1990;20:261-7. **IIa**
586. Curzen N, Rafferty P, Holgate ST. Effects of a cyclo-oxygenase inhibitor, flurbiprofen, and an H1 histamine receptor antagonist, terfenadine, alone and in combination on allergen induced immediate bronchoconstriction in man. Thorax 1987; 42:946-52. **IIa**
587. Wasserfallen JB, Leuenberger P, Pecoud A. Effect of cetirizine, a new H1 antihistamine, on the early and late allergic reactions in a bronchial provocation test with allergen. J Allergy Clin Immunol 1993;91:1189-97. **Ib**
588. Bruttmann G, Pedrali P, Arendt C, Rihoux JP. Protective effect of cetirizine in patients suffering from pollen asthma. Ann Allergy 1990;64:224-8. **Ib**
589. Takayama M, Ishii T, Hatanaka E. Cytological and histopathological studies of otitis media with effusion. Auris Nasus Larynx 1985;12(suppl 1):S166-8. **III**
590. Nguyen LH, Manoukian JJ, Sobol SE, Tewfik TL, Mazer BD, Schloss MD, et al. Similar allergic inflammation in the middle ear and the upper airway: evidence linking otitis media with effusion to the united airways concept. J Allergy Clin Immunol 2004;114:1110-5. **III**
591. Hurst DS, Venge P. The presence of eosinophil cationic protein in middle ear effusion. Otolaryngol Head Neck Surg 1993;108:711-22. **III**
592. Bikhazi P, Ryan AF. Expression of immunoregulatory cytokines during acute and chronic middle ear immune response. Laryngoscope 1995;105:629-34. **IIb**
593. Seto A, Einarson T, Koren G. Pregnancy outcome following first trimester exposure to antihistamines: meta-analysis. Am J Perinatol 1997;14:119-24. **Ia**
594. Gilbert C, Mazzotta P, Loebstein R, Koren G. Fetal safety of drugs used in the treatment of allergic rhinitis: a critical review. Drug Saf 2005;28:707-19. **IV**
595. Saxen I. Letter: Cleft palate and maternal diphenhydramine intake. Lancet 1974;1: 407-8. **IV**
596. Saxen I. Associations between oral clefts and drugs taken during pregnancy. Int J Epidemiol 1975;4:37-44. **III**
597. Aselton P, Jick H, Milunsky A, Hunter JR, Stergachis A. First-trimester drug use and congenital disorders. Obstet Gynecol 1985;65:451-5. **III**
598. Heinonen Op SD, Shapiro S. Birth Defects and drugs in pregnancy. Littleton (MA): Publishing Sciences Group; 1977. **IV**
599. Briggs Gg FR, Yaffe S. Drugs in pregnancy and lactation. 5th ed. Baltimore (MD): Williams and Wilkins; 1998. **IV**
600. Werler MM, Sheehan JE, Mitchell AA. Maternal medication use and risks of gastroschisis and small intestinal atresia. Am J Epidemiol 2002;155:26-31. **III**
601. Werler MM, Mitchell AA, Shapiro S. First trimester maternal medication use in relation to gastroschisis. Teratology 1992;45:361-7. **III**
602. Schatz M, Zeiger RS, Harden K, Hoffman CC, Chilingar L, Petitti D. The safety of asthma and allergy medications during pregnancy. J Allergy Clin Immunol 1997;100:301-6. **IIa**
603. Gluck PA, Gluck JC. A review of pregnancy outcomes after exposure to orally inhaled or intranasal budesonide. Curr Med Res Opin 2005;21:1075-84. **IV**
604. Mazzotta P, Loebstein R, Koren G. Treating allergic rhinitis in pregnancy: safety considerations. Drug Saf 1999;20:361-75. **IV**
605. Bracken MB, Triche EW, Belanger K, Saftlas A, Beckett WS, Leaderer BP. Asthma symptoms, severity, and drug therapy: a prospective study of effects on 2205 pregnancies. Obstet Gynecol 2003;102:739-52. **III**
606. Rahimi R, Nikfar S, Abdollahi M. Meta-analysis finds use of inhaled corticosteroids during pregnancy safe: a systematic meta-analysis review. Hum Exp Toxicol 2006;25:447-52. **Ia**
607. Greenberger PA, Patterson R. Beclomethasone diproprionate for severe asthma during pregnancy. Ann Intern Med 1983;98:478-80. **III**
608. Brown HM, Storey G, Jackson FA. Beclomethasone dipropionate aerosol in long-term treatment of perennial and seasonal asthma in children and adults: a report of five-and-half years' experience in 600 asthmatic patients. Br J Clin Pharmacol 1977;4(suppl 3):259S-67S. **III**
609. Blaiss MS. Management of rhinitis and asthma in pregnancy. Ann Allergy Asthma Immunol 2003;90:16-22. **IV**
610. Kallen B, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. Obstet Gynecol 1999;93:392-5. **III**
611. Namazy J, Schatz M, Long L, Lipkowitz M, Lillie MA, Voss M, et al. Use of inhaled steroids by pregnant asthmatic women does not reduce intrauterine growth. J Allergy Clin Immunol 2004;113:427-32. **III**
612. Dombrowski MP, Brown CL, Berry SM. Preliminary experience with triamcinolone acetonide during pregnancy. J Matern Fetal Med 1996;5:310-3. **III**

613. Dombrowski M, Thom E, McNellis D. Maternal-fetal medicine units (MFMU) studies of inhaled corticosteroids during pregnancy. J Allergy Clin Immunol 1999;103:S356-9. **IV**
614. The use of newer asthma and allergy medications during pregnancy. The American College of Obstetricians and Gynecologists (ACOG) and the American College of Allergy, Asthma and Immunology (ACAAI). Ann Allergy Asthma Immunol 2000;84:475-80. **IV**
615. Metzger WJ, Turner E, Patterson R. The safety of immunotherapy during pregnancy. J Allergy Clin Immunol 1978;61:268-72. **III**
616. Tan R, Corren J. Optimum treatment of rhinitis in the elderly. Drugs Aging 1995; 7:168-75. **V**
617. Edelstein DR. Aging of the normal nose in adults. Laryngoscope 1996;106: 1-25. **IV**
618. Baroody FM, Cheng CC, Moylan B, deTineo M, Haney L, Reed KD, et al. Absence of nasal mucosal atrophy with fluticasone aqueous nasal spray. Arch Otolaryngol Head Neck Surg 2001;127:193-9. **Ib**
619. Syabbalo NC, Bundgaard A, Widdicombe JG. Effects of exercise on nasal airflow resistance in healthy subjects and in patients with asthma and rhinitis. Bull Eur Physiopathol Respir 1985;21:507-13. **III**
620. Keles N. Treating allergic rhinitis in the athlete. Rhinology 2002;40:211-4. **IV**
621. Bagenstose SE, Bernstein JA. Treatment of chronic rhinitis by an allergy specialist improves quality of life outcomes. Ann Allergy Asthma Immunol 1999;83:524-8. **III**
622. Demoly P, Allaert FA, Lecasble M. ERASM, a pharmacoepidemiologic survey on management of intermittent allergic rhinitis in every day general medical practice in France. Allergy 2002;57:546-54. **III**
623. Consultation and referral guidelines citing the evidence: how the allergist-immunologist can help. J Allergy Clin Immunol 2006;117:S495-523.
624. Allergy and immunology core curriculum outline 1996. Core Curriculum Subcommittee of the Training Program Directors. American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 1996;98:1012-5. 2002 update available at: http://www.aaaai.org/professionals/dareers/training_programs.stm. **IV**
625. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36), I: conceptual framework and item selection. Med Care 1992;30:473-83. **IV**
626. Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ 1992;305:160-4. **III**
627. Jenkinson C, Wright L, Coulter A. Criterion validity and reliability of the SF-36 in a population sample. Qual Life Res 1994;3:7-12. **III**
628. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220-33. **III**
629. Feeny D, Furlong W, Boyle M, Torrance GW. Multi-attribute health status classification systems. Health Utilities Index. Pharmacoeconomics 1995;7:490-502. **IV**
630. Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q. Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2. Med Care 1996;34:702-22. **III**
631. Hunt SM, McEwen J, McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists. J R Coll Gen Pract 1985;35:185-8. **III**
632. Jenkinson C, Fitzpatrick R, Argyle M. The Nottingham Health Profile: an analysis of its sensitivity in differentiating illness groups. Soc Sci Med 1988;27:1411-4. **III**
633. Van Schayck CP, Rutten-van Molken MP, van Doorslaer EK, Folgering H, van Weel C. Two-year bronchodilator treatment in patients with mild airflow obstruction: contradictory effects on lung function and quality of life. Chest 1992;102: 1384-91. **Ib**
634. Jette AM, Davies AR, Cleary PD, Calkins DR, Rubenstein LV, Fink A, et al. The Functional Status Questionnaire: reliability and validity when used in primary care. J Gen Intern Med 1986;1:143-9. **III**
635. Parkerson GR Jr, Broadhead WE, Tse CK. The Duke Health Profile: a 17-item measure of health and dysfunction. Med Care 1990;28:1056-72. **III**
636. Raat H, Bonsel GJ, Essink-Bot ML, Landgraf JM, Gemke RJ. Reliability and validity of comprehensive health status measures in children: the Child Health Questionnaire in relation to the Health Utilities Index. J Clin Epidemiol 2002;55:67-76. **III**
637. Raat H, Botterweck AM, Landgraf JM, Hoogeveen WC, Essink-Bot ML. Reliability and validity of the short form of the child health questionnaire for parents (CHQ-PF28) in large random school based and general population samples. J Epidemiol Community Health 2005;59:75-82. **III**
638. Turner-Bowker D. A new tool for monitoring pediatric health outcomes: the SF-10 for Children. McLean (VA): International Society for Quality of Life Research; 2004. **IV**
639. Varni JW, Limbers CA, Burwinkle TM. Parent proxy-report of their childrens health-related quality of life: an analysis of 13,878 parents reliability and validity across age subgroups using the PedsQL 4.0 Generic Core Scales. Health Qual Life Outcomes 2007;5:2. **III**
640. Varni JW, Limbers CA, Burwinkle TM. How young can children reliably and validly self-report their health-related quality of life? an analysis of 8,591 children across age subgroups with the PedsQL 4.0 Generic Core Scales. Health Qual Life Outcomes 2007;5:1. **III**
641. Chan KS, Mangione-Smith R, Burwinkle TM, Rosen M, Varni JW. The PedsQL: reliability and validity of the short-form generic core scales and Asthma Module. Med Care 2005;43:256-65. **III**
642. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. Ambul Pediatr 2003;3: 329-41. **III**
643. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. Clin Exp Allergy 1991;21:77-83. **Ib**
644. Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ. Interpretation of rhinoconjunctivitis quality of life questionnaire data. J Allergy Clin Immunol 1996;98: 843-5. **Ib**
645. Juniper EF, Thompson AK, Roberts JN. Can the standard gamble and rating scale be used to measure quality of life in rhinoconjunctivitis? comparison with the RQLQ and SF-36. Allergy 2002;57:201-6. **III**
646. Juniper EF. Development and validation of the Standarized Rhiunoconjunctivitis Quality of Life Questionnairs (RQLQ[S]). Orlando: AAAAI; 1999. **IV**
647. Juniper EF. Development and validation of the Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ). Orlando: AAAAI; 1999. **IV**
648. Juniper EF, Rohrbaugh T, Meltzer EO. A questionnaire to measure quality of life in adults with nocturnal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2003;111:484-90. **III**
649. Juniper EF, Guyatt GH, Andersson B, Ferrie PJ. Comparison of powder and aerosolized budesonide in perennial rhinitis: validation of rhinitis quality of life questionnaire. Ann Allergy 1993;70:225-30. **Ib**
650. Revicki DA, Leidy NK, Brennan-Diemer F, Thompson C, Togias A. Development and preliminary validation of the multiattribute Rhinitis Symptom Utility Index. Qual Life Res 1998;7:693-702. **III**
651. Juniper EF, Howland WC, Roberts NB, Thompson AK, King DR. Measuring quality of life in children with rhinoconjunctivitis. J Allergy Clin Immunol 1998;101:163-70. **III**
652. Juniper EF, Guyatt GH, Dolovich J. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: development and testing of a questionnaire for clinical trials. J Allergy Clin Immunol 1994;93:413-23. **IIa**
653. del Cuvillo A, Mullol J, Bartra J, Davila I, Jauregui I, Montoro J, et al. Comparative pharmacology of the H1 antihistamines. J Investig Allergol Clin Immunol 2006;16(suppl 1):3-12. **IV**
654. Semprex-D. Electronic Medicines Compendium. Available at: http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=2183, 2007. **IV**
655. Mann RD, Pearce GL, Dunn N, Shakir S. Sedation with ''non-sedating'' antihistamines: four prescription-event monitoring studies in general practice. BMJ 2000;320:1184-6. **III**
656. Simons FE, Simons KJ. Clinical pharmacology of new histamine H1 receptor antagonists. Clin Pharmacokinet 1999;36:329-52. **LB**
657. Pearlman DS, Grossman J, Meltzer EO. Histamine skin test reactivity following single and multiple doses of azelastine nasal spray in patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2003;91:258-62. **Ib**
658. Affrime M, Gupta S, Banfield C, Cohen A. A pharmacokinetic profile of desloratadine in healthy adults, including elderly. Clin Pharmacokinet 2002;41(suppl 1):13-9. **III**
659. Molimard M, Diquet B, Benedetti MS. Comparison of pharmacokinetics and metabolism of desloratadine, fexofenadine, levocetirizine and mizolastine in humans. Fundam Clin Pharmacol 2004;18:399-411. **IV**
660. Simons FE, Frith EM, Simons KJ. The pharmacokinetics and antihistaminic effects of brompheniramine. J Allergy Clin Immunol 1982;70:458-64. **LB**
661. Simons FE. Histamine and H^1-antihistamihnes in allergic diseases, 2nd ed. New York: Marcel Dekker, Inc; 2002. **IV**
662. National Jewish Medical and Research Center. Allergy intradermal skin testing. 2007. Available at: http://www.njc.org/disease-info/tests/intradermal.aspx). Accessed July 3, 2008. **IV**
663. Antihistamines (systemic). In: Drug information for the health care professional. USP DI. Englewood (CO): Microdex, Inc; 2000. p. 343-53. **IV**
664. Cook TJ, MacQueen DM, Wittig HJ, Thornby JI, Lantos RL, Virtue CM. Degree and duration of skin test suppression and side effects with antihistamines: a double blind controlled study with five antihistamines. J Allergy Clin Immunol 1973;51: 71-7. **III**
665. Long WF, Taylor RJ, Wagner CJ, Leavengood DC, Nelson HS. Skin test suppression by antihistamines and the development of subsensitivity. J Allergy Clin Immunol 1985;76:113-7. **III**

666. Schran HF, Petryk L, Chang CT, O'Connor R, Gelbert MB. The pharmacokinetics and bioavailability of clemastine and phenylpropanolamine in single-component and combination formulations. J Clin Pharmacol 1996;36:911-22. **Ib**
667. Phillips MJ, Meyrick Thomas RH, Moodley I, Davies RJ. A comparison of the in vivo effects of ketotifen, clemastine, chlorpheniramine and sodium cromoglycate on histamine and allergen induced weals in human skin. Br J Clin Pharmacol 1983;15:277-86. **IIa**
668. Turner RB, Sperber SJ, Sorrentino JV, O'Connor RR, Rogers J, Batouli AR, et al. Effectiveness of clemastine fumarate for treatment of rhinorrhea and sneezing associated with the common cold. Clin Infect Dis 1997;25:824-30. **III**
669. Daly F. Antihistamines. In: POISINDEX System. Englewood: MICROMEDEX; 2001. **IV**
670. Andersen J, Sugerman K, Lockhart J, Weinberg W. Effective prophylactic therapy for cyclic vomiting syndrome in children usig amitriptyline or cyproheptadine. Am J Health Syst Pharm 1998;55:1167-9. **III**
671. Almind M, Dirksen A, Nielsen NH, Svendsen UG. Duration of the inhibitory activity on histamine-induced skin weals of sedative and non-sedative antihistamines. Allergy 1988;43:593-6. **III**
672. Cyproheptadine: Lexi-Comp. 2007. Available at: http://www.merck.com/mmpe/lexicomp/cyproheptadine.html. Accessed July 4, 2008. **IV**
673. Valoti M, Frosini M, Dragoni S, Fusi F, Sgaragli G. Pharmacokinetics of diphenhydramine in healthy volunteers with a dimenhydrinate 25 mg chewing gum formulation. Methods Find Exp Clin Pharmacol 2003;25:377-81. **LB**
674. Diphenhydramine. Available at: http://www.nhtsa.dot.gov/PEOPLE/injury/research/job185drugs/diphenhydramine.htm. Accessed July 4, 2008. **IV**
675. Strenkoski-Nix LC, Ermer J, DeCleene S, Cevallos W, Mayer PR. Pharmacokinetics of promethazine hydrochloride after administration of rectal suppositories and oral syrup to healthy subjects. Am J Health Syst Pharm 2000;57:1499-505. **LB**
676. Bagian JP, Ward DF. A retrospective study of promethazine and its failure to produce the expected incidence of sedation during space flight. J Clin Pharmacol 1994;34:649-51. **III**
677. *electronic* Medicines Compendium (*e*MC). Multi-action Actifed tablets. 2006. Available at: http://emc.medicines.org.uk. Accessed July 1, 2007. **IV**
678. Rabago D, Zgierska A, Mundt M, Barrett B, Bobula J, Maberry R. Efficacy of daily hypertonic saline nasal irrigation among patients with sinusitis: a randomized controlled trial. J Fam Pract 2002;51:1049-55. **Ib**
679. Brown CL, Graham SM. Nasal irrigations: good or bad? Curr Opin Otolaryngol Head Neck Surg 2004;12:9-13. **IV**
680. Talbot AR, Herr TM, Parsons DS. Mucociliary clearance and buffered hypertonic saline solution. Laryngoscope 1997;107:500-3. **III**
681. Fellows J, Crestodina L. Home-prepared saline: a safe, cost-effective alternative for wound cleansing in home care. J Wound Ostomy Continence, Nurs 2006;33:606-9. **III**
682. Diav-Citrin O, Shechtman S, Aharonovich A, Moerman L, Arnon J, Wajnberg R, et al. Pregnancy outcome after gestational exposure to loratadine or antihistamines: a prospective controlled cohort study. J Allergy Clin Immunol 2003;111:1239-43. **IIa**
683. Seto A, Einarson T, Koren G. Evaluation of brompheniramine safety in pregnancy. Reprod Toxicol 1993;7:393-5. **Ia**
684. Jick H, Holmes LB, Hunter JR, Madsen S, Stergachis A. First-trimester drug use and congenital disorders. JAMA 1981;246:343-6. **III**
685. Kallen B. Use of antihistamine drugs in early pregnancy and delivery outcome. J Matern Fetal Neonatal Med 2002;11:146-52. **IIa**
686. Erez S, Schifrin BS, Dirim O. Double-blind evaluation of hydroxyzine as an antiemetic in pregancy. J Reprod Med 1971;7:35-7. **IIa**
687. Einarson A, Bailey B, Jung G, Spizzirri D, Baillie M, Koren G. Prospective controlled study of hydroxyzine and cetirizine in pregnancy. Ann Allergy Asthma Immunol 1997;78:183-6. **IIa**
688. Moretti ME, Caprara D, Coutinho CJ, Bar-Oz B, Berkovitch M, Addis A, et al. Fetal safety of loratadine use in the first trimester of pregnancy: a multicenter study. J Allergy Clin Immunol 2003;111:479-83. **IIa**
689. Loebstein R, Lalkin A, Addis A, Costa A, Lalkin I, Bonati M, et al. Pregnancy outcome after gestational exposure to terfenadine: a multicenter, prospective controlled study. J Allergy Clin Immunol 1999;104:953-6. **III**
690. Demoly P, Bozonnat MC, Dacosta P, Daures JP. The diagnosis of asthma using a self-questionnaire in those suffering from allergic rhinitis: a pharmacoepidemiological survey in everyday practice in France. Allergy 2006;61:699-704. **III**
691. Aberg N, Hesselmar B, Aberg B, Eriksson B. Increase of asthma, allergic rhinitis and eczema in Swedish schoolchildren between 1979 and 1991. Clin Exp Allergy 1995;25:815-9. **III**
692. Aberg N, Engstrom I, Lindberg U. Allergic diseases in Swedish school children. Acta Paediatr Scand 1989;78:246-52. **III**
693. Aberg N, Engstrom I. Natural history of allergic diseases in children. Acta Paediatr Scand 1990;79:206-11. **III**
694. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. J Allergy Clin Immunol 2001;108:S2-8. **IV**
695. Law AW, Reed SD, Sundy JS, Schulman KA. Direct costs of allergic rhinitis in the United States: estimates from the 1996 Medical Expenditure Panel Survey. J Allergy Clin Immunol 2003;111:296-300. **III**
696. Linna O, Kokkonen J, Lukin M. A 10-year prognosis for childhood allergic rhinitis. Acta Paediatr 1992;81:100-2. **III**
697. Sibbald B, Rink E, D'Souza M. Is the prevalence of atopy increasing? Br J Gen Pract 1990;40:338-40. **III**
698. Fireman P. Allergic rhinitis. In: Fireman P, Slavin R, editors. Atlas of allergies. Philadelphia (PA): JB Lippincott; 1991. p. 9.2-9.18. **IV**
699. McMenamin P. Costs of hay fever in the United States in 1990. Ann Allergy 1994;73:35-9. **III**
700. US Census Bureau. US Census. 2008. Available at: http://www.census.gov/index.html. Accessed July 4, 2008. **IV**
701. Simpson A, Custovic A. Pets and the development of allergic sensitization. Curr Allergy Asthma Rep 2005;5:212-20. **IV**
702. Strachan DP, Cook DG. Health effects of passive smoking, 5: parental smoking and allergic sensitisation in children. Thorax 1998;53:117-23. **III**
703. Guerra S, Sherrill DL, Cottini M, Michetti G, Allegra L. On the association between date of birth and pollen sensitization: is age an effect modifier? Allergy Asthma Proc 2002;23:303-10. **III**
704. Saitoh Y, Dake Y, Shimazu S, Sakoda T, Sogo H, Fujiki Y, et al. Month of birth, atopic disease, and atopic sensitization. J Investig Allergol Clin Immunol 2001;11:183-7. **III**
705. Wjst M, Dharmage S, Andre E, Norback D, Raherison C, Villani S, et al. Latitude, birth date, and allergy. PLoS Med 2005;2:e294. **III**
706. Bjorksten B. Risk factors in early childhood for the development of atopic diseases. Allergy 1994;49:400-7. **IV**
707. Rance F, Kanny G, Dutau G, Moneret-Vautrin DA. Food hypersensitivity in children: clinical aspects and distribution of allergens. Pediatr Allergy Immunol 1999;10:33-8. **III**
708. Ross RN. The costs of allergic rhintiis. Am J Managed Care 1996;2:285-90. **III**
709. Schoenwetter WF, Dupclay L Jr, Appajosyula S, Botteman MF, Pashos CL. Economic impact and quality-of-life burden of allergic rhinitis. Curr Med Res Opin 2004;20:305-17. **IV**
710. Raphael GD, Baraniuk JN, Kaliner MA. How and why the nose runs. J Allergy Clin Immunol 1991;87:457-67. **IV**
711. KleinJan A, Willart M, van Rijt LS, Braunstahl GJ, Leman K, Jung S, et al. An essential role for dendritic cells in human and experimental allergic rhinitis. J Allergy Clin Immunol 2006;118:1117-25. **IIa**
712. Wagenmann M, Schumacher L, Bachert C. The time course of the bilateral release of cytokines and mediators after unilateral nasal allergen challenge. Allergy 2005;60:1132-8. **IIb**
713. Okano M, Fujiwara T, Sugata Y, Gotoh D, Masaoka Y, Sogo M, et al. Presence and characterization of prostaglandin D2-related molecules in nasal mucosa of patients with allergic rhinitis. Am J Rhinol 2006;20:342-8. **IIa**
714. Peters-Golden M, Gleason MM, Togias A. Cysteinyl leukotrienes: multi-functional mediators in allergic rhinitis. Clin Exp Allergy 2006;36:689-703. **IV**
715. Heppt W, Dinh QT, Cryer A, Zweng M, Noga O, Peiser C, et al. Phenotypic alteration of neuropeptide-containing nerve fibres in seasonal intermittent allergic rhinitis. Clin Exp Allergy 2004;34:1105-10. **IIb**
716. Kramer MF, Jordan TR, Klemens C, Hilgert E, Hempel JM, Pfrogner E, et al. Factors contributing to nasal allergic late phase eosinophilia. Am J Otolaryngol 2006;27:190-9. **IIb**
717. KleinJan A, Dijkstra MD, Boks SS, Severijnen LA, Mulder PG, Fokkens WJ. Increase in IL-8, IL-10, IL-13, and RANTES mRNA levels (in situ hybridization) in the nasal mucosa after nasal allergen provocation. J Allergy Clin Immunol 1999;103:441-50. **IIb**
718. Braunstahl GJ, Overbeek SE, Kleinjan A, Prins JB, Hoogsteden HC, Fokkens WJ. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. J Allergy Clin Immunol 2001;107:469-76. **IIa**
719. Juliusson S, Bende M. Priming effect of a birch pollen season studied with laser Doppler flowmetry in patients with allergic rhinitis. Clin Allergy 1988;18:615-8. **IIb**
720. Ciprandi G, Ricca V, Landi M, Passalacqua G, Bagnasco M, Canonica GW. Allergen-specific nasal challenge: response kinetics of clinical and inflammatory events to rechallenge. Int Arch Allergy Immunol 1998;115:157-61. **IIb**
721. Wachs M, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman PS, Naclerio RM. Observations on the pathogenesis of nasal priming. J Allergy Clin Immunol 1989;84:492-501. **III**
722. Kurukulaaratchy RJ, Matthews S, Arshad SH. Defining childhood atopic phenotypes to investigate the association of atopic sensitization with allergic disease. Allergy 2005;60:1280-6. **III**

723. Marinho S, Simpson A, Lowe L, Kissen P, Murray C, Custovic A. Rhinoconjunctivitis in 5-year-old children: a population-based birth cohort study. Allergy 2007; 62:385-93. **IIb**
724. Almqvist C, Larsson PH, Egmar AC, Hedren M, Malmberg P, Wickman M. School as a risk environment for children allergic to cats and a site for transfer of cat allergen to homes. J Allergy Clin Immunol 1999;103:1012-7. **IIa**
725. Lucente FE. Rhinitis and nasal obstruction. Otolaryngol Clin North Am 1989;22: 307-18. **IV**
726. Leger D, Annesi-Maesano I, Carat F, Rugina M, Chanal I, Pribil C, et al. Allergic rhinitis and its consequences on quality of sleep: an unexplored area. Arch Intern Med 2006;166:1744-8. **III**
727. Galan C, Garcia M, Alcazar H, Dominguez P. Meteorological variation effect on aerobiology: new tools on pollen forecasting. Allerg Immunol (Paris) 2006;38: 203-8. **III**
728. Antepara I, Fernandez JC, Gamboa P, Jauregui I, Miguel F. Pollen allergy in the Bilbao area (European Atlantic seaboard climate): pollination forecasting methods. Clin Exp Allergy 1995;25:133-40. **III**
729. White JF, Bernstein DI. Key pollen allergens in North America. Ann Allergy Asthma Immunol 2003;91:425-35. **IV**
730. Jelks M. Allergy plants that cause sneezing and wheezing. Tampa: Worldwide Publications; 1986. **IV**
731. Lewis W, Zenger V. Airborne and allergic pollen of North America. Baltimore: John Hopkins University Press; 1983. **V**
732. Platts-Mills TA, Hayden ML, Chapman MD, Wilkins SR. Seasonal variation in dust mite and grass-pollen allergens in dust from the houses of patients with asthma. J Allergy Clin Immunol 1987;79:781-91. **III**
733. de Ana SG, Torres-Rodriguez JM, Ramirez EA, Garcia SM, Belmonte-Soler J. Seasonal distribution of Alternaria, Aspergillus, Cladosporium and Penicillium species isolated in homes of fungal allergic patients. J Investig Allergol Clin Immunol 2006;16:357-63. **III**
734. Shusterman D, Murphy MA, Balmes J. The influence of sex, allergic rhinitis, and test system on nasal sensitivity to airborne irritants: a pilot study. Environ Health Perspect 2001;109:15-9. **IIb**
735. Sheahan P, Walsh RM, Walsh MA, Costello RW. Hyperresponsiveness of congestive nasal reflexes in allergic rhinitis. Rhinology 2006;44:68-73. **IIb**
736. Bernstein DI, Schoenwetter WF, Nathan RA, Storms W, Ahlbrandt R, Mason J. Efficacy and safety of fexofenadine hydrochloride for treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1997;79:443-8. **Ib**
737. Wachs M, Proud D. Observations on the pathogenesis of nasal priming. J Allergy Clin Immunol 1989;84:492-501. **IV**
738. Taudorf E, Moseholm L. Pollen count, symptom and medicine score in birch pollinosis: a mathematical approach. Int Arch Allergy Appl Immunol 1988;86: 225-33. **III**
739. Solomon WR, Platts-Mills TA. Aerobiology and inhalant allergnes. In: Middleton E, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, editors. Allergy: principles and practice. 5th ed. St Louis (MO): Mosby-Year Book Inc; 1998. p. 367-403. **IV**
740. Neal JS, Arlian LG, Morgan MS. Relationship among house-dust mites, Der 1, Fel d 1, and Can f 1 on clothing and automobile seats with respect to densities in houses. Ann Allergy Asthma Immunol 2002;88:410-5. **IIb**
741. Osborne M, Reponen T, Adhikari A, Cho SH, Grinshpun SA, Levin L, et al. Specific fungal exposures, allergic sensitization, and rhinitis in infants. Pediatr Allergy Immunol 2006;17:450-7. **III**
742. Carney AS, Powe DG, Huskisson RS, Jones NS. Atypical nasal challenges in patients with idiopathic rhinitis: more evidence for the existence of allergy in the absence of atopy? Clin Exp Allergy 2002;32:1436-40. **IIa**
743. Powe DG, Huskisson RS, Carney AS, Jenkins D, McEuen AR, Walls AF, et al. Mucosal T-cell phenotypes in persistent atopic and nonatopic rhinitis show an association with mast cells. Allergy 2004;59:204-12.
744. Leonardi A, Fregona IA, Gismondi M, Daniotti E, Carniel G, Secchi AG. Correlation between conjunctival provocation test (CPT) and systemic allergometric tests in allergic conjunctivitis. Eye 1990;4:760-4. **III**
745. Susini de Luca H, Favennec F, Bloch-Michel E. [Rhinoconjunctivitis: importance of a local diagnosis?]. Eur Ann Allergy Clin Immunol 2003;35:352-5. **III**
746. Bousquet J, Knani J, Hejjaoui A, Ferrando R, Cour P, Dhivert H, et al. Heterogeneity of atopy, I: clinical and immunologic characteristics of patients allergic to cypress pollen. Allergy 1993;48:183-8. **III**
747. Bielory L. Allergic diseases of the eye. Med Clin North Am 2006;90:129-48. **IV**
748. Bernstein DI, Levy AL, Hampel FC, Baidoo CA, Cook CK, Philpot EE, et al. Treatment with intranasal fluticasone propionate significantly improves ocular symptoms in patients with seasonal allergic rhinitis. Clin Exp Allergy 2004;34:952-7. **Ib**
749. Bielory L. Ocular symptom reduction in patients with seasonal allergic rhinitis treated with the intranasal cortiocosteroid mometasone furoate. Ann Allergy 2008;100:272-9. **IV**
750. Crampton HJ. Comparison of ketotifen fumarate ophthalmic solution alone, desloratadine alone, and their combination for inhibition of the signs and symptoms of seasonal allergic rhinoconjunctivitis in the conjunctival allergen challenge model: a double-masked, placebo- and active-controlled trial. Clin Ther 2003; 25:1975-87. **Ib**
751. Spangler DL, Abelson MB, Ober A, Gotnes PJ. Randomized, double-masked comparison of olopatadine ophthalmic solution, mometasone furoate monohydrate nasal spray, and fexofenadine hydrochloride tablets using the conjunctival and nasal allergen challenge models. Clin Ther 2003;25:2245-67. **Ib**
752. Abelson MB, Welch DL. An evaluation of onset and duration of action of patanol (olopatadine hydrochloride ophthalmic solution 0.1%) compared to Claritin (loratadine 10 mg) tablets in acute allergic conjunctivitis in the conjunctival allergen challenge model. Acta Ophthalmol Scand Suppl 2000;230:60-3. **Ib**
753. Discepola M, Deschenes J, Abelson M. Comparison of the topical ocular antiallergic efficacy of emedastine 0.05% ophthalmic solution to ketorolac 0.5% ophthalmic solution in a clinical model of allergic conjunctivitis. Acta Ophthalmol Scand Suppl 1999;228:43-6. **Ib**
754. Yaylali V, Demirlenk I, Tatlipinar S, Ozbay D, Esme A, Yildirim C, et al. Comparative study of 0.1% olopatadine hydrochloride and 0.5% ketorolac tromethamine in the treatment of seasonal allergic conjunctivitis. Acta Ophthalmol Scand 2003;81:378-82. **Ib**
755. Stokes TC, Feinberg G. Rapid onset of action of levocabastine eye-drops in histamine-induced conjunctivitis. Clin Exp Allergy 1993;23:791-4. **Ib**
756. Horak F, Stubner P, Zieglmayer R, Kawina A, Moser M, Lanz R. Onset and duration of action of ketotifen 0.025% and emedastine 0.05% in seasonal allergic conjunctivitis: efficacy after repeated pollen challenges in the Vienna challenge chamber. Clin Drug Investig 2003;23:329-37. **Ib**
757. Silvers WS. The skier's nose: a model of cold-induced rhinorrhea. Ann Allergy 1991;67:32-6. **Ib**
758. Papon JF, Brugel-Ribere L, Fodil R, Croce C, Larger C, Rugina M, et al. Nasal wall compliance in vasomotor rhinitis. J Appl Physiol 2006;100: 107-11. **IIb**
759. Bock SA, Lee WY, Remigio LK, May CD. Studies of hypersensitivity reactions to foods in infants and children. J Allergy Clin Immunol 1978;62:327-34. **IIa**
760. Metcalfe D. The diagnosis of food allergy: theory and practice. In: Spector S, editor. Provaocative challenge proceedures: bronchial, oral, nasal and exercise. Boca Raton: CRC Press; 1983. p. 119-25. **IV**
761. Atkins FM, Steinberg SS, Metcalfe DD. Evaluation of immediate adverse reactions to foods in adult patients, I: correlation of demographic, laboratory, and prick skin test data with response to controlled oral food challenge. J Allergy Clin Immunol 1985;75:348-55. **Ib**
762. James JM, Bernhisel-Broadbent J, Sampson HA. Respiratory reactions provoked by double-blind food challenges in children. Am J Respir Crit Care Med 1994; 149:59-64. **Ib**
763. James JM. Common respiratory manifestations of food allergy: a critical focus on otitis media. Curr Allergy Asthma Rep 2004;4:294-301. **IV**
764. Aleman A, Sastre J, Quirce S, de las Heras M, Carnes J, Fernandez-Caldas E, et al. Allergy to kiwi: a double-blind, placebo-controlled food challenge study in patients from a birch-free area. J Allergy Clin Immunol 2004;113:543-50. **IIa**
765. Mattila L, Kilpelainen M, Terho EO, Koskenvuo M, Helenius H, Kalimo K. Food hypersensitivity among Finnish university students: association with atopic diseases. Clin Exp Allergy 2003;33:600-6. **III**
766. Hendrick DJ, Davies RJ, D'Souza MF, Pepys J. An analysis of skin prick test reactions in 656 asthmatic patients. Thorax 1975;30:2-8. **III**
767. Novembre E, de Martino M, Vierucci A. Foods and respiratory allergy. J Allergy Clin Immunol 1988;81:1059-65. **IIa**
768. Pastorello E, Ortolani C, Luraghi MT, Pravettoni V, Sillano V, Froldi M, et al. Evaluation of allergic etiology in perennial rhinitis. Ann Allergy 1985;55:854-6. **III**
769. Pelikan Z, Pelikan-Filipek M. Bronchial response to the food ingestion challenge. Ann Allergy 1987;58:164-72. **III**
770. Heiner DC. Respiratory diseases and food allergy. Ann Allergy 1984;53: 657-64. **III**
771. Gwaltney JM Jr, Scheld WM, Sande MA, Sydnor A. The microbial etiology and antimicrobial therapy of adults with acute community-acquired sinusitis: a fifteen-year experience at the University of Virginia and review of other selected studies. J Allergy Clin Immunol 1992;90:457-61; discussion 62. **III**
772. Reh DD, Mace J, Robinson JL, Smith TL. Impact of age on presentation of chronic rhinosinusitis and outcomes of endoscopic sinus surgery. Am J Rhinol 2007;21:207-13. **IIb**
773. Cincik H, Ferguson BJ. The impact of endoscopic cultures on care in rhinosinusitis. Laryngoscope 2006;116:1562-8. **III**
774. Igarashi Y, Skoner DP, Doyle WJ, White MV, Fireman P, Kaliner MA. Analysis of nasal secretions during experimental rhinovirus upper respiratory infections. J Allergy Clin Immunol 1993;92:722-31. **IIa**

775. Cirillo I, Marseglia G, Klersy C, Ciprandi G. Allergic patients have more numerous and prolonged respiratory infections than nonallergic subjects. Allergy 2007; 62:1087-90. **III**
776. Armengot M, Juan G, Carda C, Montalt J, Basterra J. Young's syndrome: a further cause of chronic rhinosinusitis. Rhinology 1996;34:35-7. **III**
777. Afzelius BA. Genetics and pulmonary medicine, 6: immotile cilia syndrome: past, present, and prospects for the future. Thorax 1998;53:894-7. **III**
778. Winther B, Alper CM, Mandel EM, Doyle WJ, Hendley JO. Temporal relationships between colds, upper respiratory viruses detected by polymerase chain reaction, and otitis media in young children followed through a typical cold season. Pediatrics 2007;119:1069-75. **III**
779. Gwaltney JM Jr. Management update of acute bacterial rhinosinusitis and the use of cefdinir. Otolaryngol Head Neck Surg 2002;127:S24-9. **IV**
780. Mullarkey MF. Eosinophilic nonallergic rhinitis. J Allergy Clin Immunol 1988; 82:941-9. **III**
781. Rupp GH, Friedman RA. Eosinophilic nonallergic rhinitis in children. Pediatrics 1982;70:437-9. **III**
782. Jacobs RL, Freedman PM, Boswell RN. Nonallergic rhinitis with eosinophilia (NARES syndrome): clinical and immunologic presentation. J Allergy Clin Immunol 1981;67:253-62. **III**
783. Powe DG, Huskisson RS, Carney AS, Jenkins D, Jones NS. Evidence for an inflammatory pathophysiology in idiopathic rhinitis. Clin Exp Allergy 2001;31: 864-72. **IIb**
784. Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. Allergy 2003;58:691-706. **III**
785. Cristaudo A, Sera F, Severino V, De Rocco M, Di Lella E, Picardo M. Occupational hypersensitivity to metal salts, including platinum, in the secondary industry. Allergy 2005;60:159-64. **III**
786. Palczynski C, Walusiak J, Ruta U, Gorski P. Occupational asthma and rhinitis due to glutaraldehyde: changes in nasal lavage fluid after specific inhalatory challenge test. Allergy 2001;56:1186-91. **IIa**
787. Bernstein DI, Korbee L, Stauder T, Bernstein JA, Scinto J, Herd ZL, et al. The low prevalence of occupational asthma and antibody-dependent sensitization to diphenylmethane diisocyanate in a plant engineered for minimal exposure to diisocyanates. J Allergy Clin Immunol 1993;92:387-96. **III**
788. Hytonen M, Kanerva L, Malmberg H, Martikainen R, Mutanen P, Toikkanen J. The risk of occupational rhinitis. Int Arch Occup Environ Health 1997;69:487-90. **III**
789. Lieutier-Colas F, Meyer P, Pons F, Hedelin G, Larsson P, Malmberg P, et al. Prevalence of symptoms, sensitization to rats, and airborne exposure to major rat allergen (Rat n 1) and to endotoxin in rat-exposed workers: a cross-sectional study. Clin Exp Allergy 2002;32:1424-9. **III**
790. Banauch GI, Dhala A, Alleyne D, Alva R, Santhyadka G, Krasko A, et al. Bronchial hyperreactivity and other inhalation lung injuries in rescue/recovery workers after the World Trade Center collapse. Crit Care Med 2005;33:S102-6. **IIa**
791. Meggs WJ. RADS and RUDS: the toxic induction of asthma and rhinitis. J Toxicol Clin Toxicol 1994;32:487-501. **III**
792. Meggs WJ, Elsheik T, Metzger WJ, Albernaz M, Bloch RM. Nasal pathology and ultrastructure in patients with chronic airway inflammation (RADS and RUDS) following an irritant exposure. J Toxicol Clin Toxicol 1996;34:383-96. **LB**
793. Walker SM, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. J Allergy Clin Immunol 2001;107:87-93. **Ib**
794. Keles N. Treatment of allergic rhinitis during pregnancy. Am J Rhinol 2004;18: 23-8. **IV**
795. Sorri M, Hartikainen-Sorri AL, Karja J. Rhinitis during pregnancy. Rhinology 1980;18:83-6. **III**
796. Ellegard E, Oscarsson J, Bougoussa M, Igout A, Hennen G, Eden S, et al. Serum level of placental growth hormone is raised in pregnancy rhinitis. Arch Otolaryngol Head Neck Surg 1998;124:439-43. **III**
797. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. J Allergy Clin Immunol 2005; 115:34-46. **IV**
798. Stimpel M, Koch B, Oparil S. Antihypertensive treatment in postmenopausal women: results from a prospective, randomized, double-blind, controlled study comparing an ACE inhibitor (moexipril) with a diuretic (hydrochlorothiazide). Cardiology 1998;89:271-6. **Ib**
799. Labetalol and hydrochlorothiazide in hypertension. Labetalol/Hydrochlorothiazide Multicenter Study Group. Clin Pharmacol Ther 1985;38:24-7. **Ib**
800. Goldstein I. Oral phentolamine: an alpha-1, alpha-2 adrenergic antagonist for the treatment of erectile dysfunction. Int J Impot Res 2000;12(suppl 1):S75-80. **III**
801. Graf P. Adverse effects of benzalkonium chloride on the nasal mucosa: allergic rhinitis and rhinitis medicamentosa. Clin Ther 1999;21:1749-55. **III**
802. Dutt SN, Kameswaran M. The aetiology and management of atrophic rhinitis. J Laryngol Otol 2005;119:843-52. **IV**
803. Van Zele T, Claeys S, Gevaert P, Van Maele G, Holtappels G, Van Cauwenberge P, et al. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. Allergy 2006;61:1280-9. **IIb**
804. Sibert JR, Barton RP. Dominant inheritance in a family with primary atrophic rhinitis. J Med Genet 1980;17:39-40. **III**
805. Serrano E, Neukirch F, Pribil C, Jankowski R, Klossek JM, Chanal I, et al. Nasal polyposis in France: impact on sleep and quality of life. J Laryngol Otol 2005; 119:543-9. **IIa**
806. Valero A, Serrano C, Valera JL, Barbera A, Torrego A, Mullol J, et al. Nasal and bronchial response to exercise in patients with asthma and rhinitis: the role of nitric oxide. Allergy 2005;60:1126-31. **III**
807. Stern RC, Boat TF, Wood RE, Matthews LW, Doershuk CF. Treatment and prognosis of nasal polyps in cystic fibrosis. Am J Dis Child 1982;136: 1067-70. **IV**
808. Yung MW, Gould J, Upton GJ. Nasal polyposis in children with cystic fibrosis: a long-term follow-up study. Ann Otol Rhinol Laryngol 2002;111:1081-6. **III**
809. Larsen K. The clinical relationship of nasal polyps to asthma. Allergy Asthma Proc 1996;17:243-9. **III**
810. Claeys S, Van Hoecke H, Holtappels G, Gevaert P, De Belder T, Verhasselt B, et al. Nasal polyps in patients with and without cystic fibrosis: a differentiation by innate markers and inflammatory mediators. Clin Exp Allergy 2005;35: 467-72. **IIb**
811. Uller L, Andersson M, Greiff L, Persson CG, Erjefalt JS. Occurrence of apoptosis, secondary necrosis, and cytolysis in eosinophilic nasal polyps. Am J Respir Crit Care Med 2004;170:742-7. **IIb**
812. Weschta M, Rimek D, Formanek M, Polzehl D, Podbielski A, Riechelmann H. Topical antifungal treatment of chronic rhinosinusitis with nasal polyps: a randomized, double-blind clinical trial. J Allergy Clin Immunol 2004;113:1122-8. **Ib**
813. Katzenstein AL, Sale SR, Greenberger PA. Allergic Aspergillus sinusitis: a newly recognized form of sinusitis. J Allergy Clin Immunol 1983;72:89-93. **III**
814. deShazo RD, Swain RE. Diagnostic criteria for allergic fungal sinusitis. J Allergy Clin Immunol 1995;96:24-35. **III**
815. Khan DA, Cody DT 2nd, George TJ, Gleich GJ, Leiferman KM. Allergic fungal sinusitis: an immunohistologic analysis. J Allergy Clin Immunol 2000;106: 1096-101. **IIb**
816. Juniper EF, Stahl E, Doty RL, Simons FE, Allen DB, Howarth PH. Clinical outcomes and adverse effect monitoring in allergic rhinitis. J Allergy Clin Immunol 2005;115:S390-413. **IV**
817. Smith TL, Mendolia-Loffredo S, Loehrl TA, Sparapani R, Laud PW, Nattinger AB. Predictive factors and outcomes in endoscopic sinus surgery for chronic rhinosinusitis. Laryngoscope 2005;115:2199-205. **III**
818. Sunderman FW Jr. Nasal toxicity, carcinogenicity, and olfactory uptake of metals. Ann Clin Lab Sci 2001;31:3-24. **IV**
819. Aubart FC, Ouayoun M, Brauner M, Attali P, Kambouchner M, Valeyre D, et al. Sinonasal involvement in sarcoidosis: a case-control study of 20 patients. Medicine (Baltimore) 2006;85:365-71. **IIa**
820. Alobid I, Mullol J, Cid MC. Rhinitis of granulomatous and vasculitic diseases. Clin Allergy Immunol 2007;19:221-39. **III**
821. Mitschke H. [Oto-rhino-laryngological diseases in patients with advanced kidney failure after kidney transplantation]. Fortschr Med 1980;98:437-40. **III**
822. Botelho-Nevers E, Gouriet F, Lepidi H, Couvret A, Amphoux B, Dessi P, et al. Chronic nasal infection caused by Klebsiella rhinoscleromatis or Klebsiella ozaenae: two forgotten infectious diseases. Int J Infect Dis 2007;11:423-9. **III**
823. Tonkin SL, Partridge J, Beach D. The pharyngeal effect of partial nasal obstruction. Pediatrics 1979;63:261-71. **III**
824. Suwandhi E, Ton MN, Schwarz SM. Gastroesophageal reflux in infancy and childhood. Pediatr Ann 2006;35:259-66. **IV**
825. Canani RB, Cirillo P, Roggero P, Romano C, Malamisura B, Terrin G, et al. Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. Pediatrics 2006;117:e817-20. **IIa**
826. Suryadevara AC, Fattal M, Woods CI. Nontraumatic cerebrospinal fluid rhinorrhea as a result of pseudotumor cerebri. Am J Otolaryngol 2007;28:242-6. **IV**
827. Clark D, Bullock P, Hui T, Firth J. Benign intracranial hypertension: a cause of CSF rhinorrhoea. J Neurol Neurosurg Psychiatry 1994;57:847-9. **IV**
828. Chan DT, Poon WS, Ip CP, Chiu PW, goh KY. How useful is glucose detection in diagnosing cerebrospinal fluid leak? the rational use of CT and beta-2 transferrin assay in detection of cerebrospinal fluid fistula. Asian J Surg 2004;27:39-42. **III**
829. Schidlow DV. Primary ciliary dyskinesia (the immotile cilia syndrome). Ann Allergy 1994;73:457-68. **IV**
830. Sasaki Y, Togo Y, Wagner HN Jr, Hornick RB, Schwartz AR, Proctor DF. Mucociliary function during experimentally induced rhinovirus infection in man. Ann Otol Rhinol Laryngol 1973;82:203-11. **III**

831. Zayas JG, O'Brien DW, Tai S, Ding J, Lim L, King M. Adaptation of an amphibian mucociliary clearance model to evaluate early effects of tobacco smoke exposure. Respir Res 2004;5:9. **LB**
832. Tripathi A BB. Diagnosis of immediate hypersensitivity. In: Grammer LC, Greenberger PA, editors. Patterson's allergic diseases. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 145-57. **IV**
833. Blaiss M. Approach to the allergic patient. In: Liberman P, Anderson JA, editors. Allergic diseases. Diagnosis and treatment. Totowa (NJ): Humana Press, Inc; 1997. p. 15-26. **IV**
834. Howard W. Medical evaluation. In: Bierman CW, Pearlman DS, editors. Allergic diseases of infancy, childhood and adolescence. Philadelphia: WB Saunders Co; 2008. p. 282-8. **IV**
835. Gentile DA, Michaels M, Skoner DP. Allergy and immunology. In: Zitelli BJ, Davis HW, editors. Atlas of pediatric physical diagnosis. 4th ed. Philadelphia (PA): Mosby-Wolfe; 2002. **IV**
836. Doyle WJ, Skoner DP, Seroky JT, Fireman P, Gwaltney JM. Effect of experimental rhinovirus 39 infection on the nasal response to histamine and cold air challenges in allergic and nonallergic subjects. J Allergy Clin Immunol 1994;93: 534-42. **III**
837. Bousquet J, Duchateau J, Pignat JC, Fayol C, Marquis P, Mariz S, et al. Improvement of quality of life by treatment with cetirizine in patients with perennial allergic rhinitis as determined by a French version of the SF-36 questionnaire. J Allergy Clin Immunol 1996;98:309-16. **Ib**
838. McHorney CA. Generic health measurement: past accomplishments and a measurement paradigm for the 21st century. Ann Intern Med 1997;127:743-50. **IV**
839. Bresolin D, Shapiro GG, Shapiro PA, Dassel SW, Furukawa CT, Pierson WE, et al. Facial characteristics of children who breathe through the mouth. Pediatrics 1984;73:622-5. **III**
840. Marks M. Significance of discoloration in the lower orbitopalpebral grooves in allergic children (allergic shiners). Ann Allergy Asthma Immunol 1963;21:26-32. **IV**
841. Johansson L, Oberg D, Melen I, Bende M. Do topical nasal decongestants affect polyps? Acta Otolaryngol 2006;126:288-90. **Ib**
842. Yewell J, Haydon R, Archer S, Manaligod JM. Complications of intranasal prescription narcotic abuse. Ann Otol Rhinol Laryngol 2002;111:174-7. **IV**
843. Vilensky W. Illicit and licit drugs causing perforation of the nasal septum. J Forensic Sci 1982;27:958-62. **IV**
844. Schoelzel EP, Menzel ML. Nasal sprays and perforation of the nasal septum. JAMA 1985;253:2046. **IV**
845. Kuriloff DB, Kimmelman CP. Osteocartilaginous necrosis of the sinonasal tract following cocaine abuse. Laryngoscope 1989;99:918-24. **IV**
846. Nelson HS, Kolehmainen C, Lahr J, Murphy J, Buchmeier A. A comparison of multiheaded devices for allergy skin testing. J Allergy Clin Immunol 2004;113: 1218-9. **III**
847. Panagou P, Loukides S, Tsipra S, Syrigou K, Anastasakis C, Kalogeropoulos N. Evaluation of nasal patency: comparison of patient and clinician assessments with rhinomanometry. Acta Otolaryngol 1998;118:847-51. **IIb**
848. Jose J, Ell SR. The association of subjective nasal patency with peak inspiratory nasal flow in a large healthy population. Clin Otolaryngol Allied Sci 2003;28: 352-4. **IIb**
849. Kano S, Pedersen OF, Sly PD. Nasal response to inhaled histamine measured by acoustic rhinometry in infants. Pediatr Pulmonol 1994;17:312-9. **IIb**
850. Austin CE, Foreman JC. Acoustic rhinometry compared with posterior rhinomanometry in the measurement of histamine- and bradykinin-induced changes in nasal airway patency. Br J Clin Pharmacol 1994;37:33-7. **IIb**
851. Uzzaman A, Metcalfe DD, Komarow HD. Acoustic rhinometry in the practice of allergy. Ann Allergy Asthma Immunol 2006;97:745-51. **IV**
852. Amin K, Rinne J, Haahtela T, Simola M, Peterson CG, Roomans GM, et al. Inflammatory cell and epithelial characteristics of perennial allergic and nonallergic rhinitis with a symptom history of 1 to 3 years' duration. J Allergy Clin Immunol 2001;107:249-57. **III**
853. Rivasi F, Bergamini G. Nasal cytology in allergic processes and other syndromes caused by hyperreactivity. Diagn Cytopathol 1988;4:99-105. **IV**
854. Jean R, Delacourt C, Rufin P, Pfister A, Waernessyckle S, de Blic J, et al. Nasal cytology in rhinitis children: comparison between brushing and blowing the nose. Allergy 1996;51:932-4. **III**
855. Ventura MT, Tsungoussova O, Barbaro MP, Resta O, Carpagnano GE, Dragonieri S, et al. Validity and reproducibility of morphologic analysis of nasal secretions obtained using ultrasonic nebulization of hypertonic solution. Ann Allergy Asthma Immunol 2007;99:232-5. **III**
856. University of Texas MB. UTMB point of care testing procedures policy. 2006. Available at: http://www.utmb.edu/poc/SOP/SOP2005/PPMP/SOPnsmear05-06.pdf. Accessed July 4, 2008. **IV**
857. Ingels K, Durdurez JP, Cuvelier C, van Cauwenberge P. Nasal biopsy is superior to nasal smear for finding eosinophils in nonallergic rhinitis. Allergy 1997;52: 338-41. **III**
858. Okano M, Nishizaki K, Nakada M, Kawarai Y, Goto S, Satoskar AR, et al. Prevalence and prediction of allergic rhinitis using questionnaire and nasal smear examination in schoolchildren. Acta Otolaryngol Suppl 1999;540:58-63. **III**
859. Chen ST, Sun HL, Lu KH, Lue KH, Chou MC. Correlation of immunoglobulin E, eosinophil cationic protein, and eosinophil count with the severity of childhood perennial allergic rhinitis. J Microbiol Immunol Infect 2006;39: 212-8. **III**
860. Jang AS. Nasal eosinophilic inflammation contributes to bronchial hyperresponsiveness in patients with allergic rhinitis. J Korean Med Sci 2002;17: 761-4. **III**
861. Jousimies-Somer HR, Savolainen S, Ylikoski JS. Macroscopic purulence, leukocyte counts, and bacterial morphotypes in relation to culture findings for sinus secretions in acute maxillary sinusitis. J Clin Microbiol 1988;26:1926-33. **III**
862. Ibanez-Tallon I, Heintz N, Omran H. To beat or not to beat: roles of cilia in development and disease. Hum Mol Genet 2003;12(spec no 1):R27-35. **IV**
863. Stern DA, Riedler J, Nowak D, Braun-Fahrlander C, Swoboda I, Balic N, et al. Exposure to a farming environment has allergen-specific protective effects on TH2-dependent isotype switching in response to common inhalants. J Allergy Clin Immunol 2007;119:351-8. **III**
864. Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 2005;94:S1-S63. **V**
865. Williams JW Jr, Roberts L Jr, Distell B, Simel DL. Diagnosing sinusitis by X-ray: is a single Waters view adequate? J Gen Intern Med 1992;7:481-5. **III**
866. McAlister WH, Lusk R, Muntz HR. Comparison of plain radiographs and coronal CT scans in infants and children with recurrent sinusitis. AJR Am J Roentgenol 1989;153:1259-64. **III**
867. Clinical practice guideline: management of sinusitis. Pediatrics 2001;108: 798-808. **V**
868. McAlister WH, Parker BR, Kushner DC, Babcock DS, Cohen HL, Gelfand MJ, et al. Sinusitis in the pediatric population. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000;215(suppl):811-8. **IV**
869. Lazar RH, Younis RT, Parvey LS. Comparison of plain radiographs, coronal CT, and intraoperative findings in children with chronic sinusitis. Otolaryngol Head Neck Surg 1992;107:29-34. **III**
870. Gigante J. Tonsillectomy and adenoidectomy. Pediatr Rev 2005;26:199-202. **IV**
871. McNicholas WT, Tarlo S, Cole P, Zamel N, Rutherford R, Griffin D, et al. Obstructive apneas during sleep in patients with seasonal allergic rhinitis. Am Rev Respir Dis 1982;126:625-8. **III**
872. Portnoy J, Barnes C. Clinical relevance of spore and pollen counts. Immunol Allergy Clin North Am 2003;23:389-410. **IV**
873. Gonzalo-Garjo MA, Tormo-Molina R, Munoz-Rodriguez AF, Silva-Palacios I. Differences in the spatial distribution of airborne pollen concentrations at different urban locations within a city. J Investig Allergol Clin Immunol 2006;16:37-43. **LB**
874. Portnoy J, Barnes C, Barnes CS. The National Allergy Bureau: pollen and spore reporting today. J Allergy Clin Immunol 2004;114:1235-8. **LB**
875. Port A, Hein J, Wolff A, Bielory L. Aeroallergen prevalence in the northern New Jersey-New York City metropolitan area: a 15-year summary. Ann Allergy Asthma Immunol 2006;96:687-91. **LB**
876. Wang DY, Clement P. Pathogenic mechanisms underlying the clinical symptoms of allergic rhinitis. Am J Rhinol 2000;14:325-33. **III**
877. Toth J, Schultze-Werninghaus C, Marks B, Temmel AF, Stubner P, Jager S, et al. Environmental priming influences allergen-specific nasal reactivity. Allergy 1998; 53:1172-7. **IIb**
878. Solomon WR, Burge HA, Boise JR. Exclusion of particulate allergens by window air conditioners. J Allergy Clin Immunol 1980;65:305-8. **LB**
879. Zeghnoun A, Ravault C, Fabres B, Lecadet J, Quenel P, Thibaudon M, et al. Short-term effects of airborne pollen on the risk of allergic rhinoconjunctivitis. Arch Environ Occup Health 2005;60:170-6. **IIb**
880. Barnes C, Pacheco F, Landuyt J, Hu F, Portnoy J. Hourly variation of airborne ragweed pollen in Kansas City. Ann Allergy Asthma Immunol 2001;86:166-71. **LB**
881. Portnoy J, Chapman J, Burge H, Muilenberg M, Solomon W. Epicoccum allergy: skin reaction patterns and spore/mycelium disparities recognized by IgG and IgE ELISA inhibition. Ann Allergy 1987;59:39-43. **IIb**
882. Portnoy J, Olson I, Pacheco F, Barnes C. Affinity purification of a major Alternaria allergen using a monoclonal antibody. Ann Allergy 1990;65:109-14. **LB**
883. Arruda LK, Mann BJ, Chapman MD. Selective expression of a major allergen and cytotoxin, Asp f I, in Aspergillus fumigatus: implications for the immunopathogenesis of Aspergillus-related diseases. J Immunol 1992;149:3354-9. **LB**

884. Arruda LK, Platts-Mills TA, Longbottom JL, el-Dahr JM, Chapman MD. Aspergillus fumigatus: identification of 16, 18, and 45 kd antigens recognized by human IgG and IgE antibodies and murine monoclonal antibodies. J Allergy Clin Immunol 1992;89:1166-76. **LB**
885. Vailes L, Sridhara S, Cromwell O, Weber B, Breitenbach M, Chapman M. Quantitation of the major fungal allergens, Alt a 1 and Asp f 1, in commercial allergenic products. J Allergy Clin Immunol 2001;107:641-6. **LB**
886. Chapman MD. Challenges associated with indoor moulds: health effects, immune response and exposure assessment. Med Mycol 2006;44(suppl):29-32. **III**
887. Atkinson RW, Strachan DP, Anderson HR, Hajat S, Emberlin J. Temporal associations between daily counts of fungal spores and asthma exacerbations. Occup Environ Med 2006;63:580-90. **IIb**
888. Burch M, Levetin E. Effects of meteorological conditions on spore plumes. Int J Biometeorol 2002;46:107-17. **LB**
889. Alvarez-Fernandez JA, Quirce S, Calleja JL, Cuevas M, Losada E. Hypersensitivity pneumonitis due to an ultrasonic humidifier. Allergy 1998;53:210-2. **III**
890. Baur X, Behr J, Dewair M, Ehret W, Fruhmann G, Vogelmeier C, et al. Humidifier lung and humidifier fever. Lung 1988;166:113-24. **III**
891. Burke GW, Carrington CB, Strauss R, Fink JN, Gaensler EA. Allergic alveolitis caused by home humidifiers: unusual clinical features and electron microscopic findings. JAMA 1977;238:2705-8. **III**
892. Ganier M, Lieberman P, Fink J, Lockwood DG. Humidifier lung: an outbreak in office workers. Chest 1980;77:183-7. **III**
893. Tourville DR, Weiss WI, Wertlake PT, Leudemann GM. Hypersensitivity pneumonitis due to contamination of home humidifier. J Allergy Clin Immunol 1972;49:245-51. **III**
894. Volpe BT, Sulavik SB, Tran P, Apter A. Hypersensitivity pneumonitis associated with a portable home humidifier. Conn Med 1991;55:571-3. **III**
895. Park GM, Lee SM, Lee IY, Ree HI, Kim KS, Hong CS, et al. Localization of a major allergen, Der p 2, in the gut and faecal pellets of Dermatophagoides pteronyssinus. Clin Exp Allergy 2000;30:1293-7. **LB**
896. Pollart S, Chapman MD, Platts-Mills TA. House dust mite and dust control. Clin Rev Allergy 1988;6:23-33. **IV**
897. Causer S, Shorter C, Sercombe J. Effect of floorcovering construction on content and vertical distribution of house dust mite allergen, Der p I. J Occup Environ Hyg 2006;3:161-8; quiz D45. **LB**
898. Carayol N, Birnbaum J, Magnan A, Ramadour M, Lanteaume A, Vervloet D, et al. Fel d 1 production in the cat skin varies according to anatomical sites. Allergy 2000;55:570-3. **LB**
899. Smith TS, Hogan MB, Welch JE, Corder WT, Wilson NW. Modern prevalence of insect sensitization in rural asthma and allergic rhinitis patients. Allergy Asthma Proc 2005;26:356-60. **III**
900. Hwang KY, Park JS, Ahn HC, Nam HS. Prevalence of arthropod antibodies in Korean patients with allergic rhinitis. Korean J Parasitol 2001;39:197-9. **III**
901. Witteman AM, van den Oudenrijn S, van Leeuwen J, Akkerdaas J, van der Zee JS, Aalberse RC. IgE antibodies reactive with silverfish, cockroach and chironomid are frequently found in mite-positive allergic patients. Int Arch Allergy Immunol 1995;108:165-9. **III**
902. Kim YK, Lee MH, Jee YK, Hong SC, Bae JM, Chang YS, et al. Spider mite allergy in apple-cultivating farmers: European red mite (Panonychus ulmi) and two-spotted spider mite (Tetranychus urticae) may be important allergens in the development of work-related asthma and rhinitis symptoms. J Allergy Clin Immunol 1999;104:1285-92. **III**
903. Barnes C, Tuck J, Simon S, Pacheco F, Hu F, Portnoy J. Allergenic materials in the house dust of allergy clinic patients. Ann Allergy Asthma Immunol 2001;86:517-23. **LB**
904. Goetz DW. Harmonia axyridis ladybug hypersensitivity in clinical allergy practice. Allergy Asthma Proc 2007;28:50-7. **III**
905. Nakazawa T, Satinover SM, Naccara L, Goddard L, Dragulev BP, Peters E, et al. Asian ladybugs (Harmonia axyridis): a new seasonal indoor allergen. J Allergy Clin Immunol 2007;119:421-7. **LB**
906. Sharma K, Muldoon SB, Potter MF, Pence HL. Ladybug hypersensitivity among residents of homes infested with ladybugs in Kentucky. Ann Allergy Asthma Immunol 2006;97:528-31. **III**
907. Munir AK, Bjorksten B, Einarsson R, Schou C, Ekstrand-Tobin A, Warner A, et al. Cat (Fel d I), dog (Can f I), and cockroach allergens in homes of asthmatic children from three climatic zones in Sweden. Allergy 1994;49:508-16. **III**
908. Baker AM, Johnson DG, Levisky JA, Hearn WL, Moore KA, Levine B, et al. Fatal diphenhydramine intoxication in infants. J Forensic Sci 2003;48:425-8. **III**
909. Benadryl (diphenhydramine hydrochloride). 2006. Available at: http://www.pfizer.com/pfizer/download/uspi_benadryl.pdf. Accessed July 4, 2008. **IV**
910. Simons FE. The eternal triangle: benefit, risk, and cost of therapeutic agents. Ann Allergy Asthma Immunol 1996;77:337-40. **IV**
911. Lang DM. Management of allergic rhinitis. Geriatr Times 2002;III:41-8. **IV**
912. McCue JD. Safety of antihistamines in the treatment of allergic rhinitis in elderly patients. Arch Fam Med 1996;5:464-8. **IV**
913. Vermeeren A, O'Hanlon JF. Fexofenadine's effects, alone and with alcohol, on actual driving and psychomotor performance. J Allergy Clin Immunol 1998;101:306-11. **IIa**
914. Shamsi Z, Kimber S, Hindmarch I. An investigation into the effects of cetirizine on cognitive function and psychomotor performance in healthy volunteers. Eur J Clin Pharmacol 2001;56:865-71. **Ib**
915. Ratner P, Falques M, Chuecos F, Esbri R, Gispert J, Peris F, et al. Meta-analysis of the efficacy of ebastine 20 mg compared to loratadine 10 mg and placebo in the symptomatic treatment of seasonal allergic rhinitis. Int Arch Allergy Immunol 2005;138:312-8. **Ia**
916. Lee C, Corren J. Review of azelastine nasal spray in the treatment of allergic and non-allergic rhinitis. Expert Opin Pharmacother 2007;8:701-9. **IV**
917. Patanase (olopatadine hydrochloride). 2008. Available at: http://ecatalog.alcon.com/pi/patanase_us_en.pdf. Accessed July 4, 2008. **IV**
918. Salerno SM, Jackson JL, Berbano EP. The impact of oral phenylpropanolamine on blood pressure: a meta-analysis and review of the literature. J Hum Hypertens 2005;19:643-52. **Ia**
919. Salerno SM, Jackson JL, Berbano EP. Effect of oral pseudoephedrine on blood pressure and heart rate: a meta-analysis. Arch Intern Med 2005;165:1686-94. **Ia**
920. Fivgas GD, Newman NJ. Anterior ischemic optic neuropathy following the use of a nasal decongestant. Am J Ophthalmol 1999;127:104-6. **III**
921. Cantu C, Arauz A, Murillo-Bonilla LM, Lopez M, Barinagarrementeria F. Stroke associated with sympathomimetics contained in over-the-counter cough and cold drugs. Stroke 2003;34:1667-72. **III**
922. Magargal LE, Sanborn GE, Donoso LA, Gonder JR. Branch retinal artery occlusion after excessive use of nasal spray. Ann Ophthalmol 1985;17:500-1. **III**
923. Loewen AH, Hudon ME, Hill MD. Thunderclap headache and reversible segmental cerebral vasoconstriction associated with use of oxymetazoline nasal spray. CMAJ 2004;171:593-4. **III**
924. Greene RR. Clinical images: Afrin-induced central nervous system vasospasm and thunderclap headache. Arthritis Rheum 2005;52:3314. **II**
925. Baxi LV, Gindoff PR, Pregenzer GJ, Parras MK. Fetal heart rate changes following maternal administration of a nasal decongestant. Am J Obstet Gynecol 1985;153:799-800. **III**
926. Afrin 12 hour. Available at: http://www.mercksource.com/pp/us/cns/cns_hl_pdr.jspzQzpgzEzzSzppdocszSzuszSzcnszSzcontentzSzpdrotczSzotc_fullzSzdrugszSzfgotc013zPzhtm. Accessed July 4, 2008. **IV**
927. Pauwels R. Mode of action of corticosteroids in asthma and rhinitis. Clin Allergy 1986;16:281-8. **IV**
928. Reed CE, Marcoux JP, Welsh PW. Effects of topical nasal treatment on asthma symptoms. J Allergy Clin Immunol 1988;81:1042-7. **Ib**
929. Ratner PH, Howland WC 3rd, Arastu R, Philpot EE, Klein KC, Baidoo CA, et al. Fluticasone propionate aqueous nasal spray provided significantly greater improvement in daytime and nighttime nasal symptoms of seasonal allergic rhinitis compared with montelukast. Ann Allergy Asthma Immunol 2003;90:536-42. **Ib**
930. Pullerits T, Praks L, Skoogh BE, Ani R, Lotvall J. Randomized placebo-controlled study comparing a leukotriene receptor antagonist and a nasal glucocorticoid in seasonal allergic rhinitis. Am J Respir Crit Care Med 1999;159:1814-8. **Ib**
931. Ratner PH, van Bavel JH, Martin BG, Hampel FC Jr, Howland WC 3rd, Rogenes PR, 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;47:118-25. **Ib**
932. 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;36:676-84. **Ib**
933. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. First-line treatment of seasonal (ragweed) rhinoconjunctivitis: a randomized management trial comparing a nasal steroid spray and a nonsedating antihistamine. CMAJ 1997;156:1123-31. **Ib**
934. Fraunfelder FT, Meyer SM. Posterior subcapsular cataracts associated with nasal or inhalation corticosteroids. Am J Ophthalmol 1990;109:489-90. **III**
935. Barenholtz H. Effect of inhaled corticosteroids on the risk of cataract formation in patients with steroid-dependent asthma. Ann Pharmacother 1996;30:1324-7. **IV**
936. Wilson AM, Sims EJ, McFarlane LC, Lipworth BJ. Effects of intranasal corticosteroids on adrenal, bone, and blood markers of systemic activity in allergic rhinitis. J Allergy Clin Immunol 1998;102:598-604. **Ib**
937. Mortimer KJ, Harrison TW, Tattersfield AE. Effects of inhaled corticosteroids on bone. Ann Allergy Asthma Immunol 2005;94:15-21; quiz 2-3, 79. **IV**
938. Toogood JH, Baskerville JC, Markov AE, Hodsman AB, Fraher LJ, Jennings B, et al. Bone mineral density and the risk of fracture in patients receiving long-

term inhaled steroid therapy for asthma. J Allergy Clin Immunol 1995;96:157-66. **III**
939. Doull I, Freezer N, Holgate S. Osteocalcin, growth, and inhaled corticosteroids: a prospective study. Arch Dis Child 1996;74:497-501. **Ib**
940. Brown HM, Storey G, Jackson FA. Beclomethasone dipropionate aerosol in treatment of perennial and seasonal rhinitis: a review of five years' experience. Br J Clin Pharmacol 1977;4(suppl 3):283S-6S. **III**
941. Minshall E, Ghaffar O, Cameron L, O'Brien F, Quinn H, Rowe-Jones J, et al. Assessment by nasal biopsy of long-term use of mometasone furoate aqueous nasal spray (Nasonex) in the treatment of perennial rhinitis. Otolaryngol Head Neck Surg 1998;118:648-54. **IIb**
942. Klossek JM, Laliberte F, Laliberte MF, Mounedji N, Bousquet J. Local safety of intranasal triamcinolone acetonide: clinical and histological aspects of nasal mucosa in the long-term treatment of perennial allergic rhinitis. Rhinology 2001; 39:17-22. **Ib**
943. Taylor G, Shivalkar PR. Disodium cromoglycate: laboratory studies and clinical trial in allergic rhinitis. Clin Allergy 1971;1:189-98. **IIb**
944. Chandra RK, Heresi G, Woodford G. Double-blind controlled crossover trial of 4% intranasal sodium cromoglycate solution in patients with seasonal allergic rhinitis. Ann Allergy 1982;49:131-4. **IIa**
945. Ratner P, Meltzer E, Byas L, Block E. Randomized, double-blind, placebo-controlled evaluation of cromolyn sodium in the treatment of allergic rhinitis in young children. J Appl Res 2001;1:100-9. **Ib**
946. Meltzer EO. Efficacy and patient satisfaction with cromolyn sodium nasal solution in the treatment of seasonal allergic rhinitis: a placebo-controlled study. Clin Ther 2002;24:942-52. **Ib**
947. Ratner PH, Ehrlich PM, Fineman SM, Meltzer EO, Skoner DP. Use of intranasal cromolyn sodium for allergic rhinitis. Mayo Clin Proc 2002;77:350-4. **IV**
948. Drugs acting at synaptic and neuroeffector junctional sites. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, editors. Goodman and Gilman's The Pharmacological Basis of Therapeutics. New York (NY): McGraw-Hill; 1996. p. 148-60. **IV**
949. White MV. Muscarinic receptors in human airways. J Allergy Clin Immunol 1995;95:1065-8. **IV**
950. Druce HM, Wright RH, Kossoff D, Kaliner MA. Cholinergic nasal hyperreactivity in atopic subjects. J Allergy Clin Immunol 1985;76:445-52. **III**
951. Baroody FM, Wagenmann M, Naclerio RM. Comparison of the secretory response of the nasal mucosa to methacholine and histamine. J Appl Physiol 1993;74:2661-71. **Ib**
952. Baroody FM, Ford S, Lichtenstein LM, Kagey-Sobotka A, Naclerio RM. Physiologic responses and histamine release after nasal antigen challenge: effect of atropine. Am J Respir Crit Care Med 1994;149:1457-65. **Ib**
953. Wood CC, Fireman P, Grossman J, Wecker M, MacGregor T. Product characteristics and pharmacokinetics of intranasal ipratropium bromide. J Allergy Clin Immunol 1995;95:1111-6. **IV**
954. Kim KT, Kerwin E, Landwehr L, Bernstein JA, Bruner D, Harris D, et al. Use of 0.06% ipratropium bromide nasal spray in children aged 2 to 5 years with rhinorrhea due to a common cold or allergies. Ann Allergy Asthma Immunol 2005;94: 73-9. **IIb**
955. 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;132:164-72. **Ib**
956. Hill SL 3rd, Krouse JH. The effects of montelukast on intradermal wheal and flare. Otolaryngol Head Neck Surg 2003;129:199-203. **Ib**
957. Simons FE, Johnston L, Gu X, Simons KJ. Suppression of the early and late cutaneous allergic responses using fexofenadine and montelukast. Ann Allergy Asthma Immunol 2001;86:44-50. **Ib**
958. Nathan RA, Yancey SW, Waitkus-Edwards K, Prillaman BA, Stauffer JL, Philpot E, et al. Fluticasone propionate nasal spray is superior to montelukast for allergic rhinitis while neither affects overall asthma control. Chest 2005;128:1910-20. **Ib**
959. Fahy JV, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J, et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. Am J Respir Crit Care Med 1997;155:1828-34. **Ib**
960. Soler M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. Eur Respir J 2001;18:254-61. **Ib**
961. Corren J, Casale T, Deniz Y, Ashby M. Omalizumab, a recombinant humanized anti-IgE antibody, reduces asthma-related emergency room visits and hospitalizations in patients with allergic asthma. J Allergy Clin Immunol 2003;111:87-90. **Ib**
962. Spector SL, Toshener D, Gay I, Rosenman E. Beneficial effects of propylene and polyethylene glycol and saline in the treatment of perennial rhinitis. Clin Allergy 1982;12:187-96. **Ib**
963. Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. J Allergy Clin Immunol 2006;117:169-75. **III**
964. Bernstein DI, Wanner M, Borish L, Liss GM. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. J Allergy Clin Immunol 2004;113:1129-36. **III**
965. Reid MJ, Lockey RF, Turkeltaub PC, Platts-Mills TA. Survey of fatalities from skin testing and immunotherapy 1985-1989. J Allergy Clin Immunol 1993;92: 6-15. **III**
966. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). J Allergy Clin Immunol 1987;79:660-77. **III**
967. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. J Allergy Clin Immunol 1998;102:558-62. **IV**
968. Kohno Y, Minoguchi K, Oda N, Yokoe T, Yamashita N, Sakane T, et al. Effect of rush immunotherapy on airway inflammation and airway hyperresponsiveness after bronchoprovocation with allergen in asthma. J Allergy Clin Immunol 1998; 102:927-34. **III**
969. Frew AJ, Powell RJ, Corrigan CJ, Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006;117:319-25. **Ib**
970. Brain D. The nasal septum. In: Kerr A, Groves J, editors. Scott-Brown's otolaryngology. 5th ed. London: Butterworths; 1987. p. 154-79. **IV**
971. Lerdlum S, Vachiranubhap B. Prevalence of anatomic variation demonstrated on screening sinus computed tomography and clinical correlation. J Med Assoc Thai 2005;88(suppl 4):S110-5. **III**
972. Guyuron B, Uzzo CD, Scull H. A practical classification of septonasal deviation and an effective guide to septal surgery. Plast Reconstr Surg 1999;104:2202-9; discussion 10-2. **III**
973. Lopez MA, Westine JG, Toriumi DM. The role of powered instrumentation in rhinoplasty and septoplasty. J Long Term Eff Med Implants 2005;15:283-8. **IV**
974. Mlynski G. Surgery of the nasal septum. Facial Plast Surg 2006;22:223-9. **IV**
975. Yilmaz M, Kemaloglu YK, Baysal E, Tutar H. Radiofrequency for inferior turbinate hypertrophy: could its long-term effect be predicted with a preoperative topical vasoconstrictor drop test? Am J Rhinol 2006;20:32-5. **III**
976. Russo CA, Owens P, Steiner, C. Ambulatory surgery in US hospitals, 2003. 2007. Available at: http://www.ahrq.gov/data/hcup/factbk9/factbk9.pdf. Accessed July 3, 2008. **IV**
977. Graft D, Aaronson D, Chervinsky P, Kaiser H, Melamed J, Pedinoff A, et al. A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray. J Allergy Clin Immunol 1996;98:724-31. **Ib**
978. Craig TJ, Hanks CD, Fisher LH. How do topical nasal corticosteroids improve sleep and daytime somnolence in allergic rhinitis? J Allergy Clin Immunol 2005;116:1264-6. **IIa**
979. Van Cauwenberge P, Bachert C, Passalacqua G, Bousquet J, Canonica GW, Durham SR, et al. Consensus statement on the treatment of allergic rhinitis. European Academy of Allergology and Clinical Immunology. Allergy 2000;55: 116-34. **IV**
980. Berger WE, Schenkel EJ, Mansfield LE. Safety and efficacy of desloratadine 5 mg in asthma patients with seasonal allergic rhinitis and nasal congestion. Ann Allergy Asthma Immunol 2002;89:485-91. **IIa**
981. Horak F, Stubner UP, Zieglmayer R, Harris AG. Effect of desloratadine versus placebo on nasal airflow and subjective measures of nasal obstruction in subjects with grass pollen-induced allergic rhinitis in an allergen-exposure unit. J Allergy Clin Immunol 2002;109:956-61. **Ib**
982. Aaronson DW. Evaluation of cetirizine in patients with allergic rhinitis and perennial asthma. Ann Allergy Asthma Immunol 1996;76:440-6. **Ib**
983. Ciprandi G, Cosentino C, Milanese M, Mondino C, Canonica GW. Fexofenadine reduces nasal congestion in perennial allergic rhinitis. Allergy 2001;56:1068-70. **Ib**
984. Stern MA, Wade AG, Ridout SM, Cambell LM. Nasal budesonide offers superior symptom relief in perennial allergic rhinitis in comparison to nasal azelastine. Ann Allergy Asthma Immunol 1998;81:354-8. **Ib**
985. Gani F, Pozzi E, Crivellaro MA, Senna G, Landi M, Lombardi C, et al. The role of patient training in the management of seasonal rhinitis and asthma: clinical implications. Allergy 2001;56:65-8. **Ib**
986. Gregory C, Cifaldi M, Tanner LA. Targeted intervention programs: creating a customized practice model to improve the treatment of allergic rhinitis in a managed care population. Am J Manag Care 1999;5:485-96. **Ib**
987. Sade K, Berkun Y, Dolev Z, Shalit M, Kivity S. Knowledge and expectations of patients receiving aeroallergen immunotherapy. Ann Allergy Asthma Immunol 2003;91:444-8. **III**
988. Bonay M, Neukirch C, Grandsaigne M, Lecon-Malas V, Ravaud P, Dehoux M, et al. Changes in airway inflammation following nasal allergic challenge in patients with seasonal rhinitis. Allergy 2006;61:111-8. **Ib**

989. Sandrini A, Ferreira IM, Jardim JR, Zamel N, Chapman KR. Effect of nasal triamcinolone acetonide on lower airway inflammatory markers in patients with allergic rhinitis. J Allergy Clin Immunol 2003;111:313-20. **Ib**
990. Grembiale RD, Camporota L, Naty S, Tranfa CM, Djukanovic R, Marsico SA. Effects of specific immunotherapy in allergic rhinitic individuals with bronchial hyperresponsiveness. Am J Respir Crit Care Med 2000;162:2048-52. **Ib**
991. Slavin RG. Allergic rhinitis: managing the adult spectrum. Allergy Asthma Proc 2006;27:9-11. **IV**
992. Reiss M, Reiss G. [Rhinitis in old age]. Schweiz Rundsch Med Prax 2002;91: 353-8. **V**
993. Bende M. Blood flow with 133Xe in human nasal mucosa in relation to age, sex and body position. Acta Otolaryngol 1983;96:175-9. **III**
994. Mygind N, Borum P. Intranasal ipratropium: literature abstracts and comments. Rhinol Suppl 1989;9:37-44. **IV**
995. Alaranta A, Alaranta H, Heliovaara M, Alha P, Palmu P, Helenius I. Allergic rhinitis and pharmacological management in elite athletes. Med Sci Sports Exerc 2005;37:707-11. **III**
996. Fisher LH, Davies MJ, Craig TJ. Nasal obstruction, the airway, and the athlete. Clin Rev Allergy Immunol 2005;29:151-8. **IV**
997. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of allergic rhinitis: an analysis of randomized, prospective, single- or double-blind, placebo-controlled studies. Clin Ther 2000;22:342-50. **Ia**
998. Leung D, Schatz M. Consultation and referral guidelines citing the evidence: how the allergist-immunologist can help. J Allergy Clin Immunol 2006;117:S495-518. **IV**