Task force report

Allergen immunotherapy: A practice parameter third update

***Chief Editors*: Linda Cox, MD, Harold Nelson, MD, and Richard Lockey, MD**

***Workgroup Contributors*: Christopher Calabria, MD, Thomas Chacko, MD, Ira Finegold, MD, Michael Nelson, MD, PhD, and Richard Weber, MD**

***Task Force Reviewers*: David I. Bernstein, MD, Joann Blessing-Moore, MD, David A. Khan, MD, David M. Lang, MD, Richard A. Nicklas, MD, John Oppenheimer, MD, Jay M. Portnoy, MD, Christopher Randolph, MD, Diane E. Schuller, MD, Sheldon L. Spector, MD, Stephen Tilles, MD, and Dana Wallace, MD**

Key words: *Allergy immunotherapy, subcutaneous immunotherapy, sublingual immunotherapy, allergic rhinitis, asthma, Hymenoptera, atopic dermatitis, anaphylaxis, epinephrine, β-blockers, angiotensin-converting enzyme inhibitor, epicutaneous immunotherapy, intralymphatic immunotherapy, nasal immunotherapy*

These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology. The American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma & Immunology have jointly accepted responsibility for establishing "Allergen immunotherapy: a practice parameter third update." 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 the ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma & Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion. A current list of published practice parameters of the Joint Task Force on Practice Parameters for Allergy and Immunology can be found in Table E1 in this article's Online Repository at www.jacionline.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. The Joint Task Force gratefully acknowledges the AAAAI Board of Directors and the ACAAI Board of Regents for their review and support of this document.

The authors and editors gratefully acknowledge Susan Grupe and Jessica Karle for their administrative assistance.

CHIEF EDITORS

Linda Cox, MD
Department of Medicine Nova Southeastern University College of Osteopathic Medicine
Davie, Florida

Richard Lockey, MD
Division of Allergy and Immunology
Department of Internal Medicine

Disclosure of potential conflict of interest: L. Cox is a consultant for Genentech/Novartis, Hollister-Stier, and Stallergenes; is a speaker for Novartis; has received research support from Stallergenes; is on the Board of Directors for the American Board of Allergy and Immunology; and is on the US Food and Drug Administration (FDA)'s Allergenic Product Advisory Committee. H. Nelson is a consultant for Merck and Planet Biopharmaceuticals, is a Data and Safety Monitoring Board member of DBV Technologies, and has received research support from ALK-Abelló. M. Nelson has received research support from the Department of Defense, is a speaker for the American College of Allergy, Asthma & Immunology (ACAAI), and is a member of the FDA's Advisory Committee on Allergic Products. R. Weber is on the speakers' bureau for AstraZeneca and Genentech, has received research support from Novartis and GlaxoSmithKline, and is Committee Chair of the ACAAI. D. I. Bernstein is a consultant and on the advisory board for ALK America, is on the advisory board for Merck, and has received research support from Merck and Schering-Plough. J. Blessing-Moore is a speaker for Merck-Schering/AstraZeneca, Novartis, TEVA, and Meda Alcon and has received research support from Meda. D. A. Khan is a speaker for AstraZeneca and Merck, has received research support from the Vanberg Family Foundation and the Sellars Family Foundation, is Conjoint Board Review Chair for the ACAAI, and is a past president of the Texas Allergy, Asthma and Immunology Society. D. M. Lang is a speaker and consultant for GlaxoSmithKline; is a speaker for AstraZeneca, Merck, TEVA, Sanofi-Aventis, and Genentech/Novartis; and has received research support from Genentech/Novartis. R. A. Nicklas is a fellow for the ACAAI. J. Oppenheimer is a consultant and has provided lectures for AstraZeneca, Merck, and GlaxoSmithKline; and has received research support from AstraZeneca, Merck, GlaxoSmithKline, and Genentech. J. M. Portnoy is a speaker for Phadia, Merck, and CSL Behring; has received research support from the US Department of Housing and Urban Development; and is a board member of the ACAAI board of regents. S. L. Spector has received research support from Genentech, GlaxoSmithKline, Schering-Plough, Aventis, Novartis, Pharmaxis, Boehringer Ingelheim, AstraZeneca, Johnson & Johnson, Xyzal, Alcon, Centocor, Sepracor, UCB, Amgen, Capnia, and IVAX. S. Tilles is a speaker for Alcon; is on the advisory board for ALK, Ista, Merck, and Stallergenes; has received research support from Alcon, Amgen, Amphastar, Astellas, Boehringer Ingelheim, Ception, Genentech, Icagen, MAP Pharma, MEDA, Merck, Novartis, Roxane, and Sepracor; is Associate Editor of *Allergy Watch* and *Annals of Allergy*; and is a task force member for the Joint Task Force for Practice Parameters. D. Wallace is a speaker and advisor for Alcon, is a speaker for Merck and Sanofi-Aventis, and is President-Elect of the ACAAI. The rest of the authors have declared that they have no conflict of interest.

Received for publication September 18, 2010; accepted for publication September 23, 2010.

Reprint requests: Joint Council of Allergy, Asthma & Immunology, 50 N Brockway St, #3-3, Palatine, IL 60067. E-mail: lindaswolfcox@msn.com.

0091-6749/$36.00

© 2010 American Academy of Allergy, Asthma & Immunology

doi:10.1016/j.jaci.2010.09.034

University of South Florida College of Medicine and James A. Haley Veterans' Hospital
Tampa, Florida

Harold Nelson, MD
Department of Medicine
National Jewish Health
Denver, Colorado

WORK GROUP MEMBERS

Christopher Calabria, MD
Glen Burnie, Maryland

Thomas Chacko, MD
Roswell, Georgia

Ira Finegold, MD
New York, New York

Michael Nelson, MD, PhD
Washington, DC

Richard Weber, MD
Denver, Colorado

JOINT TASK FORCE REVIEWERS

David Bernstein, MD
Department of Medicine and Environmental Health
University of Cincinnati College of Medicine
Cincinnati, Ohio

David A. Khan, MD
Department of Internal Medicine
University of Texas Southwestern Medical Center
Dallas, Texas

Joann Blessing-Moore, MD
Departments of Medicine and Pediatrics
Stanford University Medical Center
Department of Immunology
Palo Alto, California

David M. Lang, MD
Allergy/Immunology Section
Division of Medicine Allergy and Immunology Fellowship Training Program
Cleveland Clinic Foundation
Cleveland, Ohio

Richard A. Nicklas, MD
Department of Medicine
George Washington Medical Center
Washington, DC

John Oppenheimer, MD
Department of Internal Medicine
New Jersey Medical School
Pulmonary and Allergy Associates
Morristown, New Jersey

Jay M. Portnoy, MD
Section of Allergy, Asthma & Immunology
The Children's Mercy Hospital
Department of Pediatrics
University of Missouri–Kansas City School of Medicine
Kansas City, Missouri

Christopher Randolph, MD
Yale University
New Haven, Connecticut

Diane E. Schuller, MD
Department of Pediatrics
Pennsylvania State University
Milton S. Hershey Medical College
Hershey, Pennsylvania

Sheldon L. Spector, MD
Department of Medicine
UCLA School of Medicine
Los Angeles, California

Stephen A. Tilles, MD
Department of Medicine
University of Washington School of Medicine
Redmond, Washington

Dana V. Wallace, MD
Department of Medicine
Nova Southeastern University
Davie, Florida

INVITED REVIEWERS

Don Aaronson, MD, JD, MPH
Chicago, Illinois

Desiree Larenas-Linnemann, MD
Mexico city, Mexico

Bryan Leatherman, MD
Gulfport, Mississippi

Sandra Y. Lin, MD
Johns Hopkins Department of Otolaryngology–Head & Neck Surgery
Baltimore, Maryland
Oral and sublingual immunotherapy for food hypersensitivity

Wesley Burkes, MD
Duke University
Raleigh, North Carolina
Venom hypersensitivity

David Golden, MD
Baltimore, Maryland

Theodore M. Freeman, MD
Helotes, Texas
Allergen extract section

Derek Constable, PhD
Spokane, Washington

Robert Esch, PhD
Lenoir, North Carolina

Larry Garner, CPT, BA
Spokane, Washington

Richard Lankow, PhD
Round Rock, Texas

Greg Plunkett, PhD
Round Rock, Texas

Ronald Rabin, MD
Rockville, Maryland

ASSIGNED REVIEWERS

Paul Greenberger, MD
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Bryan Martin, DO
Ohio State University
Columbus, Ohio

PREFACE

This document was developed by the Joint Task Force on Practice Parameters, which represents the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology (JCAAI).

The objective of "Allergen immunotherapy: a practice parameter third update" is to optimize the practice of allergen immunotherapy for patients with allergic diseases. This parameter is intended to establish guidelines for the safe and effective use of allergen immunotherapy while reducing unnecessary variation in immunotherapy practice. These guidelines have undergone an extensive peer-review process consistent with recommendations of the American College of Medical Quality "Policy on development and use of practice parameters for medical quality decision-making."[1]

This document builds on the previous Joint Task Force document "Allergen immunotherapy: a practice parameter second update" published in the *Journal of Allergy and Clinical Immunology* in 2007.[2] The updated practice parameter draft was prepared by a work group that included 3 of the editors from the second update, Linda Cox, MD; Hal Nelson, MD; and Richard Lockey, MD, and other workgroup members as follows: Christopher Calabria, MD; Thomas Chacko, MD; Ira Finegold, MD; Michael Nelson, MD, PhD; and Richard Weber, MD.

In preparation for the third update, the workgroup performed a comprehensive search of the medical literature, which was conducted with various search engines, including PubMed; immunotherapy, allergic rhinitis, asthma, stinging insect allergy, and related search terms were used. In addition to the published literature from the comprehensive search, information from articles known to the authors was considered. Published clinical studies were rated by category of evidence and used to establish the strength of a clinical recommendation (Table I).[3] Laboratory-based studies were not rated.

The working draft of "Allergen immunotherapy: a practice parameter third update" was reviewed by a large number of individuals. Reviewers include persons appointed by the AAAAI, ACAAI, and invited experts. Invited reviewers included those with known expertise in specific areas (eg, oral immunotherapy or immunotherapy mechanisms), the US Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research, and the American Academy of Otolaryngic Allergy, who formally endorsed the previous practice parameter update.[4] The scientific representatives of the US Allergen Extract Manufacturers were invited through their organization, the Allergenic Products Manufacturing Association, to review and comment on the allergen extract section. All of these invited reviewers who contributed to the document are acknowledged for their efforts within the particular section that they reviewed.

In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for members to review and comment. The authors carefully considered all of these comments in preparing the final version.

An annotated algorithm in this document summarizes the key decision points for the appropriate use of allergen immunotherapy (Fig 1). The section on efficacy summarizes the evidence demonstrating that allergen immunotherapy is effective in the management of properly selected patients with aeroallergen and stinging insect hypersensitivity. This document also contains recommendations for optimizing the efficacy and safety of allergen immunotherapy, including specific recommendations on prevention and management of adverse reactions and a uniform classification system for grading systemic reactions.

Specific recommendations guide the physician in selecting those patients for whom allergen immunotherapy is appropriate. Aeroallergen immunotherapy should be considered for patients who have symptoms of allergic rhinitis/conjunctivitis or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. There is also some evidence that patients with atopic dermatitis with aeroallergen sensitivity might benefit from immunotherapy.

Candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures or those experiencing unacceptable adverse effects of medications or who wish to reduce the long-term use of medications. Immunotherapy is recommended for patients with a history of a systemic reaction to Hymenoptera stings who demonstrate Hymenoptera-specific IgE antibodies. There is evidence that venom immunotherapy (VIT) might be effective in reducing large local reactions (LLRs) that might cause significant morbidity and impair quality of life.

The focus of this parameter is on allergen immunotherapy practice in the United States. Although several studies have demonstrated the efficacy of sublingual immunotherapy (SLIT), there is no FDA-approved formulation for SLIT, and this treatment route is considered investigational in the United States. Oral immunotherapy and SLIT for food hypersensitivity are also considered investigational.

This document was approved by the sponsoring organizations and represents an evidence-based, broadly accepted consensus opinion. These clinical guidelines are designed to assist clinicians by providing a framework for the evaluation and treatment of patients and are not intended to replace a clinician's judgment or establish a protocol for all patients. Not all recommendations will be appropriate for all patients. Because this document incorporates the efforts of many participants, no individual, including anyone who served on the Joint Task Force, is authorized to provide an official AAAAI or ACAAI interpretation of these guidelines. Recognizing the dynamic nature of clinical practice and practice parameters, the recommendations in this document should be considered applicable for up to 5 years after publication. Requests for information about or an interpretation of these practice parameters should be directed to the Executive Offices of

TABLE I. Classification of evidence and recommendations

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 quasiexperimental study
III	Evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports or opinions, 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 from category I evidence
C	Directly based on category III evidence or extrapolated from category I or II evidence
D	Directly based on category IV evidence or extrapolated from category I, II, or III evidence
NR	Not rated

Adapted with permission from Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. BMJ 1999;318:593-6.

the AAAAI, ACAAI and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

KEY HIGHLIGHTS OF THE UPDATE: NEW DEVELOPMENTS OR MODIFICATIONS

- **New indications for allergen immunotherapy**:
  - Atopic dermatitis in subjects with aeroallergen sensitization **(Summary Statement 8)**.
  - VIT: patients who experience recurrent bothersome LLRs **(Summary Statement 11).**
- **Measurement of baseline tryptase** is recommended in patients with moderate or severe anaphylactic reactions to stings. Increased serum tryptase levels are associated with more frequent and severe systemic reactions to VIT injections, greater failure rates during VIT, and greater relapse rates (including fatal reactions) if VIT is discontinued **(Summary Statement 10b).**
- **Patient age and initiation of allergen immunotherapy**: The update states there is no specific upper or lower age limit for initiating allergen immunotherapy. The update stresses the importance of appropriate indications, the absence of significant comorbid conditions, and the patients' ability to comply/cooperate with allergen immunotherapy.
  - **Pediatrics**: There is no specific lower limit for immunotherapy if indications are present **(Summary Statements 17 and 18)**.
  - **Elderly**: There is no specific summary statement on immunotherapy in the elderly patient in the current update. The previous update recommended that the risk/benefit assessment be carefully evaluated in the elderly population because they might have comorbid medical conditions that could increase immunotherapy risk. The current update recognizes that some of these conditions can occur more frequently in older subjects, but they can also be present in younger subjects. The current update states that the risk/benefit assessment must be evaluated in every situation, but there is no absolute upper age limit for initiation of immunotherapy **(Summary Statement 19)**.
- **Special considerations**
  - **Pregnancy**: The summary statement that states "allergen immunotherapy can be continued but usually is not initiated in the pregnant patient" is unchanged from the previous update. However, the text accompanying the summary statement includes a review of literature on the safety of immunotherapy in pregnancy. The update also suggests that discontinuation of immunotherapy should be considered if the pregnancy occurs during the build-up phase and the patient is receiving a dose unlikely to be therapeutic **(Summary Statement 20)**.
  - **Patients with HIV infection**: The summary statement stating that the "immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders" is unchanged from the previous update. However, the text accompanying the summary statement includes discussion of the published literature and case reports on patients with HIV and allergen immunotherapy **(Summary Statement 21)**.
- **Local reactions**: The current update includes several summary statements on local reactions, including discussions regarding:
  - relationship with systemic reactions (predictive value of a single local reaction or incidence of systemic reactions in patients with frequent large local reactions);
  - influence of glycerin and allergen content on local reactions; and
  - possible prevention with antihistamines and leukotriene receptor antagonists (**Summary Statements 27-30**).
- **Systemic reactions, wait period after immunotherapy, and delayed systemic reactions**: The update includes new summary statements on delayed systemic reactions, defined as occurring 30 minutes after the injection, and biphasic reactions. Delayed-onset systemic reactions might account for up to 50% of reactions. Delayed systemic reactions can occur without any preceding symptoms or can be part of a biphasic reaction. Several large studies demonstrate that life-threatening anaphylactic reactions after 30 minutes are rare. The recommendation that a patient should remain in the physician's office/medical clinic for 30 minutes after the injection is unchanged from the previous update. It is

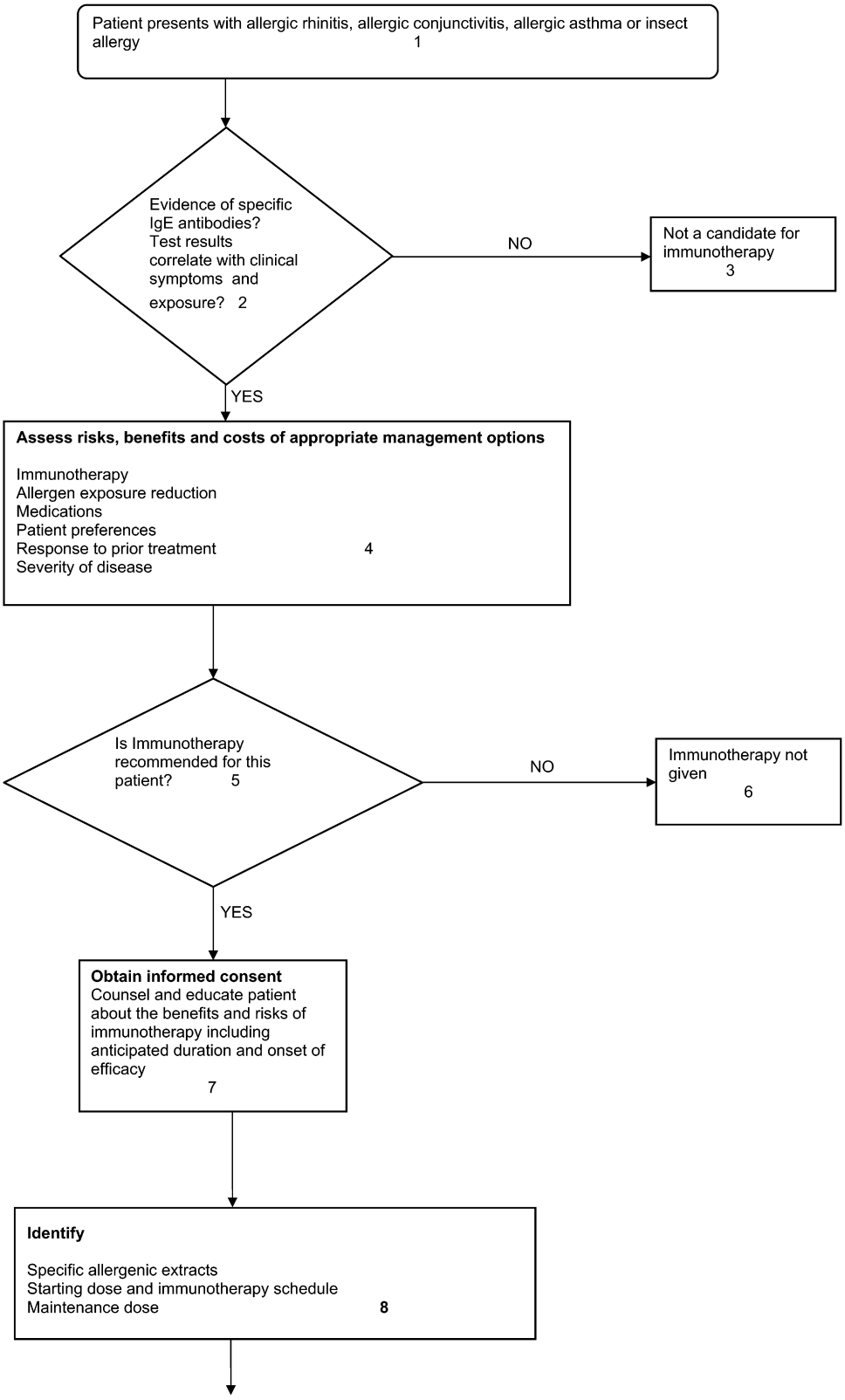


FIG 1. Algorithm for immunotherapy. (*Continued.*)

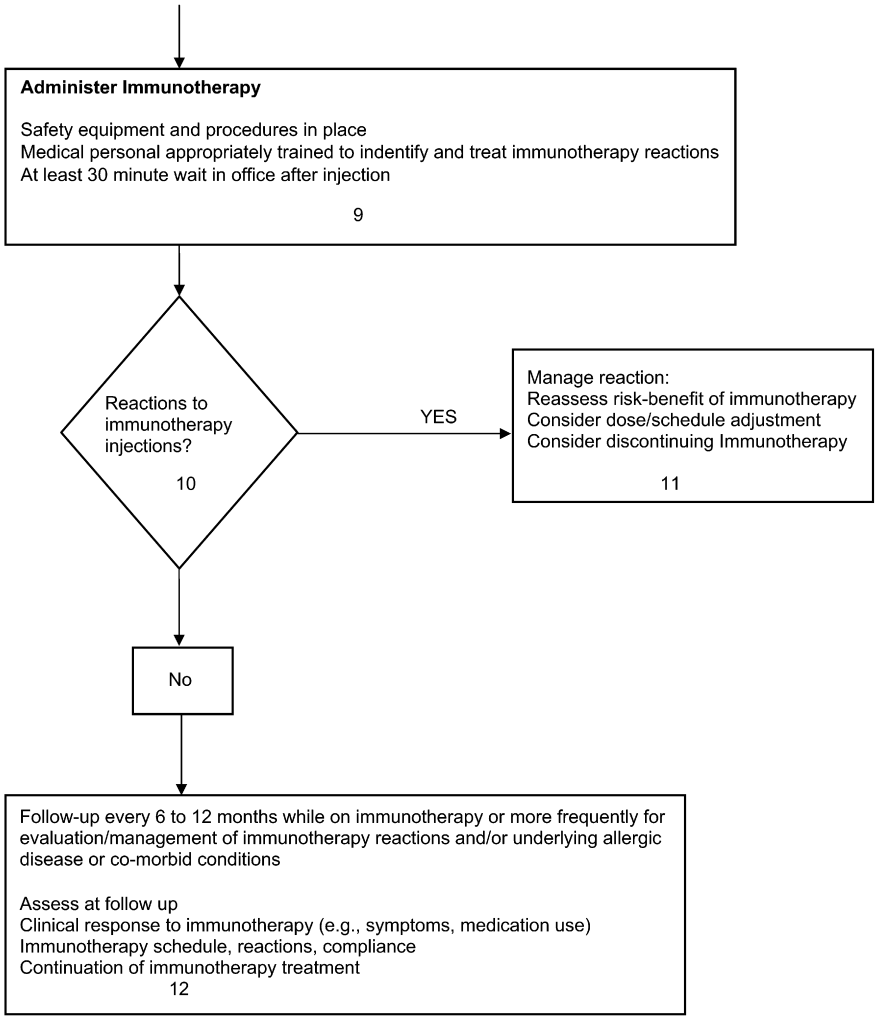


FIG 1. (*Continued*).

recommended that at the onset of immunotherapy, patients should be counseled on the possibility of immediate and delayed systemic reactions during risk communication; an action plan for such an event should be discussed. The decision to prescribe epinephrine autoinjectors to patients receiving immunotherapy should be at the physician's discretion **(Summary Statements 33-36)**.

- **β-Blocker medications**: The current update includes a discussion of cardioselective β-blockers, noting that it is not known whether there is less risk associated with immunotherapy but that there have been some severe cases of anaphylaxis from other causes reported in patients receiving cardioselective β-blockers **(Summary Statements 37-39 and 41)**.
- **Angiotensin-converting enzyme (ACE) inhibitor medications**: The update includes a new summary statement on ACE inhibitors, noting that there is some conflicting information in the published literature regarding immunotherapy risk in patients taking ACE inhibitors who receive immunotherapy. Two retrospective studies found no increased frequency of systemic reactions in patients taking ACE inhibitors receiving VIT or inhalant immunotherapy. However, a few case reports and a prospective study of 962 patients who received VIT found that ACE inhibitors were associated with more severe reactions from VIT. This update recommends that ACE inhibitor discontinuation be considered for patients receiving VIT. However, concurrent administration of VIT and an ACE inhibitor is warranted in selected cases in which there is no equally efficacious alternative and the risk/benefit assessment is favorable. **(Summary Statements 40-41)**.
- **Premedication and immunotherapy**: The update includes 3 summary statements on premedication during accelerated (rush and cluster) and conventional build-up schedules. The specific medications used in immunotherapy premedication regimens are discussed and include antihistamines, leukotriene receptor antagonists, omalizumab, and combination pretreatment. **(Summary Statements 56-58)**.
- **Rush VIT and premedication**: Because the risk of a systemic reaction from flying Hymenoptera rush VIT is relatively low, the recommendation that routine premedication is usually not necessary is unchanged from the previous update. The previous update suggested that imported fire ant rush immunotherapy had a similarly low risk. However, there are currently some conflicting data about the risk of imported fire rush immunotherapy, and premedication might be considered **(Summary Statements 55 and 57)**.

- **Aspiration before the immunotherapy injection**: The update includes a discussion of the debate regarding the need for aspiration before the immunotherapy injection (**Summary Statement 61**).
- **Cockroach immunotherapy**: The update includes a new summary statement noting that there are limited data on the efficacy of cockroach immunotherapy (**Summary Statement 71**).
- **Multiallergen immunotherapy**: A new summary statement stating that there have been few studies that have investigated the efficacy of multiallergen subcutaneous immunotherapy (SCIT) and that these studies have produced conflicting results has been included in this update (**Summary Statement 72**).
- **Allergen extract preparation**: The update includes discussion of the United States Pharmacopeia (USP) 797 allergen extract preparation guidelines, as well as the allergen extract preparation guidelines developed by the AAAAI/ACAAI/JCAAI, which was included in the previous update. The USP 797 guidelines were finalized after the previous parameter was published, and there are some differences between the 2 guidelines, one of which is that the USP 797 guidelines recommend that the preparer should wear a protective cap, face mask, and gown during the extract preparation process (**Summary Statement 77**).
- **Probable effective dosing for US-licensed standardized and nonstandardized extracts table**: The update includes a column presenting the range of major allergen content in US-licensed extracts, as well changes in the recommended dosing for nonstandardized extracts (**Summary Statement 81**).
- **Noninjection routes of immunotherapy**: Compared with the previous update, this section includes an expanded discussion of SLIT, a summary statement on oral immunotherapy for food hypersensitivity, and summary statements on epicutaneous and intralymphatic immunotherapy (**Summary Statements 92-99**).
- **Novel formulations**: This section includes summary statements on allergoids and adjuvants, the immunostimulatory oligonucleotide sequence of DNA containing a CpG motif (CpG), and 3-deacylated monophospholipid A (MPL; **Summary Statements 100-101**).

INTRODUCTION

Immunity has been defined as protection against certain diseases. The initial immunotherapeutic interventions, which included the use of preventive vaccines and xenogeneic antisera by Jenner, Pasteur, Koch, and von Behring, were effective for disease prevention. These initial efforts in immune modulation served as a model for later developments in allergen immunotherapy. From its empiric emergence in the early 1900s, when grass pollen inoculation was proposed as therapy for hay fever, allergen immunotherapy has progressed in both theory and practice from the passive immunologic approach to the active immunologic procedures pioneered by Noon[5] and Freeman.[6,7] Advances in allergen immunotherapy have depended on the improved understanding of IgE-mediated immunologic mechanisms, the characterization of specific antigens and allergens, and the standardization of allergen extracts. Proof of the efficacy of allergen immunotherapy has accumulated rapidly during the past 30 years. Numerous well-designed controlled studies demonstrate that allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma, and stinging insect hypersensitivity. Randomized controlled studies showed that allergen immunotherapy prevents the development of asthma in subjects with allergic rhinitis.[8-11] There is some evidence of immunotherapy's efficacy in the treatment of patients with atopic dermatitis with aeroallergen sensitization.[12-16]

Allergen immunotherapy is effective when appropriate doses of allergens are administered. Effective subcutaneous allergen immunotherapy appears to correlate with administration of an optimal maintenance dose in the range of 5 to 20 μg of major allergen for inhalant allergens.[17-22] It should be differentiated from unproved methods, such as neutralization-provocation therapy[23] and low-dose subcutaneous regimens based on the Rinkel technique,[24,25] which have been found to be ineffective in double-blind, placebo-controlled trials. The selection of allergens for immunotherapy is based on clinical history, the presence of specific IgE antibodies, and allergen exposure. This parameter offers suggestions and recommendations derived from known patterns of allergen cross-reactivity. Recognizing that the immunotherapy terminology used to describe extract dilutions is sometimes ambiguous, the 2003 "Allergen immunotherapy: a practice parameter" established standardized terminology for describing allergen immunotherapy extract dilutions, which is included in this and the 2007 update. These parameters also provided specific recommendations for immunotherapy maintenance doses for some standardized allergens and a suggested dosing range for nonstandardized allergen extracts.

The therapeutic preparations for allergen immunotherapy are extracted from source materials, such as pollen, mold cultures, and pelt, hence the traditional term allergen extract. The terms *allergen extract* or *extract* refer to solutions of proteins or glycoproteins extracted from source material not yet incorporated into a therapeutic allergen immunotherapy extract. The term *manufacturer's extract* refers to the allergen extract purchased from the manufacturer. The terms *stock*, *full strength*, and *concentrate* are ambiguous and should not be used. The term *maintenance concentrate* should be used to identify the allergen immunotherapy extract that contains a therapeutic effective dose for each of its individual constituents. All dilutions should be referenced to the maintenance concentrate and should be noted as a volume-to-volume dilution (eg, 1:100 vol/vol dilution of a maintenance concentrate).

This parameter reinforces the 2 previous allergen immunotherapy practice parameters' recommendations that vials of allergen immunotherapy extracts should be prepared individually for each patient and documented with standardized allergen immunotherapy prescription and administration forms. Individualized patient vials will allow for customized treatment specific to the patient's identified allergen sensitivities and reduce the risk of allergen cross-contamination and patient identification errors in administration.[26,27] Standardized prescription and administration forms will improve the safety, uniformity, and standardization of allergen immunotherapy practice. The suggested forms are found in this article's Online Repository at www.jacionline.org and on the AAAAI, ACAAI, and JCAAI Web sites (www.aaaai.org, www.acaai.org, and www.jcaai.org). The routine use of these

standardized forms should improve the quality of immunotherapy practice.

ALGORITHM AND ANNOTATIONS FOR IMMUNOTHERAPY

Fig 1 provides an algorithm for the appropriate use of allergen immunotherapy. Given below are annotations for use with the algorithm.

Box 1

Immunotherapy is effective in the management of allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity. There is some evidence it might be effective in the treatment of atopic dermatitis in patients with aeroallergen sensitivity. Allergen immunotherapy might prevent the development of asthma in subjects with allergic rhinitis. Evaluation of a patient with suspected allergic rhinitis, allergic conjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for serum specific IgE).

Box 2

Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although testing for serum specific IgE antibodies is useful under certain circumstances. Immunotherapy should be considered when positive test results for specific IgE antibodies correlate with suspected triggers and patient exposure.

Box 3

Immunotherapy should not be given to patients with negative test results for specific IgE antibodies or those with positive test results for specific IgE antibodies that do not correlate with suspected triggers, clinical symptoms, or exposure. This means that the presence of specific IgE antibodies alone does not necessarily indicate clinical sensitivity. There is no evidence from well-designed studies that immunotherapy for any allergen is effective in the absence of specific IgE antibodies.

Box 4

The management of allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity should include the evaluation of different treatment options. Each of the 3 major management approaches (allergen immunotherapy, allergen exposure reduction, and pharmacotherapy) has benefits, risks, and costs. Furthermore, the management plan must be individualized, with careful consideration given to the patient's preference. Disease severity and response (or lack of response) to previous treatment are important factors.

Box 5

The physician and patient should discuss the benefits, risks, and costs of the appropriate management options and agree on a management plan. Based on clinical considerations and the patient's preference, allergen immunotherapy might or might not be recommended. Patients with allergic rhinitis/conjunctivitis or allergic asthma whose symptoms are not well controlled by medications or avoidance measures or require high medication doses, multiple medications, or both to maintain control of their allergic disease might be good candidates for immunotherapy. Patients who experience adverse effects of medications or who wish to avoid or reduce the long-term use of medications are appropriate candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. Patients with aeroallergen-induced atopic dermatitis might benefit from immunotherapy. In general, patients with flying insect or imported fire ant hypersensitivity who are at risk for anaphylaxis should receive VIT or whole-body extract, respectively. VIT has also been shown to decrease LLRs to stinging insects.

Box 6

After careful consideration of appropriate management options, the physician and patient might decide not to proceed with immunotherapy.

Box 7

Before immunotherapy is started, patients should understand its benefits, risks, and costs. Counseling should also include the expected onset of efficacy and duration of treatment, as well as the risk of anaphylaxis and importance of adhering to the immunotherapy schedule.

Box 8

The physician prescribing immunotherapy should be trained and experienced in prescribing and administering immunotherapy. The prescribing physician must select the appropriate allergen extracts based on that particular patient's clinical history and allergen exposure history and the results of tests for specific IgE antibodies. The quality of the allergen extracts available is an important consideration. When preparing mixtures of allergen extracts, the prescribing physician must take into account the cross-reactivity of allergen extracts and the potential for allergen degradation caused by proteolytic enzymes. The prescribing physician must specify the starting immunotherapy dose, the target maintenance dose, and the immunotherapy schedule. In general, the starting immunotherapy dose is 1,000- to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 500 to 2000 allergy units (AU; eg, for dust mite) or 1000 to 4000 bioequivalent allergy units (BAU; eg, for grass or cat) for standardized allergen extracts. For nonstandardized extracts, a suggested maintenance dose is 3000 to 5000 protein nitrogen units (PNU) or 0.5 mL of a 1:100 or 1:200 wt/vol dilution of manufacturer's extract. If the major allergen concentration of the extract is known, a range between 5 and 20 μg of major allergen is the recommended maintenance dose for inhalant allergens and 100 μg for Hymenoptera venom. Immunotherapy treatment can be divided into 2 periods, which are commonly referred to as the build-up and maintenance phases.

The immunotherapy build-up schedule (also called updosing, induction, or the dose-increase phase) entails administration of gradually increasing doses during a period of approximately 8 to

28 weeks. In conventional schedules a single dose increase is given on each visit, and the visit frequency can vary from 1 to 3 times a week. Accelerated schedules, such as rush or cluster immunotherapy, entail administration of several injections at increasing doses on a single visit. Accelerated schedules offer the advantage of achieving the therapeutic dose earlier but might be associated with increased risk of a systemic reaction in some patients.

Box 9

Immunotherapy should be administered in a setting that permits the prompt recognition and management of adverse reactions. The preferred location for such administration is the prescribing physician's office. However, patients can receive immunotherapy injections at another health care facility if the physician and staff at that location are trained and equipped to recognize and manage immunotherapy reactions, particularly anaphylaxis. Patients should wait at the physician's office/medical clinic for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly if they occur.

Immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring the peak expiratory flow rate before administering an immunotherapy injection and withholding an immunotherapy injection if the peak expiratory flow rate is considered low for that patient.

Box 10

Injections of allergen immunotherapy extract can cause local or systemic reactions. Most serious systemic reactions develop within 30 minutes after the immunotherapy injection. However, immunotherapy-induced systemic reactions can occur after 30 minutes. Patients should be counseled on the possibility of immediate and delayed systemic reactions during risk communication; an action plan for such an event should be discussed. In the event of a delayed systemic reaction, the patient should be counseled on appropriate treatment based on his or her symptoms.

Box 11

Local reactions can be managed with local treatment (eg, cool compresses or topical corticosteroids) or antihistamines. Systemic reactions can be mild or severe. Epinephrine is the treatment of choice in patients with anaphylaxis.

Antihistamines and systemic corticosteroids are secondary medications that might help to modify systemic reactions but should never replace epinephrine in the treatment of anaphylaxis. Intravenous saline or supplemental oxygen might be required in severe cases. For additional details on anaphylaxis management see, "The diagnosis and management of anaphylaxis practice parameter: 2010 update."[28]

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. For some patients, the immunotherapy maintenance dose might need to be reduced. After systemic reactions to immunotherapy, the prescribing physician can re-evaluate the risk/benefit ratio of continued immunotherapy.

Box 12

Patients receiving maintenance immunotherapy should have follow-up visits at least every 6 to 12 months. Periodic visits should include a reassessment of symptoms and medication use, the medical history since the previous visit, and an evaluation of the clinical response to immunotherapy. The immunotherapy schedule and dose, reaction history, and patient compliance should also be evaluated. The physician can at this time make adjustments to the immunotherapy schedule or dose, as clinically indicated.

There are no specific markers that will predict who will remain in clinical remission after discontinuing effective allergen immunotherapy. Some patients might sustain lasting remission of their allergic symptoms after discontinuing allergen immunotherapy, but others might experience a recurrence of their symptoms. As with the decision to initiate allergen immunotherapy, the decision to discontinue treatment should be individualized, taking into account factors such as the severity of the patient's illness before treatment, the treatment benefit sustained, the inconvenience immunotherapy represents to a specific patient, and the potential effect a clinical relapse might have on the patient. Ultimately, the duration of immunotherapy should be individualized based on the patient's clinical response, disease severity, immunotherapy reaction history, and preference.

IMMUNOTHERAPY GLOSSARY

For more information on immunotherapy definitions, see the article by Kao.[29]

The *allergen immunotherapy extract* is defined as the mixture of the manufacturer's allergen extract or extracts that is used for allergen immunotherapy. Allergen extracts used to prepare the allergen immunotherapy extract can be complex mixtures containing multiple allergenic and nonallergenic macromolecules (proteins, glycoproteins, and polysaccharides) and low-molecular-weight compounds. Other terms used to describe the allergen immunotherapy extract include allergen product,[30] allergy serum, allergen vaccine,[31] and allergen solution.

Allergen immunotherapy is defined as the repeated administration of specific allergens to patients with IgE-mediated conditions for the purpose of providing protection against the allergic symptoms and inflammatory reactions associated with natural exposure to these allergens.[2] Other terms that have been used for allergen immunotherapy include hyposensitization, allergen-specific desensitization, and the lay terms allergy shots or allergy injections.[29]

Anaphylaxis is an immediate systemic reaction often occurring within minutes and occasionally as long as an hour or longer after exposure to an allergen. It can be IgE mediated, as can occur with allergen immunotherapy, or non–IgE mediated, as occurs with radiocontrast media. It is caused by the rapid release of vasoactive mediators from tissue mast cells and peripheral blood basophils.

The *build-up phase* involves receiving injections with increasing amounts of the allergen. The frequency of injections during this phase generally ranges from 1 to 3 times a week, although more rapid build-up schedules are sometimes used. The duration of this phase depends on the frequency of the injections but generally ranges from 3 to 6 months (at a frequency of 2 times and 1 time per week, respectively). Other terms used to describe the build-up phase include updosing, induction or the dose-increase phase.

TABLE II. Calculations for making extract dilutions*

All dilutions can be calculated by using the following formula:	
V1 × C1 = V2 × C2,	
where	
V1 = Final volume you want to prepare	
C1 = Concentration (wt/vol or PNU) of extract you want to prepare	
V2 = Volume of extract you will need for dilution	
C2 = Concentration of extract you will use.	
Example: Solve for V2; (V1 × C1)/C2 = V2.	
To determine the concentration of an item in a mixture:	
1. determine which formula you need to use;	
2. choose the numbers/fractions that will be inserted into the formula for V1, C1, V2, and C2;	
3. change all wt/vol fractions to a decimal number and insert into the formula (see below); and	
4. multiply first and then divide to get the answer.	
To express concentration as a percentage:	
1:10 wt/vol 1/10 = 0.1 × 100 = 10% solution	
1:20 wt/vol 1/20 = 0.05 × 100 = 5% solution	
1:40 wt/vol 1/40 = 0.025 × 100 = 2.5% solution	
Example:	
V1 = 5 mL	Final volume you want to prepare
C1 = 1:200	Concentration you want to prepare
V2 = Unknown	Volume of extract you will need for dilution
C2 = 1:10	Concentration of extract you will use
Add values into formula:	
V1 × C1 = V2 × C2	5 × (1/200) = V2 × (1/10)
	5 × (0.005) = V2 × (0.1)
V2 = (V1 × C1)/C2	V2 = 0.025/0.1 = 0.25
To determine amount of diluent needed:	
V1 − V2	5 − 0.25 = 4.75 mL

Adapted from the Greer Allergy Compendium. Lenoir (NC): Greer Laboratories; 2005. p. 71. Permission provided by Robert Esch, PhD.

Cluster immunotherapy is an accelerated build-up schedule that entails administering several injections at increasing doses (generally 2-3 per visit) sequentially in a single day of treatment on nonconsecutive days. The maintenance dose is generally achieved more rapidly than with a conventional (single injection per visit) build-up schedule (generally within 4-8 weeks).

Desensitization is the rapid administration of incremental doses of allergens or medications by which effector cells are rendered less reactive or nonreactive to an IgE-mediated immune response. Desensitization can involve IgE-mediated or other immune mechanisms. The positive skin test response to the allergens might diminish or actually convert to a negative response in some cases after this procedure. Tolerance to medications can be achieved through desensitization.

The *dose* is the actual amount of allergen administered in the injection. The volume and concentration can vary such that the same delivered dose can be given by changing the volume and concentration (ie, 0.05 mL of a 1:1 vol/vol allergen would equal 0.5 mL of a 1:10 vol/vol allergen). The dose can be calculated by using the following formula: Concentration of allergen × volume of administered dose. See Table II for calculation formula for making extract dilutions.

The *effective therapeutic dose* or *maintenance dose* is the dose that provides therapeutic efficacy without significant adverse local or systemic reactions. The effective therapeutic dose might not be the initially calculated projected effective dose (eg, 500 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose] for cat).

Hyposensitization is a term formerly used interchangeably with allergen immunotherapy. It was introduced to distinguish allergen immunotherapy from classical desensitization. Hyposensitization denotes a state of incomplete desensitization because complete desensitization is rarely accomplished with allergen immunotherapy.

Immunomodulation is a term that denotes a wide variety of drug or immunologic interventions that alter normal or abnormal immune responses by means of deletion of specific T cells, B cells, or both; immune deviation; induction of peripheral/central tolerance; or modification of various inflammatory pathways (eg, chemotaxis, adhesions, or intracytoplasmic signaling).

Immunotherapy is a treatment modality that appeared soon after adaptive immune responses were discovered and has gradually evolved to encompass any intervention that might benefit immune-induced aberrant conditions through a variety of immunologic transformations. Early definitions of the term immunotherapy included active and passive immunization to improve a host's defenses against microorganisms. Allergen immunotherapy was originally conceived as a form of active immunization, the purpose of which was to alter the host's abnormal immune responses and not augment the host's defenses against microorganisms. The modern rubric of immunotherapy includes all methods used to overcome abnormal immune responses with induction of clonal deletion, anergy, immune tolerance, or immune deviation.

Local reactions to SCIT injections can manifest as redness, pruritus, and swelling at the injection site.

The *maintenance concentrate* is a preparation that contains individual extracts or mixtures of manufacturer's allergen extracts intended for allergen immunotherapy treatment. A maintenance concentrate can be composed of a concentrated dose of a single allergen or a combination of concentrated allergens to prepare an individual patient's customized allergen immunotherapy extract mixture. Subsequent dilutions can be prepared from the maintenance concentrate for the build-up phase or if the patient cannot tolerate the maintenance concentrate.

The *maintenance dose* (or *effective therapeutic dose*) is the dose that provides therapeutic efficacy without significant adverse local or systemic reactions. The effective therapeutic dose might not be the initially calculated projected effective dose.

The *maintenance goal* (or *projected effective dose*) is the allergen dose projected to provide therapeutic efficacy. Not all patients will tolerate the projected effective dose, and some patients experience therapeutic efficacy at lower doses.

The *maintenance phase* begins when the effective therapeutic dose is reached. Once the maintenance dose is reached, the intervals between allergy injections are increased. The dose generally is the same with each injection, although modifications can be made based on several variables (ie, new vials or a persistent LLR causing discomfort). The intervals between maintenance immunotherapy injections generally range from 4 to 8 weeks for venom and every 2 to 4 weeks for inhalant allergens but can be advanced as tolerated if clinical efficacy is maintained.

A *major allergen* is an antigen that binds to the IgE sera from 50% or more of a clinically allergic group of patients. Such allergens are defined either with immunoblotting or crossed allergoimmunoelectrophoresis.

For a definition of *projected effective dose*, see the definition of maintenance goal.

Rush immunotherapy is an accelerated immunotherapy build-up schedule that entails administering incremental doses of

allergen at intervals varying between 15 and 60 minutes over 1 to 3 days until the target therapeutic dose is achieved. Rush immunotherapy schedules for inhalant allergens can be associated with a greater risk of systemic reactions, particularly in high-risk patients (eg, those with markedly positive prick/puncture or *in vitro* IgE test responses), and premedication primarily with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of stinging Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions.

For a definition of *specific immunotherapy*, see the definition of allergen immunotherapy.

A *systemic reaction* is an adverse reaction involving organ-specific systems distant from the injection site. Systemic reactions can range in severity from mild rhinitis to fatal cardiopulmonary arrest. The grading of systemic reactions is based on the organ system or systems involved and the severity.

See Table E2 in this article's Online Repository at www.jacionline.org for a list of summary statements without accompanying explanations.

IMMUNOLOGIC RESPONSES TO IMMUNOTHERAPY

Summary Statement 1: The immunologic response to subcutaneous immunotherapy is characterized by decreases in the sensitivity of end organs and changes in the humoral and cellular responses to the administered allergens. A

Summary Statement 2: Reduction in end-organ response with immunotherapy includes decreased early and late responses of the skin, conjunctiva, nasal mucosa, and bronchi to allergen challenge; decreased allergen-induced eosinophil, basophil, and mast cell infiltration; blunting of mucosal priming; and reduction of nonspecific bronchial sensitivity to histamine. A

Summary Statement 3: Shortly after initiation of immunotherapy, there is an increase in $CD4^+CD25^+$ regulatory T lymphocytes secreting IL-10 and TGF-β associated with immunologic tolerance, which is defined as a long-lived decrease in allergen-specific T-cell responsiveness. With continued immunotherapy, there is some waning of this response, and immune deviation from T_H2 to T_H1 cytokine response to the administered allergen predominates. A

Summary Statement 4: Specific IgE levels initially increase and then gradually decrease. Levels of specific IgG1, IgG4, and IgA increase. None of these changes in antibody levels have been shown to consistently correlate strongly with clinical improvement. A

Summary Statement 5: Increases in allergen-specific IgG levels are not predictive of the degree or duration of efficacy of immunotherapy. However, functional alterations in allergen-specific IgG levels, such as changes in avidity, affinity, or both for allergen, might play a role in determining clinical efficacy. LB

Immunologic changes associated with immunotherapy are complex, and the exact mechanism or mechanisms responsible for its clinical efficacy are continually being elucidated. Immunotherapy results in immunologic tolerance, which is denned as a relative decrease in antigen-specific responsiveness that might be accompanied by immune deviation, T-cell anergy, and/or T-cell apoptosis. Successful immunotherapy results in generation of a population of regulatory T cells, which are $CD4^+CD25^+$ T lymphocytes, as an early event, occurring within days or weeks. Regulatory T cells can produce inhibitory cytokines, such as IL-10, TGF-β, or both.[32-37] The presence of such regulatory cytokines has been described in allergen immunotherapy with Hymenoptera venom,[32] grass pollen,[34] and house dust mite allergen extracts.[35] Properties of IL-10 include the induction of a decrease in B-cell antigen–specific IgE production and increases in IgG4 levels; reduction in proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicitation of tolerance in T cells by means of selective inhibition of the CD28 costimulatory pathway. As a consequence, lymphoproliferative responses to allergen are reduced after immunotherapy.[38]

Data also support the concept of a later, more delayed, allergen-specific immune deviation from a T_H2 to a T_H1 cytokine profile.[39-41] Data indicate that increases in production of IL-12, a strong inducer of T_H1 responses, might contribute to this later shift.[42]

The immunologic response to SCIT is characterized by decreases in the sensitivity of end organs and changes in the humeral and cellular responses to the administered allergens. The response to allergen challenge of the conjunctiva, skin, and respiratory mucosa is reduced,[5,43-46] including both the immediate and delayed responses.[44-46] With natural allergen exposure, an enhanced sensitivity to allergen known as priming occurs. This too is reduced by immunotherapy,[45] as is the nonspecific sensitivity to bronchoconstrictive agents, such as histamine.[47,48] Eosinophils and mast cells increase in the respiratory mucosa and secretions during natural allergen exposure. These infiltrations are reduced by immunotherapy.[49-51]

In patients receiving immunotherapy, initially there is an increase in specific IgE antibody levels,[52] followed by a gradual and progressive decrease in IgE levels toward or to less than baseline levels that might continue to occur over several years. Clinical improvement occurs before subsequent decreases in IgE antibody levels, and it is clear that efficacy is not dependent on reductions in specific IgE levels.[53,54] Thus decreased levels of specific IgE do not explain the clinical response to immunotherapy.[55] Despite the persistence of significant levels of specific IgE antibody, immunotherapy usually results in a reduction in the release of mediators, such as histamine, from basophils and mast cells, a phenomenon most relevant to the immediate phase of allergic reactions. Suppression of late-phase inflammatory responses in the skin and respiratory tract generally also occur with allergen immunotherapy.[56-58]

An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, has also been associated with immunotherapy. Increased levels of allergen-specific IgA have been found in patients early in the course of immunotherapy.[35] The properties of allergen-specific IgA include the induction of IL-10 release from monocytes.[59] Although immunoreactive allergen-specific IgG levels increase, particularly IgG4 levels, the correlation between the increase in allergen-specific IgG levels and clinical improvement after immunotherapy has not been consistently demonstrated.[40,60,61] It is likely that immunotherapy alters either the affinity, specificity, or both of allergen-specific IgG.[62,63] During the initial phase of ultrarush VIT, a change in IgG specificity (ie, a change in the set of epitopes on wasp venom antigens dominantly recognized by IgG) occurred concomitantly with early clinical tolerance and was seen within 12 hours of ultrarush VIT ($P < .001$).[62] VIT resulted in a change

in IgG specificity to the major bee venom allergen phospholipase A_2 to a specificity similar to that seen in healthy nonallergic subjects.[63] This change in IgG specificity preceded the increase in IgG titers and was sustained for up to 6 months.[63]

Allergen-specific IgG induced after immunotherapy can block IgE-dependent histamine release and also IgE-facilitated antigen presentation to T cells.[64] This latter effect is dependent on allergen bound to IgE and the expression of either the low-affinity IgE receptor (CD23) on B cells, which then serve as antigen-presenting cells, or the high-affinity IgE receptor on dendritic cells, mast cells, and basophils.

Although serum immunoreactive specific IgG levels are not predictive, it is possible that functional assays of IgG, such as detection of IgG-associated serum inhibitory activity for IgE-facilitated allergen presentation, basophil histamine release, or both, might be more closely associated with the clinical response to immunotherapy, although this remains to be tested in larger clinical trials.[34,64]

A decrease in allergen-stimulated basophil histamine release has been demonstrated with immunotherapy, but it is not specific to the allergens administered.[65] Spontaneous *in vitro* release of histamine was also reduced after 4 months of immunotherapy.[66]

Immunotherapy induces an allergen-specific reduction in allergen-stimulated proliferation of PBMCs.[35,38] This was demonstrated after 70 days of SCIT to be induced by the release of IL-10 and TGF-β by $CD4^+CD25^+$ T lymphocytes.[35] The suppression of lymphocyte proliferation was accompanied by reduced release of IFN-γ, IL-5, and IL-13, indicating a suppression of both T_H1 and T_H2 lymphocyte populations. IL-10 is a general inhibitor of proliferation and cytokine responses in T cells while also inhibiting IgE and enhancing IgG4 production. TGF-β, on the other hand, induces an isotype switch to IgA, levels of which were also increased in the treated patients in this study. The IL-10 response has been shown to occur in the first few weeks of SCIT at allergen doses that are not clinically effective.[37] There is a suggestion that its secretion is not fully sustained by the end of a year of immunotherapy.[37,67]

Other studies of immunotherapy have demonstrated a decrease in the release of IL-4 and IL-13 but an increase in the release of IFN-γ from allergen-stimulated peripheral circulating T lymphocytes[68-70] or nasal mucosa.[41] After 4 years of immunotherapy, biopsies of the site of the late cutaneous reaction showed increased cells staining for mRNA for IL-12, a promoter of T_H1 differentiation of T lymphocytes.[42] The number of cells with mRNA for IL-12 correlated positively with the number staining for mRNA for IFN-γ and negatively with those staining for mRNA for IL-4 in the same biopsy specimens. Overall, the results are consistent with an early response to immunotherapy dominated by the generation of regulatory T lymphocytes that suppress both T_H1 and T_H2 responses but later a waning of this response and, instead, a dominance of immune deviation from T_H2 toward T_H1 responses to the administered allergen.

Many other changes in cells involved in the allergic response have been reported with SCIT. Numbers of B lymphocytes expressing the low-affinity IgE receptor (CD23) were increased in allergic asthmatic children, and their percentage in peripheral blood was reduced by immunotherapy.[71] Plasmacytoid dendritic cells from allergic patients showed a decreased IFN-α response to Toll-like receptor (TLR) 9 stimulation.[72] This was restored in patients on immunotherapy. Numbers of cells expressing the costimulatory molecules CD80 and CD86 were reduced at the site of the late-phase cutaneous reaction in subjects receiving immunotherapy.[73] It has not been determined whether these are primary to secondary responses to immunotherapy.

EFFICACY OF IMMUNOTHERAPY

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity

Summary Statement 6: Immunotherapy is effective for the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma, and stinging insect hypersensitivity. Therefore immunotherapy merits consideration in patients with these disorders as a possible treatment option. A

Many double-blind, placebo-controlled randomized clinical trials demonstrate a beneficial effect of immunotherapy under a variety of conditions.[74-81] Immunotherapy is effective for the treatment of allergic rhinitis[77] (including ocular symptoms[82]), allergic asthma,[74,79,81,83,84] and stinging insect hypersensitivity[78,85] and is effective in both adults and children.[86-92] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollens,[93-101] fungi,[102-107] animal allergens,[18,21,22,47,108-111] dust mites,[17,83,84,112-120] and cockroaches.[121] There have been no controlled trials of fire ant whole-body extract, but it does appear to be effective in uncontrolled trials.[122-124] A variety of different types of extracts have been evaluated in these clinical trials, including aqueous and modified extracts. Outcome measures used to measure the efficacy of immunotherapy include symptom and medication scores, organ challenge, and immunologic changes in cell markers and cytokine profiles. Several studies have also demonstrated a significant improvement in quality of life, as measured by using standardized questionnaires.[20,125-128] The magnitude of the effect depends on the outcome that is used. For dust mite, the effect size ranges from a 2.7-fold improvement in symptoms to a 13.7-fold reduction in bronchial hyperreactivity.[129]

Although many studies demonstrate the efficacy of immunotherapy, some do not. A review of the studies that do not demonstrate efficacy failed to identify a systematic deficiency.[80] Instead, this review notes that many studies evaluating immunotherapy are only marginally powered to show efficacy, making it likely that some would fail to demonstrate efficacy by chance alone, even when it is present (a type II error). Meta-analyses of the efficacy of immunotherapy both for rhinitis[77,130] and asthma[74,79,81,129] have been performed to address the issue of power. In one systematic review of 88 trials involving 3,459 asthmatic patients, SCIT resulted in significant reductions in asthma symptoms, medication use, and improvement in bronchial hyperreactivity.[74] This meta-analysis determined that it would have been necessary to treat 3 patients (95% CI, 3-5) with immunotherapy to avoid 1 deterioration in asthma symptom and 4 patients (95% CI, 3-6) with immunotherapy to avoid 1 patient requiring increased medication. These meta-analyses strongly support the efficacy of allergen immunotherapy.

Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued[93,131,132] and reduce the risk for the future development of asthma in patients with allergic rhinitis.[8,9,91,131-134] Allergen immunotherapy might also prevent the development of new allergen sensitivities in monosensitized patients.[135-138]

TABLE III. Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or asthma

Allergen immunotherapy should be considered for patients who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy might depend on a number of factors, including but not limited to: ● patient's preference/acceptability; ● adherence; ● medication requirements; ● response to avoidance measures; ● adverse effects of medications; ● coexisting allergic rhinitis and asthma; and ● possible prevention of asthma in patients with allergic rhinitis
Potential indication: atopic dermatitis, if associated with aeroallergen sensitivity:
Indications for allergen immunotherapy in patients with reactions to Hymenoptera stings: ● patients with a history of a systemic reaction to a Hymenoptera sting (especially if such a reaction is associated with respiratory symptoms, cardiovascular symptoms, or both) and demonstrable evidence of clinically relevant specific IgE antibodies; ● patients older than 16 years with a history of a systemic reaction limited to the skin and demonstrable evidence of clinically relevant specific IgE antibodies (patients ≤16 years of age who present with a history of only cutaneous symptoms to Hymenoptera stings usually do not require immunotherapy); and ● adults and children with a history of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.
Potential indication: for large local reactions in patients who have frequent and disabling large local reactions.

PATIENT SELECTION

Clinical indications for allergic rhinitis and allergic asthma

Summary Statement 7: Allergen immunotherapy should be considered for patients who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy might depend on a number of factors, including but not limited to patient's preference/acceptability, adherence, medication requirements, response to avoidance measures, and the adverse effects of medications. D

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic rhinitis.[77,130] Prospective, randomized, double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic asthma.[74,79,81,129] Allergen immunotherapy is an effective form of treatment for many allergic patients, provided they have undergone an appropriate allergy evaluation. The expected response to allergen immunotherapy is antigen specific and depends on the proper identification and selection of component allergens based on the patient's history, exposure, and diagnostic test results.

Aeroallergen immunotherapy should be considered for patients who have symptoms of allergic rhinitis, rhinoconjunctivitis, and/or asthma after natural exposure to allergens and who demonstrate specific IgE antibodies to relevant allergens (see Table III for indications for allergen immunotherapy). The severity and duration of symptoms should also be considered in assessing the need for allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. Time lost from work, emergency department or physician's office visits, and response to pharmacotherapy are important objective indicators of allergic disease severity. Symptoms interfering with sleep or work or school performance are other factors to be considered. The effect of the patient's symptoms on quality of life and responsiveness to other forms of therapy, such as allergen avoidance or medication, should also be factors in the decision to prescribe allergen immunotherapy. In addition, allergen immunotherapy should be considered if patients wish to avoid long-term pharmacotherapy. Unacceptable adverse effects of medications should favor one's decision to initiate allergen immunotherapy.

Immunotherapy does not appear to be more costly than pharmacotherapy over the projected course of treatment.[139-141] Allergen immunotherapy for allergic rhinitis has been shown to have persistent benefits after discontinuation and to reduce the risk for future development of asthma.[8-11,91,131-134]

Coexisting medical conditions should also be considered in the evaluation of a patient who might be a candidate for allergen immunotherapy. Patients with coexisting allergic rhinitis and asthma should be managed with an appropriate regimen of allergen avoidance measures and pharmacotherapy but might also benefit from allergen immunotherapy. However, the patient's asthma must be stable before allergen immunotherapy is administered.[142,143]

Atopic Dermatitis

Summary Statement 8: There are some data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. B

There are some data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[12,14,144] In a systematic review of immunotherapy for atopic dermatitis that included 4 comparable placebo-controlled studies involving a small number of patients, statistical analysis showed significant improvement in symptoms in patients with atopic dermatitis who received SCIT.[12] One randomized, double-blind study of adults with atopic dermatitis demonstrated a dose-response effect of dust mite immunotherapy on atopic dermatitis severity, as measured by using the SCORAD score ($P = .0378$) and topical corticosteroid use ($P = .0007$).[14] One open-label study of 25 patients with dust mite allergy and atopic dermatitis treated with dust mite SCIT demonstrated serologic and immunologic changes consistent with tolerance in addition to significant reductions in objective and subjective SCORAD scores.[13]

In addition, one double-blind, placebo-controlled study of 48 children with atopic dermatitis treated with dust mite SLIT reported a significant difference from baseline values in visual analog scores, SCORAD scores, and medication use only in the

mild-to-moderate severity group, whereas patients with severe disease had only a marginal benefit (see Summary Statements 93-95 for a further discussion of SLIT).[16]

Summary Statement 9: The potential for benefit in symptoms related to oral allergy syndrome with inhalant immunotherapy directed at the cross-reacting pollens has been observed in some studies but not in others. For this reason, more investigation is required to substantiate that a benefit in oral allergy symptoms will occur with allergen immunotherapy. C

The potential for benefit in symptoms related to oral allergy syndrome with cross-reacting inhalant immunotherapy, which includes the cross-reacting pollen or pollens, has been observed in some studies but not in others. One controlled prospective study demonstrated the potential to decrease oral allergy syndrome symptoms with SCIT directed against birch tree.[145] Another double-blind, double-dummy, placebo-controlled study comparing the effect of SCIT with SLIT demonstrated no significant effect on the severity of apple allergy symptoms with either method compared with the placebo group, despite a significant effect on seasonal hay fever symptoms and medication use and a decrease in IgE reactivity.[146] More investigation is required to substantiate the contention that benefits in oral symptoms will occur with immunotherapy.

Summary Statement 10a: Immunotherapy should be considered if the patient has had a systemic reaction to a Hymenoptera sting, especially if such a reaction was associated with respiratory symptoms, cardiovascular symptoms, or both and if the patient has demonstrable evidence of specific IgE. A

Systemic reactions to Hymenoptera stings, both flying and imported fire ants, especially when associated with respiratory symptoms, cardiovascular symptoms, or both and positive skin test or *in vitro* test results for specific IgE, are an indication for allergen immunotherapy.[85,147-150] In the United States patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Patients 16 years or younger who present only with a cutaneous reaction to Hymenoptera stings might not require immunotherapy.[151,152] In addition to allergen immunotherapy, patients with Hymenoptera sensitivity should be instructed in how to best avoid insect stings, be prescribed epinephrine, and be taught how and when to inject it.

Venom skin test results are positive in more than 65% of patients with a history of a systemic reaction to a Hymenoptera sting compared with 15% of those who have not had this type of a reaction.[153] In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific serum IgE is recommended.[154-156] If the venom-specific serum IgE test result is also negative, it is recommended that the skin tests, venom-specific serum IgE tests, or both be repeated 3 to 6 months later. Approximately 5% to 10% of patients with negative venom skin test results with a history of a systemic reaction have a positive venom-specific serum IgE test result.[153,157] There are no published results of the effectiveness of allergen immunotherapy in patients with negative skin test results and positive venom-specific IgE test results who have experienced systemic reactions resulting from a Hymenoptera sting. There are data to indicate that these patients might have another episode of anaphylaxis if they are restung. The chance of another systemic reaction to a sting is relatively small (5% to 10%) in adults with negative venom skin test results with a history of systemic reactions compared with the risk associated with positive venom skin test results (25% to 70%).[158] However, even though the risk is small, the reaction can be severe, and VIT is recommended for patients with negative venom skin test results and positive venom-specific serum IgE test results who have had severe anaphylaxis to an insect sting.[158]

Some patients who have negative venom-specific IgE test and skin test results are reported to have had subsequent systemic reactions to stinging insects.[155,156,159] Controlled studies designed to evaluate the efficacy of immunotherapy in these patients have not been performed. There are few anecdotal reports of patients with negative venom skin test results and negative venom-specific IgE test results being successfully treated with VIT if the selected venom is based on the results of a sting challenge. Generally, there are not sufficient data on the efficacy of immunotherapy in these patients to form conclusive recommendations.

The AAAAI Insect Committee's modified working guidelines state that a negative venom skin test result or *in vitro* assay result is not a guarantee of safety, and patients with suspected higher risk should be counseled about avoidance strategies, use of epinephrine injectors, and the emergency and follow-up care of the acute allergic reaction.[159] The AAAAI Insect Committee also acknowledged that the management of patients with a positive history and negative venom skin test results requires clinical judgment and ongoing research.

Several studies of patients with imported fire ant allergy demonstrate the effectiveness of immunotherapy with fire ant whole-body extracts.[122,123,160] Adults and children with a history of systemic reactions to the imported fire ant (*Solenopsis* species) who have positive skin test results or venom-specific IgE antibodies should be treated with allergen immunotherapy, although children 16 years or younger who have experienced only a cutaneous reaction to an imported fire ant sting might not require immunotherapy.

Although VIT is fundamentally similar to immunotherapy with inhalant allergens, there are a few noteworthy and unique features. Adverse effects are no greater in frequency or severity than with inhalant allergen immunotherapy (despite the more severe nature of the reaction to natural exposure). In contrast to inhalant rush immunotherapy, rush VIT is not associated with an increased incidence of systemic reactions. The maintenance dose and clinical protection can routinely be achieved with 8 weekly treatments, and even 2-day rush schedules can be used in most patients without an increased risk of systemic reactions. Unlike immunotherapy with inhalant allergens, the starting dose can be just 1/100 of the maintenance dose. Also, the recommended maintenance dose (100 μg of each venom) is expected to be achieved, regardless of LLRs or temporary delays caused by systemic reactions during VIT. In patients who cannot safely discontinue β-blockers but who have a history of moderate-to-severe sting-induced anaphylaxis, VIT is indicated because the risk of anaphylaxis related to a venom sting is greater than the risk of an immunotherapy-related systemic reaction.

Summary Statement 10b: Measurement of baseline serum tryptase level is recommended in patients with moderate or severe anaphylactic reactions to stings because its predictive value is useful regardless of the decision about VIT. Increased tryptase levels are associated with more frequent and more severe anaphylactic reactions to stings, as well as greater failure rates with VIT and greater relapse rates after stopping VIT. B

Measurement of baseline serum tryptase levels is recommended in patients with moderate or severe anaphylactic reactions to stings. They can be increased in more than 10% of cases and in more than 20% of those with marked hypotension.[161] An increased level of baseline serum tryptase in patients with moderate-to-severe insect sting–induced anaphylaxis is also an indicator for a possible clonal mast cell disorder, including mastocytosis.[162] Measurement of baseline serum tryptase concentrations might also identify patients with a high risk for side effects during vespid VIT. Higher baseline tryptase levels correlated with a greater frequency of severe systemic reactions during the vespid VIT build-up phase.[163] Increased baseline serum tryptase levels are associated with an increased frequency of systemic reactions to VIT injections, a greater failure rate during VIT, and a greater relapse rate (including fatal reactions) if VIT is discontinued.[162,164,165]

Summary Statement 11: Large local reactions (LLRs) to insect stings can cause significant morbidity and impair quality of life. VIT might significantly reduce the size and duration of LLRs and might be considered in patients who have frequent and disabling LLRs, particularly those with occupational exposure. B

A 4-year controlled trial designed to examine the efficacy of VIT in reducing the size and duration of large local sting reactions demonstrated significant reductions in both parameters in patients with a history of large local sting reactions.[166] Twenty-nine patients with LLRs confirmed on sting challenge (≥16 cm) were assigned to receive VIT or no treatment. There was a 42% reduction in size and a 53% reduction in duration of the large local sting reactions after 7 to 11 weeks of VIT.[166] There was further improvement after 2 years of treatment that was maintained through 4 years of VIT, with a 60% reduction in size and a 70% reduction in the duration of the LLRs.

Conditions for which immunotherapy is investigational

Food hypersensitivity. Summary Statement 12: Clinical trials do not support the use of subcutaneous immunotherapy for food hypersensitivity. A

Summary Statement 13: The safety and efficacy of oral and sublingual immunotherapy for food hypersensitivity is currently investigational. NR

The use of allergen immunotherapy for subjects with the potential for IgE-mediated reactions (anaphylaxis) to foods should be regarded as investigational at this time.[167-170] There are studies demonstrating efficacy in food hypersensitivity, the first using aqueous subcutaneous injections of peanut.[170,171] Studies with SLIT with hazelnut[172] and milk[173] and oral immunotherapy with peanut,[174] egg,[175,176] and milk[176-178] have demonstrated increased tolerance to these foods (see Summary Statement 103 for further discussion).

In the subcutaneous peanut immunotherapy study there was increased tolerance to oral peanut challenge in all of the treated patients, but there were repeated systemic reactions in most patients, even during maintenance injections, and the authors concluded that a modified peanut extract is needed for clinical application of this method of treatment.[170] There are no FDA-approved formulations for oral immunotherapy or SLIT, and this route of allergen immunotherapy is considered investigational at this time.

Conditions for which immunotherapy is not indicated

Urticaria and angioedema. Summary Statement 14: Clinical studies do not support the use of allergen immunotherapy for chronic urticaria, angioedema, or both. Therefore allergen immunotherapy for patients with chronic urticaria, angioedema, or both is not recommended. D

There is no allergic basis for the vast majority of patients with chronic urticaria or angioedema. There is no evidence supporting the efficacy of immunotherapy for subjects with chronic urticaria, angioedema, or both.

Measures of efficacy

Summary Statement 15: Clinical parameters, such as symptoms and medication use, might be useful measures of the efficacy of immunotherapy in a clinical setting; however, repetitive skin testing of patients receiving immunotherapy is not recommended. A

Whether immunotherapy is effective can be determined by measuring objective and subjective parameters.[179] Objective measures, such as an increase in allergen-specific IgG levels and decreased skin test reactivity, as measured by means of skin test titration, are changes generally associated with effective immunotherapy but, at present, are not practical for routine clinical use.[115] Nonquantitative skin testing or serum specific IgE antibody testing of patients during immunotherapy is not recommended because it has not been demonstrated that skin test reactivity (to a single dilution) or specific IgE antibody levels correlate closely with a patient's clinical response. For that reason, most allergists rely on subjective assessments, such as a patient's report that he or she is feeling better during a season previously causing symptoms. Although subjective assessments are the most common means by which physicians judge the result of immunotherapy, they might not be reliable, given the strong placebo-like effect (Hawthorne effect) associated with any treatment.

A more objective means for determining efficacy, which has been validated in controlled clinical studies, is the use of clinical symptom scores and the amount of medication required to control symptoms, maintain peak flow rates or pulmonary function test results within acceptable limits, or both. Successful immunotherapy often results in a reduction in medication use, as well as improvement in symptoms. Guidelines for allergen immunotherapy clinical trials recommend that the combined symptom-medication score be used as the primary outcome measure.[180,181] These guidelines also provide examples of scoring systems for measuring symptoms (eg, a 4-point rating scale, where 0 = absent to 3 = severe) and medication use (a point system that might vary with type of medication and duration of use).[180,181] Sequential measurements of disease-specific quality of life also might be helpful.[179,181]

Special precautions in patients with asthma

Summary Statement 16: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. C

Patients with severe or uncontrolled asthma are at increased risk for systemic reactions to immunotherapy injections.[142,143,182]

TABLE IV. Actions to reduce immunotherapy risk

- Assess the patient's general medical condition at the time of injection (eg, recent asthma exacerbation and increased asthma symptoms).
- In addition to assessing asthma symptoms, consider obtaining a PEF for patients with a history of asthma before administration of the injection. The intention of assessing PEF is to alert the provider to the need for a more in-depth assessment of asthma control. If the PEF is substantially reduced compared with the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.
- The patient should not receive his or her immunotherapy injection if his or her asthma is poorly controlled.
- Adjust the immunotherapy dose or injection frequency if symptoms of anaphylaxis occur and immunotherapy is continued.
- Use appropriately diluted initial allergen immunotherapy extract in patients who appear to have increased sensitivity on the basis of history or tests for specific IgE antibodies.
- Instruct patients to wait in the physician's office/medical facility for 30 minutes after an immunotherapy injection. Patients at greater risk of reaction from allergen immunotherapy (eg, patients who have previously had a systemic reaction) might need to wait longer.
- Educate the patient on signs and symptoms of systemic reactions and instruct them to report symptoms immediately if in the office/medical facility or to report any delayed systemic reactions to his or her physician.
- Ensure procedures to avoid clerical or nursing errors (eg, careful checking of patient identification).
- Recognize that dosage adjustments downward are usually necessary with a newly prepared allergen immunotherapy extract or a patient who has had a significant interruption in the immunotherapy schedule.

PEF, Peak expiratory flow rate measurement.

Three surveys found that fatal and near-fatal reactions (NFRs) from immunotherapy injections were more common in patients with severe/labile asthma.[143,183-185] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2] Assessment of asthma control should be considered at each injection visit (Table IV).

SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

Allergen immunotherapy in children

Summary Statement 17: Immunotherapy for children is effective and well tolerated. It has been shown to prevent the new onset of allergen sensitivities in monosensitized patients, as well as progression from allergic rhinitis to asthma. Therefore immunotherapy should be considered along with pharmacotherapy and allergen avoidance in the management of children with allergic rhinitis/rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. B

Immunotherapy for children has been shown to be effective and well tolerated,[106,186,187] although at least 1 study did not show efficacy.[188] However, this study did not include an important allergen, cockroach, which has been shown to correlate with asthma severity in other studies of inner-city asthmatic children.[189] In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (Table III). Studies of children receiving allergen immunotherapy have demonstrated significant:

- improvement in symptom control for asthma[86,88,90,91] and allergic rhinitis[87];
- increase in PC_{20} to histamine[90];
- increase in PC_{20} to cat and house dust mite allergens[17,90];
- decrease in the risk of asthma[8,9,132-134,190];
- decrease in the development of new sensitivities[135,136,138];
- modification in the release of mediators in children receiving immunotherapy that correlates with decreased clinical symptoms[92]; and
- reduction in pharmacy, outpatient, and total health care costs.[139,140]

Summary Statement 18: Immunotherapy can be initiated in young children. Indications are similar to those of other age groups. D

Although there is some disagreement about the role of allergen immunotherapy in children younger than 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.[86,91] In children with allergic rhinitis, allergen immunotherapy might prevent asthma.[8,9,132-134] However, allergen immunotherapy for inhalant allergens is usually not considered in infants and toddlers because (1) there might be difficulty in communicating with the child regarding systemic reactions and (2) injections can be traumatic to very young children. Therefore each case should be considered individually by weighing the benefits and risks. For children who have had a history of anaphylaxis to stinging insects or have severe allergic disease, the benefits of allergen immunotherapy might outweigh the risks.

Immunotherapy can be initiated in young children less than 5 years of age if indicated. Indications should be based on the severity of the disease, risk/benefit ratios, and the ability of the physician to correlate the clinical presentation with appropriate and obtainable allergy testing. There have been several reports of efficacy and safety with immunotherapy in children as young as 3 years. A randomized, double-blind, placebo-controlled study assessing the efficacy of grass pollen–specific allergen immunotherapy over 2 pollen seasons showed that immunotherapy was effective for childhood seasonal allergic asthma in children aged 3 to 16 years.[191] The subjects were children sensitized to grass pollen and requiring at least 200 μg of inhaled beclomethasone equivalent per day. The primary outcome measure was a combined asthma symptom-medication score during the second pollen season. Secondary outcome measures included end point titration skin prick testing, conjunctival and bronchial provocation testing to allergen, sputum eosinophilia, exhaled nitric oxide, and adverse events. Of the 39 patients enrolled, 35 provided data. In the SCIT-treated group there was a substantial reduction in asthma symptom-medication scores compared with those seen in the placebo group ($P = .04$). There was also a significant decrease in cutaneous ($P = .002$), conjunctival ($P = .02$), and bronchial ($P = .01$) reactivity to allergen in the SCIT group compared with that seen in the placebo group. The 2 groups had similar levels of airway inflammation, despite a trend toward less inhaled steroid use in the active group. No serious adverse events were reported, and no subjects withdrew because of adverse events.

Another study examined the safety of immunotherapy in 239 children less than 5 years of age.[192] Immunotherapy was

prescribed according to the immunotherapy guidelines of the World Health Organization (except for age). In this prospective study there was 1 systemic reaction among 6,689 injections in 239 patients, with 18 children younger than 2 years, 29 between the ages of 2 and 3 years, 33 between the ages of 3 and 4 years, and 52 between the ages of 4 and 5 years. The systemic reaction occurred in a 3-year-old with severe allergic rhinitis after 1 AU of mite mix. Generalized urticaria and rhinitis occurred 1.5 hours after the injection and were "easily" treated with epinephrine and an antihistamine medication. The authors conclude as follows: "We consider specific immunotherapy in patients less than five years of age to be a safe treatment that should increase research of its efficacy and preventive effects against asthma and new sensitizations."

Young children have been thought to present problems unique to their age with regard to immunotherapy and complications. However, young children seldom present difficulties in the diagnosis of a systemic reaction, and there have been no studies that indicate that children are more at risk to conventional SCIT.[193]

Summary Statement 19: In patients who otherwise have the indication for specific immunotherapy, there is no absolute upper age limit for initiation of immunotherapy. D

Immunotherapy can be considered in the treatment of patients of all ages, and the risk/benefit assessment must be evaluated in every situation. Some patients might be taking medications that could make treatment of anaphylaxis with epinephrine more difficult, such as β-blockers, or might have significant comorbid medical conditions, such as hypertension, coronary artery disease, cerebrovascular disease, and/or cardiac arrhythmias. Some of these conditions can occur more frequently in older subjects.

However, immunotherapy can provide significant benefits in the older adult population and should be considered if the appropriate indications are present and there are no significant comorbid conditions. A study that compared the clinical efficacy of immunotherapy in 2 age populations (>54 years vs <54 years) found a similar reduction in medication use and improvement in symptoms in the 2 age groups.[194]

The patient's age alone should not preclude the consideration of allergen immunotherapy, and clinical benefits have been reported.

Immunotherapy in pregnancy

Summary Statement 20a: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. C

Summary Statement 20b: If pregnancy occurs during the build-up phase and the patient is receiving a dose unlikely to be therapeutic, discontinuation of immunotherapy should be considered. D

The physician must be aware of the benefits versus potential risks of immunotherapy in pregnant patients. Allergen immunotherapy is usually not initiated during pregnancy because of concerns about the potential adverse effects of systemic reactions and their resultant treatment on the fetus, mother, or both (eg, spontaneous abortion, premature labor, or fetal hypoxia).[195] If pregnancy occurs during the build-up phase and the patient is receiving a dose unlikely to be therapeutic, discontinuation of immunotherapy should be considered.

There have been no large prospective studies investigating the safety of immunotherapy in pregnancy. However, several retrospective studies suggest that there is no greater risk of prematurity, fetal abnormality, or other adverse pregnancy outcome in women who receive immunotherapy during pregnancy.[195,196]

One retrospective study of the allergy clinic records of 109 pregnant patients who received immunotherapy and 60 pregnant patients who refused immunotherapy revealed a higher incidence of abortion, prematurity, and toxemia in the group that did not receive immunotherapy compared with the immunotherapy group.[196]

Another retrospective study of 121 pregnancies in atopic patients who had received immunotherapy during pregnancy found the incidence of prematurity, toxemia, abortion, neonatal death, and congenital malformation was no greater than that for the general population.[195] The incidence of these adverse events was also similar to that seen in a group of 147 pregnancies in atopic patients who did receive immunotherapy, except for a greater incidence of abortion in the untreated group. Similar safety was demonstrated with VIT during pregnancies.[197]

In addition to improving the pregnant patient's allergic condition, 2 studies suggest that allergen immunotherapy might prevent allergic sensitization in the child.[198,199] One demonstrated an absence of allergen-specific IgE in paired cord blood,[199] and the other demonstrated an inhibitory effect on immediate skin reactivity to grass allergens in some of the offspring.[198]

Both studies showed similar levels of allergen-specific IgG in paired cord blood and maternal blood samples.[198,199] More research is needed to elucidate the effect of allergen immunotherapy during pregnancy on the subsequent development of allergen sensitization in the child.

Allergen immunotherapy maintenance doses can be continued during pregnancy. The initiation of immunotherapy might be considered during pregnancy when the clinical indication for immunotherapy is a high-risk medical condition, such as anaphylaxis caused by Hymenoptera hypersensitivity. When a patient receiving immunotherapy reports that she is pregnant, the dose of immunotherapy is usually not increased.

The recommended precautions for the prevention of adverse reactions are important in the pregnant patient because of the possible effect on the fetus, as well as the patient (see Table IV on reducing immunotherapy risk).

There is no evidence of an increased risk of prescribing or continuing allergen immunotherapy for a mother while breastfeeding and no risk for the breast-fed child.

Immunotherapy in patients with immunodeficiency and autoimmune disorders

Summary Statement 21: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. C

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with immunodeficiency or autoimmune disorders. Concern about the increased risk of immunotherapy in such patients is largely hypothetical.

A review article suggested guidelines for treatment of HIV-positive patients who meet the criteria for allergen immunotherapy. Immunotherapy was recommended for pollen and mite allergy in patients who have early to middle HIV disease, which is defined as a peripheral CD4 count of 400 or more cells/μL with no history of opportunistic infections or other AIDS-associated pathology and no evidence of plasma HIV viremia.[200] Close monitoring is recommended monthly for the first 3 months and then

quarterly. Cases of allergen immunotherapy in patients with HIV controlled with highly active antiretroviral therapy are reported.[201,202] In 1 case report, allergen immunotherapy appeared to induce a transient T-cell proliferation and modest increase in RNA viral load, which resolved with highly active antiretroviral therapy.[201] In another patient a 3.5-year course of immunotherapy for tree pollen–induced allergic rhinitis was successful in reducing the reported visual analog scale for subjective symptoms and medication use by almost 90%.[202] During therapy, his CD4 cell count remained greater than 350 cells/μL, and his HIV RNA level remained less than 50 copies/mL. His symptoms remained well controlled 3 years after discontinuation of immunotherapy.

Although concern about the safety of allergen immunotherapy in patients with autoimmune disorders has been raised in the past, there is no substantive evidence that such treatment is harmful in patients with these diseases. Therefore the benefits and risks of allergen immunotherapy in patients with HIV infection, other immunodeficiencies, or autoimmune disorders must be assessed on an individual basis.

FOLLOW-UP CARE AND DURATION OF TREATMENT

Continuing care

Time course of improvement. Summary Statement 22: Clinical and physiological improvement can be demonstrated very shortly after the patient reaches a maintenance dose. A

Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose.[20,103,111,203] One study of patients with cat allergy who achieved the maintenance dose in 5 weeks with a cluster schedule reported the results of titrated nasal allergen challenge, titrated skin prick testing, and allergen-specific IgG4 measurement with cat immunotherapy at 5 weeks were predictive of the response at 1 year.[22]

Improvement might not be observed for several reasons, including (1) failure to remove significant allergenic exposures (eg, a cat in the household), (2) exposure to high levels of allergen, (3) continued exposure to nonallergen triggers (eg, tobacco smoke), (4) incomplete identification and treatment of clinically relevant allergens, or (5) failure to treat with adequate doses of each allergen. If clinical improvement is not apparent after 1 year of maintenance therapy, possible reasons for lack of efficacy should be evaluated. If none are found, discontinuation of immunotherapy should be considered, and other treatment options should be pursued.

Follow-up visits. Summary Statement 23: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. D

Patients should be evaluated at least every 6 to 12 months while receiving immunotherapy:

- to assess efficacy;
- to implement and reinforce its safe administration and to monitor adverse reactions;
- to assess the patient's compliance with treatment;
- to determine whether immunotherapy can be discontinued; and
- to determine whether adjustments in the immunotherapy dosing schedule or allergen content are necessary.

Patients might need more frequent office visits for evaluation and management of immunotherapy (eg, treatment of local reactions, systemic reactions, or both or changes in their immunotherapy vials or lots) or changes in the management of underlying allergic disease or comorbid conditions.

Duration of treatment. Summary Statement 24: The patient's response to immunotherapy should be evaluated on a regular basis. A decision about continuation of effective immunotherapy should generally be made after the initial period of 3 to 5 years of treatment. Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. The severity of disease, benefits sustained from treatment, and convenience of treatment are all factors that should be considered in determining whether to continue or stop immunotherapy for any individual patient. D

The patient's response to immunotherapy should be evaluated on a regular basis. The severity of disease, benefits obtained from treatment, and convenience of treatment are all factors that should be considered in determining whether to continue or stop immunotherapy for any patient. If allergen immunotherapy is effective, treatment might be continued for longer than 3 years, depending on the patient's ongoing response to treatment. Some patients experience a prolonged remission after discontinuation, but others might relapse after discontinuation of immunotherapy. Therefore the decision to continue or stop immunotherapy must be individualized.

Summary Statement 25: Although there are no specific tests to distinguish which patients will relapse after discontinuing VIT, there are clinical features that are associated with a higher chance of relapse, notably a history of a very severe reaction to a sting, an increased baseline serum tryptase level, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. C

There have been few studies designed specifically to look at the question of when to discontinue effective allergen immunotherapy or the duration of immunotherapy efficacy after termination of treatment. The duration of allergen immunotherapy efficacy has probably been most extensively studied in Hymenoptera hypersensitivity. Long-term follow-up studies suggest that a 5-year immunotherapy treatment course for Hymenoptera hypersensitivity might be sufficient for most allergic subjects.[204-206] However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported.[205,206] Nevertheless, systemic reactions to stings after discontinuing VIT are generally much milder than pretreatment reactions and are rarely severe.

There are conflicting data on the optimal duration of VIT. Two studies did not find a difference in relapse rates between the patients treated for 3 years compared with those treated for 5 years,[205,207] but the limited number of patients who were treated for 3 years or less in one study did not allow for any conclusions regarding the risk of stopping therapy after 3 years of treatment.[205] Two studies reported better outcomes in terms of re-sting reactions in patients who received 4 or more years of VIT compared with those who received shorter treatment courses.[206,208]

Change in skin test reactivity does not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who had a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE.[207,209] Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment.[209]

The relapse rate and the frequency of severe reactions are greater in patients who had a history of very severe reactions to stings before treatment, those with increased baseline tryptase levels, those who had systemic reactions during VIT (to a sting or a venom injection), those with honeybee allergy, and those who had less than 5 years of treatment.

Summary Statement 26: At present, 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 duration of treatment should be determined by the physician and patient after considering the risks and benefits associated with discontinuing or continuing immunotherapy. D

The duration of aeroallergen immunotherapy efficacy has not been as extensively studied as that for VIT.[210] Some studies suggest that a 3- to 5-year treatment duration is sufficient for inhalant allergen immunotherapy, but others have reported a significant relapse rate within 3 years of discontinuing allergen immunotherapy.

One prospective controlled study was designed to study the immunotherapy relapse rate during the 3-year period after discontinuation of immunotherapy in 40 asthmatic patients who had been treated with immunotherapy with a standardized dust mite *(Dermatophagoides pteronyssinus)* extract for 12 to 96 months.[89] Fifty-five percent of the patients relapsed. The duration of efficacy was related to the reduction of skin test reactivity at the end of immunotherapy treatment ($P = .003$) and the duration of immunotherapy treatment. The relapse rate was 62% in the group treated for less than 35 months compared with 48% in the group treated for greater than 36 months ($P = .04$). Prolonged clinical efficacy was demonstrated in a double-blind, placebo-controlled study of patients with severe grass pollen–induced allergic rhinitis who had been treated for 3 to 4 years with immunotherapy.[93] There was a switch to placebo in half the group (16 patients) after 3 to 4 years of immunotherapy, and efficacy parameters were monitored over the next 3 years. Seasonal symptom scores and the use of rescue medication remained low for 3 to 4 years after the discontinuation of immunotherapy, and there was no significant difference between patients who continued and those who discontinued immunotherapy. Similar sustained clinical benefits with accompanying immunologic changes in grass pollen–specific serum IgG4 levels and IgE-blocking factor were demonstrated 1 year after discontinuation of a 3-year course of grass pollen tablets in one double-blind, placebo-controlled study of 257 patients with allergic rhinitis.[211]

Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained clinical remission after discontinuing inhalant immunotherapy. Therefore the duration of treatment should be determined by the physician and patient after considering the benefits and risks associated with discontinuing or continuing inhalant immunotherapy.

A form to document indications for continuation of immunotherapy can be found at www.aaaai.org, www.jcaai.org, or www.acaai.org.

SAFETY OF IMMUNOTHERAPY

Local reactions

Summary Statement 27: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with a greater frequency of large local reactions might be at an increased risk for future systemic reactions. C

In a survey of 249 patients undergoing immunotherapy, 71% reported experiencing a local reaction.[212] Of the patients experiencing local reactions, 84.7% reported reactions smaller than the palm of the hand, and 81.9% deemed local reactions not to be bothersome at all or only slightly bothersome. Ninety-six percent of the local reactors stated they would not stop immunotherapy because of the local reactions.

Local reactions associated with allergen immunotherapy are fairly common, with a frequency ranging from 26% to 82% of patients and 0.7% to 4% of injections.[213-215] Two retrospective studies compared the effect of not adjusting the immunotherapy dose based on LLRs on the immunotherapy systemic reaction rate with dose-adjustment protocols.[215,216] Both studies found no statistical difference between the dose-adjustment and no-dose-adjustment protocols in terms of immunotherapy-induced systemic reactions. Both authors concluded that local reactions were poor predictors of subsequent systemic reactions at the next injection, and dose reductions for most local reactions are unnecessary.

However, a retrospective review of a large, multicenter allergy practice group's database comparing the frequency of LLRs (defined as ≥25 mm) in patients who had experienced systemic reactions with age-, sex-, and allergen sensitivity–matched control subjects who had not had allergen immunotherapy–induced systemic reactions found the rate of LLRs was 4 times higher among the 258 patients who had experienced a systemic reaction compared with those who had never experienced a systemic reaction.[217] Patients who had experienced systemic reactions had LLRs in 35.2% of visits compared with 8.9% of visits in the matched control group without systemic reactions (difference between groups, $P < .001$). Individual LLRs were not predictive of future systemic reactions, but LLRs preceded systemic reactions in approximately one third of the systemic reactions. These differences suggest that subjects with a greater frequency of LLRs might be at greater risk for systemic reactions. Of note, it was the policy of this practice group to repeat the dose for LLRs between 25 and 30 mm size and reduce the dose for LLRs between 30 and 50 mm.

A case-cohort study based on a 3-year retrospective chart review of patients receiving imported fire ant immunotherapy identified LLRs, "…defined as local reactions larger than the patient's palm (average adult, 8-10 cm)," as a risk factor for a systemic reaction to imported fire ant immunotherapy (odds ratio, 34.5; 95% CI, 6.52-182).[218]

Prospective studies investigating the sensitivity and specificity of LLRs and the effect of immunotherapy protocol modifications based on them are needed.

Summary Statement 28: Local reactions were found to not predict local reactions at the next injection in a retrospective study. C

A 12-month study at a single site demonstrated that local reactions did not predict local reactions at the next injection.[219] The clinic did not perform routine dose adjustments for local reactions and did not control for antihistamine use. A total number of 9,678 injections were administered to 360 patients. Small local reactions (the size of the patient's palm or less), LLRs (larger than the patient's palm), and whether a local reaction was followed by a local reaction were recorded. At least 1 local reaction was experienced by 78.3% of patients, and 7.5% had an LLR. The total

local reaction rate was 16.3% per injection, the small local reaction rate was 15.9%, and the LLR rate was 0.4% per injection. Overall, 27% of all local reactions were followed by another local reaction, whereas 6% of LLRs were followed by a subsequent LLR. The sensitivity and positive predictive value for a local reaction predicting a local reaction at the next injection were 26.2% and 27.2%, respectively. The sensitivity, positive predictive value, and specificity for an LLR predicting an LLR at the subsequent injection were 5.2%, 6.0%, and 99.6%, respectively.

This study suggests that local reactions do not predict local reactions at the next immunotherapy injection.

Summary Statement 29: Glycerin concentrations of up to 50% were not associated with significantly higher local reaction rates. Higher glycerin concentrations are associated with injection pain, which correlates with the total amount of glycerin injected. C

Glycerin is a preservative used in allergen extracts that might have some irritant properties that can produce injection pain. Despite its irritating properties, a 1-year retrospective study at a single site demonstrated that higher glycerin concentrations (even 50%) were not associated with significantly higher small or LLR rates.[220] Small local reaction (the size of the patient's palm or less) but not LLR (larger than size of the patient's palm) rates increased with higher allergen concentration, number, and volume. The study also demonstrated that although small local reactions increased with allergen content, LLRs did not.[220]

Local reaction rates were similar for aeroallergen, flying Hymenoptera, and imported fire ant injections. Because flying Hymenoptera did not contain any glycerin and had comparable local reaction rates, this, along with the aforementioned findings, suggests that the allergen content and the not the glycerin plays a larger role in the cause of local reactions. This study suggests that LLRs are not associated with the glycerin concentration or allergen content of immunotherapy extracts. However, a prospective study demonstrated that pain associated with glycerin increases in proportion to glycerin concentration and injection volume.[221] The glycerin concentrations in this study ranged from 0% to 30%, and the volume injected ranged from 0.1 to 1.0 mL. Although clinically important pain was unusual when the injected total dose of glycerin (volume × concentration) was less than 0.05 mL, the frequency of bothersome pain increased as the total glycerin dose increased. The extract manufacturers' package insert advises care when administering a volume greater than 0.2 mL of an extract in 50% glycerin because of the potential discomfort and pain it might cause.

Management of LLRs

Summary Statement 30: Antihistamines have been demonstrated to be beneficial in decreasing local reactions during cluster and rush protocols, whereas leukotriene antagonists were shown to be effective in a rush protocol. Although commonly used, the effect of these medications in reducing local reactions during conventional build-up and maintenance immunotherapy injections has not been extensively reported. A

Oral antihistamines are effective in decreasing local reactions during cluster regimens[222] and rush protocols with VIT.[223-225] One study that demonstrated a decrease in the frequency of LLRs with fexofenadine premedication found no additional benefit with the addition of the H2 antihistamine ranitidine.[225]

The only other drug class studied for immunotherapy local reaction prevention are the leukotriene antagonists. A double-blind, placebo-controlled pilot study of 15 patients that compared the effect of placebo, montelukast, or desloratadine premedication on local reactions with rush VIT demonstrated a significant delay in the onset and decrease in the size of local reactions in the montelukast group compared with the placebo group, whereas there was no difference between the desloratadine and placebo groups in these parameters.[226]

Systemic reactions

Summary Statement 31: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. A

The prevalence of severe systemic reactions after allergen immunotherapy ranges from less than 1% of patients receiving conventional immunotherapy to greater than approximately 34% of patients in some studies of rush immunotherapy.[182,227-229] A review of the SCIT systemic reaction rates reported in studies published within the past 15 years found that the percentage of systemic reactions per injection with conventional schedules is approximately 0.2%.[230]

In a 2006 survey of allergen immunotherapy–induced fatal reactions and NFRs sent to physician members of the AAAAI, 273 of 646 respondents reported NFRs during the period of 1990 to 2001.[185] The incidence of unconfirmed NFRs was 23 per year (5.4 events per million injections). Administration during the height of the pollen season (46% of respondents) and immunotherapy dosing errors (25% of respondents) were cited as the 2 most important contributing factors in the NFRs. The most severe NFR was respiratory failure (10% of NFRs). One patient with an NFR was receiving a β-blocker, and none were taking concomitant ACE inhibitors. Ninety-three percent of the NFRs occurred in clinics staffed by allergists, and none occurred in medically unsupervised settings.

In a retrospective analysis of the incidence and characteristics of nonfatal SCIT-induced systemic reactions in 435,854 injections administered to 4,000 patients over a 20-year period (1981-2000), there were 115 systemic reactions (5.2% of patients and 0.06% of injections) in the first 10 years and 26 systemic reactions (1.08% of patients and 0.01% of injections) in the second 10 years.[231,232] There were significantly less asthma and urticaria reactions in the second period.[232]

In a prospective multicenter study there were 53 systemic reactions in 17,526 doses administered to 423 patients (0.3% per injection and 3.7% of patients).[233] All systemic reactions were mild to moderate and responded well to treatment. Five patients experienced more than 3 systemic reactions (total of 36 reactions), and the authors noted that 40% of the systemic reactions would have been avoided if patients experiencing the third systemic reaction had been withdrawn.

In the previously mentioned AAAAI physician members' survey of fatal reactions and NFRs from immunotherapy injections, there were 41 fatalities identified in the initial brief survey.[143] The estimated fatality rate was 1 per 2.5 million injections (average of 3.4 deaths per year), which is similar to 2 previous surveys of AAAAI physician members.[183,184] In a subsequent 3-year AAAAI/ACAAI Immunotherapy Safety Surveillance study, data were provided by 806 practices representing 1922 SCIT prescribers (>50% response

rate).[234] There were no fatalities reported in 2008 for the approximately 8.1 million injections administered, although respondents voluntarily reported 6 SCIT fatalities from 2001 to 2007 that occurred in other practices.

Therefore although severe systemic reactions to allergen immunotherapy are uncommon, serious systemic reactions (some fatal) can occur.

Summary Statement 32: An assessment of the patient's current health status should be made before administration of the allergy immunotherapy injection to determine whether there were any health changes that might require modifying or withholding that patient's immunotherapy treatment. Poorly controlled asthma has been identified as a risk factor for a severe immunotherapy-induced reaction. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma symptoms. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. B

In the AAAAI's survey of physician members on immunotherapy- and skin testing–induced fatal reactions and NFRs during the period of 1990-2001, 15 of the 17 fatalities occurred in patients with asthma, and in 9 patients not optimally controlled asthma was considered the susceptibility factor that contributed to the fatal outcome.[143] The most severe NFR, respiratory failure, occurred exclusively in asthmatic patients, and 4 (57%) of 7 asthmatic patients had a baseline FEV_1 of less than 70% of predicted value.[185]

In the most comprehensive evaluation of fatalities associated with allergen immunotherapy (1945-1987), there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[184] Sufficient information for complete analysis was provided for 30 patients. Ten fatalities occurred during seasonal exacerbation of the patient's disease, 4 in patients who had been symptomatic at the time of the injection, 2 of whom had been receiving β-adrenergic blockers. Of the 24 fatalities associated with immunotherapy, 4 had experienced previous reactions, 11 manifested a high degree of sensitivity, and 4 had been injected with newly prepared extracts.

In a prospective study of 125 asthmatic patients with mite allergy that used a 3-day rush immunotherapy protocol, FEV_1 was identified as a predictor for systemic reactions.[182] In this study 73.3% of the patients with an FEV_1 of less than 80% of predicted value experienced an asthma reaction during rush immunotherapy, whereas only 12.6% of patients with an FEV_1 of greater than 80% of predicted value had asthmatic reactions ($P < .0001$).The authors noted that if the patients with an FEV_1 of less than 80% of predicted value had been excluded from the study, the systemic reaction rate would have been 19.7% instead of 36%. These studies suggest that labile asthma, severe asthma, or both is a risk factor for immunotherapy.

In addition to symptomatic asthma and injections administered during periods of exacerbation of symptoms, other risk factors for immunotherapy that have been identified include the presence of a high degree of hypersensitivity, use of β-blockers, injections from new vials, and dosing errors.[31] With the exception of dosing errors and a high degree of hypersensitivity, these risk factors can be minimized by performing a preinjection health screen before the administration of the allergy immunotherapy injection. This preinjection evaluation might include a health inquiry administered verbally or as a written questionnaire directed to determine whether there were any health changes that might require modifying or withholding that patient's immunotherapy treatment. The preinjection health inquiry might include questions regarding the presence of asthma symptom exacerbation, β-blocker use, change in health status (including pregnancy), or an adverse reaction to the previous allergen immunotherapy injection. The preinjection evaluation might also include a peak flow measurement to assess the airway function of asthmatic patients (an example of a written preinjection questionnaire can be found in the members section of www.aaaai.org).

A patient's asthma must be stable before the allergen immunotherapy injection is administered, and patients with significant systemic illness generally should not receive an allergy immunotherapy injection.

Timing of anaphylactic reactions to immunotherapy injections

Summary Statement 33: The majority of safety data on allergen immunotherapy reactions are in the context of 30 minutes. Because most serious systemic reactions from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office/medical clinic for at least 30 minutes after the immunotherapy injection. C

A review of the literature indicates that most systemic reactions occur within 30 minutes after an injection.[230,235] Although some studies reported up to 50% of systemic reactions occurring after 30 minutes,[236-238] almost all severe systemic reactions (equivalent to grade 4 in the World Allergy Organization SCIT Systemic Reaction Grading System, Table V) began within 30 minutes after the injection.[235,236,239]

In a review of 14 studies that reported immunotherapy systemic reaction rates published between 1995-2009, 10 of 12 studies that reported the timing of the system reactions reported the incidence in terms of greater than or less than 30 minutes (see Table E3 in this article's Online Repository at www.jacionline.org).[230] The other 2 studies reported systemic reaction timing as an average and a range: one reported an average time of systemic reactions as 20 minutes (range, 1-60 minutes), and the other reported that 6 reactions occurred between 20 and 55 minutes. Few studies have provided comparative safety data on the incidence of systemic reactions in the first 20 minutes versus the 20- to 30-minute time period.

In the AAAAI's fatal reaction and NFR surveys previously discussed, 10 (77%) patients with fatal reactions and 65 (96%) patients with NFRs for whom information on the timing of the onset of symptoms was available had symptoms within 30 minutes of the injection.[143,185] The onset of symptoms before the fatal immunotherapy reaction was greater than 30 minutes in 3 patients. In 1 patient the reaction began within 35 minutes after the injection, but treatment was not administered until 45 minutes after the injection. A second late reaction occurred after the patient had left the clinic early, and it was estimated that treatment was initiated at least 50 minutes after the injection. A third late reaction occurred in the office of a primary care physician and began 30 to 40 minutes after the injection, but treatment was initiated 20 minutes after the onset of symptoms. The timing of the reaction was unknown in 4 of the fatal reactions.

In an earlier AAAAI survey, 17 fatalities associated with allergen immunotherapy were reported for the years 1985-1989.[183] Onset of anaphylaxis occurred within 20 minutes in 11 patients, within 20 to 30 minutes in 1 patient, and after more than 30 minutes in 1 patient. Four patients did not wait after the

TABLE V. Subcutaneous systemic reaction grading system*

World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (see text)				
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Symptom(s)/ sign(s) of one organ system present[i] **Cutaneous** Generalized pruritus, urticaria, flushing or sensation of heat or warmth[ii] **or** Angioedema (not laryngeal, tongue or uvular) **or** **Upper respiratory** Rhinitis (e.g., sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) **or** Throat-clearing (itchy throat) **or** Cough perceived to come from the upper airway, not the lung, larynx, or trachea **or** **Conjunctival** Conjunctival erythema, pruritus or tearing **Other** Nausea, metallic taste, or headache	*Symptom(s)/ sign(s) of more than one organ system present* **or** **Lower respiratory** Asthma: cough, wheezing, shortness of breath (e.g., less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator) **or** **Gastrointestinal** Abdominal cramps, vomiting, or diarrhea or **Other** Uterine cramps	**Lower respiratory** Asthma (e.g., 40% PEF or FEV1 drop, NOT responding to an inhaled bronchodilator) **or** **Upper respiratory** Laryngeal, uvula or tongue edema with or without stridor	**Lower or Upper respiratory** Respiratory failure with or without loss of consciousness **or** **Cardiovascular** Hypotension with or without loss of consciousness	Death

Patients might also have a feeling of impending doom, especially in grades 2, 3, or 4.

Note: Children with anaphylaxis seldom convey a sense of impending doom, and their behavior changes might be a sign of anaphylaxis, such as becoming very quiet or irritable and cranky.

Scoring includes a suffix that denotes if and when epinephrine is or is not administered in relationship to symptoms/signs of the systemic reaction: *a*, 5 minutes or less; *b*, greater than 5 minutes to 10 minutes or less; *c*, greater 10 minutes to 20 minutes or less; *d*, greater than 20 minutes; *z*, epinephrine not administered.

The final grade of the reaction will not be determined until the event is over, regardless of the medication administered. The final report should include the first symptom(s)/sign(s) and the time of onset after the subcutaneous allergen immunotherapy injection[iii] and a suffix reflecting if and when epinephrine was or was not administered (eg, Grade2a:rhinitis:10 minutes).

Final report: Grade a-d,or z _____ First symptom_____Time of onset of first symptom_____

Comments[iv]

[i] Each grade is based on the organ system involved and severity. Organ systems are defined as follows: cutaneous, conjunctival, upper respiratory, lower respiratory, gastrointestinal, cardiovascular, and other. A reaction from a single organ system, such as cutaneous, conjunctival, or upper respiratory, but not asthma, gastrointestinal, or cardiovascular, is classified as grade 1. Symptom(s)/sign(s) from more than 1 organ system or asthma, gastrointestinal, or cardiovascular are classified as grades 2 or 3. Respiratory failure or hypotension, with or without loss of consciousness, is defined as grade 4 and death as grade 5. The grade is determined by the physician's clinical judgment.

[ii] This constellation of symptoms can rapidly progress to a more severe reaction.

[iii] Symptoms occurring within the first minutes after the injection might be a sign of severe anaphylaxis. Mild symptoms can progress rapidly to severe anaphylaxis and death.

[iv] If signs or symptoms are not included in the table or the differentiation between a systemic reaction and a vasovagal (vasodepressor) reaction, which can occur with any medical intervention, is difficult, please include comment, as appropriate.

*This is the World Allergy Organization Subcutaneous Systemic Reaction Grading System, which has been endorsed by the AAAAI and ACAAI (from Cox L, Larenas-Linnemann D, Lockey RF, et al. J Allergy Clin Immunol 125:569-574, e567; reprinted with permission from Elsevier Inc).

injection, and the onset of their systemic reaction symptoms is not known.

In a prospective study a total of 20,588 extract injections were administered to 628 patients, resulting in 52 systemic reactions in 42 patients, with 38% of the systemic reactions occurring from 30 minutes to 6 hours after the allergy vaccine administration.[240] In another prospective study 8% of systemic reactions occurred more than 2 hours after injection.[241]

Most of the extract manufacturers' package inserts recommend a wait period of either 20 to 30 minutes or 30 minutes after administration of the immunotherapy injection. The European Academy of Allergy and Clinical Immunology's recommended observation period after an allergen immunotherapy injection is 30 minutes.[30] Most of the safety data on allergen immunotherapy reactions are in the context of 30 minutes, and thus 30 minutes continues to be the recommended wait period after the immunotherapy injection.

Patients should remain in the physician's office/medical clinic for at least 30 minutes after receiving an injection, but longer waits are reasonable, as directed by the physician. Some physicians might request that patients considered at increased risk of a serious systemic reaction outside of the office/medical clinic carry injectable epinephrine. These patients should be instructed in the use of epinephrine to treat a systemic reaction that occurs after they have left the physician's office or other location where the injection was given. The risks and benefits of continuing allergen immunotherapy in patients who have had a severe systemic reaction should be carefully considered.

Summary Statement 34: Delayed systemic reactions, defined as occurring after the 30-minute wait period, can occur and, in general, are not severe. B

Delayed systemic reactions, defined as the onset of a systemic reaction after the 30-minute wait period, have been reported to account for 27% to 50% of all systemic reactions.[235-239,242,243] Although several studies reported no severe delayed reactions[236,237] or no delayed reactions with hypotension,[235] others reported delayed reactions associated with urticaria,[239,243] wheezing, and stridor[243] and abnormal peak flow readings.[238] In a retrospective study that reported 50% of the systemic reactions as delayed, the authors concluded that their findings support "…30 minutes as an optimal wait time for immunotherapy" because all serious reactions occurred within 30 minutes.[236]

Summary Statement 35: Biphasic immunotherapy reactions, defined as resolution of the initial reaction with recurrence at 2 to 24 hours, were reported in up to 23% of patients who experienced a systemic reaction after allergen immunotherapy in one study. Biphasic reactions were typically less severe than the initial reaction. C

Biphasic anaphylactic reactions are characterized by complete clinical resolution of initial symptoms followed by onset of late-phase symptoms, usually within 24 hours.[244] Biphasic anaphylactic reactions are reported to occur 1% to 20% of the time. Two prospective studies report that biphasic reactions occur in 10%[245] and 23%[246] of immunotherapy reactions. Biphasic immunotherapy reactions occurred more frequently in women and were more common in patients who required more than 1 dose of epinephrine during the initial reaction. No specific symptoms during the initial reaction predicted a biphasic reaction. Biphasic reactions were typically less severe than the initial reaction, and none required additional epinephrine. Patients should be counseled on the possibility of a biphasic reaction and a management plan outlined with instructions on when to seek medical care.

Summary Statement 36: Several large studies demonstrate that life-threatening anaphylactic reactions after the first 30 minutes are rare. Delayed and biphasic immunotherapy-induced systemic reactions can occur outside of a supervised medical facility. Thus patients should be educated regarding the possible signs and symptoms of systemic reactions and to contact their health care professional or seek emergency medical attention, as indicated. The decision to prescribe epinephrine autoinjectors to patients receiving allergen immunotherapy is up to the physician's discretion and is based on a number of considerations. C

At the onset of immunotherapy, patients should be counseled on the possibility of immediate and delayed systemic reactions during risk communication; an action plan for such an event should be discussed. In the event of a delayed systemic reaction, the patient should be counseled on appropriate treatment based on their symptoms. They should be instructed to contact their health care professional or seek emergency medical attention, as indicated. After a delayed systemic reaction, the physician should evaluate the risks and benefits of continuing immunotherapy; consider some treatment modifications, such as a longer wait period; or both. The length of the longer wait time will depend on the clinical history of the delayed systemic reaction. Physicians might also want to consider prescribing an epinephrine autoinjector to treat such future reactions.

β-Blockers and ACE inhibitors

Summary Statement 37: Exposure to β-adrenergic blocking agents is a risk factor for more serious and treatment-resistant anaphylaxis. Concomitant use of β-blockers and allergen immunotherapy should be carefully considered from an individualized risk/benefit standpoint and incorporate the patient's preferences in the medical decision-making process. C

β-blockade can enhance mediator release in the setting of IgE-mediated and non–IgE-mediated anaphylactic reactions[247,248]; might intensify pulmonary, cardiovascular, and cutaneous end-organ effects of mediators; and has been associated with increased mortality in experimental anaphylaxis induced by either immunologic or nonimmunologic mechanisms.[249,250] Patients who are receiving β-adrenergic blockers might be at heightened risk should they experience a systemic reaction to an allergen immunotherapy injection because epinephrine might be less efficacious; epinephrine administration might also paradoxically worsen anaphylaxis through facilitating unopposed α-adrenergic and vagotonic effects.[247,251-257]

There are 3 potential elements of risk that can be influenced by β-blockers in the setting of allergen immunotherapy administration. Reactions might be (1) more frequent, (2) more severe, and (3) refractory to treatment.

A prospective cohort study that investigated anaphylactoid reactions from contrast media found no statistically significant increase in risk associated with β-blocker exposure; however, few severe reactions occurred in this study.[258] A case-control study found that β–blocker use was a significant risk factor for anaphylactoid reactions from intravenous radiocontrast media infusions, which were more likely to be severe and refractory to treatment.[255] An expanded case-control study with both retrospective

and concurrent subject selection found patients receiving β-blockers were almost 8 times more likely to be hospitalized after an anaphylactoid reaction and had a greater risk for a severe anaphylactoid reaction with bronchospasm.[256] In this study nonasthmatic patients with cardiovascular disorders receiving β-blockers were at greater risk for bronchospasm with severe reactions. This case-control study generated data from a stimulus associated with non–IgE-mediated anaphylaxis, radiocontrast media. In considering the risk for more serious anaphylaxis in patients receiving allergen immunotherapy, it is assumed that the anaphylactogenic stimulus of radiocontrast media is generalizable to the stimulus of allergen immunotherapy administration.

Two retrospective studies on immunotherapy risk factors with VIT[238,259] and inhalant immunotherapy[238] found no increase in the frequency of systemic reactions in patients taking β-blockers. A prospective cohort study of 3,178 patients receiving inhalant immunotherapy and VIT found no increased risk for more frequent systemic reactions in patients taking β-blockers compared with those who were not.[260] Overall, 87% of reactions in this study were categorized as mild and 2 (1%) as severe, and no reactions with hypotension were observed. These data provide support for the contention that β-blocker exposure does not increase the frequency of systemic reactions from allergen immunotherapy; however, these data do not allow a determination as to the additional 2 elements of risk, severe and refractory to treatment, because few severe reactions were observed in this study.

β-Blockers have important differences in receptor affinity, receptor selectivity, lipophilicity, and intrinsic sympathomimetic agonism.[261] It is unknown whether these dissimilarities translate into meaningful differences in the setting of β-blocker–associated anaphylaxis. Topical β-blockers have markedly less systemic effects than orally administered β-blockers but can still promote systemic β-adrenergic antagonism. Cardioselective β-blockers, which mainly affect β_1 receptors, are less likely to promote bronchospasm than nonselective β-blockers, which inhibit both β_1 and β_2 adrenoceptors. Unusually, severe anaphylaxis in patients taking ophthalmic and cardioselective β-blockers has been described[262-266]; for this reason, the absence of increased β-blocker risk in association with either ophthalmic or cardioselective β-adrenergic antagonists in patients receiving allergen immunotherapy cannot be assumed.

In patients who are taking β-blockers for whom inhalant allergen immunotherapy is being considered or administered, it is appropriate to incorporate patients' values and preferences into the decision-making process to determine whether the β-blocker should be replaced with an acceptable alternative. Many patients will place a higher value on reducing the risk for severe reaction from immunotherapy and will prefer discontinuing the β-blocker if an alternative is available; others might accept this added risk and place a higher value on the benefits of continuing the β-blocker. The evidence reviewed above implies that a cautious attitude should be adopted toward the concomitant use of β-blockers and inhalant allergen immunotherapy. In patients taking β-blockers for whom an acceptable alternative is not available (eg, secondary cardioprotection), withholding immunotherapy is generally the most prudent management option.

Summary Statement 38: The balance of possible risks and benefits is not the same for patients with the potential for life-threatening stinging insect reactions who are also taking a β-blocker. In patients who are unable to replace a β-blocker with an equally efficacious alternative, concomitant administration of venom immunotherapy and a β-blocker is warranted. C

It is appropriate to regard venom and inhalant allergen immunotherapy differently from the standpoint of potential risks and benefits when making management decisions regarding concomitant administration of immunotherapy and β-blockers. Management decisions concerning β-blockers in patients receiving or who are candidates for allergen immunotherapy are contingent on an individualized assessment of possible risks compared with benefits. For patients taking a β-blocker for uncomplicated hypertension, an equally efficacious alternative antihypertensive agent can generally be prescribed, which would permit administration of allergen immunotherapy without heightened risk. In some situations there might be no equivalent substitute for β-blockers, such as when a patient requires a β-blocker for myocardial reinfarction prophylaxis. In such situations the management decision should balance the risk associated with continuing β-blocker treatment with the potential untoward effects resulting from β-blocker discontinuation.

When managing patients who are candidates for VIT, there is greater risk from withholding this therapy, and the benefit associated with this intervention might be life-saving.[85] When such patients are unable to replace a β-blocker with an equally efficacious alternative, concomitant administration of VIT and a β-blocker is indicated.

Summary Statement 39: Glucagon might be efficacious for the treatment of refractory β-blocker–associated anaphylaxis. C

Glucagon can exert salutary effects in the setting of treatment-resistant, β-blocker–associated anaphylaxis based on increasing cyclic AMP levels through noncatecholamine mechanisms and exertion of potent chronotropic and inotropic effects.[267] Improvement of refractory hypotension in patients with β-blocker–associated refractory anaphylaxis has been reported after administration of intravenous glucagon.[262]

Summary Statement 40: ACE inhibitors have been associated with greater risk for more severe reaction from venom immunotherapy, as well as field stings. ACE inhibitor discontinuation should be considered for patients receiving venom immunotherapy. Concurrent administration of venom immunotherapy and an ACE inhibitor is warranted in selected cases in which no equally efficacious alternative for an ACE inhibitor exists and this is judged to be favorable from an individualized risk/benefit standpoint and consideration of patients' preferences. No evidence exists that angiotensin receptor blockers are associated with greater risk for anaphylaxis from allergen immunotherapy. C

ACE inhibitors and angiotensin receptor blockers inhibit the metabolism of angiotensin, bradykinin, and substance P.[268] Greater risk for more serious anaphylaxis might exist in patients receiving these drugs because of possible compromise in compensatory activation of the renin-angiotensin system. In patients taking an ACE inhibitor, breakdown of vasoactive kinins generated during anaphylaxis might be impaired. Bradykinin is a potent vasoactive mediator that can contribute to the hypovolemia and hypotension observed in patients with severe anaphylaxis.[269]

Anaphylaxis occurred in 2 patients receiving VIT while ACE inhibitors were being taken, did not occur when these drugs were withheld, and then recurred with resumption of ACE inhibitor treatment.[270] There have been other cases of unusually severe anaphylaxis in patients receiving VIT while taking an ACE

inhibitor, which did not recur after the ACE inhibitor was discontinued.[271] No cases such as this have been reported in association with angiotensin receptor blockers.

Two retrospective cohort studies did not find an association between ACE inhibitor use and systemic reactions to either inhalant immunotherapy[238] or VIT.[272] These data provide support for the contention that ACE inhibitor use is not associated with increased frequency of systemic reactions to allergen immunotherapy; however, greater risk for a more serious reaction might still exist.

A large multicenter study of patients receiving VIT found that ACE inhibitor exposure was associated with a statistically significant increase in the risk for more severe anaphylaxis.[161] In patients with anaphylactic potential to Hymenoptera venom, patients receiving VIT, or both, it is prudent to consider ACE inhibitor discontinuation to reduce the risk for severe reactions while substituting an equally efficacious non–ACE inhibitor alternative. For patients who require an ACE inhibitor for an indication for which there is no equally effective alternative medication available, a management decision by the physician prescribing VIT should be approached cautiously from an individualized risk/benefit standpoint, including consideration of patients' preferences. It is also important to note that the Hymenoptera venom package insert contains a warning that patients who "… undergo desensitization treatment while under concomitant therapy with ACE inhibitors may have an increased risk of life-threatening anaphylactic reactions."[273] The stinging insect practice parameter[158] and the ACE inhibitor package inserts carry a similar warning about the potential increased risk of systemic reactions to VIT in patients receiving ACE inhibitors.

There is no evidence that greater risk for anaphylaxis, for more serious anaphylaxis, or for recalcitrant anaphylaxis is present in association with angiotensin receptor blockers. For this reason, suspension of an angiotensin receptor blocker in patients receiving VIT is not necessary.

Summary Statement 41: β-blockers and ACE inhibitors are frequently prescribed in combination. Concomitant administration of both of these medications in a patient who requires venom immunotherapy might be warranted, if favorable, from an individualized assessment of potential risks and benefits and patients' preferences. D

β-Blockers and ACE inhibitors are commonly prescribed in combination for patients with heart failure[274] and for secondary prevention of myocardial infarction.[275] Each drug has been associated with prolonged survival. Patients receiving both drugs are at heightened risk from VIT because the potential for anaphylaxis that is more severe, treatment resistant, or both might be additive; however, an individualized risk/benefit assessment favors concomitant administration of VIT along with these medications because this intervention offers the potential for greater benefit than the alternatives of either withholding VIT or drug suspension.

Patient requirements and contraindications

Summary Statement 42: Patients selected for immunotherapy should be cooperative and compliant. D

Patients who are mentally or physically unable to communicate clearly with the physician and patients who have a history of noncompliance might be poor candidates for immunotherapy. If a patient cannot communicate clearly with the physician, it will be difficult for the patient to report signs and symptoms, especially early symptoms, suggestive of systemic reactions.

Special precautions in patients with asthma

Summary Statement 43: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable. C

Patients with severe or uncontrolled asthma are at increased risk for systemic reactions to immunotherapy injections.[142,143,182] Three surveys found that deaths from immunotherapy were more common in patients with asthma that was symptomatic, labile, or both.[143,183,184] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2,30]

Summary Statement 44: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications for allergen immunotherapy. Examples include severe asthma uncontrolled by pharmacotherapy and significant cardiovascular disease. C

Alternatives to allergen immunotherapy should be considered in patients with any medical condition that reduces the patient's ability to survive a systemic allergic reaction. Examples include patients with markedly compromised lung function (either chronic or acute), poorly controlled asthma, unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension. Under some circumstances, immunotherapy might be indicated for high-risk patients, such as those with Hymenoptera hypersensitivity and cardiac disease being treated with β-blocker medications.

Reducing the risk of anaphylaxis to immunotherapy injections

Summary Statement 45: Allergen immunotherapy should be administered in a setting where procedures that can reduce the risk of anaphylaxis are in place and where the prompt recognition and treatment of anaphylaxis is ensured. C

The major risk of allergen immunotherapy is anaphylaxis, which in rare cases can be fatal, despite optimal management. Therefore allergen immunotherapy should be administered in a setting where anaphylaxis will be promptly recognized and treated by a physician, qualified physician extender (nurse practitioner or physician assistant), or both appropriately trained in emergency treatment (Table VI).

Before allergen immunotherapy is chosen as a treatment, the physician should educate the patient about the benefits and risks of immunotherapy, as well as the methods for minimizing risks. The patient also should be told that despite appropriate precautions, reactions can occur without warning signs or symptoms. Informed consent should include a discussion of the potential immunotherapy-induced adverse reactions, and this discussion should be documented in the patient's medical record.

Management of immunotherapy-induced systemic reactions

Summary Statement 46: Epinephrine is the treatment of choice for immunotherapy-induced systemic reactions. Risk

TABLE VI. Recommended equipment and medications to treat immunotherapy systemic reactions

Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur. The following are suggested equipment and medications for the management of immunotherapy systemic reactions. Modifications of this suggested list might be based on anticipated emergency medical services' response time and physician's airway management skills:

- stethoscope and sphygmomanometer;
- tourniquet, syringes, hypodermic needles, and intravenous catheters (eg, 14-18 gauge);
- aqueous epinephrine HCL 1:1,000 wt/vol;
- equipment to administer oxygen by mask;
- intravenous fluid set-up;
- antihistamine for injection (second-line agents for anaphylaxis, but H1 and H2 antihistamines work better together than either one alone);
- corticosteroids for intramuscular or intravenous injection (second-line agents for anaphylaxis);
- equipment to maintain an airway appropriate for the supervising physician's expertise and skill; and
- glucagon kit available for patients receiving β-blockers.

For a detailed listing of recommended equipment and medication for treatment of anaphylaxis, see Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol 2010;126:477-80, e1-42.

factors for fatal immunotherapy-induced reactions include delayed administration of epinephrine. B

The physician and health care professional who administers immunotherapy injections should be able to recognize and treat the early symptoms and signs of anaphylaxis and administer emergency treatment, if necessary. For further discussion of the treatment of anaphylaxis, see "The diagnosis and management of anaphylaxis practice parameter: 2010 update".[28]

Epinephrine is the first-line treatment for anaphylaxis.[276] There is no contraindication to epinephrine administration in patients with anaphylaxis. It is important to administer epinephrine early in the management of anaphylaxis. Fatalities during anaphylaxis usually result from delayed administration of epinephrine and from severe respiratory complications, cardiovascular complications, or both.

Aqueous epinephrine (1:1000 dilution, 0.2-0.5 mL [0.01 mg/kg in children; maximum, 0.3-mg dose]) should be administered every 5 minutes, as necessary, to control symptoms and increase blood pressure. If the clinician deems it appropriate, the 5-minute interval between injections can be liberalized to permit more frequent injections. Physicians and other health care professionals should know the potential pharmacologic benefits, risks, and routes of administration of epinephrine, as well as the potential reasons for lack of response.[28,277-279]

Studies in children not experiencing anaphylaxis have demonstrated that plasma levels of epinephrine reach higher levels more rapidly when epinephrine is administered intramuscularly in the thigh compared with subcutaneous administration in the arm.[279] Intramuscular injection in the thigh in adults who were not experiencing anaphylaxis produced significantly higher peak plasma epinephrine concentrations more rapidly than epinephrine injected intramuscularly or subcutaneously in the upper arm, the pharmacokinetic profile for which was similar.[278] Whether the same pharmacokinetic profile is seen in patients with anaphylaxis is not known. It is also not clear whether the pharmacokinetic profile observed after intramuscular administration in the thigh is preferred compared with subcutaneous administration in the arm for treatment of protracted or biphasic anaphylaxis. There are no studies evaluating outcomes in immunotherapy-induced anaphylaxis that compared sites of epinephrine administration, particularly in this circumstance, when the antigen is introduced into the arm.

Appropriate personnel, equipment, and medications should be immediately available to treat anaphylaxis, should it occur. Suggested actions to reduce the risk of anaphylaxis and recommended equipment and medications to treat anaphylaxis are listed in Tables IV and VI, respectively.

IMMUNOTHERAPY SCHEDULES AND DOSES

Starting doses

Summary Statement 47: The starting dose for build-up is usually a 1,000-fold or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. D

There are 2 phases of allergen immunotherapy administration: the initial build-up phase, when the dose and concentration of allergen immunotherapy extract are increased, and the maintenance phase, when the patient receives an effective therapeutic dose over a period of time. If the starting dose is too dilute, an unnecessarily large number of injections will be needed, resulting in a delay in achieving a therapeutically effective dose. On the other hand, if the starting dose is too concentrated, the patient might be at increased risk of having a systemic reaction.

When choosing the starting dose, most allergists/immunologists start at a dilution of the maintenance concentrate that is appropriate based on the sensitivity of the patient to the allergens in the extract, which, in turn, is based on the history and skin test reactivity.

Common starting dilutions from the maintenance concentrate are 1:10,000 (vol/vol) or 1:1,000 (vol/vol), although more diluted concentrations frequently are used for patients who are highly sensitive, as indicated by history or skin test reactions.

Frequency of build-up injections

Summary Statement 48: The frequency of allergen immunotherapy administration during a conventional build-up phase is generally 1 to 3 injections per week. D

A number of schedules are used for the build-up phase of immunotherapy. The most commonly used schedule is for increasing doses of allergen immunotherapy extract to be administered 1 to 3 times per week (see Table E4 in this article's Online Repository at www.jacionline.org for an example of a conventional immunotherapy schedule). This weekly schedule is recommended in most of the allergen extract package inserts. With this schedule, a typical patient can expect to reach a maintenance dose in 3 to 6 months, depending on the starting dilution and the occurrence of reactions. It is acceptable for patients to receive injections more frequently. The interval between injections is

empiric but might be as short as 1 day without any increase in the occurrence of systemic reactions[280] if there is a need to achieve a maintenance dose (eg, allergy season is approaching) or for practical reasons (eg, patient's schedule). Alternatively, accelerated treatment schedules, such as rush or cluster regimens, can be used that more rapidly achieve maintenance dosing. These cluster and rush dosing schedules are discussed in Summary Statements 52 through 55.

Allergen immunotherapy extracts used during the build-up phase usually consist of three or four 10-fold dilutions of the maintenance concentrate. The volume generally is increased at a rate that depends on several factors, including (1) the patient's sensitivity to the extract, (2) the history of prior reactions, and (3) the concentration being delivered (with smaller percentage increments being given at higher concentrations).

In the case of VIT, the aim is to achieve a uniform maintenance dose of 100 μg of each venom; to this end, patients might be expected to tolerate relatively large local reactions that might not be considered acceptable with inhalant immunotherapy.Dose adjustments for systemic reactions

Summary Statement 49: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. D

It is customary to either reduce the dose if a systemic reaction has occurred or consider discontinuation of immunotherapy, especially if the reaction has been severe. Although there are no evidence-based guidelines on dose adjustment after a systemic reaction, many allergists/immunologists reduce the dose to one that was previously tolerated or an even lower dose if the reaction was severe. Once the patient tolerates a reduced dose, a cautious increase in subsequent doses can be attempted. It is important for the physician who prescribed the allergen immunotherapy extract to review the course of immunotherapy to determine whether the risk/benefit assessment justifies continuation of immunotherapy. If there are recurrent systemic reactions at the maintenance dose, one management consideration would be to decrease the maintenance dose provided the dose is still high enough to benefit the patient.

Reductions during periods of exacerbation of symptoms

Summary Statement 50: Immunotherapy given during periods when the patient is exposed to increased levels of allergens to which they are highly sensitive might be associated with an increased risk of a systemic reaction. However, although survey data have noted this to be a risk factor for severe reactions, several published studies have not found an association between pollen seasons and systemic reactions. C

Injections administered during periods when a patient is exposed to increased levels of allergen to which they are highly sensitive might be associated with an increased risk of a systemic reaction, especially if the patient is experiencing a significant exacerbation of symptoms and, in particular, asthma symptoms. Therefore it is reasonable to consider not increasing or even reducing the dose of the allergen immunotherapy extract during seasons when the patient is exposed to increased levels of allergen to which they are highly sensitive, especially if their symptoms are poorly controlled.

However 2 large studies did not demonstrate an increase in systemic reactions during the pollen season. The first was a prospective study of 4,578 patients who received 346,251 injections.[235] There was no direct correlation between pollen counts and the occurrence of systemic reactions. They did note a correlation between the number of systemic reactions and mean monthly mold counts from August to October. The second prospective study conducted from 1976 to 1989 and involving 513,368 injections did not note an increase in systemic reactions during the grass and ragweed seasons among patients receiving grass or ragweed immunotherapy.[237] Therefore although some highly sensitive patients might experience systemic reactions during their pollen season, most patients do well without dose adjustment.

Dose adjustments for late injections

Summary Statement 51: There is no retrospective or prospective published evidence to support modification of doses of allergen immunotherapy because of treatment gaps during the build-up or maintenance immunotherapy phases. However, it is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. D

There are no evidence-based guidelines on dose adjustments for missed immunotherapy doses. During the build-up phase, it is customary to repeat or even reduce the dose of allergen immunotherapy extract if there has been a substantial time interval between injections. This might depend on (1) the concentration of allergen immunotherapy extract that is to be administered, (2) whether there is a previous history of systemic reactions, and (3) the degree of variation from the prescribed interval of time, with longer intervals since the last injection leading to greater reductions in the dose to be administered. See Table E5 in this article's Online Repository at www.jacionline.org for an example of an immunotherapy dose-adjustment schedule for unscheduled gaps in allergen immunotherapy injection intervals.

A pilot observational study of 16 missed-dose adjustment protocols illustrated the wide variation of missed-dose adjustments used.[281] In this study half the protocols calculated the late interval from the date of the last dose received, whereas the other half calculated the late interval from the date of the missed scheduled dose. The author noted that a stepwise reduction (with the late interval beginning with the date of the missed dose) beginning at 3 weeks late for build-up (reduce 1 dose per week late) and 1 week late for maintenance fell within the interquartile ranges of all protocols.

Cluster schedules

Summary Statement 52: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. C

Cluster schedules are designed to accelerate the build-up phase of immunotherapy. Cluster immunotherapy usually is characterized by visits for administration of allergen immunotherapy extract 1 or 2 times per week with a schedule that contains fewer total injections than are used with conventional immunotherapy. With cluster immunotherapy, 2 or more injections are given per visit on nonconsecutive days.[18,22] The injections are typically given at 30-minute intervals, but longer intervals have also been used in some protocols. This schedule can permit a patient to reach a maintenance dose in as brief a period of time as 4 weeks. Controlled studies have shown symptomatic improvement shortly

after reaching maintenance doses by using cluster schedules.[22,113,282,283] See Table E6 in this article's Online Repository at www.jacionline.org for an example of a cluster build-up schedule.

Summary Statement 53: Studies with single allergens using a cluster schedule demonstrated a similar or increased frequency of systemic reactions compared with immunotherapy with conventional schedules. A

The cluster schedule is associated with the same[113,128,283-285] or an increased[222] frequency of systemic reactions compared with immunotherapy administered with more conventional schedules. Most studies comparing the safety of cluster schedules with conventional schedules use single allergens.[286,287] In a review article that analyzed 29 studies using a cluster schedule with venom or aeroallergens, the authors conclude that the optimal tolerance of cluster schedules is associated with: (1) use of premedication (antihistamine), (2) use of a depot preparation, (3) use of no more than 4 administrations per cluster, (4) use of a total of 4 to 6 clusters, and (5) administration of 1 to 2 clusters per week.[287] The review also notes that the twice-a-week cluster might be associated with less adverse effects than the once-a-week cluster based on the significant difference in systemic reaction rates in 2 separate grass pollen cluster studies with virtually identical protocols, except for the frequency of clusters. In the once-a-week cluster the systemic reaction rate was 33% in the premedicated group versus 79% in the group without premedication.[222] The systemic reaction rate in the twice-a-week cluster was 18% in the premedicated group versus 22% in the placebo group.[128]

The occurrence of both local and systemic reactions to cluster immunotherapy might be reduced with antihistamine premedication.[222]

Rush schedules

Summary Statement 54: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. A

Rush schedules are more rapid than cluster immunotherapy. An early study used a schedule that permitted patients to achieve a maintenance dose in 6 days; however, patients were required to remain in the hospital.[288] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.[182,229,289-291]

The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections over the course of 4 hours.[292] Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours.[293-295] The advantage of a cluster or rush schedule is that it permits patients to attain a therapeutically effective maintenance dose more rapidly than with a conventional schedule. Controlled studies have shown symptomatic improvement shortly after reaching maintenance doses by using rush schedules.[103,203]

Summary Statement 55: Rush schedules with inhalant allergens are associated with an increased risk of systemic reactions. However, rush protocols for administration of stinging Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions. A

The advantage of rush immunotherapy is that the therapeutic maintenance dose is achieved with fewer office visits in a shorter period of time. However, there is an increased risk of local and systemic reactions. The systemic reaction rate with rush immunotherapy schedules ranged from 15% to 100% of patients who did not receive premedication to 3% to 79% of premedicated patients in 1 review.[286] In one double-blind, placebo-controlled study comparing the effect of premedication before rush immunotherapy, systemic reactions were experienced by 27% by premedicated versus 73% of placebo-premedicated patients.[229] Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing.[292]

Systemic reactions with rush schedules have been reported to occur up to 2 hours after the final injection. For that reason, subjects receiving rush immunotherapy should remain under a physician's supervision for a longer waiting period than the usual 30 minutes recommended for conventional schedules (eg, 1.5-3 hours after allergen immunotherapy extract administration during rush immunotherapy).

Rush protocols for administration of flying Hymenoptera venom have generally not been associated with a similarly high incidence of systemic reactions.[293,295-297] There has been some conflicting data on the safety of rush immunotherapy with imported fire ant venom. One study demonstrated no significant difference between the premedicated and placebo-premedicated group during a 2-day rush protocol.[124] In another study conducted at the same medical center, 24% of patients experienced a systemic reaction during a 1-day rush protocol that did not include premedication.[298]

Premedication and immunotherapy-induced systemic reactions

Premedication and weekly immunotherapy. Summary Statement 56: Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. A

There is concern that antihistamines might mask a minor reaction that would otherwise alert a physician to an impending systemic reaction if taken before an immunotherapy injection during a conventional build-up. However, one randomized controlled study demonstrated that premedication reduced the frequency of severe systemic reactions caused by conventional immunotherapy and increased the proportion of patients who achieved the target maintenance dose.[299]

In the *post hoc* analysis of a study designed to investigate omalizumab's effect on the tolerability of cluster immunotherapy in patients with moderate-to-severe asthma, there was a similar incidence of systemic reactions in the patients who received antihistamine premedication compared with those who did not; however, use of antihistamines was not randomized but rather based on the physician's discretion.[300] Thus patients might still experience systemic reactions despite antihistamine premedication treatment. Because many patients might take an antihistamine as part of their overall allergy management, it is important to determine whether they have taken it on the day that they receive an allergen immunotherapy extract injection for consistency in interpretation of reactions. It also might be desirable that they consistently either take their antihistamine or avoid it on days when they receive immunotherapy. Other attempts to reduce the occurrence of systemic reactions, such as the addition of epinephrine to the allergen immunotherapy extract or use of concomitant corticosteroids, are not justified and might delay the onset of a systemic reaction beyond the waiting time when the patient is in the physician's office, thus increasing the risk (see summary statements 57 and 58 for further discussion on premedication).

Premedication with accelerated immunotherapy schedules. Summary Statement 57: Premedication before cluster and rush immunotherapy with aeroallergens might reduce the rate of systemic reactions. Combination therapy is effective in reducing systemic and local reactions during accelerated immunotherapy build-up protocols. A

Oral antihistamines. Oral antihistamines have been shown to be effective in decreasing local and systemic reactions during rush VIT protocols.[223-225] Premedication with a nonsedating antihistamine (loratadine) 2 hours before the first injection of each visit reduced both the number and severity of systemic reactions during cluster immunotherapy with birch or grass pollen extract.[222] Although rush VIT–induced systemic reaction rates are typically low,[293,295-297] some studies have demonstrated that the addition of antihistamines decreased the frequency of systemic reactions compared with placebo.[225] Antihistamines also decreased the frequency of LLRs over the first 4 weeks of treatment compared with placebo, although the addition of ranitidine to terfenadine did not provide additional benefit compared with terfenadine alone.[225] Two additional rush VIT studies demonstrated that antihistamine pretreatment decreased LLRs and cutaneous symptoms of pruritus, urticaria, and angioedema but did not decrease the frequency of respiratory, gastrointestinal, or cardiovascular reactions.[223,224] Finally, a retrospective study reported that premedication with terfenadine during rush VIT might improve efficacy because the treatment group had fewer systemic reactions to field stings and sting challenges over an average of 3 years.[301] However, this finding was not confirmed on prospective study.[302]

The effect of antihistamines in decreasing local and systemic reactions when using conventional schedules has been less documented. Antihistamine pretreatment was demonstrated to decrease the frequency of severe systemic reactions in a study using a conventional build-up schedule.[299] The effect of oral antihistamines on LLRs in this study was not reported, although the antihistamine group more frequently attained the target maintenance dose. No other study has reported the effect of antihistamines on LLRs or systemic reactions during conventional build-up or maintenance injections with inhalant allergens. For VIT, pretreatment with antihistamines did not reduce LLR rates during conventional monthly maintenance injections after they decreased LLRs during the initial rush protocol.[224,225]

Leukotriene antagonists. A pilot study demonstrates that premedication with montelukast delays the onset and decreases the size of local reactions during rush VIT, but no controlled studies have investigated the effect of leukotriene antagonists on the incidence of systemic reactions.[226]

Combination pretreatment. Combination pretreatment with ketotifen, methylprednisolone, and theophylline used during a 3-day rush treatment with pollen immunotherapy decreased the frequency of systemic reactions.[303] Premedication with prednisone, an H_1 histamine receptor antagonist, and an H2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.[229] The number of local reactions were also decreased, as was the size of the erythema and but not the wheal.

During a 2-day imported fire ant rush protocol evaluating the effect of combination therapy with antihistamines and steroids, there were no statistically significant differences in systemic reaction rates between the premedication group (3.6%) and the placebo group (6.7%).[124] However, a recent 1-day imported fire ant rush protocol involving 37 patients performed without premedication reported higher systemic reaction rates (24.3%) than the 2-day regimen, with most reactions involving urticaria and pruritus.[298]

Because the risk of a systemic reaction from rush immunotherapy with the flying Hymenoptera venoms is relatively low, routine premedication is usually unnecessary. Further studies are needed to clarify the risk of fire ant rush immunotherapy, and premedication might be considered.

Omalizumab in combination with immunotherapy

Summary Statement 58: Omalizumab pretreatment has been shown to improve the safety and tolerability of cluster and rush immunotherapy schedules in patients with moderate persistent asthma and allergic rhinitis, respectively. Additionally, omalizumab used in combination with immunotherapy has been shown to be effective in improving symptom scores compared with immunotherapy alone. A

Omalizumab used in combination with immunotherapy 2 weeks before and during the grass season was compared with immunotherapy alone. The combination therapy improved symptom load and asthma control, with more patients reporting good or excellent efficacy.[304] Additionally, omalizumab added to standard maintenance doses of birch and grass immunotherapy resulted in decreased rescue medication use and symptomatic days compared with omalizumab or immunotherapy alone.[305]

In addition to symptom improvement, omalizumab has also been shown to reduce systemic reactions to rush immunotherapy. The use of omalizumab 9 weeks before and in conjunction with ragweed rush immunotherapy improved symptom severity scores during the ragweed season compared with immunotherapy alone. Furthermore, omalizumab pretreatment resulted in a 5-fold decrease in the risk of anaphylaxis during rush immunotherapy.[306] Additionally, a prospective study examined the effect of 16 weeks of treatment with omalizumab or placebo on the incidence of systemic reactions during cluster immunotherapy in 248 subjects with asthma.[300] Eligible subjects were required to have perennial asthma that was not well controlled despite inhaled corticosteroids and to be sensitive to cat, dog, and/or house dust mite. After 13 weeks of pretreatment with omalizumab or placebo, subjects received immunotherapy to 1, 2, or 3 allergens (cat, dog, and dust mite) through a 4-week cluster regimen, which overlapped with continued omalizumab/placebo treatment for 3 weeks. This was followed by 7 weeks of maintenance injections during which the omalizumab or placebo was not given. Compared with placebo, omalizumab pretreatment reduced the rate of systemic reactions during cluster immunotherapy from 26.2% to 13.5%. There were no systemic reactions during maintenance therapy.

There have been a few case reports regarding patients with bee venom allergy who were unable to tolerate VIT because of anaphylaxis but were subsequently able to tolerate VIT with omalizumab.[307,308] There is also evidence that omalizumab might improve the tolerability of VIT in patients with mastocytosis.[309,310] Although not specifically approved as a pretreatment for allergen immunotherapy, the use of omalizumab in these scenarios might be beneficial for high-risk patients. It should be

noted that omalizumab has been associated with anaphylaxis in 0.09% to 0.2% of patients.[311,312]

Maintenance schedules

Summary Statement 59: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased, as tolerated, up to an interval of 4 weeks for inhalant allergens and up to 8 weeks for venom. Some subjects might tolerate longer intervals between maintenance dose injections. A

Once a patient who is receiving inhalant allergen immunotherapy reaches a maintenance dose, an interval of 2 to 4 weeks between injections is recommended, provided clinical improvement is maintained. Some subjects might tolerate longer intervals between maintenance dose injections.

The interval between flying Hymenoptera venom injections can be safely increased up to 8 weeks or even 3 months in some patients without loss of efficacy. Although studies have demonstrated effectiveness at 3-month intervals,[313-315] 6-month intervals between injections resulted in an increase in reactions to field stings.[316] For imported fire ant immunotherapy, there are no studies demonstrating efficacy beyond standard maintenance injection intervals. In other patients, greater efficacy, fewer reactions, or both might occur with shorter intervals between injections. Therefore the interval between allergen immunotherapy injections should be individualized to provide the greatest efficacy and safety for each patient.

Injection techniques

Summary Statement 60: Allergen immunotherapy extract injections should be given with a calibrated small-volume syringe with a 26- to 27-gauge ½- or 3/8-inch nonremovable needle. C

Immunotherapy should be administered with a 26- to 27-gauge syringe with a ½- or 3/8-inch nonremovable needle. Syringes specifically designed for immunotherapy are available from medical supply companies. Although recent Occupational Safety and Health Administration guidelines mandate the use of safety needles with allergy injections, recent publications indicate a potential increase in accidental needle sticks with the use of safety needles compared with standard syringes.[317-319]

Antigens from different vials should not be combined in a single syringe.

Summary Statement 61: The injection should be given subcutaneously in the lateral or posterior portion of the arm. D

Immunotherapy should be given subcutaneously. Subcutaneous injections result in formation of a reservoir of allergen immunotherapy extract that is slowly absorbed. Absorption that is too rapid, such as after an intramuscular injection, could lead to a systemic reaction. The skin should be pinched and lifted off of the muscles to avoid intramuscular or intravenous injection and to increase access to the subcutaneous tissues.

Each immunotherapy injection should be given in the posterior portion of the middle third of the arm at the junction of the deltoid and triceps muscles. This location tends to have a greater amount of subcutaneous tissue than adjacent areas. The skin should be wiped with an alcohol swab before giving the immunotherapy injection. This does not sterilize the area, but it does remove gross contamination from the skin surface.

The syringe can be aspirated as an extra safety step to check for blood return before injecting. It has been debated whether syringe aspiration is a necessary step. The Centers for Disease Control and Prevention's "General recommendations on immunization recommendations of the Advisory Committee on Immunization Practices" does not support or recommend aspiration, stating that "aspiration before injection of vaccines or toxoids (ie, pulling back on the syringe plunger after needle insertion, before injection) is not required because no large blood vessels exists at the recommended injection sites."[320]

A retrospective study reported no episodes of blood aspiration were noted by "…experienced allergy nurses" who were asked if they "had ever seen blood in the syringe after aspiration" during the previous 3 years in 25,285 immunotherapy injections and 3,540 immunizations.[321] To avoid recall bias, a subsequent 1-year prospective study in the clinic was performed and again demonstrated that no episodes of blood while aspirating during immunotherapy were noted in 6,642 immunotherapy injections or 683 immunizations. The author concluded that aspiration before immunotherapy injection is not required. Others have challenged these findings and shared their own anecdotal experiences with the aspiration of blood into the syringe during immunotherapy.[322,323] These authors state that although rare, the benefit of aspirating for blood still outweighs the potential risks.

If blood is present in the aspirate, the syringe should be removed and discarded in an appropriate container ("sharps" box). Another dose of the allergen extract should be drawn into a new syringe, and a different site should be chosen for the injection. In theory, removal of the syringe when blood is present reduces the likelihood of intravenous administration, which could lead to a systemic reaction. The plunger should be depressed at a rate that does not result in wheal formation or excessive pain. Mild pressure should then be applied to the injection site for about 1 minute immediately after removal of the needle. This reduces the chance of leakage of the allergen extract, which theoretically could result in a local reaction.

LOCATION OF ALLERGEN IMMUNOTHERAPY ADMINISTRATION

Supervising medical personnel

Summary Statement 62: Regardless of the location, allergen immunotherapy should be administered under the direct supervision of an appropriately trained physician, qualified physician extender (nurse practitioner or physician assistant), or both in a facility with the appropriate equipment, medications, and personnel to treat anaphylaxis. D

The physician and personnel administering immunotherapy should be aware of the technical aspects of this procedure and have available appropriately trained personnel, resuscitative equipment/medicines, and storage facilities for allergen immunotherapy extract. Physicians and other health care professionals should be able to recognize early signs and symptoms of anaphylaxis and administer emergency medications as necessary.

The physician and staff should be aware of situations that might place the patient at greater risk for systemic reactions (eg, concomitant medications that can interfere with emergency treatment, such as β-blockers; acute illness; and asthma exacerbations at the time of allergen immunotherapy extract injection).

Appropriate adjustment of dose should be made, as clinically indicated. The physician whose office prepared the patient's

allergen immunotherapy extract should provide adequately labeled allergen immunotherapy extract vials, detailed directions regarding the dosage schedule for build-up and maintenance, and instructions on adjustments that might be necessary under the following circumstances:

- when providing patients with new vials;
- during seasonal exposure to allergens that are in the patient's allergen immunotherapy extract to which the patient is very sensitive;
- if the patient has missed injections; and
- when reactions occur to the allergen immunotherapy extract.

Any systemic reaction to allergen immunotherapy should be treated immediately with epinephrine, and the physician whose office prepared the allergen immunotherapy extract should be informed. This might require a return to the allergist/immunologist's office for treatment and re-evaluation.

Prescribing physician's office

Summary Statement 63: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. D

The preferred location of allergen immunotherapy administration is in the office of the physician who prepared the patient's allergen immunotherapy extract. The physician's office should have the expertise, personnel, and procedures in place for the safe and effective administration of immunotherapy. However, in many cases it might be necessary to administer the allergen immunotherapy extract in another physician's office. Allergen immunotherapy should be administered with the same care wherever it is administered. A physician or qualified physician extender (nurse practitioner or physician's assistant) should be present and immediately available and be prepared to treat anaphylaxis when immunotherapy injections are administered. Regular practice drills with the office staff for handling systemic reactions to immunotherapy reactions should be considered.

Summary Statement 64: Patients at high risk of systemic reactions, where possible, should receive immunotherapy in the office of the physician who prepared the patient's allergen immunotherapy extract. D

Patients at high risk of systemic reactions (highly sensitive, severe symptoms, comorbid conditions, and history of recurrent systemic reactions), where possible, should receive immunotherapy in the allergist/immunologist's office.[324] The allergist/immunologist who prepared the patient's allergen immunotherapy extract and his or her support staff should have the experience and procedures in place for the administration of allergen immunotherapy to such patients.[185] The early signs of an allergic reaction are more likely to be recognized and early treatment initiated, which will decrease the possibility of a serious outcome. Modifications in the patient's immunotherapy schedule, total treatment program, or both might be more frequently necessary in these high-risk patients.

Outside medical facilities

Home administration. Summary Statement 65: In rare and exceptional cases when allergen immunotherapy cannot be administered in a medical facility and withholding this therapy would result in a serious detriment to the patient's health (eg, VIT for a patient living in a remote area), careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual basis. If this approach is used, informed consent should be obtained from the patient, and the person administering the injection to the patient must be educated about how to administer immunotherapy and recognize and treat anaphylaxis. D

Allergen immunotherapy should be administered in a medical facility with trained staff and medical equipment capable of recognizing and treating anaphylaxis. Under rare circumstances, when the benefit of allergen immunotherapy clearly outweighs the risk of withholding immunotherapy (eg, patients with a history of venom-induced anaphylaxis living in a remote region), at-home administration of allergen immunotherapy can be considered on an individual basis. In this instance there should be a discussion with the patient, with careful consideration of the potential benefits and risks involved in home administration and alternatives. Informed consent should be obtained from the patient and appropriate family members after this discussion. Under these circumstances, another adult person should be trained to administer the injection and to treat anaphylaxis, should it occur. It should be noted, however, that the package insert approved by the FDA that accompanies all allergen extracts, including venom, implies that allergy injections should be administered in a clinical setting under the supervision of a physician. Intuitively, the risk from administering allergenic extracts outside a clinical setting would appear to be greater. Recognition and treatment of anaphylaxis might be delayed or less effective than in a clinical setting in which personnel, medications, supplies, and equipment are more optimal to promptly recognize and treat anaphylaxis (Table VI). Home administration should only be considered in the rare circumstance when the benefit of immunotherapy clearly outweighs the risks. Frequent or routine prescription of home immunotherapy is not appropriate under any circumstances.

Transferring allergen immunotherapy care

Summary

Statement 66: If a patient receiving immunotherapy transfers from one physician to another, a decision must be made by the physician to whom the patient has transferred as to whether to continue immunotherapy. D

Summary

Statement 67: If immunotherapy is continued, a decision must then be made about whether to continue unchanged the immunotherapy program initiated by the previous physician or to start a new immunotherapy program. Patients can continue to receive the immunotherapy extract prepared by the patient's previous physician if this is acceptable to the transferring and accepting physicians. D

Patients may transfer from one physician (previous physician) to another (current physician) while receiving allergen immunotherapy. When this occurs, a decision must be made by the current physician about whether to continue immunotherapy and, if so, what allergen immunotherapy extract and schedule should be used: the one that the patient received from the previous physician (ie, an unchanged immunotherapy program) or one to be prepared by the current physician (ie, a new immunotherapy program).

The current physician might choose to prepare a new allergen immunotherapy extract formulation based on the immunotherapy prescription or allergy test results from the previous physician, if the records provide adequate details. If there is inadequate information in the immunotherapy prescription documentation to continue the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract formulation might be prescribed.

Summary Statement 68: A detailed documentation of the patient's schedule and allergen extract content must accompany a patient when he or she transfers responsibility for immunotherapy care from one physician to another. In addition, a record of previous response to and compliance with this program should be communicated to the patient's new physician. D

If the patient transfers from one physician to another and continues on the previous immunotherapy program without changing either the schedule or allergen immunotherapy extract, he or she is not at substantially increased risk of having systemic reactions as long as there is a clear and detailed documentation of the patient's previous schedule and the contents of the allergen immunotherapy extract. The patient's immunotherapy administration documentation must accompany the patient who transfers responsibility for the immunotherapy program from one physician to another. This should include a record of any reactions to immunotherapy and how they were managed, as well as the patient's response to immunotherapy. Under these circumstances, immunotherapy can be continued with the allergen immunotherapy extract that the patient was previously receiving if (1) the previous physician is willing and able to continue to provide the patient with the allergen immunotherapy extract, (2) the patient has shown significant improvement on this immunotherapy program, (3) the contents of the allergen immunotherapy extract are appropriate for the area in which the patient is now living, and (4) all extracts are well identified and the records are clear (see Tables E7-E15 in this article's Online Repository at www.jacionline.org for documentation guidelines and examples of allergen immunotherapy prescription and administration forms).

Summary Statement 69: An allergen immunotherapy extract must be considered different if there is any change. There is potentially an increased risk of a systemic reaction if the immunotherapy extract is changed because of the possible variability in the composition and potency of allergen extracts. If the allergen immunotherapy extract is changed, the patient might need to be retested for specific IgE sensitivity and started on an immunotherapy formulation and schedule that is based on this re-evaluation. D

An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the allergen immunotherapy extract. These include changes in the lot, manufacturer, extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is potentially an increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient's dose is not modified. This increased risk might be due to the significant variability in content and potency of extracts and the variability in methods used by physicians to prepare the patient's immunotherapy extract. For example, the strength of a given concentration of nonstandardized extracts might vary significantly from lot to lot. The risk of systemic reactions might be greater with nonstandardized extracts because of this potential variability in the composition and/or potency.

If the allergen immunotherapy extract is to be changed, the patient might need to be retested for allergen-specific IgE and started on an immunotherapy schedule and immunotherapy extract formulation that is appropriate. In this situation the starting dose should be comparable with the initial dose that would be used if the patient had not previously been receiving immunotherapy. If the information that accompanies the patient is thorough, the current physician can prepare an allergen immunotherapy extract identical or almost identical to that provided by the previous physician. In such a case all that might be required is a decrease in the dose from the patient's previous injection if there has not been too long an interval since the last injection. For lot changes from the same manufacturer, the physician can consider decreasing the dose by 50% to 90% of the previous dose. For changes in manufacturer and nonstandardized extracts, a greater decrease in dose might be necessary.

ALLERGEN EXTRACT SELECTION AND HANDLING

Specific allergens

Summary Statement 70: Immunotherapy is effective for pollen, animal allergens, dust mite, mold/fungi, and Hymenoptera hypersensitivity. Therefore immunotherapy should be considered as part of the management program in patients who have symptoms related to exposure to these allergens, as supported by the presence of specific IgE antibodies. A

Pollen. Pollen extracts have been shown to be safe and effective in many controlled clinical trials.[74,130] It seems reasonable to extrapolate information about pollen extracts that have been studied to those that have not been subjected to rigorous investigation and to assume that the latter are also safe and effective. Less information is available with respect to mixtures of pollen extracts. However, those studies that have been conducted with mixtures have demonstrated clinical effectiveness (see Summary Statement 72).[82,91]

Mold/fungi. Several studies with *Alternaria* and *Cladosporium* species suggest that allergen immunotherapy with fungi might be effective.[102-107] However, the allergen content of most commercially available mold extracts is variable but generally low.[325,326]

Extracts for some potentially clinically important fungi are not available.[327] For example, there are no commercially available extracts for many fungal ascospores, even though they frequently are the dominant type of airborne bioparticulate during certain seasons. Another example is the lack of basidiospore (mushroom) extracts, especially given the evidence that such exposures can be associated with epidemics of asthma in the late fall. It is important that the practicing physician distinguishes between molds that are predominantly found indoors (eg, *Penicillium* and *Aspergillus* genera) and many other molds that are found either exclusively outdoors or both indoors and outdoors and be able to assess the potential clinical effect of each.

There is evidence that proteolytic enzymes present in some mold extracts could digest other antigens, such as pollens or dust mites, when combined in a mixture.[328-330] For this reason, it is desirable to separate pollen and other extracts from extracts with high proteolytic activity when using mixtures (see Summary Statement 84).

Animal dander. Although the best treatment for animal allergy is avoidance, this is not always possible. Exposure to both dog and cat allergen has been shown to be ubiquitous and can

occur even without an animal in the home, making avoidance even more difficult.[331]

Because immunotherapy has been shown to be effective for cat[18,22,47,108-110,332,333] and dog,[21,47] the decision to include dog or cat allergen in an allergen immunotherapy extract should be considered in those circumstances in which there is exposure. However, the major allergen content of cat extracts is relatively low, requiring larger amounts to be given than for pollens or house dust mite. The major allergen content of most dog extracts is too low to allow effective dosing, even with undiluted manufacturers' extracts. However, in one study using an extract containing approximately 161 μg/mL Can f 1 (Hollister-Stier Laboratories, Spokane, Wash), there was a significant dose response of immunologic parameters similar to that demonstrated with other allergens.[21]

Dust mites. Crude house dust extract is generally an inappropriate substitute for house dust mite extract because the protein content is not restricted to dust mite allergens, nor does it necessarily guarantee inclusion of dust mite proteins. Immunotherapy with standardized dust mite is generally more effective than that with crude house dust allergens. The house dust mites *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* contain 2 major allergen groups that are immunologically cross-reactive: Der p 1 and Der f 1 and Der p 2 and Der f 2. Sixty percent or more of mite-sensitive patients react to these 2 major allergen dust mite groups. Allergens from other species of mites (eg, *Blomia tropicalis* and *Euroglyphus maynei*) partially cross-react with allergens from *Dermatophagoides* species.[334,335] Only 50% of the projected amounts of each of the 2 house dust mites (*D pteronyssinus* and *D farinae*) needs to be included when preparing an allergen immunotherapy extract based on the high degree of cross-allergenicity between the major allergens in these 2 species. Immunotherapy for dust mites is effective[17,112,115,116,118] and should be considered in conjunction with avoidance measures in patients who have symptoms consistent with dust mite allergy and specific IgE antibodies for dust mite allergens.

The addition of dust mite immunotherapy after a year of pharmacologic treatment and house dust mite avoidance provided additional clinical benefits in a double-blind, placebo-controlled study of patients with dust mite allergy with mild-to moderate asthma.[112] After an observational year of pharmacologic treatment and allergen avoidance, patients were randomized to receive dust mite SCIT or placebo for 3 years. There was a significant decrease in rescue bronchodilator use, an increase in morning and evening peak expiratory flow rates, and reduction in skin test reactivity in the immunotherapy group compared with values in the placebo group. A similar improvement in asthma symptoms has been demonstrated with dust mite SLIT.[336]

Dust mite hypersensitivity should particularly be considered in patients who have perennial symptoms exacerbated by dusty environments.

Hymenoptera venom. Randomized, double-blind, placebo-controlled studies show that immunotherapy with Hymenoptera venom is effective in dramatically reducing the risk of anaphylaxis to honeybee, yellow jacket, hornet, and wasp stings.[85,158,337] Efficacy has also been demonstrated with immunotherapy using whole-body extracts of imported fire ants.[122,123]

Cockroach

Summary Statement 71: There are limited data on the efficacy of cockroach immunotherapy. B

There are no placebo-controlled trials evaluating the efficacy of cockroach immunotherapy for allergic rhinitis or asthma. One controlled trial demonstrated significant reductions in symptom scores and medication use in asthmatic patients with cockroach hypersensitivity compared with untreated control subjects.[121] This suggests that cockroach immunotherapy might be effective. Although commercially available extracts are "…relatively low in potency, immunotherapeutic doses should be achievable."[338]

Immunotherapy can be considered in conjunction with aggressive avoidance measures, particularly in patients living in the inner city who have perennial allergic symptoms and specific IgE antibodies to cockroach allergens. If immunotherapy with cockroach extract is prescribed, only glycerinated extracts should be used.

The most common species of cockroach identified in dwellings are the German cockroach, *Blatella germanica*, and the American cockroach, *Periplaneta americana.* Allergens derived from *B germanica* include Bla g 2, Bla g 4, and Bla g 5 and that for *P americana* is Per a 1. Partial cross-reactivity between cockroach allergens exists, but each regionally relevant species should be represented in the immunotherapy extract.[339]

Multiallergen immunotherapy

Summary Statement 72: There are few studies that have investigated the efficacy of multiallergen subcutaneous immunotherapy. These studies have produced conflicting results, with some demonstrating significant clinical improvement compared with placebo and others showing no benefit over optimal pharmacotherapy and environmental control measures. Thus it is important to treat the patients only with relevant allergens. B

The vast majority of clinical immunotherapy trials have been with single allergens.[74,130] The limited number of studies investigating the efficacy of multiallergen immunotherapy have produced conflicting results. In general, multiallergen trials have demonstrated efficacy,[47,82,90,340] although some failed to provide results specific to the multiallergens.[9,109,341,342]

A review of the immunotherapy literature identified 13 studies that used 2 or more unrelated allergen extracts: 11 subcutaneous, 2 sublingual, and 1 with both.[343] Four of the 7 studies that used 2 non–cross-reacting allergens reported superior efficacy compared with placebo and comparable efficacy when compared with single-allergen extract treatment. However, the other 3 studies did not report the results between single and multiple allergens separately. In the 5 studies that used multiple allergens, the practice most commonly used by US allergists, 3 demonstrated efficacy,[82,100,344] and 2 did not.[95,188]

The considerable heterogeneity of these clinical trials makes comparison difficult, and the failure of some studies to provide results specific to each allergen makes it difficult to evaluate the efficacy of multiallergen immunotherapy. Further research on the efficacy of multiallergen immunotherapy is needed. It is also important to treat the patients only with relevant allergens.

Basis of allergen extract selection

Summary Statement 73: The selection of the components of an allergen immunotherapy extract should be based on a careful history in correlation with positive allergy skin test results or serum specific IgE antibodies. The allergen

immunotherapy extract should contain only clinically relevant allergens. In choosing the components for a clinically relevant allergen immunotherapy extract, the physician should be familiar with local and regional aerobiology and indoor and outdoor allergens, paying special attention to potential allergens in the patient's own environment. D

A careful history, noting environmental exposures and an understanding of the local and regional aerobiology of suspected allergens, such as pollen, mold/fungi, animal dander, dust mite, and cockroach, is required in the selection of the components for a clinically relevant allergen immunotherapy extract. Although the relationship between day-to-day outdoor pollen and fungi exposure and the development of clinical symptoms is not always clear, symptoms that occur during periods of increased exposure to allergens, in association with positive allergy skin test results or serum specific IgE antibodies, provide good evidence that such exposures are relevant. Because North America is botanically and ecologically diverse, it is not possible to devise a common list of appropriate allergen extracts for each practice location. Only clinically relevant allergens should be included in the allergen immunotherapy treatment.

The clinical relevance of an aeroallergen depends on certain key properties: (1) its intrinsic allergenicity, (2) its aerodynamic properties, (3) whether it is produced in large enough quantities to be sampled, (4) whether it is sufficiently buoyant to be carried long distances, and (5) whether the plant releasing the pollen is widely and abundantly prevalent in the region. The primary allergens used for immunotherapy are derived from plant (grasses, trees, and weeds), arthropod (house dust mites), fungus, animal (cat and dog), insect (cockroach), and Hymenoptera venom source materials. Information concerning regional and local aerobiology is available on various Web sites or through the National Allergy Bureau at http://www.aaaai.org/nab.

A patient's lifestyle can produce exposure to a wide variety of aeroallergens from different regions, necessitating inclusion in the extract of multiple allergens from different geographic areas. Determination of the significance of indoor allergens for a particular patient might be difficult to determine. Historical factors, such as the presence of a furry animal in the home or a history of insect infestation, might be helpful. Animals in the home were associated with much higher dander levels, cockroach sightings correlated with significant cockroach allergen in the home, and dampness in houses has been a risk factor for respiratory symptoms, including asthma. However, some studies have demonstrated significant indoor levels of cat and dog allergen in households without pets[331] and significant levels of murine allergen in suburban[345] and inner-city homes[346] of asthmatic children. In the National Cooperative Inner-City Asthma Study, 33% of the homes had detectable rat allergen (Rat n 1), and a correlation between rat allergen sensitization and increased asthma morbidity in inner-city children was found.[347] Fur-bearing pets and the soles of shoes are also conduits by which molds and other "outdoor" allergens can enter the home.

Several commercial immunoassays to measure the presence of indoor allergens (eg, dust mite, cat, cockroach, and dog) in settled house dust samples are available and might provide useful estimates of indoor allergen exposure.

The omission of clinically relevant allergens from an allergic patient's allergen immunotherapy extract contributes to the decreased effectiveness of allergen immunotherapy. Conversely, inclusion of all allergens to which IgE antibodies are present, without establishing the possible clinical relevance of these allergens, might dilute the content of other allergens in the allergen immunotherapy extract and make allergen immunotherapy less effective.

Inclusion of allergens to which the patient does not have demonstrable specific IgE (ie, nonrelevant allergens) might result in new sensitization rather than induction of tolerance.[348,349] The physician should therefore select those aeroallergens for testing and treatment that are clinically relevant.

As is the case in interpreting positive immediate hypersensitivity skin test results, there must be a clinical correlation with the demonstration of *in vitro* allergen-specific IgE levels and a clinical history of an allergic disease. There is no evidence to support the administration of immunotherapy based solely on results of serum specific IgE testing, as is being done by both commercial laboratories and some physician's offices. This is promoting the remote practice of allergy, which is not recommended.

There are no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma.

Skin tests and serum specific IgE antibody tests

Summary Statement 74: Skin testing has been the primary diagnostic tool in clinical studies of allergen immunotherapy. Therefore in most patients skin testing should be used to determine whether the patient has serum specific IgE antibodies. Appropriately interpreted serum specific IgE antibodies can also be used. C

The use of standardized allergens has greatly increased the consistency of skin test results for these antigens. Controlled studies in which the clinical history has correlated with skin test results have demonstrated the efficacy of immunotherapy for relevant allergens.[17,21,22,47,82,99,103,104,109,121] Skin testing can also provide the physician with useful information about the appropriate starting dose of selected allergens. On rare occasions, systemic reactions can occur after skin testing in a highly sensitive subject.[237,350,351] In addition, skin tests might be difficult to perform in patients with dermatographism or atopic dermatitis. Serum specific IgE tests are particularly useful in such patients.

Studies indicate that skin testing might be more sensitive than *in vitro* tests in detecting allergen-specific IgE.[352-357] Based on nasal/bronchial challenge test results, skin tests have greater sensitivity than serum specific IgE measurement.[356-358] The comparability of skin tests and serum specific IgE antibodies depends on the allergen being tested. For these reasons, skin testing is preferable as a method for selection of allergens for inclusion in immunotherapy and determining the starting dose for an immunotherapy program. Among the skin testing techniques available, a properly applied percutaneous (prick/puncture) test consistently produces reproducible results. Generally, skin prick testing is sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass[359] and cat,[354] are used.

Intradermal/intracutaneous skin testing might be required for some allergen extracts. It is appropriate in some patients to use serum specific IgE tests as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, atopic dermatitis, and stinging insect hypersensitivity. Serum specific IgE tests can also be used to define the allergens that should be used in allergen immunotherapy.

In the case of Hymenoptera venom, immunotherapy can be started even without a live sting challenge in patients with

negative skin test results and positive *in vitro* test results. However, there are no published results of the effectiveness of Hymenoptera VIT in patients with negative skin test results and positive serum venom-specific IgE antibody results.

Allergen extract selection

Summary Statement 75: Nonstandardized extracts can vary widely in biologic activity and composition, regardless of a particular weight/volume or PNU potency, and should not be considered equipotent. B

An allergen extract is a solution of elutable materials derived from allergen source materials, such as pollens or molds. They consist of complex mixtures of proteins and glycoproteins to which antibodies can bind. Cockroach and animal dander contain between 10 and 20 antigens,[360,361] house dust mites between 20 and 40 antigens,[362] and pollens between 30 and 50 antigens,[363-365] and a fungal extract can contain as many as 80 antigens.[366]

Nonstandardized extracts are labeled as weight/volume, which expresses weight in grams per volume in milliliters; that is, a potency of 1:100 indicates that 1 gram of dry allergen (eg, ragweed) was added to 100 mL of a buffer for extraction.

Nonstandardized extracts can also be labeled in PNU, where 1 PNU equals 0.01 g of protein nitrogen. Neither method confers any direct or comparative information about an extract's biologic potency. Nonstandardized extracts can have a wide range of potencies. Extracts labeled with a particular weight/volume or PNU potency can have widely varying biologic activities.[367-369] Therefore they should not be considered equipotent.

Nonstandardized manufacturer's extracts usually are available at concentrations of between 1:10 and 1:50 wt/vol or 20,000 and 100,000 PNU.

Summary Statement 76: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. A

Allergen extracts are commercially available for most of the commonly recognized allergens. Allergen extract potency variability and product composition inconsistency have several potential consequences. Diagnostic allergy skin testing and allergen immunotherapy efficacy and safety are dependent on the quality of the allergen extracts. When possible, standardized extracts should be used to prepare allergen immunotherapy treatment sets.[2,370,371] The advantage of standardized extracts is that the biologic activity is more consistent, and therefore the risk of an adverse reaction caused by extract potency variability should be diminished.

US-licensed extracts can be obtained in aqueous, glycerinated, lyophilized, and acetone- and alum-precipitated formulations. Some commonly used allergens are standardized. These include extracts for cat hair, cat pelt, *D pteronyssinus*, *D farinae*, short ragweed, Bermuda grass, Kentucky bluegrass, perennial rye grass, orchard grass, timothy grass, meadow fescue, red top, sweet vernal grass, and Hymenoptera venoms (yellow jacket, honeybee, wasp, yellow hornet, and white-faced hornet). However, most allergen extracts are not yet standardized. Allergen standardization comprises 2 components: (1) selection of a reference extract and (2) selection of an assay or procedure to compare the manufactured extract with the reference extract. Allergen standardization in the United States is based on assessment of the potency of allergen extracts by using quantitative skin tests and reported as BAU values. The quantitative test method is called the intradermal dilution for 50 mL sum of erythema ($ID_{50}EAL$) system for determining BAU values.[372] The $ID_{50}EAL$ method entails preparing a series of 3-fold dilutions of a candidate reference extract and injecting 0.05 mL intradermally to 15 to 20 "highly sensitive" allergic subjects. The dilution that results in an erythema with the sum of the longest diameter and midpoint (orthogonal) diameter equaling 50 mm is considered the end point (D_{50}). The mean D_{50} is calculated, and the potency of the extract is assigned.

Standardized extracts are available with biologic potencies of 10,000 and 100,000 BAU for grasses; 5,000 and 10,000 BAU for cat allergen; 5,000, 10,000, and 30,000 AU for dust mite; and 100,000 AU or 1:10 and 1:20 wt/vol for short ragweed, with the Amb a 1 concentration listed in FDA units on the label of the weight/volume extracts.

Cat and short ragweed extracts were originally standardized based on the estimate of major allergen content: Fel d 1 and Amb a 1, respectively. The concentrations of Fel d 1 and Amb a 1 were shown to correlate with the overall biological activity of the cat and short ragweed extracts, as determined by means of quantitative skin testing.[367,373]

Short ragweed extract is sold as weight/volume or AU per milliliter, with the Amb a 1 content reported in FDA units: 1 FDA unit of Amb a 1 equals 1 μg of Amb a 1, and 350 units of Amb a 1/mL is approximately equivalent to 100,000 AU/mL. Cat extracts are available as 5,000 and 10,000 BAL/mL, which contain 10 to 19.9 FDA units of Fel d 1/mL: 1 FDA unit of Fel d 1 equals 2 to 4 μg of Fel d 1.[371,373,374] Approximately 22% of subjects with cat allergy have specific IgE antibodies to cat albumin.[375] Cat pelt extracts have a greater amount of albumin than cat hair extracts.[376]

Dust mites were originally standardized in AU by means of the RAST assay. Subsequent $ID_{50}EAL$ testing indicates that the AU is bioequivalent to the BAU, and therefore the original AU nomenclature was retained.[377] Thus dust mite extracts are still labeled in AU.

Allergen extract preparation

Summary Statement 77: Allergen immunotherapy extract preparation should be performed by persons experienced and trained in handling allergenic products. A customized allergen immunotherapy extract should be prepared from a manufacturer's extract or extracts in accordance to the patient's clinical history and allergy test results and might contain single or multiple allergens. D

Allergen immunotherapy extracts carry the risk for anaphylaxis. Compounding personnel should be appropriately trained health professionals, including, but not limited to, registered nurses, licensed practical nurses, medical technicians, medical assistants, physician assistants, advanced practice nurses, and physicians. The compounding personnel should use the allergen extract preparation guidelines, the revised USP 797 pharmaceutical compounding guidelines, or both (Tables VII and VIII).[2,378] The physician is responsible for providing general oversight and supervision of compounding, as well ensuring that the compounding personnel are appropriately trained in the allergen extract preparation guidelines. These guidelines recommend that compounding personnel complete a media-fill test, which is a procedure used to assess the quality of the aseptic technique. The USP 797 guidelines require compounding personnel to perform and pass a media-fill test on at least an annual basis.[379] Both guidelines also recommend that compounding personnel take and pass a written test. The test is available online at

TABLE VII. Allergen immunotherapy extract preparation guidelines

1. **Qualifications of extract preparation personnel**:
   - Compounding personnel must pass a written test on aseptic technique and extract preparation.
   - Compounding personnel must be trained in preparation of allergenic products.
   - Compounding personnel must annually pass a media-fill test, as described in Addendum A.
   - Compounding personnel who fail written or media-fill tests would be reinstructed and re-evaluated.
   - Compounding personnel must be able to demonstrate understanding of antiseptic hand cleaning and disinfection of mixing surfaces.
   - Compounding personnel must be able to correctly identify, measure, and mix ingredients.
   - Compounding personnel should be appropriately trained health professionals, including, but not limited to, registered nurses, licensed practical nurses, medical technicians, medical assistants, physicians' assistants, advanced practice nurses, and physicians.
2. **Physician responsibility**: A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in preparation of immunotherapy with aseptic techniques as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files. The physician is responsible for providing general oversight and supervision of compounding.
3. **Bacteriostasis**: Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if the phenol concentration is less than 0.25%, the extract must have a glycerin concentration of at least 20%.
4. **Dilutions prepared in accordance with manufacturer's instructions**: Allergen extracts must be diluted in accordance with the antigen manufacturer's instructions.
5. **Potency**: The manufacturer's expiration dates must be followed. Beyond-use dates for allergy extract dilutions should be based on the best available clinical data.
6. **Mixing of extracts with high and low proteolytic enzymes**: Cross-reactivity of antigens: Separation of aqueous extracts with high proteolytic enzyme activities from other extracts is recommended.
7. **Storage**: Extracts should be stored at 4°C to reduce the rate of potency loss or according to the manufacturer's directions. Extracts beyond the expiration date of the manufacturer are to be discarded. Storage must be in a designated refrigerator for medications and not used for food or specimens.
8. **Subcutaneous injection**: Allergen extracts can only be administered intradermally or through subcutaneous injection unless FDA-approved package inserts or accepted standards of clinical practice permit another route of administration.
9. **Aseptic technique**: Preparation of allergy immunotherapy shall follow aseptic manipulations defined as follows:
   - The physician must designate a specific site, such as a countertop, in an area of the practice facility where personnel traffic is restricted and activities that might contribute to microbial contamination (eg, eating, food preparation, and placement of used diagnostic devices and materials and soiled linens) are prohibited.
   - The extract preparation area must be sanitized with 70% isopropanol that does not contain added ingredients, such as dyes and glycerin.
   - Extract preparation personnel must thoroughly wash hands to wrists with detergent or soap and potable water. Substitution of hand washing by mean of treatment with sanitizing agents containing alcohol, 70% isopropanol, or both is acceptable.
   - Necks of ampules to be opened and stoppers of vials to be needle punctured must be sanitized with isopropanol.
   - Direct contact contamination of sterile needles, syringes, and other drug-administration devices and sites on containers of manufactured sterile drug products from which drugs are administered must be avoided. Sources of direct contact contamination include but are not limited to touch by personnel and nonsterile objects, human secretions, blood, and exposure to other nonsterile materials.
   - After mixing is complete, visual inspection is to be performed for physical integrity of the vial.
10. **Labeling**: Immunotherapy vials are to be clearly labeled with the patient's name and the beyond-use date of the vial.
11. **Mixing log**: A mixing log is to be kept with information on the patient's name, extract used for mixing, mixing date, and expiration date and lot numbers.
12. **Policy and procedure manual**: Practices preparing allergy extracts must maintain a policy and procedure manual for the procedures to be followed in mixing, diluting, or reconstituting of sterile products and for the training of personnel in the standards described above.

Addendum A. Example of a media-fill test procedure

This or an equivalent test is performed at least annually by each person authorized to compound allergen immunotherapy extracts under conditions that closely simulate the most challenging or stressful conditions encountered during compounding of allergen immunotherapy extracts. Once begun, this test is completed without interruption.

A double-concentrated medium, such as from Valiteq, is transferred in ten 0.5-mL increments with a sterile syringe to a sterile 10-mL vial. Five milliliters of sterile water (preservative free) is added. This is the "concentrate." The vial is incubated within a range of 20°C to 35°C for 14 days. Failure is indicated by visible turbidity in the medium on or before 14 days.

www.JCAAI.org along with an allergen extract preparation handbook that can be used to prepare for the test (http://www.jcaai.org).

Policies, procedures, and processes intended for conventional drugs and medications might be inappropriate for allergenic products. For example, substitution with differing lots, manufacturers, or dose formulations might be routine for conventional drugs and medications but could lead to anaphylactic reactions with allergenic products because of significant differences in the composition, potency, or both of the new extract.

Prepared allergenic products usually have expiration dates of 3 to 12 months from the date of preparation but should not extend beyond the shortest expiration date of the individual components (see Summary Statement 89 for further discussion of allergen extract dilution expiration dates). Allergen immunotherapy extracts are prepared by using sterile manufacturer's extracts and sterile diluents containing antibacterial constituents (usually phenol). There are no reports of infections associated with allergen immunotherapy injections.[380-382]

Extracts obtained from extract-manufacturing companies should be called the manufacturer's extract. Vials of manufacturer's extract contain individual or limited mixtures of allergens that can be used alone as a concentrated dose of single allergen or combined with other concentrated allergens to prepare an individual patient's customized allergen mixture, designated as the patient's maintenance concentrate.

TABLE VIII. USP Chapter 797 sterile compounding standards for allergy vaccine preparation[378,379]

Allergen extracts as compounding sterile preparations (CSPs) are single- and multiple-dose intradermal or subcutaneous injections that are prepared by specially trained physicians and personnel under their direct supervision. Allergen extracts as CSPs are not subject to the personnel, environmental, and storage requirements for all CSP Microbial Contamination Risk Levels in this chapter only when all of the following criteria are met:
1. Before beginning compounding activities, personnel perform a thorough hand-cleansing procedure by removing debris from under fingernails (using a nail cleaner under running warm water), followed by vigorous hand and arm washing to the elbows for at least 30 seconds with either nonantimicrobial or antimicrobial soap and water.
2. Compounding personnel wear hair covers, facial hair covers, gowns, and face masks.
3. Compounding personnel perform antiseptic hand cleansing with an alcohol-based surgical hand scrub with persistent activity.
4. Compounding personnel wear powder-free sterile gloves that are compatible with sterile 70% isopropyl alcohol before beginning compounding manipulations.
5. Compounding personnel disinfect their gloves intermittently with sterile 70% isopropyl alcohol when preparing multiple allergenic extract as CSPs.
6. Ampule necks and vial stoppers on packages of manufactured sterile ingredients are disinfected by careful wiping with sterile 70% isopropyl alcohol swabs to ensure that the critical sites are wet for at least 10 seconds and allowed to dry before they are used to compound allergen extract as CSPs.
7. The label of each multidose vial of allergen extract as CSPs lists the name of one specific patient, a beyond-use date, and a storage temperature range that is assigned based on the manufacturer's recommendations or peer-reviewed publications.
8. Single-dose allergen extract as CSPs shall not be stored for subsequent additional use.

A copy of the complete USP Chapter _77 guidelines can be accessed at http://www.usp.org/USPNF/pf/generalChapter797.html.

The main factor that limits how concentrated an allergen immunotherapy extract can be is the tendency of highly concentrated antigen solutions to develop precipitates. This is an unpredictable and poorly understood phenomenon. Although there is no evidence that such precipitates adversely affect the extract, the FDA does not permit a manufacturer to ship an extract that has a precipitate.

Principles of mixing allergen immunotherapy

Summary Statement 78: Consideration of the following principles is necessary when mixing allergen extracts: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. B

Once the relevant allergen or allergens for each patient are identified, a mixture that contains these allergens can be formulated. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts. Several factors need to be considered when combining extracts, including (1) cross-reactivity of allergens, (2) the need to include the optimal dose for each constituent, and (3) potential interaction between different types of allergens, when mixed, that could lead to degradation of allergen extract components because of proteolytic enzymes.

Cross-reactivity of allergen extract

Summary Statement 79: The selection of allergens for immunotherapy should be based in part on the cross-reactivity of clinically relevant allergens. Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial might be necessary to attain optimal therapeutic doses of each of the components. Many botanically related pollens contain allergens that are cross-reactive. When pollens are substantially cross-reactive, selection of a single pollen within the cross-reactive genus or subfamily might suffice. When pollen allergens are not substantially cross-reactive, testing for and treatment with multiple locally prevalent pollens might be necessary. B

Allergenic cross-reactivity is the recognition by the patient's immune system of different extracts' constituents as the same or similar. When one allergen elicits the same immunologic responses as another cross-reacting allergen, it is not necessary or even desirable to include both in the same mixture.[383] Such a practice might result in the addition of too much of a given allergen, which could lead to an adverse reaction, as well as the unnecessary dilution of other allergens, with a resultant reduction in efficacy. A knowledge of each allergen's classification according to species and the fact that there is immunologic cross-reactivity within allergens of the same genus or subfamily allows one to select components of the allergen immunotherapy extract that are maximally effective. In general, the patterns of allergenic cross-reactivities among pollens follow their taxonomic relationships (see Fig E5 in this article's Online Repository at www.jacionline.org for patterns of allergen cross-reactivity).

Cumulative data, both *in vitro* and *in vivo*, concerning cross-reactivity offer a practical advantage in the selection of several categories of pollen allergens for immunotherapy. However, because cross-reactivity is variable for many grass and weed pollens, their intrinsic allergenicity, prevalence, and aerobiologic characteristics within a specific region should be considered.[384,385] Because many temperate pasture grasses (subfamily Pooideae; eg, fescue, rye, timothy, blue, and orchard, which are widely distributed throughout the United States) share major allergens, inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[386-393] Grasses in other subfamilies (eg, Bermuda, Bahia, and Johnson) show greater diversity and should be evaluated separately.[394-396] Bermuda and Johnson grasses are important in the South, and Bahia has become an important allergenic grass in the lower southern states. Because it is uncertain whether palms, sedges, and cattails have the ability to trigger allergy symptoms, immunotherapy with these allergens is generally not recommended.

Although cross-reactivity among tree pollens is not as pronounced as that among grass or ragweed pollens, it does occur. Pollen from members of the cypress family (Cupressaceous; eg, juniper, cedar, and cypress) strongly cross-react.[383,397-399] Therefore pollen from one member of this family should be adequate for skin testing and immunotherapy. The closely related birch family (Betulaceae; eg, birch, alder, hazel, hornbeam, and hop hornbeam) and oak (Fagaceae; eg, beech, oak, and chestnut) have strong cross-allergenicity.[400,401] Significant cross-reactivity between Betulaceae pollens and oak of the Fagaceae family has been demonstrated with percutaneous skin testing.[386] RAST

inhibition studies have shown cross-inhibition between oaks and other *Fagales* species.[402] IgE immunoblot inhibition experiments have demonstrated that the *Fagales* species might be strongly inhibited by birch species.[403] The use of one of the locally prevalent members (eg, birch and alder) should be adequate.[404]

Ash and European olive trees are strongly cross-reactive; the extract that is the most prevalent in the region and best correlates with symptoms could be used.[405,406] Maple and box elder trees are found throughout the United States, except for the arid southwest. Although in the same genus as maple (ie, *Acer*), box elders appear different and should be considered separately. Oaks and elms (eg, Chinese, Siberian, some American) are prevalent in eastern and central states but have a more limited distribution west of the continental divide. The distribution of other trees is variable enough to require botanical observation in a given locale.

There is strong cross-reactivity between major allergens of common ragweed species (eg, short, giant, false, and western). However, southern and slender ragweed do not cross-react as well,[385,407] and there are allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.[408]

Weeds other than ragweed, such as marsh elders, sages, and mugwort, have an abundant distribution, predominantly in the western states. These weeds and sages (*Artemisia* species) must be treated separately from the ragweeds. Sages are strongly cross-reactive, and a single member can provide adequate coverage of the group.[409] Similarly, Chenopod-Amaranth families have wide ranges in the western regions but are present throughout North America.[410] Current information on the cross-reactivity of these families is limited.[411,412] Skin testing suggests strong cross-reactivity across Chenopod and Amaranth family boundaries. The Amaranth family also seems to have strong cross-reactivity by means of RAST inhibition and immunodiffusion.[413] The use of a single Amaranth extract should be sufficient to cover this family. Similarly, *Atriplex* species (eg, saltbushes and scales) show near identity, and use of a single member is adequate.[414,415] Among other subfamily Chenopod members, Russian thistle appears to have the most cross-allergenicity.

The most prevalent house dust mites, *D pteronyssinus* and *D farinae*, are ubiquitous except in arid or semiarid climates and regions of higher altitudes. *D pteronyssinus* and *D farinae* are members of the same family and genus. They have allergens with extensive cross-reacting epitopes, as well as unique allergenic epitopes. Generally, *D pteronyssinus* and *D farinae* are considered individually. Establishing the practical importance of various allergenic fungi involves many of the same problems encountered in treating pollen allergy. In general, the genera of Deuteromycetes occur in all but the coldest regions. For clinical purposes, molds often are characterized as outdoor (eg, *Alternaria*, *Cladosporium*, and *Drechslera [Helminthosporium]* species) or indoor (eg, *Aspergillus* and *Penicillium* species).

Immunotherapy with standardized extracts of cat hair (Fel d 1 only) or pelt (Fel d 1 plus cat albumin) is available for cat allergy. Although German cockroaches are most likely to occur in American homes, an extract representing an equal mixture of German and American cockroaches might be appropriate for immunotherapy.[416,417] Flying Hymenoptera insects occur throughout the United States. On the other hand, the imported fire ant is found only in the Gulf Coast states, Texas, and some other southern and western states. Likewise, it appears that imported fire ants have become endemic in parts of mainland China, Hong Kong, and parts of Australia, and anaphylaxis has been reported in Europe.[418-420] Commercial venom extracts are available for some Hymenoptera species, except the fire ant, for which only whole-body extract is available.

Dose selection

Summary Statement 80: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. A

The maintenance dose of allergen immunotherapy must be adequate.[17-22,97,421] Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000, 1:100,000, and 1:10,000 vol/vol). A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy extract. Failure to do so will reduce the efficacy of immunotherapy. This might occur because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased.

Summary Statement 81: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The maintenance concentrate vial is the highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial). The projected effective dose is called the maintenance goal. Some subjects unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The maintenance dose is the dose that provides therapeutic efficacy without significant adverse local or systemic reactions and might not always reach the initially calculated projected effective dose. This reinforces that allergy immunotherapy must be individualized. A

The highest concentration of an allergen extract mixture that is projected to be used as the therapeutic effective dose is called the maintenance concentrate. The maintenance concentrate (if a mixture of extracts) should either be obtained from the manufacturer as a customized mixture or should be prepared by the physician under sterile conditions by adding an appropriate volume of the individual manufacturer's extracts. The maintenance concentrate should be formulated to deliver a full projected therapeutic dose of each of its constituent components. However, some patients might not tolerate the targeted therapeutic dose because of local reactions, systemic reactions, or both, and their maintenance dose would be lower (eg, 500 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose] for cat). Such patients might need weaker dilutions of their maintenance concentrate. Subjects who have systemic reactions with doses that are less than the projected effective dose should be maintained on the highest tolerated dose, providing this dose is effective. The highest tolerated effective therapeutic dose is called the maintenance dose. The maintenance dose of immunotherapy for a particular patient must be individualized.

Nonetheless, the original projected maintenance concentration of the allergen immunotherapy extract is still referred to as the maintenance concentrate, and the specific patient's therapeutic dose is called the maintenance dose. The consistent use of this nomenclature system is essential because errors in choosing the correct vial are a reason for systemic reactions, especially when the patient transfers from one physician to another. A new office might be unfamiliar with the nomenclature system used by the previous physician. Therefore it is important that standard

TABLE IX. Probable effective dose range for standardized and nonstandardized US- licensed allergen extracts

Allergenic extract	Labeled potency or concentration	Probable effective dose range	Range of estimated major allergen content in US-licensed extracts
Dust mites: *D farinae* and *D pteronyssinus*	3,000, 5,000, 10,000, and 30,000 AU/mL	500-2,000 AU	10,000 AU/mL 20-160 μg/mL Der p 1, Der f 1* 2-180 μg/mL Der p 2, Der f 2* 78-206 μg/mL Der p 1, Der f 1† 13-147 μg/mL Der p 2, Der f 2†
Cat hair	5,000 and 10,000 BAU/mL	1,000-4,000 BAU	10,000 BAU/mL 20-50 μg/mL Fel d 1*‡ 30-100 μg/mL cat albumin§
Cat pelt	5,000-10,000 BAU/mL	1,000-4,000 BAU	10,000 BAU/mL 20-50 μg/mL Fel d 1*‡ 400-2,000 μg/mL cat albumin§
Grass, standardized	100,000 BAU/mL	1,000-4,000 BAU	100,000 BAU/mL 425-1,100 μg/mL Phl p 5* 506-2,346 μg/mL group 1‖
Bermuda	10,000 BAU/mL	300-1,500 BAU	10,000 BAU/mL 141-422 Cyn d 1 μg/mL*
Short ragweed	1:10, 1:20 wt/vol, 100,000 AU/mL	6-12 μg of Amb a 1 or 1,000-4,000 AU	1:10 wt/vol 300 μg/mL Amb a 1‡ Concentration of Amb a 1 is on the label of wt/vol extracts
Nonstandardized AP Dog	1:100 wt/vol	15 μg of Can f 1	80-400 μg/mL Can f 1† 10-20 μg/mL dog albumin¶
Nonstandardized extract, dog	1:10 and 1:20 wt/vol	15 μg of Can f 1	0.5 to 10 μg/mL Can f 1† <12-1,500 μg/mL dog albumin¶
Nonstandardized extracts: pollen	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	0.5 mL of 1:100 or 1:200 wt/vol	NA
Nonstandardized extracts: mold/fungi, cockroach	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose	NA
Hymenoptera venom	100 μg/mL single venom 300 μg/mL in mixed vespid extract	50-200 μg of each venom	100-300 μg/mL of venom protein
Imported fire ant	1:10 to 1:20 wt/vol whole-body extract	0.5 mL of a 1:100 wt/vol to 0.5 mL of a 1:10 wt/vol extract	NA

NA, Information not available.
*ALK-Abelló ELISA.
†Indoor Biotechnology ELISA.
‡FDA radial immunodiffusion assay.
§Greer Radial Immunodiffusion assay.
‖Greer ELISA.
¶Hollister-Stier ELISA using Innovative Research, Inc, reagents.

terminology be adopted by all physicians who prescribe allergen immunotherapy.

The therapeutically effective doses used in controlled clinical studies are the basis of the recommended dosage range of standardized extracts presented in Tables IX and X. For allergens that have not been standardized, the effective dose must be estimated and individualized. It is important to keep a separate record of the contents of each extract, including final dilutions of each of the constituents. Although early improvement in symptoms has been documented with these doses, long-term benefit appears to be related not only to the individual maintenance dose but also the duration of treatment.[99,135]

Because a full dose-response curve has not been determined for most allergens, it is possible (and supported by expert opinion) that therapeutic response can occur with doses lower than those that have been shown to be effective in controlled studies. In general, however, low doses are less likely to be effective, and very low doses usually are ineffective.[18,20,21,24,25,97] Although administration of a higher maintenance dose of immunotherapy increases the likelihood of clinical effectiveness, it also increases the risk of systemic reactions. In particular, highly sensitive patients might be at increased risk of a systemic reaction to immunotherapy injections with higher maintenance doses.

The concept of highest tolerated dose does not apply for VIT, and all patients are expected to achieve the full recommended dose for the necessary degree of protection. There are conflicting data over whether lower doses (50 mg) are less effective, but there are also data showing that 200 mg is more reliably effective.[421] In the case of VIT, patients are expected to tolerate LLRs to achieve the full dose, even though with inhalant immunotherapy the dose can be reduced for such LLRs to minimize the patient's discomfort.

The allergist/immunologist might need to prepare more than 1 maintenance concentrate to provide a therapeutic dose of each of the allergens for the polysensitized patient.

TABLE X. Basis for allergen extract dosing recommendations

Major allergen content: Multiple studies demonstrate that the efficacious dose for allergen immunotherapy is between 5 and 20 μg of the major allergen per injection. Two extracts licensed in the United States are standardized based on major allergen content (measured by means of radial immunodiffusion): short ragweed (Amb a 1) and cat (Fel d 1). Patients might also have IgE sensitivity to multiple allergens in the extracts.

Currently, only the Amb a 1 and Fel d 1 FDA-issued radial immunodiffusion test reagents are standardized and used by all US manufacturers for short ragweed and cat hair and pelt extracts. The house dust mite, grass pollen, and dog hair major allergen assays are not standardized by the FDA and are either purchased or used internally by individual manufacturers.

Nonstandardized extracts: The labeled concentrations for the nonstandardized extracts have no established standards for biologic potency. Nonstandardized extracts are labeled on the basis of PNU values or the weight of the source material extracted with a given volume of extracting fluid (wt/vol). There are no dose-response studies with nonstandardized extracts. When analyzed, the nonstandardized pollen extracts demonstrate potency that is similar to that of grass and ragweed, although with a wider range. A target dose of 0.5 mL of a 1:100 or 1:200 wt/vol of nonstandardized extract is reasonable.

Cockroach and mold/fungi extracts are generally of low potency and vary considerably in composition. Only glycerinated cockroach or mold/fungi extracts should be used, and they should be used at higher doses than the nonstandardized pollens.

Dust mites: There are no dose-response studies with US-licensed dust mite extracts, and dosing recommendations in AUs are extrapolated from published European studies that use aqueous[475] and alum-precipitated extracts.[17,118] One study, designed to investigate the effect of 3 doses of an alum-precipitated *D pteronyssinus* extract (0.7, 7, and 21 μg of Der p 1), found a dose-response effect on efficacy and side effects.[17] The authors suggested that the optimal maintenance dose is 7 μg of Der p 1. Corresponding doses are based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Appropriate dose reductions would need to be made when combining antigens that have a strong degree of cross-reactivity, such as *D pteronyssinus* and *D farinae*.

Cat hair and pelt: The major cat allergen Fel d 1 is reported in FDA units (Fel d 1 U) with 1 Fel d 1 U equal to approximately 2 to 4 μg of Fel d 1.[370,374,476] The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 U to 19.9 U/mL. One study demonstrates clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 (or highest tolerated) dose in terms of decreased cat extract PD_{20}, titrated skin test results, and allergen-specific IgE and IgG.[332,333] In a study that investigated the efficacy in terms of immunologic changes of 3 doses of a US-licensed cat extract (0.6, 3, and 15 μg of Fel d 1 from ALK-Abelló, Round Rock, Tex) there was significant effect on titrated skin prick tests, allergen-specific IgG4 levels, and $CD4^+$/IL-4 only in the group treated with 15 μg of Fed 1, although the 3-μg dose group did demonstrate a significant change in titrated skin test response and an increase in cat-specific IgG4 levels.[18]

Grass: There have been no dose-response studies with US-licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,[99] alum-precipitated,[20,128] and calcium phosphate–precipitated grass pollen extracts.[477] One of these studies compared a dose of 2 μg with 20 μg of major timothy grass allergen (Phl p 5) and found clinical efficacy at both doses.[20] The efficacy was greater in the dose of 20 μg of Phl p 5, but the systemic reaction rate was also higher in the high-dose group. The package inserts for US-licensed grass pollen extracts contain a table to convert the nonstandardized units (wt/vol and PNU) for which there have been studies that have demonstrated efficacy into BAUs. Appropriate dose reductions would need to be made when combining antigens that have a strong degree of cross-reactivity, such as the Northern pasture grasses (subfamily Pooideae; eg, perennial rye, meadow fescue, or timothy).

Bermuda grass: Bermuda grass has an assigned potency of 10,000 BAU, which is 10-fold less than the other standardized grasses. However, the major allergen content of Bermuda grass according to one extract manufacturer (ALK-Abelló) was 348 μg/mL of Cyn d 1 with a range of 141 to 422 μg/mL, and this is similar to the major allergen content of the other standardized grasses.[478] It has been speculated that the apparent discrepancy in assigned potency to Bermuda grass extract was the result of standardization (ID_{50}EAL testing) undertaken in a nonendemic area for Bermuda grass.

Short ragweed: Short ragweed is reported in FDA units, with 1 U of Amb a 1 equaling 1 μg of Amb a 1. The potency units for short ragweed extracts were originally assigned based on their Amb a 1 content. Subsequent data suggest that 1 U of Amb a 1 is equivalent to 1 μg of Amb a 1, and 350 Amb a 1 U/mL is approximately equivalent to 100,000 AU/mL.[376] The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2,000 AU, with a range of 1,000 to 4,000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrates a significant improvement in ragweed nasal challenge in patients treated with a mean dose of 6 μg of Amb a 1 for 3 to 5 years compared with an untreated matched control group.[479] A ragweed dose-response study (0.6, 12.4, and 24.8 μg Amb a 1) demonstrates efficacy as measured by nasal challenge at 12 and 24 μg Amb a 1.[97] The efficacy of the 24-μg dose was not significantly better than that of the 12-μg dose, and the authors concluded that the optimal dose for ragweed extract is greater than 0.6 μg but not more than 12.4 μg of Amb a 1.

Dog hair or pelt extracts: Dog hair or pelt extracts are not standardized, and potency is reported as wt/vol or PNU per milliliter. One dose-response study with a US-licensed dog hair extract investigated the efficacy of 3 doses (AP dog hair; Hollister-Stier; 0.6, 3, and 15 μg of Can f 1) in terms of immunologic changes and found the dose of 15 μg of Can f 1 to be most efficacious.[21] The 3-μg dose also demonstrated significant efficacy, although not as great as the 15-μg dose. The extract used in the dosing study was assayed at 160 μg/mL. Subsequent lots assayed ranged between 80.4 and 396.3 μg/mL Can f 1 (110 lots; mean of 170.8 μg/mL Can f 1 [SD, 52.3 μg/mL]); information provided by the extract manufacturer, Hollister-Stier, by using references calibrated back to Indoor Biotechnologies ST-CF1 standard to maintain consistency with original clinical trial recommendations.

Hymenoptera venom: The recommended maintenance dose for stinging Hymenoptera venom immunotherapy is 100 μg of each insect venom.[158] However, there is some controversy about the optimum maintenance dose. Initial studies used 100 μg as the maintenance dose. One investigator has used the 50-μg maintenance dose in patients with yellow jacket allergy successfully,[147] although some believe that this dose offers a lesser degree of protection. Increasing the maintenance dose up to 200 μg per dose has been effective in achieving protection in some patients who have experienced sting reactions while receiving a 100-μg maintenance dose of VIT.[421] (see "Stinging insect hypersensitivity: a practice parameter update II" for a more detailed discussion of venom and imported fire ant immunotherapy dosing).

Imported fire ant: The optimal dose for fire ant whole-body extract immunotherapy is less well defined. Most reports have recommended 0.5 mL of a 1:100 wt/vol extract with either *Solenopsis invicta* or a mixture of *Solenopsis invicta* and *Solenopsis richteri* extract, although there are some recommendations for a dose as high as 0.5 mL of a 1:10 wt/vol extract.[122,123,152,298]

Proteolytic enzymes and mixing

Summary Statement 82: Studies designed to investigate the effect of combining extracts with high proteolytic activity, such as cockroach and mold/fungi, with extracts such as pollen, dander, and dust mite, have demonstrated a significant loss of potency with some of these extracts. Separation of extracts with high proteolytic enzyme activities from other extracts is recommended. It might be necessary to prepare 2 or more vials

to provide allergen immunotherapy containing an optimal dose of each component while avoiding allergen extract combinations that might result in degradation of some or all of the components. B

Many allergen extracts contain mixtures of proteins and glycoproteins. Proteolytic enzymes can degrade other allergenic proteins. There have been reports of interactions between extracts when mixed together.[328-330,422,423] Extracts such as *Alternaria* species have been shown to reduce the IgE-binding activity of timothy grass extract when mixed together. Studies designed to investigate the effect of combining mold/fungi extracts with pollen extracts have demonstrated a significant loss of potency of grass pollen, cat, birch, white oak, box elder, dog, and some weeds.[329,330,422,423] Cockroach had a similar deleterious effect on pollen extract potency.[422,424] The evidence on mixing cockroach extract with dust mite and ragweed extracts is conflicting.[329,330,422] Short ragweed appeared resistant to the effects of the proteolytic enzymes in one study,[330] but another study found short ragweed Amb a 1 was susceptible to proteases present in *Penicillium* and *Alternaria* species extracts at relatively low (10%) glycerin levels.[329]

Dust mite extracts do not appear to have a deleterious effect on pollen extracts.[329,330,422,424] These studies suggest that pollen, dust mite, and cat extracts can be mixed together.[328] The effect of the combination of high proteolytic-containing extracts on each other or the extent of self-degradation of allergenic proteins has not been extensively studied, and the clinical relevance of the changes is also unclear.

Because such interactions between extracts have not been fully delineated, consideration should be given to keeping extracts that tend to have high proteolytic enzyme activities, such as fungi and cockroach extracts, separate from those extracts susceptible to their action, such as pollen.[328]

It is not recommended to mix venoms together (eg, wasps or honeybee with yellow jacket), even though yellow jacket and hornet venom are available premixed as a mixed-vespid extract.

Preparing allergen immunotherapy extracts that contain an optimal dose of each allergen extract, a determinant of efficacy, which does not contain allergen extract combinations that result in degradation of some of all or all of the components, might require preparation of 2 or more vials.

Therefore 2 or more injections might be needed to be given at each patient's visit depending on whether all of the relevant extracts can be mixed into a single vial and still deliver an optimal dose of each allergen.

Allergen immunotherapy extract handling

Storage. Summary Statement 83: Allergen immunotherapy extracts should be stored at 4°C to 8°C to reduce the rate of potency loss. B

Because the efficacy and safety of immunotherapy depend on the use of allergen immunotherapy extracts with reasonably predictable biologic activity, it is important that they be stored under conditions that preserve such activity. The potency of allergen immunotherapy extracts is affected by several factors, including the passage of time, temperature, concentration, number of allergens in a vial, volume of the storage vial, and presence of stabilizers and preservatives. Allergen immunotherapy extracts, including reconstituted lyophilized extracts, should be stored at 4°C to 8°C to minimize the rate of potency loss because storage at higher temperatures (eg, room temperature) can result in rapid deterioration.[425]

Summary Statement 84: Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions. It is the responsibility of each supplier or manufacturer to ship extracts under validated conditions that are shown not to adversely affect the product's potency or safety. C

Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions (personal communication, Robert Esch, PhD, Greer, Lenoir, NC). These studies include actual shipments made by their carriers to places like Phoenix in the summer and Alaska in the winter. One study that evaluated the potency of standardized timothy grass extracts mailed round trip between San Antonio, Texas, and Phoenix, Arizona, during August produced no significant reductions in relative potencies *(in vitro)* or skin test reactivity *(in vivo)* in 3 sensitive patients.[426] The results of these studies are on file under each manufacturer's product licenses. Each study is specific to each manufacturer because the packaging (eg, use of insulation) varies from company to company. It is the responsibility of each supplier or manufacturer to ship allergen extracts under validated conditions that have been shown not to adversely affect the product's potency or safety.

Allergen extract expiration dates. Summary Statement 85: In determining the allergen immunotherapy extract expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by several factors separately and collectively, including (1) storage temperature, (2) presence of stabilizers and bactericidal agents, (3) concentration, (4) presence of proteolytic enzymes, and (5) volume of the storage vial. D

The potency of concentrated allergen immunotherapy extracts (1:1 vol/vol up to 1:10 vol/vol) when kept at 4°C is relatively constant and allows the extract to be used until the expiration date that is present on the label. Less concentrated allergen immunotherapy extracts are more sensitive to the effects of temperature and might not maintain their potency until the listed expiration date.[425,427]

The mixing of other allergens might decrease the loss of potency with time because the additional allergens might prevent adherence of proteins to the vial's glass wall. Thus highly concentrated extracts are more stable than diluted ones. Extracts are prepared as aqueous, glycerinated, freeze-dried, and alum formulations. Aqueous and glycerin diluents are compatible for mixing standardized with nonstandardized products. Lyophilization is used to maintain the strength of the dry powder, but once the allergen immunotherapy extract is reconstituted, stabilizing agents, such as human serum albumin (0.03%) or 50% glycerin, are needed to maintain potency.[427] Phenol is a preservative added to extracts to prevent growth of microorganisms.

Phenol can denature proteins in allergen extracts.[428,429] Human serum albumin might protect against the deleterious effect of phenol on allergen extracts.[428] Human serum albumin might also prevent the loss of potency within storage vials by preventing absorption of allergen on the inner surface of the glass vial. Glycerin is also a preservative. At a concentration of 50%, glycerin appears to prevent loss of allergenic potency, possibly through inhibition of the activity of proteolytic and glycosidic enzymes that are present in certain extracts. However, it might cause discomfort when injected.[221]

There are few studies that have investigated the potency of dilutions of allergen extract mixtures over time. Expiration dates for allergen extract dilutions are somewhat empiric and not strongly evidence based. A study undertaken by the AAAAI's Immunotherapy and Allergy Diagnostic committee designed to study the stability of a mixture of standardized extracts in 4 conditions of storage (with and without intermittent room temperature exposure and diluted in normal saline or human serum albumin) found that short ragweed at 1:10 vol/vol dilution, as measured by means of radial immunodiffusion, was stable in all conditions of storage over 12 months.[430] Dust mite and cat at 1:10 and 1:100 vol/vol dilutions were also stable in all conditions of storage over 12 months, as measured by using an ELISA assay with an mAb for Der p 1, Der f 1, and Fel d 1.

The expiration date of any dilution should not exceed the expiration date of the earliest expiring constituent that is added to the mixture.

Customized individualized allergen immunotherapy extracts

Summary Statement 86: Administration of an incorrect injection is a potential risk of allergen immunotherapy. An incorrect injection is an injection given to the wrong patient or a correct patient receiving an injection of an incorrect dose. A customized individual maintenance concentrate of the allergen immunotherapy extract and serial dilutions, whether a single extract or a mixture of extracts, prepared and labeled with the patient's name and birth date might reduce the risk of incorrect (ie, wrong patient) injection. D

Summary Statement 87: The mixing of antigens in a syringe is not recommended because of the potential for treatment errors and cross-contamination of extracts. C

Individually prepared and labeled vials are recommended because they have several potential advantages over shared vials (ie, vials of allergen extract used for multiple patients). These potential advantages include being able to prepare labels with specific patient identifiers, less distractions during mixing, and less frequent mixing.

Labels on patient-specific vials can provide at least 2 patient identifiers (eg, birth date and patient name), which would be consistent with the recommendations of the Joint Commission National for Patient Safety Goals: "Goal 1: Improve the accuracy of patient identification. Use at least two patient identifiers when providing care, treatment or services."[27] Acceptable identifiers include the patient's name, birth date, assigned identification number, telephone number, or other person-specific identifier.[27] The risk of errors of administration might be reduced because the individually prepared allergen immunotherapy vials labeled with the patient's name and birth date will allow the person administering the extract and the patient an opportunity to verify the name/birth date on the label before administering the injection.[26,27]

In a survey endorsed by the AAAAI and JCAAI of 1,717 allergists, 57% of the 476 respondents reported at least 1 wrong-patient injection, and 74% of the 473 respondents reported at least 1 wrong-dose injection in the previous 5 years.[26] The incorrect injections resulted in 1 death, 29 hospital admissions, and 59 emergency department visits. In addition to patient identifiers on vial labels, the authors cited several other reasons why patient-specific vials might reduce incorrect injection errors. One reason was that they can be prepared in a confined laboratory setting, which might provide substantially fewer distractions than a situation in which a nurse is trying to concentrate on drawing up the injection correctly while in the room with the patient.

With individually prepared vials, the specific components are mixed once, whereas the mixing would be repeated on every injection visit if the allergen extract were withdrawn from different stock solutions, as it in the mixing of antigens in the syringe (also referred to as "off-the-board"). In addition, the mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. This procedure might pose an increased risk for dosing error if the nurse is drawing up the injections from multiple solutions of different composition or dilution with similar labels (eg, mold mix I 1:10 and mold mix II 1:100).

Some allergists/immunologists prefer to administer immunotherapy doses drawn directly from a stock dilution of an individual allergen extract or mixture of allergens and inject the extract into the patient (shared- patient vials). If shared-patient vials are used, it is essential that policies and procedures are developed to verify that the correct allergen and correct dose is administered to the correct patient. Data are not available to determine whether treatment errors are more common with this method of administration.

If the allergen immunotherapy is administered from vials without specific patient identifiers, measures to reduce the likelihood of a wrong injection error that might result from similar labels (eg, weed mix I 1:10 and weed mix II 1:100) should be implemented.

To improve the safety of using medications, the Joint Commission recommends that an "… [organization] identifies and at a minimum, annually reviews a list of look-alike/sound-alike medications used by the [organization] and takes action to prevent errors involving the interchange of these medications."[27]

Allergen extract dilution labeling and nomenclature

Summary Statement 88: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. D

In preparation for the build-up phase of immunotherapy, serial dilutions should be produced from each maintenance concentrate. Typically, these are 10-fold dilutions, although other dilutions occasionally are used. These dilutions should be labeled in terms of volume/volume to indicate that they are dilutions derived from the maintenance concentrate. For example, serial 10-fold dilutions from the maintenance concentrate would be labeled as 1:10 (vol/vol) or 1:100 (vol/vol). Alternatively, the vial dilutions can be labeled in actual units (eg, 1,000 BAU or 100 BAU), but this system can be complicated if allergens with different potency units are used (eg, weight/volume, BAU, AU, or PNU), and this can make it difficult to easily interpret the vial label.

Instructions on how to prepare various allergen extract dilutions are shown in Table XI. If the final volume of the diluted allergen immunotherapy extract to be produced is 10 mL, then one tenth of that final volume, or 1.0 mL, should be removed from the more concentrated allergen immunotherapy extract and added to a new bottle containing 9.0 mL of diluent.

TABLE XI. Procedure for dilutions from the maintenance concentrate (1:1 vol/vol)

Dilution from maintenance concentrate vaccine	Extract volume (mL)	Diluent volume (mL)	Final volume (mL)	Final concentration
1:1 (vol/vol)	1.0	0.0	1.0	1:1 (vol/vol)
1:1 (vol/vol)	2.0	8.0	10.0	1:5 (vol/vol)
1:1 (vol/vol)	1.0	9.0	10.0	1:10 (vol/vol)
1:10 (vol/vol)	1.0	9.0	10.0	1:100 (vol/vol)
1:100 (vol/vol)	1.0	9.0	10.0	1:1000 (vol/vol)

All dilutions are expressed as vol/vol from the maintenance concentrate.

TABLE XII. Suggested nomenclature for labeling dilutions from the maintenance concentrate

Dilution from maintenance concentrate	Vol/vol label	No.	Color
Maintenance concentrate	1:1	1	Red
10-fold	1:10	2	Yellow
100-fold	1:100	3	Blue
1,000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

Effect of dilution on dose

Summary Statement 89: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. A

The more antigens that are added to the maintenance concentrate, the more there is the potential to dilute other antigens in the allergen immunotherapy extract, thereby limiting the ability to deliver a therapeutic effective dose for any given allergen.

If the appropriate concentration of each allergen extract is added, then adding additional allergens to the maintenance concentration will have no effect on the concentration of the other allergens, as long as the additional allergens are replacing diluent. For example, if the desired maintenance concentration for cat is 2,000 BAU/mL, 2 mL of the manufacturer's extract (10,000 BAU/mL for cat) can be added to 8 mL of diluent or 8 mL of other allergens, and the final concentration of cat will be 2,000 BAU/mL in both mixtures. Once the diluent is all replaced, addition of further allergens will result in undesirable dilution of all allergens in the maintenance mixture.

Summary Statement 90: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. D

During the build-up phase of immunotherapy, several dilutions of the patient's maintenance concentrate are needed. Use of one labeling system to indicate dilutions might help to avoid administration errors (Table XII). In addition to the labeled dilution from the maintenance concentrate (volume/volume), a numbering system, a color-coding system, or an alphabetical system should be used. If this uniform labeling system is used, it is essential that it be used in the same way by all physicians to reduce potential administration errors by staff unfamiliar with the labeling system. If the current labeling system is different, the transition toward the uniform labeling system should be gradually phased in to reduce potential errors, and the staff involved with preparation and administration of allergen immunotherapy should be involved with the planning of this transition.

If a numbering system is used, the highest concentration should be numbered 1. This is necessary to provide consistency in labeling because if larger numbers are used to indicate more concentrated extracts, the number of the maintenance concentrate would vary from patient to patient depending on the number of dilutions made. If a color-coding system is used, it should be consistent (eg, the highest concentration should be red, the next highest yellow, followed by blue, green, and silver in that order; Figs 2 and 3).

Regardless of the labeling system used for indicating dilutions from the maintenance concentrate, the specific contents of each allergen immunotherapy extract should be listed separately. The volume and concentration of each of its constituents should be listed on the immunotherapy prescription form.

Consistency is essential as a basis for adoption of a standardized system. Some allergists/immunologists, however, have found it helpful to use letters for designating different component mixtures of extracts (eg, trees [T], grasses [G], and molds [M]; see Table E9 in this article's Online Repository at www.jacionline.org).

Documentation and record keeping

Summary Statement 91: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be documented. D

An immunotherapy injection should not be given unless adequate documentation is available in the patient's medical record. This also means that patients who receive injections in a health care facility other than the office of the prescribing physician must have appropriate documentation. The recommended documentation for informed consent to allergy immunotherapy, examples of prescription and administration forms, and other similar sample documents can be found in this article's Online Repository at www.jacionline.org. These forms, along with examples of immunotherapy consent and instruction forms, can also be found at http://www.aaaai.org and http://www.acaai.org.

NONINJECTION ROUTES OF IMMUNOTHERAPY

Summary Statement 92: Allergen extracts can be administered through several routes in addition to the subcutaneous route. Currently, there are no FDA-approved formulations for a noninjection immunotherapy extract. A

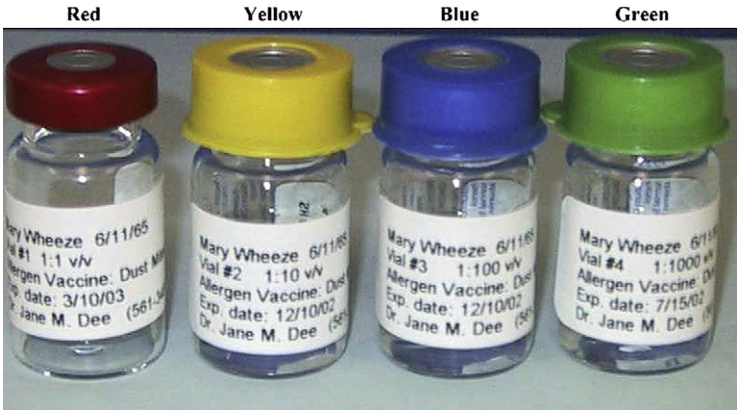


FIG 2. Example of color-coded vials of allergen immunotherapy maintenance.

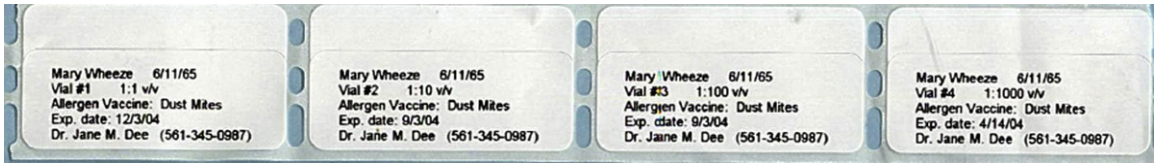


FIG 3. Example of labels for allergen immunotherapy maintenance concentrate and dilutions.

Favorable results have been reported with intranasal,[431] intrabronchial,[432] sublingual,[433-435] oral,[436] intralymphatic,[437] and epicutaneous[438] administration. With intranasal and intrabronchial allergen administration, local symptoms were decreased by use of pretreatment with sodium cromoglycate. Despite reported clinical successes, both approaches have been largely abandoned. Intralymphatic and epicutaneous administration are newly described approaches, which will be discussed in a later section. Administration of pollen allergen extracts through the oral route reduces symptoms caused by natural pollen exposure, but the dose required is much greater compared with that required through the subcutaneous route; gastrointestinal side effects are frequent. The oral approach has been largely abandoned for inhalant allergens but has been pursued for treatment of food allergy in children.[174,176,439,440] Presently, immunotherapy for inhalant allergens through the oral route is limited to sublingual administration, with subsequent swallowing of the extract (SLIT).

The efficacy and safety of SLIT for aeroallergen-induced allergic rhinitis with or without asthma is currently under investigation in the United States. Clinical trials evaluating the safety and efficacy of oral immunotherapy and SLIT for food hypersensitivity are also being conducted in the United States.

Summary Statement 93: Randomized controlled clinical trials with dust mite and pollen sublingual immunotherapy have demonstrated significant improvement in symptoms and medication use in patients with allergic rhinitis and asthma. A

Several meta-analyses conclude that SLIT is effective in the treatment of allergic rhinitis[441,442] and allergic asthma[443,444] in adults and children. Although these meta-analyses are criticized because of discrepancies, inconsistencies, and lack of robustness,[445] they conclude that SLIT is effective, as confirmed by several studies, each with hundreds of subjects. These large studies have been conducted primarily in grass-sensitive subjects with allergic rhinitis.[211,433,446] Two studies used daily doses of grass pollen extract containing 15 to 25 μg of group 5 allergen for a monthly cumulative dose 22.5 to 37.5 times the monthly maintenance dose proved effective by means of injection. Doses one third of the effective dose were not superior to placebo in 2 of these studies.[211,433] The grass pollen extract in these studies was administered as early as 4 months before the pollen season or as late as the first day of the grass pollen season.[446] As opposed to the clear dose responses in these studies, other studies with various allergens administered by means of SLIT report both positive and negative results with doses ranging from 2 to 375 times the cumulative monthly doses used by means of injection.[447] Thus the appropriate dose for SLIT with most inhalant allergens is not established. Also not established is the relative efficacy of SLIT versus SCIT because the few comparative studies available are underpowered.

Studies of SLIT have shown that it can reduce new sensitization, methacholine sensitivity, and the onset of asthma.[448,449] Improvement in allergic rhinitis persists for at least 1 year after discontinuation of 3 years of SLIT with grass pollen extract.[211,446] SLIT improves mild-to-moderate atopic dermatitis caused by house dust mite sensitivity[16] and increases the tolerance to hazelnuts in allergic subjects, some of whom have had anaphylactic reactions.[172,450]

Adverse reactions to SLIT

Summary Statement 94: Local reactions, primarily oral-mucosal, are common with sublingual immunotherapy. Systemic reactions can occur, and a few have been reported in subjects who were unable to tolerate subcutaneous immunotherapy. A few reported cases have been of a severity to be categorized as anaphylaxis. A

Local reactions to SLIT are common. In a study of 316 subjects receiving grass tablets without build-up, oral pruritus was reported by 46%, and edema of the mouth was reported by 18%.[451] Most of these local symptoms were reported to be mild

to moderate in severity and did not persist with continued treatment; fewer than 4% of subjects discontinued the study because of side effects. Local reactions are no more common when there is no initial build-up in dosing.[447] There are no deaths reported with SLIT; however, systemic reactions occur, and a few have been of a severity to be categorized as anaphylaxis.[452-455] Notable are 2 subjects who did not tolerate SCIT who had anaphylactic reactions with the first dose of SLIT.[456] Other authors also report systemic reactions to SLIT in patients who had not tolerated SCIT.[457]

Summary Statement 95: Clinical trials evaluating the safety and efficacy of sublingual immunotherapy for patients with ragweed- and grass pollen–induced allergic rhinitis. Currently, there are no FDA-approved formulations for sublingual immunotherapy. A

It was estimated in 2009 that 45% of specific immunotherapy in Europe was administered as SLIT.[458] In the United States SLIT is used much less commonly. A survey of 828 US practicing allergists in 2007 revealed that 66% had tried SLIT, but only a quarter of them reported extensive experience.[459] The respondents report that the major limiting factors for the use of SLIT in the United States were the lack of allergy extracts approved by the FDA for sublingual administration (61.7%) and the lack of knowledge of effective doses (27.5%). Because there are no approved extracts for SLIT, no billing codes exist. Another problem for the use of SLIT in the United States is that most double-blind, placebo-controlled studies demonstrating efficacy used a single allergen extract. A preliminary study comparing timothy grass monotherapy with the same dose of timothy grass administered in combination with 9 other pollen extracts suggests that efficacy might be seriously reduced with administration of multiple allergen extracts sublingually.[460] The typical allergen extract for use in the United States contains 8 unique allergen extracts.[461] Until these limitations are overcome, the administration of allergen immunotherapy through the sublingual route must be considered as "investigational" in the United States.

Intranasal immunotherapy

Summary Statement 96: Randomized controlled studies have demonstrated that nasal immunotherapy with dust mite and pollen extracts is effective in reducing symptoms and medication use. Local adverse reactions are common with this approach and are the most frequently cited reason for discontinuation of treatment in one large prospective study. The use of this approach has decreased considerably since the introduction of SLIT. C

Randomized placebo-controlled studies demonstrate that intranasal administration of allergen extracts improves symptoms of allergic rhinitis both to pollens[431,462-466] and house dust mites.[467] Allergic symptoms caused by the topical administration of allergens are greatly reduced by premedication with topical cromolyn sodium. A study of 3 unrelated weed extracts demonstrates efficacy for this multiallergen mixture.[466] A 3-year study with *Parietaria judaica* reports persistent benefits for up to 12 months after conclusion of nasal immunotherapy.[465] Local reactions are fairly common with this approach and are the most common reason for discontinuation of treatment in a 3-year prospective study of 2,774 children investigating compliance with nasal immunotherapy, SCIT, and SLIT.[468] By the end of the first year, 43.9% of the children discontinued nasal immunotherapy, with 56.6% citing "unpleasant" as the reason. The use of this approach to immunotherapy has essentially stopped since the introduction of SLIT, and no recent clinical trials of either intranasal or intrabronchial immunotherapy are available.

Intralymphatic

Summary Statement 97: A 3-injection course of intralymphatic immunotherapy was as effective as a 3-year course of conventional subcutaneous immunotherapy in a noncontrolled study. NR

A noncontrolled study was conducted with 165 patients with grass pollen allergy, comparing 3 injections of grass allergen extract into the inguinal lymph nodes at 4-week intervals with 3 years of conventional SCIT.[437] The total extract dose was more than 1,000-fold less with the intralymphatic injections. Systemic reactions were less frequent, but nasal tolerance to allergen increased more rapidly with intralymphatic injections. After 3 years, there were no clinical differences in outcomes between the 2 treatments.

Epicutaneous

Summary Statement 98: Epicutaneous immunotherapy resulted in significantly higher treatment success in a placebo-controlled study. However, there were no significant differences in the primary outcome and nasal provocation test scores between the groups. NR

A placebo-controlled trial has been reported of application of grass pollen extract in the form of a patch applied once weekly for 12 weeks and left in place for 48 hours each time.[438] Treatment was initiated 4 weeks before and continued through the 2006 grass pollen season. Subjects receiving active treatment reported fewer symptoms than the placebo-treated subjects for both the 2006 and 2007 grass pollen seasons. However, there were no significant differences in the primary outcome, nasal provocation scores, between the placebo and treatment groups. The major adverse effect was an eczematous reaction at the application sites.

Oral immunotherapy and SLIT for food hypersensitivity

Summary Statement 99: Several clinical trials with oral and sublingual immunotherapy demonstrate an increased tolerance to oral food challenge in subjects with food hypersensitivity while receiving therapy. Oral and sublingual food immunotherapy is investigational. NR

At present, the only treatment for food hypersensitivity is avoidance, but clinical trials suggest that tolerance can be achieved with oral immunotherapy and SLIT. There was diminished IgE reactivity associated with increased IgG4 reactivity to the major kiwi allergen Act c 1 in Western blots after 5 years of continuous treatment in a case of a woman with kiwi-associated anaphylaxis treated with a kiwi-pulp SLIT extract.[469] The patient tolerated resumption of SLIT after 4 months of interrupted treatment, which suggests that this treatment can produce a persistent state of tolerance. Clinical trials with SLIT demonstrate an increased tolerance to oral food challenge with hazelnut[172,450] and milk.[173]

A study examining the safety of peanut oral immunotherapy in 28 patients with peanut allergy found that most adverse reactions occurred during the initial escalation day, with upper respiratory tract (79%) and abdominal (68%) symptoms being the most common adverse reactions.[440] The probability of adverse reactions after the build-up phase dose was 46%, 29% of which were upper respiratory tract symptoms and 24% of which were skin symptoms. Fifty-one percent of subjects experienced some mild side effects, which were "…easily controlled by the oral administration of antihistamines or sodium cromolyn" in a study of 59 patients with food allergy treated with oral immunotherapy for 18 months.[470]

Clinical trials with peanut,[174] egg,[175,176] and milk[176,177] oral immunotherapy demonstrate an increased tolerance to treated food. In an open-label peanut oral immunotherapy trial, 27 (93%) children with peanut allergy were able to tolerate the target total peanut dose of 3.9 g after 4 to 22 months.[174] Treatment was associated with a significant reduction in titrated skin prick test responses, basophil activation, and other humoral and cellular changes associated with immunologic tolerance.

NOVEL FORMULATIONS: ALLERGOIDS AND ADJUVANTS

Summary Statement 100: Allergoids are modified allergen extracts processed in a way that reduces the extract's allergenicity while preserving its antigenicity. B

Allergoids are chemically modified extracts that reduce IgE-binding capacity. These extracts potentially reduce the allergenicity of the allergens but retain antigenicity. However, one study comparing the tolerability of a standardized grass pollen extract with an allergoid reported a higher percentage of systemic reactions in the allergoid group during rush build-up and the maintenance phase.[96] Allergoids are used, on average, in 20% of SCIT treatments prescribed in Europe, but the use varies in different countries.[458] There are no FDA-approved allergoids in the United States.

Summary Statement 101: Adjuvants might enhance the effectiveness of allergen immunotherapy by shifting the immune response toward T_H1 production. The 2 adjuvants most extensively studied with allergen immunotherapy are an immunostimulatory oligonucleotide sequence of DNA containing a CpG motif (CpG) and 3-deacylated monophospholipid A (MPL). Clinical trials with these adjuvants, in combination with ragweed (CPG and MPL) and grasses (MPL), demonstrate significant improvement in allergic rhinitis symptoms with 4 to 6 injections administered preseasonally. Neither of these adjuvants are available as FDA-approved allergen extracts. NR

Efforts to develop safer and more effective allergen immunotherapy extracts have resulted in several modifications to the allergen extracts. Adjuvants enhance the effectiveness of allergen immunotherapy primarily by shifting the immune response toward T_H1 production through their action on TLRs. The receptor for CpG DNA, TLR9, which is expressed primarily on plasmacytoid dendritic cells, can lead to production of IL-10, IgG isotope switching, and inhibition of other immune responses mediated by T_H2 cells when activated.[471] TOLAMBA, a TLR9 agonist, is a CpG adjuvant that is covalently linked to the major ragweed allergen Amb a 1. A randomized double-blind, placebo-controlled, phase 2 trial of 25 adults with ragweed-induced allergic rhinitis randomized to receive 6 increasing doses of TOLAMBA (0.06, 0.3, 1.2, 3.0, 6.0, and 12 μg) or placebo before the ragweed season demonstrated a significant reduction in total nasal symptom scores during the peak season in the TOLAMBA group compared with the placebo-treated patients in both the first and second ragweed season with no "pattern of vaccine-associated systemic reactions or clinically significant laboratory abnormalities."[472] However, there was no difference in the primary outcome (ie, albumin levels in nasal lavage fluid after nasal allergen provocation). The development of a CpG ragweed vaccine was discontinued by the company after interim analysis of a subsequent large trial indicated that neither the placebo nor CpG groups showed symptoms during the ragweed season, making it impossible to assess the therapeutic efficacy of the CpG vaccine.[473]

MPL, the other adjuvant used in allergen immunotherapy, is a TLR4 agonist derived from the LPS of *Salmonella minnesota*, which induces T_H1 cytokines in human and animal studies. MPL is used in an allergen vaccine product composed of a tyrosine-absorbed (delays absorption) glutaraldehyde-modified allergoid (Pollinex Quattro; Allergy Therapeutics Ltd, West Sussex, England), which is administered as 4 injections given at 1- to 2-week intervals and ending 2 to 4 weeks before the start of the season. The highest and cumulative doses were equivalent to 24 and 60 μg of group 1 grass pollen allergen, respectively.[474] The treatment resulted in significant reductions in symptoms and combined symptom-medication scores in a double-blind, placebo-controlled, multicenter study of 141 patients with tree- or grass pollen–induced allergic rhinitis with no difference in systemic adverse events between the active and placebo groups.[474]

AUTHORS' NOTE

Examples of allergen immunotherapy prescription and administration forms, immunotherapy labels, conventional and cluster build-up schedules, immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals, summaries of documentation guidelines, systemic reaction reporting sheets, and patterns of allergen cross-reactivity can be found in the tables and figures in this article's Online Repository at www.jacionline.org. Some of these forms, along with examples of immunotherapy instruction and consent forms, preinjection health questionnaires, and indications for beginning and continuing immunotherapy forms, the allergen extraction preparation guidelines, can also be found at www.aaaai.org, www.acaai.org, or www.jcaai.org.

REFERENCES

1. American College of Medical Quality's policy on development and use of practice parameters for medical quality decision-making. Available at: http://www.acmq.orq/profess/PDFs/policy5.pdf. Accessed September 26, 2006. NR
2. Cox L, Li J, Lockey R, Nelson H. Allergen immunotherapy: a practice parameter second update. J Allergy Clin Immunol 2007;120(suppl):S25-85, IV.
3. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. BMJ 1999;318:593-6, NR.
4. Fass P. American Academy of Otolaryngic Allergy endorses the Allergen Immunotherapy Practice Parameter. J Allergy Clin Immunol 2008;121:269-70, NR.
5. Noon L. Prophylactic inoculation against hay fever. Lancet 1911;1:1572-3, NR.
6. Freeman J. Further observations of the treatment of hay fever by hypodermic inoculations of pollen vaccine. Lancet 1911;2:814-7, NR.
7. Freeman J. "Rush Inoculation," with special reference to hay fever treatment. Lancet 1930;1:744-7, NR.

8. Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy 2007;62:943-8, Ib.
9. Moller C, Dreborg S, Ferdousi HA, 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.
10. 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.
11. Polosa R, Li Gotti F, Mangano G, et al. Effect of immunotherapy on asthma progression, BHR and sputum eosinophils in allergic rhinitis. Allergy 2004;59: 1224-8, Ib.
12. Bussmann C, Böckenhoff A, Henke H, Werfel T, Novak N. Does allergen-specific immunotherapy represent a therapeutic option for patients with atopic dermatitis? J Allergy Clin Immunol 2006;118:1292-8, IV.
13. Bussmann C, Maintz L, Hart J, et al. Clinical improvement and immunological changes in atopic dermatitis patients undergoing subcutaneous immunotherapy with a house dust mite allergoid: a pilot study. Clin Exp Allergy 2007;37:1277-85, III.
14. Werfel T, Breuer K, Rueff F, et al. Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multi-centre, randomized, dose-response study. Allergy 2006;61:202-5, Ia.
15. Novak N. Allergen specific immunotherapy for atopic dermatitis. Curr Opin Allergy Clin Immunol 2007;7:542-6, NR.
16. Pajno GB, Caminiti L, Vita D, et al. Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized, double-blind, placebo-controlled study. J Allergy Clin Immunol 2007;120:164-70, Ib.
17. 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.
18. 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.
19. Creticos PS, Van Metre TE, Mardiney MR, Rosenberg GL, Norman PS, Adkinson NF Jr. Dose response of IgE and IgG antibodies during ragweed immunotherapy. J Allergy Clin Immunol 1984;73:94-104, IIb.
20. Frew AJ, Powell RJ, Corrigan CJ. Durham systemic reaction. 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.
21. Lent AM, Harbeck R, Strand M, et al. Immunologic response to administration of standardized dog allergen extract at differing doses. J Allergy Clin Immunol 2006;118:1249-56, Ib.
22. Nanda A, O'Connor M, Anand M, 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.
23. Teuber SS, Porch-Curren C. Unproved diagnostic and therapeutic approaches to food allergy and intolerance. Curr Opin Allergy Clin Immunol 2003;3:217-21.
24. Van Metre TE, Adkinson NF, Amodio FJ, et al. A comparative study of the effectiveness of the Rinkel method and the current standard method of immunotherapy for ragweed pollen hay fever. J Allergy Clin Immunol 1980;66:500-13, IIb.
25. Van Metre TE, Adkinson NF, Lichtenstein LM, et al. A controlled study of the effectiveness of the Rinkel method of immunotherapy for ragweed pollen hay fever. J Allergy Clin Immunol 1980;65:288-97, IIa.
26. Aaronson DW, Gandhi TK. Incorrect allergy injections: allergists' experiences and recommendations for prevention. J Allergy Clin Immunol 2004;113:1117-21, III.
27. The Joint Commission on Accreditation of Healthcare Organizations 2010 National Patient Safety Goals. Available at: http://www.jointcommission.org/PatientSafety/NationalPatientSafetyGoals/. Accessed August 22, 2010. NR
28. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol 2010; 126:477-80, e1-42. NR.
29. Kao N. Terminology used for allergen immunotherapy. Ann Allergy Asthma Immunol 2000;84:273-4, NR.
30. Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E. Standards for practical allergen-specific immunotherapy. Allergy 2006;61 (suppl 82):1-20, NR.
31. Allergen immunotherapy: therapeutic vaccines for allergic diseases. Geneva: January 27-29, 1997. Allergy 1998;53:1-42, NR.
32. Bellinghausen I, Metz G, Enk AH, Christmann S, Knop J, Saloga J. Insect venom immunotherapy induces interleukin-10 production and a Th2-to-Th1 shift, and changes surface marker expression in venom-allergic subjects. Eur J Immunol 1997;27:1131-9, LB.
33. Blaser K, Akdis CA. Interleukin-10, T regulatory cells and specific allergy treatment. Clin Exp Allergy 2004;34:328-31, LB.
34. Francis JN, Till SJ, Durham SR. Induction of IL-10+CD4+CD25+ T cells by grass pollen immunotherapy. J Allergy Clin Immunol 2003;111:1255-61, LB.
35. Jutel M, Akdis M, Budak F, et al. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. Eur J Immunol 2003;33:1205-14, LB.
36. Savolainen J, Laaksonen K, Rantio-Lehtimaki A, Terho EO. Increased expression of allergen-induced in vitro interleukin-10 and interleukin-18 mRNA in peripheral blood mononuclear cells of allergic rhinitis patients after specific immunotherapy. Clin Exp Allergy 2004;34:413-9, LB.
37. Francis J, James L, Paraskevopoulos G, et al. Grass pollen immunotherapy: IL-10 induction and suppression of late responses precedes IgG4 inhibitory antibody activity. J Allergy Clin Immunol 2008;121:1120-5, e2. LB.
38. Evans R, Pence H, Kaplan H, Rocklin RE. The effect of immunotherapy on humoral and cellular responses in ragweed hayfever. J Clin Invest 1976;57: 1378-85, LB.
39. Till SJ, Durham SR. Immunological responses to allergen immunotherapy. Clin Allergy Immunol 2004;18:85-104, NR.
40. Till SJ, Francis JN, Nouri-Aria K, Durham SR. Mechanisms of immunotherapy. J Allergy Clin Immunol 2004;113:1025-35, NR.
41. Durham SR, Ying S, Varney VA, et al. Grass pollen immunotherapy inhibits allergen-induced infiltration of CD4+ T lymphocytes and eosinophils in the nasal mucosa and increases the number of cells expressing messenger RNA for interferon-gamma. J Allergy Clin Immunol 1996;97:1356-65, Ib.
42. Hamid QA, Schotman E, Jacobson MR, Walker SM, Durham SR. Increases in IL-12 messenger RNA+ cells accompany inhibition of allergen-induced late skin responses after successful grass pollen immunotherapy. J Allergy Clin Immunol 1997;99:254-60, IIb.
43. Bousquet J, Maasch H, Martinot B, Hejjaoui A, Wahl R, Michel FB. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. II. Comparison between parameters assessing the efficacy of immunotherapy. J Allergy Clin Immunol 1988;82:439-46, Ia.
44. Van Bever HP, Bosmans J, De Clerck LS, Stevens WJ. Modification of the late asthmatic reaction by hyposensitization in asthmatic children allergic to house dust mite *(Dermatophagoides pteronyssinus)* or grass pollen. Allergy 1988;43: 378-85, IIa.
45. Iliopoulos O, Proud D, Adkinson NF Jr, et al. Effects of immunotherapy on the early, late, and rechallenge nasal reaction to provocation with allergen: changes in inflammatory mediators and cells. J Allergy Clin Immunol 1991;87:855-66, IIa.
46. Nish WA, Charlesworth EN, Davis TL, et al. The effect of immunotherapy on the cutaneous late phase response to antigen. J Allergy Clin Immunol 1994;93:484-93, III.
47. Hedlin G, Graff-Lonnevig V, Heilborn H, 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.
48. Pichler CE, Helbling A, Pichler WJ. Three years of specific immunotherapy with house-dust-mite extracts in patients with rhinitis and asthma: significant improvement of allergen-specific parameters and of nonspecific bronchial hyperreactivity. Allergy 2001;56:301-6, IIb.
49. Wilson DR, Irani AM, Walker SM, et al. Grass pollen immunotherapy inhibits seasonal increases in basophils and eosinophils in the nasal epithelium. Clin Exp Allergy 2001;31:1705-13, Ib.
50. Rak S, Bjornson A, Hakanson L, Sorenson S, Venge P. The effect of immunotherapy on eosinophil accumulation and production of eosinophil chemotactic activity in the lung of subjects with asthma during natural pollen exposure. J Allergy Clin Immunol 1991;88:878-88, IIa.
51. Nouri-Aria KT, Pilette C, Jacobson MR, Watanabe H, Durham SR. IL-9 and c-Kit+ mast cells in allergic rhinitis during seasonal allergen exposure: effect of immunotherapy. J Allergy Clin Immunol 2005;116:73-9, IIb.
52. Lichtenstein LM, Ishizaka K, Norman PS, Sobotka AK, Hill BM. IgE antibody measurements in ragweed hay fever. Relationship to clinical severity and the results of immunotherapy. J Clin Invest 1973;52:472-82, IIb.
53. Bousquet J, Braquemond P, Feinberg J, Guerin B, Maasch H, Michel FB. Specific IgE response before and after rush immunotherapy with a standardized allergen or allergoid in grass pollen allergy. Ann Allergy 1986;56:456-9, LB.
54. Gleich GJ, Zimmermann EM, Henderson LL, Yunginger JW. Effect of immunotherapy on immunoglobulin E and immunoglobulin G antibodies to ragweed antigens: a six-year prospective study. J Allergy Clin Immunol 1982;70:261-71, IIa.
55. Norman PS, Lichtenstein LM, Marsh DG. Studies on allergoids from naturally occurring allergens. IV. Efficacy and safety of long-term allergoid treatment of ragweed hay fever. J Allergy Clin Immunol 1981;68:460-70, IIb.
56. Rak S, Lowhagen O, Venge P. The effect of immunotherapy on bronchial hyperresponsiveness and eosinophil cationic protein in pollen-allergic patients. J Allergy Clin Immunol 1988;82:470-80, IIb.

57. Sadan N, Rhyne MB, Mellitis ED, et al. Immunotherapy of pollinosis in children. Investigation of the immunologic basis of clinical improvement. N Engl Med 1969;280:623-7, IIb.
58. Varney VA, Hamid QA, Gaga M, et al. Influence of grass pollen immunotherapy on cellular infiltration and cytokine mRNA expression during allergen-induced late-phase cutaneous responses. J Clin Invest 1993;92:644-51, IIb.
59. Pilette C, Nouri-Aria KT, Jacobson MR, et al. Grass pollen immunotherapy induces an allergen-specific IgA2 antibody response associated with mucosal TGF-beta expression. J Immunol 2007;178:4658-66, IIa.
60. Ewan PW, Deighton J, Wilson AB, Lachmann PJ. Venom-specific IgG antibodies in bee and wasp allergy: lack of correlation with protection from stings. Clin Exp Allergy 1993;23:647-60, IIb.
61. Djurup R, Malling HJ. High IgG4 antibody level is associated with failure of immunotherapy with inhalant allergens. Clin Allergy 1987;17:459-68, IIb.
62. Michils A, Baldassarre S, Ledent C, Mairesse M, Gossart B, Duchateau J. Early effect of ultrarush venom immunotherapy on the IgG antibody response. Allergy 2000;55:455-62, IIb.
63. Michils A, Mairesse M, Ledent C, Gossart B, Baldassarre S, Duchateau J. Modified antigenic reactivity of anti-phospholipase A2 IgG antibodies in patients allergic to bee venom: conversion with immunotherapy and relation to subclass expression. J Allergy Clin Immunol 1998;102:118-26, IIb.
64. Wachholz PA, Soni NK, Till SJ, Durham SR. Inhibition of allergen-IgE binding to B cells by IgG antibodies after grass pollen immunotherapy. J Allergy Clin Immunol 2003;112:915-22, Ib.
65. Lichtenstein LM, Levy DA. Is desensitization for ragweed hay fever immunologically specific? Int Arch Allergy Appl Immunol 1972;42:615-26, NR.
66. Wantke F, Gotz M, Jarisch R. Spontaneous histamine release in whole blood in patients before and after 4 months of specific immunotherapy. Clin Exp Allergy 1993;23:992-5, LB.
67. Savolainen J, Jacobsen L, Valovirta E. Sublingual immunotherapy in children modulates allergen-induced in vitro expression of cytokine mRNA in PBMC. Allergy 2006;61:1184-90, LB.
68. Lack G, Nelson HS, Amran D, et al. Rush immunotherapy results in allergen-specific alterations in lymphocyte function and interferon-gamma production in CD4+ T cells. J Allergy Clin Immunol 1997;99:530-8, LB.
69. Majori M, Caminati A, Corradi M, Brianti E, Scarpa S, Pesci A. T-cell cytokine pattern at three time points during specific immunotherapy for mite-sensitive asthma. Clin Exp Allergy 2000;30:341-7, LB.
70. Gabrielsson S, Soderlund A, Paulie S, van der Pouw Kraan TC, Troye-Blomberg M, Rak S. Specific immunotherapy prevents increased levels of allergen-specific IL-4- and IL-13-producing cells during pollen season. Allergy 2001;56:293-300, Ib.
71. Jung CM, Prinz JC, Rieber EP, Ring J. A reduction in allergen-induced Fc epsilon R2/CD23 expression on peripheral B cells correlates with successful hyposensitization in grass pollinosis. J Allergy Clin Immunol 1995;95:77-87, LB.
72. Tversky JR, Bieneman AP, Chichester KL, Hamilton RG, Schroeder JT. Subcutaneous allergen immunotherapy restores human dendritic cell innate immune function. Clin Exp Allergy 2010;40:94-102, LB.
73. Plewako H, Arvidsson M, Oancea I, Hasseus B, Dahlgren U, Rak S. The effect of specific immunotherapy on the expression of costimulatory molecules in late phase reaction of the skin in allergic patients. Clin Exp Allergy 2004;34:1862-7, LB.
74. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. Cochrane Database Syst Rev 2010;8:CD001186.Ia.
75. Bousquet J, Lockey R, Malling HJ, et al. Allergen immunotherapy: therapeutic vaccines for allergic diseases. World Health Organization. American academy of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 1998;81: 401-5, NR.
76. Lockey RF. "ARIA": global guidelines and new forms of allergen immunotherapy. J Allergy Clin Immunol 2001;108:497-9, IV.
77. 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.
78. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of hymenoptera venom hypersensitivity: a meta-analysis. Clin Ther 2000;22:351-8, Ia.
79. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of asthma: a meta-analysis of prospective, randomized, double-blind, placebo-controlled studies. Clin Ther 2000;22:329-41, Ia.
80. Portnoy JM. Immunotherapy for asthma: unfavorable studies. Ann Allergy Asthma Immunol 2001;87:28-32, IV.
81. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. Cochrane Database Syst Rev 2003;4:CD001186.Ia.
82. Lowell FC, Franklin W. A double-blind study of the effectiveness and specificity of injection therapy in ragweed hay fever. N Engl J Med 1965;273:675-9, Ib.
83. 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.
84. Bonno M, Fujisawa T, Iguchi K, 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.
85. Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. N Engl J Med 1978;299:157-61, IIa.
86. 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.
87. Cantani A, Micera M. Is specific immunotherapy safe and effective in children? Eur Rev Med Pharmacol Sci 2000;4:139-43, IV.
88. Cools M, Van Bever HP, Weyler JJ, Stevens WJ. Long-term effects of specific immunotherapy, administered during childhood, in asthmatic patients allergic to either house-dust mite or to both house-dust mite and grass pollen. Allergy 2000; 55:69-73, IIa.
89. Des Roches A, Paradis L, Knani J, 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.
90. Hedlin G, Wille S, Browaldh L, et al. Immunotherapy in children with allergic asthma: effect on bronchial hyperreactivity and pharmacotherapy. J Allergy Clin Immunol 1999;103:609-14, Ib.
91. Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children—a 14-year study. Pediatrics 1968;42:793-802, IIa.
92. Ohashi Y, Nakai Y, Tanaka 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.
93. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999;341:468-75, Ib.
94. 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.
95. Bousquet J, Becker WM, Hejjaoui A, 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, IIa.
96. Bousquet J, Hejjaoui A, Skassa-Brociek W, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. I. Rush immunotherapy with allergoids and standardized orchard grass-pollen extract. J Allergy Clin Immunol 1987;80:591-8, Ib.
97. Creticos PS, Marsh DG, Proud D, et al. Responses to ragweed-pollen nasal challenge before and after immunotherapy. J Allergy Clin Immunol 1989;84:197-205, Ib.
98. Creticos PS, Reed CE, Norman PS, et al. Ragweed immunotherapy in adult asthma. N Engl J Med 1996;334:501-6, Ib.
99. 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.
100. Franklin W, Lowell FC. Comparison of two dosages of ragweed extract in the treatment of pollinosis. JAMA 1967;201:915-7, III.
101. Ortolani C, Pastorello EA, Incorvaia C, et al. A double-blind, placebo-controlled study of immunotherapy with an alginate-conjugated extract of *Parietaria judaica* in patients with *Parietaria* hay fever. Allergy 1994;49:13-21, IIa.
102. 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, LB.
103. 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, IIa.
104. Malling HJ, Dreborg S, Weeke B. Diagnosis and immunotherapy of mould allergy. V. Clinical efficacy and side effects of immunotherapy with *Cladosporium herbarum*. Allergy 1986;41:507-19, Ib.
105. Malling HJ. Diagnosis and immunotherapy of mould allergy. IV. Relation between asthma symptoms, spore counts and diagnostic tests. Allergy 1986;41: 342-50, III.
106. Karlsson R, Agrell B, Dreborg S, 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.
107. 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.
108. 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.
109. Haugaard L, Dahl R. Immunotherapy in patients allergic to cat and dog dander. I. Clinical results. Allergy 1992;47:249-54, IIa.
110. 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.
111. 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.
112. 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.
113. Tabar AI, Echechipia S, Garcia BE, et al. Double-blind comparative study of cluster and conventional immunotherapy schedules with *Dermatophagoides pteronyssinus*. J Allergy Clin Immunol 2005;116:109-18, Ib.
114. Pichler CE, Marquardsen A, Sparholt S, et al. Specific immunotherapy with *Dermatophagoides pteronyssinus* and *D. farinae* results in decreased bronchial hyperreactivity. Allergy 1997;52:274-83, Ib.
115. Bousquet J, Calvayrac P, Guerin 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, Ib.
116. Bousquet J, Hejjaoui A, Clauzel AM, et al. Specific immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. II. Prediction of efficacy of immunotherapy. J Allergy Clin Immunol 1988;82:971-7, IIa.
117. 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.
118. 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.
119. Pauli G, Bessot JC, Bigot H, 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.
120. Wang H, Lin X, Hao C, et al. A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients. Allergy 2006;61:191-7, Ib.
121. Kang BC, Johnson J, Morgan C, Chang JL. The role of immunotherapy in cockroach asthma. J Asthma 1988;25:205-18, Ib.
122. Freeman TM, Hylander R, Ortiz A, Martin ME. Imported fire ant immunotherapy: effectiveness of whole body extracts. J Allergy Clin Immunol 1992;90:210-5, IIa.
123. Triplett RF. Sensitivity to the imported fire ant: successful treatment with immunotherapy. South Med J 1973;66:477-80, III.
124. Tankersley MS, Walker RL, Butler WK, Hagan LL, Napoli DC, Freeman TM. Safety and efficacy of an imported fire ant rush immunotherapy protocol with and without prophylactic treatment. J Allergy Clin Immunol 2002;109:556-62, Ib.
125. Corrigan CJ, Kettner J, Doemer C, Cromwell O, Narkus A. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. Allergy 2005;60:801-7, Ib.
126. Ferrer M, Burches E, Pelaez A, et al. Double-blind, placebo-controlled study of immunotherapy with *Parietaria judaica*: clinical efficacy and tolerance. J Investig Allergol Clin Immunol 2005;15:283-92, Ib.
127. Jutel M, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O. Allergen-specific immunotherapy with recombinant grass pollen allergens. J Allergy Clin Immunol 2005;116:608-13, Ib.
128. 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.
129. Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. Am J Respir Crit Care Med 1995;151:969-74, Ia.
130. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database Syst Rev 2007;1:CD001936.Ia.
131. 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.
132. 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.
133. Eng PA, Reinhold M, Gnehm HP. Long-term efficacy of preseasonal grass pollen immunotherapy in children. Allergy 2002;57:306-12, IIa.
134. Jacobsen L. Preventive aspects of immunotherapy: prevention for children at risk of developing asthma. Ann Allergy Asthma Immunol 2001;87:43-6, IV.
135. 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, IIa.
136. 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, IIa.
137. Purello-D'Ambrosio F, Gangemi S, Merendino RA, 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.
138. Inal A, Altintas DU, Yilmaz M, Karakoc GB, Kendirli SG, Sertdemir Y. Prevention of new sensitizations by specific immunotherapy in children with rhinitis and/or asthma monosensitized to house dust mite. J Investig Allergol Clin Immunol 2007;17:85-91, III.
139. Hankin CS, Cox L, Lang D, et al. Allergen immunotherapy and health care cost benefits for children with allergic rhinitis: a large-scale, retrospective, matched cohort study. Ann Allergy Asthma Immunol 2010;104:79-85, III.
140. Hankin CS, Cox L, Lang D, et al. Allergy immunotherapy among Medicaid-enrolled children with allergic rhinitis: patterns of care, resource use, and costs. J Allergy Clin Immunol 2008;121:227-32, III.
141. Ariano R, Berto P, Tracci D, Incorvaia C, Frati F. Pharmacoeconomics of allergen immunotherapy compared with symptomatic drug treatment in patients with allergic rhinitis and asthma. Allergy Asthma Proc 2006;27:159-63, III.
142. Lockey RF, Nicoara-Kasti GL, Theodoropoulos DS, Bukantz SC. Systemic reactions and fatalities associated with allergen immunotherapy. Ann Allergy Asthma Immunol 2001;87:47-55, III.
143. 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.
144. Glover MT, Atherton DJ. A double-blind controlled trial of hyposensitization to *Dermatophagoides pteronyssinus* in children with atopic eczema. Clin Exp Allergy 1992;22:440-6, Ib.
145. Bucher X, Pichler WJ, Dahinden CA, Helbling A. Effect of tree pollen specific, subcutaneous immunotherapy on the oral allergy syndrome to apple and hazelnut. Allergy 2004;59:1272-6, IIa.
146. Hansen KS, Khinchi MS, Skov PS, Bindslev-Jensen C, Poulsen LK, Malling HJ. Food allergy to apple and specific immunotherapy with birch pollen. Mol Nutr Food Res 2004;48:441-8, Ib.
147. Reisman RE, Livingston A. Venom immunotherapy: 10 years of experience with administration of single venoms and 50 micrograms maintenance doses. J Allergy Clin Immunol 1992;89:1189-95, III.
148. Reisman RE. Insect stings. N Engl J Med 1994;331:523-7, IV.
149. Valentine MD. Allergy to stinging insects. Ann Allergy 1993;70:427-32, IV.
150. Valentine MD. Insect venom allergy: diagnosis and treatment. J Allergy Clin Immunol 1984;73:299-304, IV.
151. Valentine MD, Schuberth KC, Kagey-Sobotka A, et al. The value of immunotherapy with venom in children with allergy to insect stings. N Engl J Med 1990;323:1601-3, III.
152. Moffitt JE, Barker JR, Stafford CT. Management of imported fire ant allergy: results of a survey. Ann Allergy Asthma Immunol 1997;79:125-30, III.
153. Golden DB, Marsh DG, Kagey-Sobotka A, et al. Epidemiology of insect venom sensitivity. JAMA 1989;262:240-4, III.
154. Goldberg A, Confino-Cohen R. Timing of venom skin tests and IgE determinations after insect sting anaphylaxis. J Allergy Clin Immunol 1997;100:182-4, IV.
155. Golden DB, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM. Insect sting allergy with negative venom skin test responses. J Allergy Clin Immunol 2001;107:897-901, III.
156. Reisman RE. Insect sting allergy: the dilemma of the negative skin test reactor. J Allergy Clin Immunol 2001;107:781-2, IV.
157. Golden DB. Insect sting allergy and venom immunotherapy: a model and a mystery. J Allergy Clin Immunol 2005;115:439-48, IV.
158. Moffitt JE, Golden DB, Reisman RE, et al. Stinging insect hypersensitivity: a practice parameter update. J Allergy Clin Immunol 2004;114:869-86, NR.
159. Golden DB, Tracy JM, Freeman TM, Hoffman DR. Negative venom skin test results in patients with histories of systemic reaction to a sting. J Allergy Clin Immunol 2003;112:495-8, IV.
160. Duplantier JE, Freeman TM, Bahna SL, Good RA, Sher MR. Successful rush immunotherapy for anaphylaxis to imported fire ants. J Allergy Clin Immunol 1998;101:855-6, III.

161. Ruëff F, Przybilla B, Biló MB, et al. Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum tryptase—a study of the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity. J Allergy Clin Immunol 2009;124:1047-54, III.
162. Bonadonna P, Perbellini O, Passalacqua G, et al. Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum tryptase levels. J Allergy Clin Immunol 2009;123:680-6, III.
163. Rueff F, Przybilla B, Bilo MB, et al. Predictors of side effects during the build-up phase of venom immunotherapy for Hymenoptera venom allergy: the importance of baseline serum tryptase. J Allergy Clin Immunol 2010;126:105-11, e5. III.
164. Muller UR. Elevated baseline serum tryptase, mastocytosis and anaphylaxis. Clin Exp Allergy 2009;39:620-2, IV.
165. Haeberli G, Bronnimann M, Hunziker T, Muller U. Elevated basal serum tryptase and hymenoptera venom allergy: relation to severity of sting reactions and to safety and efficacy of venom immunotherapy. Clin Exp Allergy 2003;33: 1216-20, III.
166. Golden DB, Kelly D, Hamilton RG, Craig TJ. Venom immunotherapy reduces large local reactions to insect stings. J Allergy Clin Immunol 2009;123:1371-5, III.
167. Sampson HA. Food anaphylaxis. Br Med Bull 2000;56:925-35, IV.
168. Rance F. [Current childhood food allergies]]. Allerg Immunol (Paris) 2000;32: 366-76, IV.
169. Bannon GA, Cockrell G, Connaughton C, et al. Engineering, characterization and in vitro efficacy of the major peanut allergens for use in immunotherapy. Int Arch Allergy Immunol 2001;124:70-2, LB.
170. Nelson HS, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. J Allergy Clin Immunol 1997;99:744-51, Ib.
171. Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. J Allergy Clin Immunol 1992;90: 256-62, Ib.
172. Enrique E, Malek T, Pineda F, et al. Sublingual immunotherapy for hazelnut food allergy: a follow-up study. Ann Allergy Asthma Immunol 2008;100:283-4, Ib.
173. de Boissieu D, Dupont C. Sublingual immunotherapy for cow's milk protein allergy: a preliminary report. Allergy 2006;61:1238-9, III.
174. Jones SM, Pons L, Roberts JL, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol 2009;124:292-300, e1-97. III.
175. Buchanan AD, Green TD, Jones SM, et al. Egg oral immunotherapy in nonanaphylactic children with egg allergy. J Allergy Clin Immunol 2007;119:199-205, Ib.
176. Staden U, Rolinck-Werninghaus C, Brewe F, Wahn U, Niggemann B, Beyer K. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. Allergy 2007;62:1261-9, III.
177. Narisety SD, Skripak JM, Steele P, et al. Open-label maintenance after milk oral immunotherapy for IgE-mediated cow's milk allergy. J Allergy Clin Immunol 2009;124:610-2, III.
178. Longo G, Barbi E, Berti I, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J Allergy Clin Immunol 2008;121: 343-7, Ib.
179. Pfaar O, Anders C, Klimek L. Clinical outcome measures of specific immunotherapy. Curr Opin Allergy Clin Immunol 2009;9:208-13, IV.
180. Casale TB, Canonica GW, Bousquet J, et al. Recommendations for appropriate sublingual immunotherapy clinical trials. J Allergy Clin Immunol 2009;124: 665-70, IV.
181. Canonica GW, Baena-Cagnani CE, Bousquet J, et al. Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. Allergy 2007;62:317-24, IV.
182. Bousquet J, Hejjaoui A, Dhivert H, Clauzel AM, Michel FB. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. Systemic reactions during the rush protocol in patients suffering from asthma. J Allergy Clin Immunol 1989;83:797-802, IIa.
183. 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.
184. 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.
185. Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. J Allergy Clin Immunol 2006;117:169-75, III.
186. Bertelsen A, Andersen JB, Christensen J, Ingemann L, Kristensen T, Ostergaard PA. Immunotherapy with dog and cat extracts in children. Allergy 1989;44:330-5, Ib.
187. Larenas-Linnemann D. Subcutaneous and sublingual immunotherapy in children: complete update on controversies, dosing, and efficacy. Curr Allergy Asthma Rep 2008;8:465-74, IV.
188. Adkinson NF Jr, Eggleston PA, Eney D, et al. A controlled trial of immunotherapy for asthma in allergic children. N Engl J Med 1997;336:324-31, Ib.
189. Rosenstreich DL, Eggleston P, Kattan M, et al. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. N Engl J Med 1997;336:1356-63, III.
190. Niggemann B, Jacobsen L, Dreborg S, 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.
191. Roberts G, Hurley C, Turcanu V, Lack G. Grass pollen immunotherapy as an effective therapy for childhood seasonal allergic asthma. J Allergy Clin Immunol 2006;117:263-8, Ib.
192. Rodriguez Perez N, Ambriz Moreno Mde J. Safety of immunotherapy and skin tests with allergens in children younger than five years. Rev Alerg Mex 2006; 53:47-51, III.
193. Finegold I. Immunotherapy: when to initiate treatment in children. Allergy Asthma Proc 2007;28:698-705, IV.
194. Asero R. Efficacy of injection immunotherapy with ragweed and birch pollen in elderly patients. Int Arch Allergy Immunol 2004;135:332-5, III.
195. Metzger WJ, Turner E, Patterson R. The safety of immunotherapy during pregnancy. J Allergy Clin Immunol 1978;61:268-72, III.
196. Shaikh WA. A retrospective study on the safety of immunotherapy in pregnancy. Clin Exp Allergy 1993;23:857-60, III.
197. Schwartz HJ, Golden DB, Lockey RF. Venom immunotherapy in the Hymenoptera-allergic pregnant patient. J Allergy Clin Immunol 1990;85: 709-12, III.
198. Glovsky MM, Ghekiere L, Rejzek E. Effect of maternal immunotherapy on immediate skin test reactivity, specific rye I IgG and IgE antibody, and total IgE of the children. Ann Allergy 1991;67:21-4, III.
199. Flicker S, Marth K, Kofler H, Valenta R. Placental transfer of allergen-specific IgG but not IgE from a specific immunotherapy-treated mother. J Allergy Clin Immunol 2009;124:1358-60, e1. NR.
200. Marshall GD Jr. AIDS, HIV-positive patients, and allergies. Allergy Asthma Proc 1999;20:301-4, IV.
201. Randhawa IS, Junaid I, Klaustermeyer WB. Allergen immunotherapy in a patient with human immunodeficiency virus: effect on T-cell activation and viral replication. Ann Allergy Asthma Immunol 2007;98:495-7, NR.
202. Steiner U, Furrer H, Helbling A. Specific Immunotherapy in a Pollen-Allergic Patient With Human Immunodeficiency Virus Infection. World Allergy Organization Journal 2009;2:57-8, NR.
203. Kohno Y, Minoguchi K, Oda N, 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, IIa.
204. The discontinuation of Hymenoptera venom immunotherapy. J Allergy Clin Immunol 1998;101:573-5, IV.
205. Golden DBK, Kagey-Sobotka A, Lichtenstein LM. Survey of patients after discontinuing venom immunotherapy. J Allergy Clin Immunol 2000;105:385-90, III.
206. Lerch E, Müller UR. Long-term protection after stopping venom immunotherapy: results of re-stings in 200 patients. J Allergy Clin Immunol 1998;101:606-12, III.
207. van Halteren HK, van der Linden PW, Burgers JA, Bartelink AK. Discontinuation of yellow jacket venom immunotherapy: follow-up of 75 patients by means of deliberate sting challenge. J Allergy Clin Immunol 1997;100:767-70, III.
208. Keating MU, Kagey-Sobotka A, Hamilton RG, Yunginger JW. Clinical and immunologic follow-up of patients who stop venom immunotherapy. J Allergy Clin Immunol 1991;88:339-48, III.
209. Golden DBK, Kwiterovich KA, Kagey-Sobotka A, Lichtenstein LM. Discontinuing venom immunotherapy: extended observations. J Allergy Clin Immunol 1998; 101:298-302, III.
210. Cox L, Cohn JR. Duration of allergen immunotherapy in respiratory allergy: when is enough, enough? Ann Allergy Asthma Immunol 2007;98:416-26, IV.
211. Durham SR, Emminger W, Kapp A, et al. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. J Allergy Clin Immunol 2010;125:131-8, e1-7. Ib.
212. Coop CA, Tankersley MS. Patient perceptions regarding local reactions from allergen immunotherapy injections. Ann Allergy Asthma Immunol 2008;101:96-100, III.
213. Nelson BL, Dupont LA, Reid MJ. Prospective survey of local and systemic reactions to immunotherapy with pollen extracts. Ann Allergy 1986;56:331-4, III.
214. Prigal SJ. A ten-year study of repository injections of allergens: local reactions and their management. Ann Allergy 1972;30:529-35, III.
215. Tankersley MS, Butler KK, Butler WK, Goetz DW. Local reactions during allergen immunotherapy do not require dose adjustment. J Allergy Clin Immunol 2000;106:840-3, III.
216. Kelso JM. The rate of systemic reactions to immunotherapy injections is the same whether or not the dose is reduced after a local reaction. Ann Allergy Asthma Immunol 2004;92:225-7, III.

217. Roy SR, Sigmon JR, Olivier J, Moffitt JE, Brown DA, Marshall GD. Increased frequency of large local reactions among systemic reactors during subcutaneous allergen immunotherapy. Ann Allergy Asthma Immunol 2007;99:82-6, III.
218. La Shell MS, Calabria CW, Quinn JM. Imported fire ant field reaction and immunotherapy safety characteristics: the IFACS study. J Allergy Clin Immunol 2010; 125:1294-9, III.
219. Calabria CW, Coop CA, Tankersley MS. The LOCAL Study: Local reactions do not predict local reactions in allergen immunotherapy. J Allergy Clin Immunol 2009;124:739-44, III.
220. Calabria CW, Coop CA, Tankersley M. The GILL study: Glycerin-induced local reactions in immunotherapy. J Allergy Clin Immunol 2008;121:222-6, IIb.
221. Van Metre TE Jr, Rosenberg GL, Vaswani SK, Ziegler SR, Adkinson NF. Pain and dermal reaction caused by injected glycerin in immunotherapy solutions. J Allergy Clin Immunol 1996;97:1033-9, IIa.
222. Nielsen L, Johnsen CR, Mosbech H, Poulsen LK, Malling HJ. Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. J Allergy Clin Immunol 1996;97:1207-13, Ib.
223. Berchtold E, Maibach R, Muller U. Reduction of side effects from rush-immunotherapy with honey bee venom by pretreatment with terfenadine. Clin Exp Allergy 1992;22:59-65, Ib.
224. Reimers A, Hari Y, Muller U. Reduction of side-effects from ultrarush immunotherapy with honeybee venom by pretreatment with fexofenadine: a double-blind, placebo-controlled trial. Allergy 2000;55:484-8, Ib.
225. Brockow K, Kiehn M, Riethmuller C, Vieluf D, Berger J, Ring J. Efficacy of antihistamine pretreatment in the prevention of adverse reactions to Hymenoptera immunotherapy: a prospective, randomized, placebo-controlled trial. J Allergy Clin Immunol 1997;100:458-63, Ib.
226. Wohrl S, Gamper S, Hemmer W, Heinze G, Stingl G, Kinaciyan T. Premedication with montelukast reduces local reactions of allergen immunotherapy. Int Arch Allergy Immunol 2007;144:137-42, Ib.
227. Bernstein DI, Epstein T, Murphy-Berendts K, Liss GM. Surveillance of systemic reactions to subcutaneous immunotherapy injections: year 1 outcomes of the ACAAI and AAAAI collaborative study. Ann Allergy Asthma Immunol 2010; 104:530-5, III.
228. Windom H, Lockey R. An update on the safety of specific immunotherapy. Curr Opin Allergy Clin Immunol 2008;8:571-6, IV.
229. Portnoy J, Bagstad K, Kanarek H, Pacheco F, Hall B, Barnes C. Premedication reduces the incidence of systemic reactions during inhalant rush immunotherapy with mixtures of allergenic extracts. Ann Allergy 1994;73:409-18, Ib.
230. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. J Allergy Clin Immunol 2010;125:569-74, e7. IV.
231. Ragusa FV, Passalacqua G, Gambardella R, et al. Nonfatal systemic reactions to subcutaneous immunotherapy: a 10-year experience. J Investig Allergol Clin Immunol 1997;7:151-4, III.
232. Ragusa VF, Massolo A. Non-fatal systemic reactions to subcutaneous immunotherapy: a 20-year experience comparison of two 10-year periods. Allerg Immunol (Paris) 2004;36:52-5, III.
233. Moreno C, Cuesta-Herranz J, Fernandez-Tavora L, Alvarez-Cuesta E. Immunotherapy safety: a prospective multi-centric monitoring study of biologically standardized therapeutic vaccines for allergic diseases. Clin Exp Allergy 2004;34: 527-31, III.
234. Bernstein DI, Epstein T, Murphy-Berendts K, Liss GM. Surveillance of systemic reactions to subcutaneous immunotherapy injections: year 1 outcomes of the ACAAI and AAAAI collaborative study. Ann Allergy Asthma Immunol 2010;104:530-5, III.
235. Tinkelman DG, Cole WQ 3rd, Tunno J. Immunotherapy: a one-year prospective study to evaluate risk factors of systemic reactions. J Allergy Clin Immunol 1995; 95:8-14, III.
236. DaVeiga SP, Caruso K, Golubski S, Lang DM. A retrospective survey of systemic reaction from allergen immunotherapy. J Allergy Clin Immunol 2008;121(suppl): S124, III.
237. Lin MS, Tanner E, Lynn J, Friday GA Jr. Nonfatal systemic allergic reactions induced by skin testing and immunotherapy. Ann Allergy 1993;71:557-62, III.
238. Rank MA, Oslie CL, Krogman JL, Park MA, Li JT. Allergen immunotherapy safety: characterizing systemic reactions and identifying risk factors. Allergy Asthma Proc 2008;29:400-5, III.
239. Winther L, Arnved J, Malling HJ, Nolte H, Mosbech H. Side-effects of allergen-specific immunotherapy: a prospective multi-centre study. Clin Exp Allergy 2006; 36:254-60, III.
240. Greenberg MA, Kaufman CR, Gonzalez GE, Rosenblatt CD, Smith LJ, Summers RJ. Late and immediate systemic-allergic reactions to inhalant allergen immunotherapy. J Allergy Clin Immunol 1986;77:865-70, III.
241. Matloff SM, Bailit IW, Parks P, Madden N, Greineder DK. Systemic reactions to immunotherapy. Allergy Proc 1993;14:347-50, III.
242. Gastaminza G, Algorta J, Audicana M, Etxenagusia M, Fernandez E, Munoz D. Systemic reactions to immunotherapy: influence of composition and manufacturer. Clin Exp Allergy 2003;33:470-4, III.
243. Greenberg MA, Kaufman CR, Gonzalez GE, Trusewych ZP, Rosenblatt CD, Summers RJ. Late systemic-allergic reactions to inhalant allergen immunotherapy. J Allergy Clin Immunol 1988;82:287-90, III.
244. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol 2010; 126:477-80, e1-42. IV.
245. Confino-Cohen R, Goldberg A. Allergen immunotherapy-induced biphasic systemic reactions: incidence, characteristics, and outcome: a prospective study. Ann Allergy Asthma Immunol 2010;104:73-8, III.
246. Scranton SE, Gonzalez EG, Waibel KH. Incidence and characteristics of biphasic reactions after allergen immunotherapy. J Allergy Clin Immunol 2009;123:493-8, III.
247. Toogood JH. Risk of anaphylaxis in patients receiving beta-blocker drugs. J Allergy Clin Immunol 1988;81:1-5, IV.
248. Lang DM. Do beta-blockers really enhance the risk of anaphylaxis during immunotherapy? Curr Allergy Asthma Rep 2008;8:37-44, IV.
249. Nisam MR, Zbinden A, Chesrown S, Barnett D, Gold WM. Distribution and pharmacological release of histamine in canine lung in vivo. J Appl Physiol 1978;44: 455-63, NR.
250. Matsumura Y, Tan EM, Vaughan JH. Hypersensitivity to histamine and systemic anaphylaxis in mice with pharmacologic beta adrenergic blockade: protection by nucleotides. J Allergy Clin Immunol 1976;58:387-94, LB.
251. Bickell WH, Dice WH. Military antishock trousers in a patient with adrenergic-resistant anaphylaxis. Ann Emerg Med 1984;13:189-90, NR.
252. Jacobs RL, Rake GW Jr, Fournier DC, Chilton RJ, Culver WG, Beckmann CH. Potentiated anaphylaxis in patients with drug-induced beta-adrenergic blockade. J Allergy Clin Immunol 1981;68:125-7, NR.
253. Javeed N, Javeed H, Javeed S, Moussa G, Wong P, Rezai F. Refractory anaphylactoid shock potentiated by beta-blockers. Catheter Cardiovasc Diagn 1996;39: 383-4, NR.
254. Kivity S, Yarchovsky J. Relapsing anaphylaxis to bee sting in a patient treated with beta-blocker and Ca blocker. J Allergy Clin Immunol 1990;85:669-70, NR.
255. Lang DM, Alpern MB, Visintainer PF, Smith ST. Increased risk for anaphylactoid reaction from contrast media in patients on beta-adrenergic blockers or with asthma. Ann Intern Med 1991;115:270-6, III.
256. Lang DM, Alpern MB, Visintainer PF, Smith ST. Elevated risk of anaphylactoid reaction from radiographic contrast media is associated with both beta-blocker exposure and cardiovascular disorders. Arch Intern Med 1993;153:2033-40, III.
257. Newman BR, Schultz LK. Epinephrine-resistant anaphylaxis in a patient taking propranolol hydrochloride. Ann Allergy 1981;47:35-7, NR.
258. Greenberger PA, Meyers SN, Kramer BL. Effects of beta-adrenergic and calcium antagonists on the development of anaphylactoid reactions from radiographic contrast media during cardiac angiography. J Allergy Clin Immunol 1987;80: 698-702, III.
259. Muller UR, Haeberli G. Use of beta-blockers during immunotherapy for Hymenoptera venom allergy. J Allergy Clin Immunol 2005;115:606-10, III.
260. Hepner MJ, Ownby DR, Anderson JA, Rowe MS, Sears-Ewald D, Brown EB. Risk of systemic reactions in patients taking beta-blocker drugs receiving allergen immunotherapy injections. J Allergy Clin Immunol 1990;86:407-11, III.
261. Frishman WH. Beta-adrenergic blockers. Med Clin North Am 1988;72:37-81, IV.
262. Zaloga GP, DeLacey W, Holmboe E, Chernow B. Glucagon reversal of hypotension in a case of anaphylactoid shock. Ann Intern Med 1986;105:65-6, NR.
263. Laxenaire MC, Torrens J, Moneret-Vautrin DA. Fatal anaphylactic shock in a patient treated with beta-blockers. Ann Fr Anesth Reanim 1984;3:453-5, NR.
264. Benitah E, Nataf P, Herman D. [Anaphylactic complications in patients treated with beta-blockers. Apropos of 14 cases]]. Therapie 1986;41:139-42, NR.
265. Odeh M, Oliven A, Bassan H. Timolol eyedrop-induced fatal bronchospasm in an asthmatic patient. J Fam Pract 1991;32:97-8, NR.
266. Cornaille G, Leynadier F, Modiano, Dry J. [Severity of anaphylactic shock in patients treated with beta-blockers]]. Presse Med 1985;14:790-1, NR.
267. Pollack CV Jr. Utility of glucagon in the emergency department. J Emerg Med 1993;11:195-205, IV.
268. Kaplan AP, Joseph K, Silverberg M. Pathways for bradykinin formation and inflammatory disease. J Allergy Clin Immunol 2002;109:195-209, NR.
269. Smith PL, Kagey-Sobotka A, Bleecker ER, et al. Physiologic manifestations of human anaphylaxis. J Clin Invest 1980;66:1072-80, NR.
270. Tunon-de-Lara JM, Villanueva P, Marcos M, Taytard A. ACE inhibitors and anaphylactoid reactions during venom immunotherapy. Lancet 1992;340:908, NR.
271. Ober AI, MacLean JA, Hannaway PJ. Life-threatening anaphylaxis to venom immunotherapy in a patient taking an angiotensin-converting enzyme inhibitor. J Allergy Clin Immunol 2003;112:1008-9, NR.

272. White KM, England RW. Safety of angiotensin-converting enzyme inhibitors while receiving venom immunotherapy. Ann Allergy Asthma Immunol 2008; 101:426-30, III.
273. Hollister-Stier. Instructions and dosage schedule for allergenic extracts hymenoptera venom products [package insert]. Spokane (WA): Hollister-Stier; Feb. 2005, NR
274. Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): the Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:1115-40, IV.
275. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation 2004;110:588-636, IV.
276. Kemp SF, Lockey RF, Simons FE. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy 2008;63:1061-70, IV.
277. Simons FE. Apparent lack of response to epinephrine in anaphylaxis. J Allergy Clin Immunol 2005;115:640, NR.
278. Simons FE, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. J Allergy Clin Immunol 2001;108:871-3, Ib.
279. Simons FE, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. J Allergy Clin Immunol 1998;101:33-7, Ib.
280. Tipton WR, Nelson HS. Experience with daily immunotherapy in 59 adult allergic patients. J Allergy Clin Immunol 1982;69:194-9, IIa.
281. Montgomery JR. The need for standardizing the aeroallergen immunotherapy missed-dose adjustment protocol. Allergy Asthma Proc 2008;29:425-6, III.
282. Tabar AI, Fernandez-Tavora L, Alonso R, et al. Olerance of a cluster schedule with a house dust mite extract quantified in mass units: multicentre study. J Investig Allergol Clin Immunol 2004;14:193-7.
283. Zhang L, Wang C, Han D, Wang X, Zhao Y, Liu J. Comparative study of cluster and conventional immunotherapy schedules with *Dermatophagoides pteronyssinus* in the treatment of persistent allergic rhinitis. Int Arch Allergy Immunol 2009;148:161-9, IIb.
284. Martinez-Canavate A, Eseverri JL, Rodenas R, et al. Evaluation of paediatric tolerance to an extract of *Alternaria alternata* under two treatment regimes. A multicentre study. Allergol Immunopathol (Madr) 2005;33:138-41, III.
285. Serrano P, Justicia JL, Sanchez C, et al. Systemic tolerability of specific subcutaneous immunotherapy with index-of-reactivity-standardized allergen extracts administered using clustered regimens: a retrospective, observational, multicenter study. Ann Allergy Asthma Immunol 2009;102:247-52, III.
286. Cox L. Advantages and disadvantages of accelerated immunotherapy schedules. J Allergy Clin Immunol 2008;122:432-4, IV.
287. Parmiani S, Fernandez Tavora L, Moreno C, Guardia P, Rico P. Clustered schedules in allergen-specific immunotherapy. Allergol Immunopathol (Madr) 2002;30: 283-91, IV.
288. Miller DL, Mansmann HC Jr. Rapid injection therapy in children with intractable asthma: safety and technique. Ann Allergy 1971;29:178-86, III.
289. Portnoy J, King K, Kanarek H, Horner S. Incidence of systemic reactions during rush immunotherapy. Ann Allergy 1992;68:493-8, III.
290. Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80, III.
291. Hejjaoui A, Dhivert H, Michel FB, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. IV. Systemic reactions according to the immunotherapy schedule. J Allergy Clin Immunol 1990;85:473-9, III.
292. Harvey SM, Laurie S, Hilton K, Khan DA. Safety of rush immunotherapy to multiple aeroallergens in an adult population. Ann Allergy Asthma Immunol 2004;92: 414-9, III.
293. Bernstein JA, Kagen SL, Bernstein DI, Bernstein IL. Rapid venom immunotherapy is safe for routine use in the treatment of patients with Hymenoptera anaphylaxis. Ann Allergy 1994;73:423-8, III.
294. Jutel M, Skrbic D, Pichler WJ, Muller UR. Ultra rush bee venom immunotherapy does not reduce cutaneous weal responses to bee venom and codeine phosphate. Clin Exp Allergy 1995;25:1205-10, III.
295. Roll A, Hofbauer G, Ballmer-Weber BK, Schmid-Grendelmeier P. Safety of specific immunotherapy using a four-hour ultra-rush induction scheme in bee and wasp allergy. J Investig Allergol Clin Immunol 2006;16:79-85, III.
296. Goldberg A, Confino-Cohen R. Rush venom immunotherapy in patients experiencing recurrent systemic reactions to conventional venom immunotherapy. Ann Allergy Asthma Immunol 2003;91:405-10, III.
297. Schiavino D, Nucera E, Pollastrini E, et al. Specific ultrarush desensitization in Hymenoptera venom-allergic patients. Ann Allergy Asthma Immunol 2004;92: 409-13, III.
298. Dietrich JJ, Moore LM, Nguyen S, Hagan LL, Tankersley MS. Imported fire ant hypersensitivity: a 1-day rush immunotherapy schedule without premedication. Ann Allergy Asthma Immunol 2009;103:535-6, III.
299. Ohashi Y, Nakai Y, Murata K. Effect of pretreatment with fexofenadine on the safety of immunotherapy in patients with allergic rhinitis. Ann Allergy Asthma Immunol 2006;96:600-5, Ib.
300. Massanari M, Nelson H, Casale T, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. J Allergy Clin Immunol 2010;125:383-9, Ib.
301. Muller U, Hari Y, Berchtold E. Premedication with antihistamines may enhance efficacy of specific-allergen immunotherapy. J Allergy Clin Immunol 2001;107:81-6, Ib.
302. Muller U, Golden DB, Lockey RF, Shin B. Immunotherapy for hymenoptera venom hypersensitivity. Clin Allergy Immunol 2008;21:377-92.
303. Hejjaoui A, Ferrando R, Dhivert H, Michel FB, Bousquet J. Systemic reactions occurring during immunotherapy with standardized pollen extracts. J Allergy Clin Immunol 1992;89:925-33, III.
304. Kopp MV, Brauburger J, Riedinger F, et al. The effect of anti-IgE treatment on in vitro leukotriene release in children with seasonal allergic rhinitis. J Allergy Clin Immunol 2002;110:728-35, Ib.
305. Kuehr J, Brauburger J, Zielen S, et al. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. J Allergy Clin Immunol 2002;109: 274-80, Ib.
306. Casale TB, Busse WW, Kline JN, et al. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. J Allergy Clin Immunol 2006;117:134-40, Ib.
307. Galera C, Soohun N, Zankar N, Caimmi S, Gallen C, Demoly P. Severe anaphylaxis to bee venom immunotherapy: efficacy of pretreatment and concurrent treatment with omalizumab. J Investig Allergol Clin Immunol 2009;19:225-9.
308. Schulze J, Rose M, Zielen S. Beekeepers anaphylaxis: successful immunotherapy covered by omalizumab. Allergy 2007;62:963-4, NR.
309. Kontou-Fili K. High omalizumab dose controls recurrent reactions to venom immunotherapy in indolent systemic mastocytosis. Allergy 2008;63:376-8, NR.
310. Kontou-Fili K, Filis CI. Prolonged high-dose omalizumab is required to control reactions to venom immunotherapy in mastocytosis. Allergy 2009;64:1384-5, NR.
311. Cox L, Platts-Mills TA, Finegold I, Schwartz LB, Simons FE, Wallace DV. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. J Allergy Clin Immunol 2007;120:1373-7, IV.
312. Limb SL, Starke PR, Lee CE, Chowdhury BA. Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. J Allergy Clin Immunol 2007;120:1378-81, IV.
313. Goldberg A, Reisman RE. Prolonged interval maintenance venom immunotherapy. Ann Allergy 1988;61:177-9, III.
314. Kochuyt AM, Stevens EA. Safety and efficacy of a 12-week maintenance interval in patients treated with Hymenoptera venom immunotherapy. Clin Exp Allergy 1994;24:35-41, III.
315. Goldberg A, Confino-Cohen R. Maintenance venom immunotherapy administered at 3-month intervals is both safe and efficacious. J Allergy Clin Immunol 2001;107:902-6, III.
316. Goldberg A, Confino-Cohen R. Effectiveness of maintenance bee venom immunotherapy administered at 6-month intervals. Ann Allergy Asthma Immunol 2007;99:352-7, III.
317. Kanter L. Accidental needle stick prevention: an important, costly, unsafe policy revisited. Ann Allergy Asthma Immunol 2006;97:7-9, IV.
318. Kanter LJ, Siegel C. Needle sticks and adverse outcomes in office-based allergy practices. Ann Allergy Asthma Immunol 2003;90:389-92, III.
319. Wolf BL, Marks A, Fahrenholz JM. Accidental needle sticks, the Occupational Safety and Health Administration, and the fallacy of public policy. Ann Allergy Asthma Immunol 2006;97:52-4, III.
320. Centers for Disease Control and Prevention: general recommendations on immunization recommendations of the Advisory Committee on Immunization Practices (ACIP). Morb Mortal Wkly Rep 2006;55:14-6, IV.
321. Waibel KH. Aspiration before immunotherapy injection is not required. J Allergy Clin Immunol 2006;118:525-6, III.
322. Guarneri F. Aspiration before subcutaneous immunotherapy injection: unnecessary or advisable? J Allergy Clin Immunol 2007;119:512-3, IV.
323. Miller JD, Bell JB, Lee RJ, Tarvin F. Blood return on aspiration before immunotherapy injection. J Allergy Clin Immunol 2007;119:512, IV.
324. Position statement on the administration of immunotherapy outside of the prescribing allergist facility. Drugs and Anaphylaxis Committee of the American College of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 1998;81:101-2, IV.

325. Esch RE. Manufacturing and standardizing fungal allergen products. J Allergy Clin Immunol 2004;113:210-5, LB.
326. 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.
327. Salvaggio JE, Burge HA, Chapman JA. Emerging concepts in mold allergy: what is the role of immunotherapy? J Allergy Clin Immunol 1993;92:217-22, IV.
328. Esch RE. Allergen immunotherapy: what can and cannot be mixed? J Allergy Clin Immunol 2008;122:659-60, IV.
329. Grier TJ, LeFevre DM, Duncan EA, Esch RE. Stability of standardized grass, dust mite, cat, and short ragweed allergens after mixing with mold or cockroach extracts. Ann Allergy Asthma Immunol 2007;99:151-60, LB.
330. Nelson HS, Ikle D, Buchmeier A. Studies of allergen extract stability: the effects of dilution and mixing. J Allergy Clin Immunol 1996;98:382-8, LB.
331. Arbes SJ Jr, Cohn RD, Yin M, Muilenberg ML, Friedman W, Zeldin DC. Dog allergen (Can f 1) and cat allergen (Fel d 1) in US homes: results from the National Survey of Lead and Allergens in Housing. J Allergy Clin Immunol 2004;114:111-7, III.
332. Van Metre TE Jr, Marsh DG, Adkinson NF Jr, et al. Immunotherapy for cat asthma. J Allergy Clin Immunol 1988;82:1055-68, Ib.
333. Van Metre TE Jr, Marsh DG, Adkinson NF Jr, et al. Immunotherapy decreases skin sensitivity to cat extract. J Allergy Clin Immunol 1989;83:888-99, Ib.
334. Stanaland BE, Fernandez-Caldas E, Jacinto CM, Trudeau WL, Lockey RF. Sensitization to *Blomia tropicalis*: skin test and cross-reactivity studies. J Allergy Clin Immunol 1994;94:452-7, LB.
335. Arlian LG, Rapp CM, Fernandez-Caldas E. Allergenicity of *Euroglyphus maynei* and its cross-reactivity with *Dermatophagoides* species. J Allergy Clin Immunol 1993;91:1051-8, LB.
336. Niu CK, Chen WY, Huang JL, Lue KH, Wang JY. Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: A multi-center, double-blind, randomized, and placebo-controlled study in Taiwan. Respir Med 2006;100: 1374-83, Ib.
337. Golden DB, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM. Outcomes of allergy to insect stings in children, with and without venom immunotherapy. N Engl J Med 2004;351:668-74, III.
338. Slater JE, James R, Pongracic JA, et al. Biological potency of German cockroach allergen extracts determined in an inner city population. Clin Exp Allergy 2007; 37:1033-9, LB.
339. Schou C, Lind P, Fernandez-Caldas E, Lockey RF, Lowenstein H. Identification and purification of an important cross-reactive allergen from American *(Periplaneta americana)* and German *(Blattella germanica)* cockroach. J Allergy Clin Immunol 1990;86:935-46, LB.
340. Alvarez-Cuesta E, Aragoneses-Gilsanz E, Martin-Garcia C, Berges-Gimeno P, Gonzalez-Mancebo E, Cuesta-Herranz J. Immunotherapy with depigmented glutaraldehyde-polymerized extracts: changes in quality of life. Clin Exp Allergy 2005;35:572-8, Ib.
341. Moncayo Coello CV, Rosas Vargas MA, del Rio Navarro BE, Lerma Ortiz L, Velazquez Armenta Y, Sienra Monge JJ. [Quality of life in children with allergic rhinitis before and after being treated with specific immunotherapy (cases and controls)]]. Rev Alerg Mex 2003;50:170-5, III.
342. Guardia P, Moreno C, Justicia JL, et al. Tolerance and short-term effect of a cluster schedule with pollen-extracts quantified in mass-units. Allergol Immunopathol (Madr) 2004;32:271-7, IIa.
343. Nelson HS. Multiallergen immunotherapy for allergic rhinitis and asthma. J Allergy Clin Immunol 2009;123:763-9, IV.
344. Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children—a 14-year study. Pediatrics 1968;42:793-802, Ib.
345. Matsui EC, Wood RA, Rand C, Kanchanaraksa S, Swartz L, Eggleston PA. Mouse allergen exposure and mouse skin test sensitivity in suburban, middle-class children with asthma. J Allergy Clin Immunol 2004;113:910-5, III.
346. Matsui EC, Simons E, Rand C, et al. Airborne mouse allergen in the homes of inner-city children with asthma. J Allergy Clin Immunol 2005;115:358-63, III.
347. Perry T, Matsui E, Merriman B, Duong T, Eggleston P. The prevalence of rat allergen in inner-city homes and its relationship to sensitization and asthma morbidity. J Allergy Clin Immunol 2003;112:346-52, III.
348. Modrzynski M, Zawisza E, Moverare R, et al. Development of new IgE specificities to allergenic components in birch pollen extract during specific immunotherapy studied with immunoblotting and Pharmacia CAP System. Przegl Lek 2003; 60:130-2, IIa.
349. Moverare R, Elfman L, Vesterinen E, Metso T, Haahtela T. Development of new IgE specificities to allergenic components in birch pollen extract during specific immunotherapy studied with immunoblotting and Pharmacia CAP System. Allergy 2002;57:423-30, IIa.
350. Bagg A, Chacko T, Lockey R. Reactions to prick and intradermal skin tests. Ann Allergy Asthma Immunol 2009;102:400-2, III.
351. Valyasevi MA, Maddox DE, Li JT. Systemic reactions to allergy skin tests. Ann Allergy Asthma Immunol 1999;83:132-6, III.
352. Berg TL, Johansson SG. Allergy diagnosis with the radioallergosorbent test: a comparison with the results of skin and provocation tests in an unselected group of children with asthma and hay fever. J Allergy Clin Immunol 1974;54:209-21, IIb.
353. van der Zee JS, de Groot H, van Swieten P, Jansen HM, Aalberse RC. Discrepancies between the skin test and IgE antibody assays: study of histamine release, complement activation in vitro, and occurrence of allergen-specific IgG. J Allergy Clin Immunol 1988;82:270-81, IIb.
354. Wood RA, Phipatanakul W, Hamilton RG, Eggleston PA. A comparison of skin prick tests, intradermal skin tests, and RASTs in the diagnosis of cat allergy. J Allergy Clin Immunol 1999;103:773-9, IIa.
355. Bernstein DI, Biagini RE, Karnani R, et al. In vivo sensitization to purified *Hevea brasiliensis* proteins in health care workers sensitized to natural rubber latex. J Allergy Clin Immunol 2003;111:610-6, IIb.
356. Koskela H, Taivainen A, Tukiainen H, Chan HK. Inhalation challenge with bovine dander allergens: who needs it? Chest 2003;124:383-91, IIb.
357. Sharma HP, Wood RA, Bravo AR, Matsui EC. A comparison of skin prick tests, intradermal skin tests, and specific IgE in the diagnosis of mouse allergy. J Allergy Clin Immunol 2008;121:933-9, IIb.
358. Escudero AI, Sanchez-Guerrero IM, Mora AM, et al. Cost-effectiveness of various methods of diagnosing hypersensitivity to *Alternaria*. Allergol Immunopathol (Madr) 1993;21:153-7, IIb.
359. Nelson HS, Oppenheimer J, Buchmeier A, Kordash TR, Freshwater LL. An assessment of the role of intradermal skin testing in the diagnosis of clinically relevant allergy to timothy grass. J Allergy Clin Immunol 1996;97:1193-201, IIa.
360. Lowenstein H. Domestic allergens. In: Kerr J, editor. Procedures of the XI International Congress of Allergology & Clinical Immunology, 1983London: MacMillan; 1983. p. 545-8, NR.
361. Pomes A. Cockroach and other inhalant insect allergens. Clin Allergy Immunol 2008;21:183-200, NR.
362. Lind P, Weeke B, Lowenstein H. A reference allergen preparation of the house dust mite *D. pteronyssinus*, produced from whole mite culture—a part of the DAS 76 study. Comparison with allergen preparations from other raw materials. Allergy 1984;39:259-74, LB.
363. Lowenstein H, King TP, Goodfriend L, Hussain R, Roebber M, Marsh DG. Antigens of *Ambrosia elatior* (short ragweed) pollen. II. Immunochemical identification of known antigens by quantitative immunoelectrophoresis. J Immunol 1981; 127:637-42, LB.
364. Lowenstein H, Marsh DG. Antigens of *Ambrosia elatior* (short ragweed) pollen. I. Crossed immunoelectrophoretic analyses. J Immunol 1981;126:943-8, LB.
365. Lowenstein H, Marsh DG. Antigens of *Ambrosia elatior* (short ragweed) pollen. III. Crossed radioimmunoelectrophoresis of ragweed-allergic patients' sera with special attention to quantification of IgE responses. J Immunol 1983;130: 727-31, LB.
366. Aukrust L. Crossed radioimmunoelectrophoretic studies of distinct allergens in two extracts of *Cladosporium herbarum*. Int Arch Allergy Appl Immunol 1979; 58:375-90, LB.
367. Baer H, Godfrey H, Maloney CJ, Norman PS, Lichtenstein LM. The potency and antigen E content of commercially prepared ragweed extracts. J Allergy 1970;45: 347-54, LB.
368. Baer H, Maloney CJ, Norman PS, Marsh DG. The potency and group I antigen content of six commercially prepared grass pollen extracts. J Allergy Clin Immunol 1974;54:157-64, LB.
369. Greenert S, Bernstein IL, Michael JG. Immune responses of non-atopic individuals to prolonged immunisation with ragweed extract. Lancet 1971;2:1121-3, IIb.
370. The use of standardized allergen extracts. American Academy of Allergy, Asthma and Immunology (AAAAI). J Allergy Clin Immunol 1997;99:583-6, IV.
371. Nelson HS. The use of standardized extracts in allergen immunotherapy. J Allergy Clin Immunol 2000;106:41-5, IV.
372. Turkeltaub P. Allergenic extracts. II. In vivo standardization. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, editors. Allergy: principles and practice. 3rd edSt. Louis: CV Mosby; 1988. p. 388-401, NR.
373. Ohman JL Jr, Lowell FC, Bloch KJ, Kendall S. Allergens of mammalian origin V. Properties of extracts derived from the domestic cat. Clin Allergy 1976;6:419-28, NR.
374. Lombardero M, Carreira J, Duffort O. Monoclonal antibody based radioimmunoassay for the quantitation of the main cat allergen (Fel d I or Cat-1). J Immunol Methods 1988;108:71-6, LB.
375. Cabanas R, Lopez-Serrano MC, Carreira J, et al. Importance of albumin in cross-reactivity among cat, dog and horse allergens. J Investig Allergol Clin Immunol 2000;10:71-7, LB.
376. Lockey R, Slater J, Esch E. Preparation of standardization of allergen extracts. In: Adkinson F, Yunginger J, Busse W, Bochner B, Holgate S, Simmons E, editors.

Middleton's allergy: principles and practice. Sixth edSt Louis: Mosby; 2003. p. 573-84, NR.
377. Slater JE. Standardized allergen vaccines in the United States. Clin Allergy Immunol 2008;21:273-81, IV.
378. Lin SY, Houser SM, Gross G, Aaronson D. Impact of newly revised sterile medication compounding guidelines USP {797} on allergy vial preparation. Otolaryngol Head Neck Surg 2008;139:5-6, IV.
379. USP 797 guidebook to pharmaceutical compounding—sterile preparations, 2008. Available at: http://www.usp.org/products/797Guidebook/. Accessed March 21, 2010. NR
380. Lay PC, Bass R, Lin SY. Allergen vial mixing and immunotherapy: risks of infections and vial contamination. Otolaryngol Head Neck Surg 2007;137:243-5, LB.
381. Lay PC, Bass R, Hughes LF, Lin SY. Risks of allergy vial contamination: comparison of mixing in-office versus under ventilation hood. Otolaryngol Head Neck Surg 2008;139:364-6, LB.
382. Lin SY, Lay PC, Hughes LF, Bass R. The safety of multi-dose vials in allergy immunotherapy. Otolaryngol Head Neck Surg 2008;139:195-7, LB.
383. Barletta B, Afferni C, Tinghino R, Mari A, Di Felice G, Pini C. Cross-reactivity between *Cupressus arizonica* and *Cupressus sempervirens* pollen extracts. J Allergy Clin Immunol 1996;98:797-804, LB.
384. Leiferman KM, Gleich GJ. The cross-reactivity of IgE antibodies with pollen allergens. I. Analyses of various species of grass pollens. J Allergy Clin Immunol 1976;58:129-39, LB.
385. Leiferman KM, Gleich GJ, Jones RT. The cross-reactivity of IgE antibodies with pollen allergens. II. Analyses of various species of ragweed and other fall weed pollens. J Allergy Clin Immunol 1976;58:140-8, LB.
386. Bernstein IL, Perera M, Gallagher J, Michael JG, Johansson SG. In vitro cross-allergenicity of major aeroallergenic pollens by the radioallergosorbent technique. J Allergy Clin Immunol 1976;57:141-52, LB.
387. Fahlbusch B, Muller WD, Rudeschko O, Jager L, Cromwell O, Fiebig H. Detection and quantification of group 4 allergens in grass pollen extracts using monoclonal antibodies. Clin Exp Allergy 1998;28:799-807, LB.
388. Gonzalez RM, Cortes C, Conde J, et al. Cross-reactivity among five major pollen allergens. Ann Allergy 1987;59:149-54, LB.
389. Karl S, Rakoski J. Hyposensitization with cross-reacting pollen allergens. Z Hautkr 1988;63(suppl 4):55-7, LB.
390. Leavengood DC, Renard RL, Martin BG, Nelson HS. Cross allergenicity among grasses determined by tissue threshold changes. J Allergy Clin Immunol 1985;76: 789-94, LB.
391. Lowenstein H. Timothy pollen allergens. Allergy 1980;35:188-91, NR.
392. Martin BG, Mansfield LE, Nelson HS. Cross-allergenicity among the grasses. Ann Allergy 1985;54:99-104, NR.
393. van Ree R, van Leeuwen WA, Aalberse RC. How far can we simplify in vitro diagnostics for grass pollen allergy?: a study with 17 whole pollen extracts and purified natural and recombinant major allergens. J Allergy Clin Immunol 1998;102: 184-90, LB.
394. Blaher B, Suphioglu C, Knox RB, Singh MB, McCluskey J, Rolland JM. Identification of T-cell epitopes of Lol p 9, a major allergen of ryegrass *(Lolium perenne)* pollen. J Allergy Clin Immunol 1996;98:124-32, LB.
395. Eusebius NP, Papalia L, Suphioglu C, et al. Oligoclonal analysis of the atopic T cell response to the group 1 allergen of *Cynodon dactylon* (Bermuda grass) pollen: pre- and post-allergen-specific immunotherapy. Int Arch Allergy Immunol 2002;127:234-44, LB.
396. Phillips JW, Bucholtz GA, Fernandez-Caldas E, Bukantz SC, Lockey RF. Bahia grass pollen, a significant aeroallergen: evidence for the lack of clinical cross-reactivity with timothy grass pollen. Ann Allergy 1989;63:503-7, LB.
397. Black J. Cedar hay fever. J Allergy 1929;1:71-3, NR.
398. Pham NH, Baldo BA, Bass DJ. Cypress pollen allergy. Identification of allergens and crossreactivity between divergent species. Clin Exp Allergy 1994;24:558-65, LB.
399. Yoo TJ, Spitz E, McGerity JL. Conifer pollen allergy: studies of immunogenicity and cross antigenicity of conifer pollens in rabbit and man. Ann Allergy 1975;34: 87-93, LB.
400. Lowenstein H. Cross reactions among pollen antigens. Allergy 1980;35:198-200, NR.
401. Zetterstrom O, Fagerberg E, Wide L. An investigation of pollen extracts from different deciduous trees in patients with springtime allergy in Sweden. Acta Allergol 1972;27:15-21, LB.
402. Eriksson NE, Wihl JA, Arrendal H, Strandhede SO. Tree pollen allergy. III. Cross reactions based on results from skin prick tests and the RAST in hay fever patients. A multi-centre study. Allergy 1987;42:205-14, LB.
403. Niederberger V, Pauli G, Gronlund H, et al. Recombinant birch pollen allergens (rBet v 1 and rBet v 2) contain most of the IgE epitopes present in birch, alder, hornbeam, hazel, and oak pollen: a quantitative IgE inhibition study with sera from different populations. J Allergy Clin Immunol 1998;102:579-91, LB.
404. White JF, Bernstein DI. Key pollen allergens in North America. Ann Allergy Asthma Immunol 2003;91:425-36, 92. IV.
405. Bousquet J, Guerin B, Hewitt B, Lim S, Michel FB. Allergy in the Mediterranean area. III: cross reactivity among *Oleaceae* pollens. Clin Allergy 1985;15:439-48, NR.
406. Kernerman SM, McCullough J, Green J, Ownby DR. Evidence of cross-reactivity between olive, ash, privet, and Russian olive tree pollen allergens. Ann Allergy 1992;69:493-6, LB.
407. Yunginger JW, Gleich GJ. Measurement of ragweed antigen E by double antibody radioimmunoassay. J Allergy Clin Immunol 1972;50:326-37, LB.
408. Asero R, Weber B, Mistrello G, Amato S, Madonini E, Cromwell O. Giant ragweed specific immunotherapy is not effective in a proportion of patients sensitized to short ragweed: analysis of the allergenic differences between short and giant ragweed. J Allergy Clin Immunol 2005;116:1036-41, IIa.
409. Katial RK, Lin FL, Stafford WW, Ledoux RA, Westley CR, Weber RW. Mugwort and sage *(Artemisia)* pollen cross-reactivity: ELISA inhibition and immunoblot evaluation. Ann Allergy Asthma Immunol 1997;79:340-6, LB.
410. Lewis W, Vinay P, Zenger VE. Airborne and Allergenic Pollen of North America. Baltimore (MD): The John Hopkins University Press; 1983. LB.
411. Gomez J, Mansfield LE, Frederick RW, Rael ED. Analysis of the individual allergens of Russian thistle pollen by an enzyme-linked immunoblotting technique. J Asthma 1989;26:243-50, LB.
412. Shafiee A, Yunginger JW, Gleich GJ. Isolation and characterization of Russian thistle *(Salsola pestifer)* pollen allergens. J Allergy Clin Immunol 1981;67: 472-81, LB.
413. Weber RW, Nelson HS. Pollen allergens and their interrelationships. Clin Rev Allergy 1985;3:291-318, NR.
414. Weber R. Cross-reactivity among Chenopod-Amaranth weeds: skin test correlation. Ann Allergy 1987;58:287, NR.
415. Weber RWNH. Chenopod-Amaranth cross-allergenicity: evaluated by RAST inhibition. Ann Allergy 1984;52:226, NR.
416. Helm RM, Squillace DL, Jones RT, Brenner RJ. Shared allergenic activity in Asian *(Blattella asahinai)*, German *(Blattella germanica)*, American *(Periplaneta americana)*, and Oriental *(Blatta orientalis)* cockroach species. Int Arch Allergy Appl Immunol 1990;92:154-61, LB.
417. Jeong KY, Lee J, Lee IY, Ree HI, Hong CS, Yong TS. Allergenicity of recombinant Bla g 7, German cockroach tropomyosin. Allergy 2003;58:1059-63, LB.
418. Solley GO, Vanderwoude C, Knight GK. Anaphylaxis due to red imported fire ant sting. Med J Aust 2002;176:521-3, NR.
419. Fernandez-Melendez S, Miranda A, Garcia-Gonzalez JJ, Barber D, Lombardero M. Anaphylaxis caused by imported red fire ant stings in Malaga, Spain. J Investig Allergol Clin Immunol 2007;17:48-9, NR.
420. Wong SS, Yuen KY. Red imported fire ants in Hong Kong. Hong Kong Med J 2005;11:131-2, NR.
421. Rueff F, Wenderoth A, Przybilla B. Patients still reacting to a sting challenge while receiving conventional Hymenoptera venom immunotherapy are protected by increased venom doses. J Allergy Clin Immunol 2001;108:1027-32, III.
422. Kordash TR, Amend MJ, Williamson SL, Jones JK, Plunkett GA. Effect of mixing allergenic extracts containing *Helminthosporium, D. farinae*, and cockroach with perennial ryegrass. Ann Allergy 1993;71:240-6, LB.
423. Grier TJ, LeFevre DM, Duncan EA, Esch RE. Stability and mixing compatibility of dog epithelia and dog dander allergens. Ann Allergy Asthma Immunol 2009; 103:411-7, LB.
424. Esch RE. Role of proteases on the stability of allergenic extracts. Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf A M 1992;171-9, LB.
425. Anderson MC, Baer H. Antigenic and allergenic changes during storage of a pollen extract. J Allergy Clin Immunol 1982;69:3-10, LB.
426. Moore M, Tucker M, Grier T, Quinn J. Effects of summer mailing on in vivo and in vitro relative potencies of standardized timothy grass extract. Ann Allergy Asthma Immunol 2010;104:147-51, LB.
427. Sridhara S, Singh BP, Arora N, Verma J, Gangal SV. A study on antigenic and allergenic changes during storage in three different biological extracts. Asian Pac J Allergy Immunol 1992;10:33-8, LB.
428. Niemeijer NR, Kauffman HF, van Hove W, Dubois AE, de Monchy JG. Effect of dilution, temperature, and preservatives on the long-term stability of standardized inhalant allergen extracts. Ann Allergy Asthma Immunol 1996;76: 535-40, LB.
429. Vijay HM, Young NM, Bernstein IL. Studies on *Alternaria* allergens. VI. Stability of the allergen components of *Alternaria tenuis* extracts under a variety of storage conditions. Int Arch Allergy Appl Immunol 1987;83:325-8, LB.
430. Support for practicing allergists Extract stability study yields key data. AAAAI Academy News May 2006. LB.
431. Passalacqua G, Albano M, Ruffoni S, et al. Nasal immunotherapy to *Parietaria*: evidence of reduction of local allergic inflammation. Am J Respir Crit Care Med 1995;152:461-6, IIa.

432. Tari MG, Mancino M, Monti G. Immunotherapy by inhalation of allergen in powder in house dust allergic asthma—a double-blind study. J Investig Allergol Clin Immunol 1992;2:59-67, IIa.
433. Didier A, Malling HJ, Worm M, 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.
434. Durham S, Yang W, Pedersen M, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: A randomized controlled trial in seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006;117:802-9, Ib.
435. Canonica GW, Bousquet J, Casale T, et al. Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. Allergy 2009;64(suppl 91):1-59, IV.
436. Taudorf E, Laursen LC, Lanner A, et al. Oral immunotherapy in birch pollen hay fever. J Allergy Clin Immunol 1987;80:153-61, IIb.
437. Senti G, Prinz Vavricka BM, Erdmann I, et al. Intralymphatic allergen administration renders specific immunotherapy faster and safer: a randomized controlled trial. Proc Natl Acad Sci U S A 2008;105:17908-12, III.
438. Senti G, Graf N, Haug S, et al. Epicutaneous allergen administration as a novel method of allergen-specific immunotherapy. J Allergy Clin Immunol 2009;124:997-1002, Ib.
439. Varshney P, Steele PH, Vickery BP, et al. Adverse reactions during peanut oral immunotherapy home dosing. J Allergy Clin Immunol 2009;124:1351-2, III.
440. Hofmann AM, Scurlock AM, Jones SM, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. J Allergy Clin Immunol 2009; 124:286-91, e1-6. III.
441. Penagos M, Compalati E, Tarantini F, et al. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials. Ann Allergy Asthma Immunol 2006;97:141-8, Ia.
442. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. Allergy 2005;60:4-12, Ia.
443. Calamita Z, Saconato H, Pela AB, Atallah AN. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. Allergy 2006;61:1162-72, Ia.
444. Penagos M, Passalacqua G, Compalati E, et al. Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. Chest 2008;133:599-609, Ia.
445. Nieto A, Mazon A, Pamies R, Bruno L, Navarro M, Montanes A. Sublingual immunotherapy for allergic respiratory diseases: an evaluation of meta-analyses. J Allergy Clin Immunol 2009;124:157-61, e1-32. IV.
446. Ott H, Sieber J, Brehler R, et al. Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study. Allergy 2009;64:179-86, Ib.
447. Lombardi C, Incorvaia C, Braga M, Senna G, Canonica GW, Passalacqua G. Administration regimens for sublingual immunotherapy to pollen allergens: what do we know? Allergy 2009;64:849-54, Iv.
448. Marogna M, Tomassetti D, Bernasconi A, et al. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. Ann Allergy Asthma Immunol 2008;101:206-11, III.
449. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Randomized controlled open study of sublingual immunotherapy for respiratory allergy in real-life: clinical efficacy and more. Allergy 2004;59:1205-10, Ib.
450. Enrique E, Pineda F, Malek T, et al. Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. J Allergy Clin Immunol 2005;116:1073-9, Ib.
451. Dahl R, Kapp A, Colombo G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006;118:434-40, Ib.
452. Blazowski L. Anaphylactic shock because of sublingual immunotherapy overdose during third year of maintenance dose. Allergy 2008;63:374, NR.
453. Antico A, Pagani M, Crema A. Anaphylaxis by latex sublingual immunotherapy. Allergy 2006;61:1236-7, NR.
454. Eifan AO, Keles S, Bahceciler NN, Barlan IB. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. Allergy 2007;62:567-8, NR.
455. Dunsky EH, Goldstein MF, Dvorin DJ, Belecanech GA. Anaphylaxis to sublingual immunotherapy. Allergy 2006;61:1235, NR.
456. de Groot H, Bijl A. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. Allergy 2009;64:963-4, NR.
457. Cochard MM, Eigenmann PA. Sublingual immunotherapy is not always a safe alternative to subcutaneous immunotherapy. J Allergy Clin Immunol 2009;124: 378-9, NR.
458. Cox L, Jacobsen L. Comparison of allergen immunotherapy practice patterns in the United States and Europe. Ann Allergy Asthma Immunol 2009;103:451-61, 95. IV.
459. Tucker MH, Tankersley MS. Perception and practice of sublingual immunotherapy among practicing allergists. Ann Allergy Asthma Immunol 2008;101:419-25, III.
460. Amar SM, Harbeck RJ, Sills M, Silveira LJ, O'Brien H, Nelson HS. Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract. J Allergy Clin Immunol 2009;124:150-6, e1-5. Ib.
461. Esch RE. Specific immunotherapy in the U.S.A.: general concept and recent initiatives. Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf A M 2003;94): 17-23, IV.
462. Andri L, Senna G, Andri G, et al. Local nasal immunotherapy for birch allergic rhinitis with extract in powder form. Clin Exp Allergy 1995;25:1092-9, Ib.
463. Andri L, Senna G, Betteli C, et al. Local nasal immunotherapy with extract in powder form is effective and safe in grass pollen rhinitis: a double-blind study. J Allergy Clin Immunol 1996;97:34-41, Ib.
464. Andri L, Senna GE, Betteli C, et al. Local nasal immunotherapy in allergic rhinitis to *Parietaria*. A double-blind controlled study. Allergy 1992;47:318-23, Ib.
465. Passalacqua G, Albano M, Pronzato C, et al. Long-term follow-up of nasal immunotherapy to *Parietaria*: clinical and local immunological effects. Clin Exp Allergy 1997;27:904-8, Ib.
466. Gaglani B, Borish L, Bartelson BL, Buchmeier A, Keller L, Nelson HS. Nasal immunotherapy in weed-induced allergic rhinitis. Ann Allergy Asthma Immunol 1997;79:259-65, Ib.
467. Andri L, Senna G, Betteli C, Givanni S, Andri G, Falagiani P. Local nasal immunotherapy for *Dermatophagoides*-induced rhinitis: efficacy of a powder extract. J Allergy Clin Immunol 1993;91:987-96, Ib.
468. Pajno GB, Vita D, Caminiti L, et al. Children's compliance with allergen immunotherapy according to administration routes. J Allergy Clin Immunol 2005;116: 1380-1, III.
469. Kerzl R, Simonowa A, Ring J, Ollert M, Mempel M. Life-threatening anaphylaxis to kiwi fruit: protective sublingual allergen immunotherapy effect persists even after discontinuation. J Allergy Clin Immunol 2007;119:507-8, NR.
470. Patriarca G, Nucera E, Roncallo C, et al. Oral desensitizing treatment in food allergy: clinical and immunological results. Aliment Pharmacol Ther 2003;17: 459-65, III.
471. Casale TB, Stokes JR. Immunomodulators for allergic respiratory disorders. J Allergy Clin Immunol 2008;121:288-96, IV.
472. Creticos PS, Schroeder JT, Hamilton RG, et al. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. N Engl J Med 2006;355: 1445-55, Ib.
473. Dynavax Reports Interim TOLAMBA TM Ragweed Allergy Results from DARTT Trial 01/08/2007 press release. http://investors.dynavax.com/releasedetail.cfm?ReleaseID=231013. In; 2007.
474. Drachenberg KJ, Wheeler AW, Stuebner P, Horak F. A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections. Allergy 2001;56: 498-505, III.
475. Ewan PW, Alexander MM, Snape C, Ind PW, Agrell B, Dreborg S. Effective hyposensitization in allergic rhinitis using a potent partially purified extract of house dust mite. Clin Allergy 1988;18:501-8, Ib.
476. Ohman JL Jr, Sundin B. Standardized allergenic extracts derived from mammals. Clin Rev Allergy 1987;5:37-47, IV.
477. Leynadier F, Banoun L, Dollois B, et al. Immunotherapy with a calcium phosphate-adsorbed five-grass-pollen extract in seasonal rhinoconjunctivitis: a double-blind, placebo-controlled study. Clin Exp Allergy 2001;31:988-96, Ib.
478. Cox L. Standardized allergen extracts: past, present and future. Expert Rev Clin Immunol 2005;1:579-88, IV.
479. Creticos PS, Adkinson NF Jr, Kagey-Sobotka A, et al. Nasal challenge with ragweed pollen in hay fever patients: effect of immunotherapy. J Clin Invest 1985;76: 2247-53, III.

Table E1. List of the published practice parameters of the Joint Task Force on Practice Parameters for Allergy and Immunology

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.

14 9. Parameters for the diagnosis and management of sinusitis. J Allergy Clin Immunol 1998;102(suppl): S107-S144.

15 10. Stinging insect hypersensitivity: a practice parameter. J Allergy Clin Immunol 1999;103:963-80.

16 11. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999;83(suppl): S665–S700.

17 12. Diagnosis and management of urticaria: a practice parameter. Ann Allergy 2000;85(suppl):S521-S544.

18 13. Allergen immunotherapy: a practice parameter. Ann Allergy 2003;90(suppl):SI-S540.

19 14. Symptom severity assessment of allergic rhinitis: part I. Ann Allergy 2003;91:105-14.

20 15. Disease management of atopic dermatitis: an updated practice parameter. Ann Allergy 2004;93(suppl): S1-S21.

21 16. Stinging insect hypersensitivity: a practice parameter update. J Allergy Clin Immunol 2004;114:869-86.

22 17. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol

23 2005;115(suppl):S483-S523.

24 18. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy 2005;

25 94(suppl):S1-S63.

26 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 2005; 116(suppl):S13-S47.
21. Food allergy: a practice parameter. Ann Allergy Asthma Immunol 2006;96(suppl 2):S1-S68.
22. Contact dermatitis: a practice parameter. Ann Allergy Asthma Immunol 2006;97(suppl 2):S1-S38.
23. Cox L, Li JT, Nelson H, Lockey R. Allergen immunotherapy: A practice parameter second update. J Allergy Clin Immunol 2007; 120:S25-85.
24. Bernstein IL, Li JT, Bernstein DI, et al. Allergy Diagnostic Testing-An Updated Practice Parameter. Ann Allergy 100; March 2008:S1-S148
25. Wallace D, Dykewicz M, Bernstein D, et al. The diagnosis and management of rhinitis: An updated practice parameter. The Journal of Allergy and Clinical Immunology 2008;122:S1-S84.
26. Kelso JM, Li JT, Nicklas RA, et al. Adverse Reactions to Vaccines. Ann Allergy 2009; 103(4)S1-S16.
27. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol 2010;126:477-80 e1-42.
28. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol 2010;105:259-73.

42

43

44 Table E2. List of summary statements without accompanying explanations

45 Summary Statement 1: The immunologic response to subcutaneous immunotherapy is characterized by decreases in the
46 sensitivity of end organs and changes in the humeral and cellular responses to the administered allergens. A

47 Summary Statement 2: Reduction in end organ response with immunotherapy includes decreased early and late response
48 of the skin, conjunctiva, nasal mucosa and bronchi to allergen challenge, decrease in allergen induced eosinophil,
49 basophil and mast cell infiltration, blunting of mucosal priming, and reduction of non-specific bronchial sensitivity to
50 histamine. A

51 Summary Statement 3: Shortly after initiation of immunotherapy there is an increase in CD4+CD25+ regulatory T-
52 lymphocytes secreting IL-10 and TGF-B associated with immunologic tolerance, defined as a long-lived decrease in
53 allergen-specific T-cell responsiveness. With continued immunotherapy there is some waning of this response and
54 immune deviation from Th_2 to Th_1 cytokine response to the administered allergen predominates. A

55 Summary Statement 4: Specific- IgE levels initially rise, then gradually fall. Levels of specific IgG_1 IgG_4 and IgA rise.
56 None of these changes in antibody levels have been shown to correlate strongly with clinical improvement. A

57 Summary Statement 5: Increases in allergen-specific IgG are not predictive of the degree or duration of efficacy of
58 immunotherapy. However, functional alterations in allergen-specific IgG such as changes in avidity and/or affinity for
59 allergen might play a role in determining clinical efficacy. LB

60 Summary Statement 6: Immunotherapy is effective for treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma,
61 and stinging insect hypersensitivity. Therefore, immunotherapy merits consideration in patients with these disorders as a
62 possible treatment option. A

63 Summary Statement 7: Allergen immunotherapy should be considered for patients who have demonstrable evidence of
64 specific-IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy may depend on a
65 number of factors, including but not limited to: patient preference/acceptability, adherence, medication requirements,
66 response to avoidance measures, and the adverse effects of medications. D

67 Summary Statement 8: There are some data indicating that immunotherapy can be effective for atopic dermatitis when this
68 condition is associated with aeroallergen sensitivity. B

69 Summary Statement 9: The potential for benefit in symptoms related to oral allergy syndrome with inhalant immunotherapy
70 directed at the cross-reacting pollens has been observed in some studies but not in others. For this reason, more
71 investigation is required to substantiate that a benefit in oral allergy symptoms will occur with allergen immunotherapy. C

72 Summary Statement 10a: Immunotherapy should be considered if the patient has had a systemic reaction to a
73 Hymenoptera sting, especially if such a reaction was associated with respiratory symptoms, cardiovascular symptoms, or
74 both and if the patient has demonstrable evidence of specific-IgE. A

75 Summary Statement 10b: Measurement of baseline serum tryptase level is recommended in patients with moderate or
76 severe anaphylactic reactions to stings because its predictive value is useful regardless of the decision about VIT.
77 Elevated tryptase is associated with more frequent and more severe anaphylactic reactions to stings, as well as greater
78 failure rates with VIT and greater relapse rates after stopping VIT.B

79 Summary Statement 11: Large local reactions (LLR) to insect stings may cause significant morbidity and impair quality of
80 life. VIT may significantly reduce the size and duration of large local reactions and may be considered in patients who
81 have frequent and disabling LLR, particularly those with occupational exposure. B

82 Summary Statement 12: Clinical trials do not support the use of subcutaneous immunotherapy for food hypersensitivity. A

83 Summary Statement 13: The safety and efficacy of oral and sublingual immunotherapy for food hypersensitivity is
84 currently investigational.NR

85 Summary Statement 14: Clinical studies do not support the use of allergen immunotherapy for chronic urticaria,
86 angioedema or both. Therefore, allergen immunotherapy for patients with chronic urticaria or angioedema, or both is
87 not recommended. D

88 Summary Statement 15: Clinical parameters, such as symptoms and medication use, might be useful measures of the
89 efficacy of immunotherapy in a clinical setting; however, repetitive skin testing of patients receiving immunotherapy is
90 not recommended. A

91 Summary Statement 16: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma
92 is stable with pharmacotherapy. C

93 Summary Statement 17: Immunotherapy for children is effective and well tolerated. It has been shown to prevent the new
94 onset of allergen sensitivities in monosensitized patients as well as progression from allergic rhinitis to asthma. Therefore
95 immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of
96 children with allergic rhinitis/ rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. B

97 Summary Statement 18: Immunotherapy may be initiated in young children. Indications are similar to those of other
98 age groups. D

99 Summary Statement 19: In patients, who otherwise have the indication for specific immunotherapy, there is no
100 absolute upper age limit for initiation of immunotherapy. D

101 Summary Statement 20a: Allergen immunotherapy may be continued but is usually not initiated in the pregnant patient. C

102 Summary Statement 20b: If pregnancy occurs during the build-up phase and the patient is on a dose unlikely to be
103 therapeutic, discontinuation of immunotherapy should be considered. D

104 Summary Statement 21: Immunotherapy can be considered in patients with immunodeficiency and autoimmune
105 disorders. C

106 Summary Statement 22: Clinical and physiological improvement can be demonstrated very shortly after the patient
107 reaches a maintenance dose. A

108 Summary Statement 23: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. D

109 Summary Statement 24: The patient's response to immunotherapy should be evaluated on a regular basis. A decision
110 about continuation of effective immunotherapy should generally be made after the initial period of 3 to 5 years of
111 treatment. Some patients may experience sustained clinical remission of their allergic disease after discontinuing
112 immunotherapy, but others may relapse. The severity of disease, benefits sustained from treatment, and convenience of
113 treatment are all factors that should be considered in determining whether to continue or stop immunotherapy for any
114 individual patient. D

115 Summary Statement 25: Although there are no specific tests to distinguish, which patients will relapse after discontinuing
116 VIT, there are clinical features that are associated with a higher chance of relapse, notably a history of a very severe
117 reaction to a sting, elevated baseline serum tryptase level, a systemic reaction during VIT (to a sting or a venom injection),
118 honeybee venom allergy, and treatment duration of less than 5 years. C

119 Summary Statement 26: At present, there are no specific tests or clinical markers that will distinguish between patients
120 who will relapse and those who will remain in long-term clinical remission after discontinuing effective inhalant allergen
121 immunotherapy, and the duration of treatment should be determined by the physician and patient after considering the
122 risks and benefits associated with discontinuing or continuing immunotherapy. D

123 Summary Statement 27: Published studies indicate that individual local reactions do not appear to be predictive of
124 subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an
125 increased risk for future systemic reactions. C

126 Summary Statement 28: Local reactions were found to not predict local reactions at the next injection in one retrospective
127 study. C

128 Summary Statement 29: Glycerin concentrations up to 50% were not associated with significantly higher local reaction
129 rates. Higher glycerin concentrations are associated with injection pain, which correlates with the total amount of glycerin
130 injected. C

131 Summary Statement 30: Antihistamines have been demonstrated to be beneficial in decreasing local reactions during
132 cluster and rush protocols, while leukotriene antagonists were shown effective in a rush protocol. Though commonly
133 utilized, the effect of these medications in reducing local reactions during conventional build-up and maintenance
134 immunotherapy injections has not been extensively reported. A

135 Summary Statement 31: Although there is a low risk of severe systemic reactions with appropriately administered allergen
136 immunotherapy, life-threatening and fatal reactions do occur. A

137 Summary Statement 32: An assessment of the patient's current health status should be made before administration of the
138 allergy immunotherapy injection to determine whether there were any health changes that might require modifying or
139 withholding that patient's immunotherapy treatment. Poorly controlled asthma has been identified as a risk factor for a
140 severe immunotherapy reaction. Before the administration of the allergy injection, the patient should be evaluated for the
141 presence of asthma symptoms. One might also consider an objective measure of airway function (eg, peak flow) for the
142 asthmatic patient before allergy injections. B

143 Summary Statement 33: The majority of safety data on allergen immunotherapy reactions is in the context of 30 minutes.
144 Because most serious systemic reactions from allergen immunotherapy occur within 30 minutes after an injection, patients
145 should remain in the physician's office /medical clinic for at least 30 minutes after the immunotherapy injection. C

146 Summary Statement 34: Delayed systemic reactions, defined as occurring after the 30 minute wait period, may occur and,
147 in general, are not severe. B

148 Summary Statement 35: Biphasic immunotherapy reactions, defined as resolution of the initial reaction with recurrence 2
149 to 24 hours, were reported in up to 23% of patients, who experienced a systemic reaction after allergen immunotherapy in
150 one study. Biphasic reactions were typically less severe than the initial reaction. C

151 Summary Statement 36: Several large studies demonstrate that life- threatening anaphylactic reactions after the first 30
152 minutes are rare. Delayed and biphasic immunotherapy systemic reactions may occur outside of a supervised medical
153 facility. Thus, patients should be educated regarding the possible signs and symptoms of systemic reactions and to
154 contact their health care professional or seek emergency medical attention, as indicated. The decision to prescribe
155 epinephrine autoinjectors to patients receiving allergen immunotherapy is up to the physician's discretion and is based on
156 a number of considerations. C

157 Summary Statement 37: Exposure to β-adrenergic blocking agents is a risk factor for more serious and treatment-resistant
158 anaphylaxis. Concomitant use of β-blockers and allergen immunotherapy should be carefully considered from an
159 individualized risk/benefit standpoint, and incorporate patient preferences in the medical decision-making process. C

160 Summary Statement 38: The balance of possible risks and benefits is not the same for patients with the potential for life-
161 threatening stinging insect reaction who are also taking a β-blocker. In patients who are unable to replace a β-blocker with
162 an equally efficacious alternative, concomitant administration of venom immunotherapy and a β-blocker is warranted. C

163 Summary Statement 39: Glucagon may be efficacious for the treatment of refractory β-blocker associated anaphylaxis. C

164 Summary Statement 40: ACE inhibitors have been associated with greater risk for more severe reaction from venom
165 immunotherapy as well as field stings. ACE inhibitor discontinuation should be considered for patients receiving venom
166 immunotherapy. Concurrent administration of venom immunotherapy and an ACE inhibitor is warranted in selected cases
167 in which no equally efficacious alternative for an ACE inhibitor exists, and this is judged to be favorable from an
168 individualized risk/benefit standpoint and consideration of patient preferences. No evidence exists that angiotensin
169 receptor blockers are associated with greater risk for anaphylaxis from allergen immunotherapy. C

170 Summary Statement 41: β-blocker and ACE Inhibitors are frequently prescribed in combination. Concomitant
171 administration of both of these medications in a patient who requires venom immunotherapy may be warranted, if
172 favorable, from an individualized assessment of potential risks and benefits and patient preferences. D

173 Summary Statement 42: Patients selected for immunotherapy should be cooperative and compliant. D

174 Summary Statement 43: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's
175 asthma is stable. C

176 Summary Statement 44: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or
177 the resultant treatment are relative contraindications for allergen immunotherapy. Examples include severe asthma
178 uncontrolled by pharmacotherapy and significant cardiovascular disease. C

179 Summary Statement 45: Allergen immunotherapy should be administered in a setting where procedures that can
180 reduce the risk of anaphylaxis are in place and where the prompt recognition and treatment of anaphylaxis is ensured.
181 C

182 Summary Statement 46: Epinephrine is the treatment of choice for immunotherapy systemic reactions. Risk factors for
183 fatal immunotherapy reactions include delayed administration of epinephrine. B

184 Summary Statement 47: The starting dose for build-up is usually a 1000-fold or 10,000-fold dilution of the maintenance
185 concentrate, although a lower starting dose might be advisable for highly sensitive patients. D

186 Summary Statement 48: The frequency of allergen immunotherapy administration during a conventional build-up phase
187 is generally 1 to 3 injections per week. D

188 Summary Statement 49: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic
189 reaction if immunotherapy is continued. D

190 Summary Statement 50: Immunotherapy given during periods when the patient is exposed to increased levels of
191 allergen(s) to which they are highly sensitive may be associated with an increased risk of a systemic reaction.
192 However, while survey data have noted this to be a risk factor for severe reactions, several published studies have not
193 found an association between pollen seasons and systemic reactions. C

194 Summary Statement 51: There is no retrospective or prospective published evidence to support modification of doses
195 of allergen immunotherapy because of treatment gaps during the build-up or maintenance immunotherapy phase.
196 However, it is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is
197 prolonged. D

198 Summary Statement 52: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a
199 maintenance dose more rapidly than with conventional schedules. C

200 Summary Statement 53: Studies with single allergens utilizing a cluster schedule demonstrated a similar or increased
201 frequency of systemic reactions compared with immunotherapy with conventional schedules. A

202 Summary Statement 54: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. A

203 Summary Statement 55: Rush schedules with inhalant allergens are associated with an increased risk of systemic
204 reactions. However, rush protocols for administration of stinging Hymenoptera have not been associated with a
205 similarly high incidence of systemic reactions. A

206 Summary Statement 56: Premedication may reduce the frequency of systemic reactions caused by conventional
207 immunotherapy. A

208 Summary Statement 57: Premedication before cluster and rush immunotherapy with aeroallergens may reduce the rate
209 of systemic reactions. Combination therapy is effective in reducing systemic and local reactions during accelerated
210 immunotherapy build-up protocols. A

211 Summary Statement 58: Omalizumab pretreatment has been shown to improve the safety and tolerability of cluster
212 and rush immunotherapy schedules in patients with moderate-persistent asthma and allergic rhinitis, respectively.
213 Additionally, omalizumab used in combination with immunotherapy has been shown to be effective in improving
214 symptom scores compared to immunotherapy alone. A

215 Summary Statement 59: Once a patient reaches a maintenance dose, the interval between injections often can be
216 progressively increased as tolerated up to an interval of 4 weeks for inhalant allergens and up to 8 weeks for venom.
217 Some individuals might tolerate longer intervals between maintenance dose injections. A

218 Summary Statement 60: Allergen immunotherapy extract injections should be given using a calibrated small volume
219 syringe with a 26-to 27-gauge 1/2 or 3/8 inch non-removable needle. C

220 Summary Statement 61: The injection should be given subcutaneously in the lateral or posterior portion of the arm. D

221 Summary Statement 62: Regardless of the location, allergen immunotherapy should be administered under the direct
222 supervision of an appropriately trained physician and/ or qualified physician extender in a facility with the appropriate
223 equipment, medications and personnel to treat anaphylaxis. D

224 Summary Statement 63: The preferred location for administration of allergen immunotherapy is in the office of the
225 physician who prepared the patient's allergen immunotherapy extract. D

226 Summary Statement 64: Patients at high risk of systemic reactions, where possible, should receive immunotherapy in the
227 office of the physician who prepared the patient's allergen immunotherapy extract. D

228 Summary Statement 65: In rare and exceptional cases, when allergen immunotherapy cannot be administered in a
229 medical facility and withholding this therapy would result in a serious detriment to the patients' health (eg, VIT for a patient
230 living in a remote area), careful consideration of potential benefits and risks of at-home administration of allergen
231 immunotherapy should be made on an individual patient basis. If this approach is used, informed consent should be
232 obtained from the patient, and the person administering the injection to the patient must be educated about how to
233 administer immunotherapy and recognize and treat anaphylaxis. D

234 Summary Statement 66: If a patient on immunotherapy transfers from one physician to another, a decision must be made
235 by the physician to whom the patient has transferred as to whether to continue immunotherapy. D

236 Summary Statement 67: If immunotherapy is continued, a decision must then be made about whether to continue
237 unchanged the immunotherapy program initiated by the previous physician or to start a new immunotherapy program.

238 Patients may continue to receive the immunotherapy extract prepared by the patient's previous physician if this is
239 acceptable to the transferring and accepting physicians. D

240 Summary Statement 68: A detailed documentation of the patient's schedule and allergen extract content must accompany
241 a patient when he or she transfers responsibility for their immunotherapy care from one physician to another. In addition, a
242 record of previous response to and compliance with this program should be communicated to the patient's new physician.
243 D

244 Summary Statement 69: An allergen immunotherapy extract must be considered different if there is any change. There is
245 potentially an increased risk of a systemic reaction if the immunotherapy extract is changed because of the possible
246 variability in composition and potency of allergen extracts. If the allergen immunotherapy extract is changed, the patient
247 may need to be retested for specific-IgE sensitivity and started on an immunotherapy formulation and schedule that is
248 based on this reevaluation.D

249 Summary Statement 70: Immunotherapy is effective for pollen, animal allergens, dust mite, mold/ fungi and Hymenoptera
250 hypersensitivity. Therefore, immunotherapy should be considered as part of the management program in patients who
251 have symptoms related to exposure to these allergens, as supported by the presence of specific IgE antibodies. A

252 Summary Statement 71: There is limited data on the efficacy of cockroach immunotherapy. B

253 Summary Statement 72: There are few studies that have investigated the efficacy of multiallergen subcutaneous
254 immunotherapy. These studies have produced conflicting results, with some demonstrating significant clinical
255 improvement compared with placebo and others showing no benefit over optimal pharmacotherapy and environmental
256 control measures. Thus, it is important to treat the patients only with relevant allergens. B

257 Summary Statement 73: The selection of the components of an allergen immunotherapy extract should be based on a
258 careful history in correlation with positive allergy skin tests or serum specific- IgE antibodies. The allergen immunotherapy
259 extract should contain only clinically relevant allergens. In choosing the components for a clinically relevant allergen
260 immunotherapy extract, the physician should be familiar with local and regional aerobiology and indoor and outdoor
261 allergens, paying special attention to potential allergens in the patient's own environment D

262 Summary Statement 74: Skin testing has been the primary diagnostic tool in clinical studies of allergen immunotherapy.
263 Therefore, in most patients, skin testing should be used to determine whether the patient has serum specific- IgE
264 antibodies. Appropriately interpreted serum specific-IgE antibodies can also be used. C

265 Summary Statement 75: Nonstandardized extracts can vary widely in biologic activity and composition, regardless of a
266 particular wt/vol or PNU potency and should not be considered equipotent. B

267 Summary Statement 76: When possible, standardized extracts should be used to prepare the allergen immunotherapy
268 extract treatment sets. A

269 Summary Statement 77: Allergen immunotherapy extract preparation should be performed by individuals experienced and
270 trained in handling allergenic products. A customized individual allergen immunotherapy extract should be prepared from a
271 manufacturer's extract or extracts in accordance to the patient's clinical history and allergy test results and may contain
272 single or multiple allergens. D

273 Summary Statement 78: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-
274 reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. B

275 Summary Statement 79: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of
276 clinically relevant allergens. Knowledge of allergen cross-reactivity is important in the selection of allergens for
277 immunotherapy because limiting the number of allergens in a treatment vial may be necessary to attain optimal
278 therapeutic doses of each of the components. Many botanically related pollens contain allergens that are cross-reactive.
279 When pollens are substantially cross-reactive, selection of a single pollen within the cross-reactive genus or subfamily may
280 suffice. When pollen allergens are not substantially cross-reactive, testing for and treatment with multiple locally prevalent
281 pollens might be necessary. B

282 Summary Statement 80: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the
283 constituents in the allergen immunotherapy extract. A

284 Summary Statement 81: The maintenance concentrate should be formulated to deliver a dose considered to be
285 therapeutically effective for each of its constituent components. The maintenance concentrate vial is the highest-
286 concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial). The projected effective dose is called the maintenance goal.

287 Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The
288 maintenance dose is the dose that provides therapeutic efficacy without significant adverse local or systemic reactions and
289 might not always reach the initially calculated projected effective dose. This reinforces that allergy immunotherapy must be
290 individualized. A

291 Summary Statement 82: Studies designed to investigate the effect of combining extracts with high proteolytic activity, such
292 as cockroach and mold/fungi, with extracts such as pollen, dander and dust mite extracts, have demonstrated a significant
293 loss of potency with some of these extracts. Separation of extracts with high proteolytic enzyme activities, from other
294 extracts is recommended. It may be necessary to prepare two or more vials to provide allergen immunotherapy containing
295 an optimal dose of each component, while avoiding allergen extract combinations that may result in degradation of some
296 or all of the components. B

297 Summary Statement 83: Allergen immunotherapy extracts should be stored at 4 to 8ºC to reduce the rate of potency loss.
298 B

299 Summary Statement 84: Extract manufacturers conduct stability studies with standardized extracts that expose them to
300 various shipping conditions. It is the responsibility of each supplier or manufacturer to ship extracts under validated
301 conditions that are shown not to adversely affect the product's potency or safety. C

302 Summary Statement 85: In determining the allergen immunotherapy extract expiration date, consideration must be given
303 to the fact that the rate of potency loss over time is influenced by several separately and collectively, including (1) storage
304 temperature, (2) presence of stabilizers and bactericidal agents, (3) concentration, (4) presence of proteolytic enzymes,
305 and (5) volume of the storage vial. D

306 Summary Statement 86: Administration of an incorrect injection is a potential risk of allergen immunotherapy. An incorrect
307 injection is an injection given to the wrong patient or a correct patient receiving an injection of an incorrect dose. A
308 customized individual maintenance concentrate of the allergen immunotherapy extract and serial dilutions, whether a
309 single extract or a mixture of extracts, prepared and labeled with the patient's name and birth date might reduce the risk of
310 incorrect (i.e., wrong patient) injection. D

311 Summary Statement 87: The mixing of antigens in a syringe is not recommended because of the potential for treatment
312 errors and cross-contamination of extracts. C

313 Summary Statement 88: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up
314 phase of immunotherapy. D

315 Summary Statement 89: Dilution limits the number of antigens that can be added to a maintenance concentrate if a
316 therapeutic dose is to be delivered. A

317 Summary Statement 90: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce
318 errors in administration and therefore is recommended. D

319 Summary Statement 91: The allergen immunotherapy extract contents, informed consent for immunotherapy, and
320 administration of extracts should be documented. D

321 Summary Statement 92: Allergen extracts can be administered by several routes in addition to the subcutaneous route.
322 Currently, there are no FDA-approved formulations for a noninjection immunotherapy extract. A

323 Summary Statement 93: Randomized, controlled clinical trials with dust mite and pollen sublingual immunotherapy have
324 demonstrated significant improvement in symptoms and medication use in patients with allergic rhinitis and asthma. A

325 Summary Statement 94: Local reactions, primarily oral-mucosal, are common with sublingual immunotherapy. Systemic
326 reactions may occur and a few have been reported in individuals, who were unable to tolerate subcutaneous
327 immunotherapy. A few reported cases have been of a severity to be categorized as anaphylaxis A

328 Summary Statement 95: Clinical trials evaluating the safety and efficacy of sublingual immunotherapy for ragweed and
329 grass-pollen allergic rhinitis. Currently, there are no FDA-approved formulation for sublingual immunotherapy. A

330 Summary Statement 96: Randomized, controlled studies have demonstrated that nasal immunotherapy with dust mite and
331 pollen extracts is effective in reducing symptom and medication use. Local adverse reactions are common with this
332 approach and are the most frequently cited reason for discontinuation of treatment in one large prospective study. The use
333 of this approach has decreased considerably since the introduction of SLIT. C

334 Summary Statement 97: A 3-injection course of intralymphatic immunotherapy is as effective as a 3-year course of
335 conventional subcutaneous immunotherapy in one non-controlled study. NR

336 Summary Statement 98: Epicutaneous immunotherapy resulted in significantly higher treatment success in one placebo-
337 controlled study. However, there were no significant differences in the primary outcome and nasal provocation test scores
338 between the groups. NR

339 Summary Statement 99: Several clinical trials with oral and sublingual immunotherapy demonstrate an increased
340 tolerance to oral food challenge in individual with food hypersensitivity while on therapy. Oral and sublingual food
341 immunotherapy is investigational. NR

342 Summary Statement 100: Allergoids are modified allergen extracts processed in a way that reduces the extract's
343 allergenicity while preserving its antigenicity. B

344 Summary Statement 101: Adjuvants may enhance the effectiveness of allergen immunotherapy by shifting the immune
345 response toward Th_1 production. Two adjuvants most extensively studied with allergen immunotherapy are an
346 immunostimulatory oligonucleotide sequence of DNA containing a CpG motif (CpG) and 3-deacylated monophospholipid A
347 (MPL). Clinical trials with these adjuvants, in combination with ragweed (CPG and MPL) and grasses (MPL), demonstrate

348 significant improvement in allergic rhinitis symptoms with 4 to 6 injections administered pre-seasonally. Neither of these

349 adjuvants are available as FDA-approved allergen extracts. NR

350

351 **Table E3. Systemic reactions reported with subcutaneous immunotherapy and skin testing with aeroallergens and**

352 **venom in some publications from 1995 to 2009[E1]**

P/R*	Author (year)	Location	Duration observation period	Schedule Allergen	Nº patients / Nº of injections	Systemic reaction rate		Time, minutes (range)
						Patients (%)	Injections (%)	
R	Phillips[E2] (2009)	USA	6 months	Conventional Inhalant & Venom	883/ 14,000	17 (1.9)	18 (0.13)	20 average(1-60min)

R	DaVeiga[E3] (2008)	USA	Jul/02-Mar/07	Conventional Inhalant	830/ 9659	15 (1.8)	36 (0.37)	50% <30min, 8% > 1 hour All severe reactions < 30min
R	Rank[E4] (2008)	USA	2004-2006	Conventional Inhalant	338/10497	25 (7.4)	29 (0.28)	50% > 30min, all more severe SR >30min
R	Roy[E 5] (2007)	USA, multicenter	2 years	Conventional Inhalant	12,963/ 1,108,621	258 (2)	283(0.026)	ND
R	Harvey[E6]	USA	Jan /97-7/02	Rush Inhalant	65	25/65 (38)	Does not	5 Moderate

	(2004)						apply	20-45min 1 severe started mild at 55min
P	Tinkelman[E7] (1995)	USA	Jan-Dec 1991	Conventional Inhalant	4,512/ 156,800	96 (2.1)	98 (0.06)	All severe reactions < 30min
R	Brehler[E8] (2000)	Germany	2-day 9 injections	Rush venom	403/ 3,627	43 (10.7)	ND	ND
R	Serrano[E9] (2009)	Spain, multicenter	1996-2006	Cluster Depot Inhalants	1,147/6,982	39** (3.4)	42** (0.6)	23% <30min (10-360)***
P	Schiappoli[E10] (2009) [1]	Italy, multi-center	Up to 2006	Depot	1,738/60,785	57 (3.28)	95 (0.156)	44% <30min (one grade 4), 56%

								>30min (span 45min-24h)
P	Winther[E11] (2006) [2]	Denmark	3 years	Depot, modified cluster	1038/23,047	341 (32.8)	582 (2.5)	50%<30min (all grade 4 were <30min), 50% >30min
P	Moreno[E12] (2004)	Spain, multicenter	1996-97	Conventional Inhalant	423/17,526	18 (3.7)	53(0.3)	All <30min, except 2 AD flares
R	Ragusa[E13 E14] (1997, 2004)	Italy	1981-90 1991-2000	Conventional Inhalant	4000/435,854	115 (5.2) 26 (1.1)	115 (0.06) 26 (0.01)	Almost all SR within 30min
R	Gastaminza[E15] (2003)	Spain	5 years	Conventional Inhalant & Venom	1212/29,762	60 (5)	79 (0.27)	73% < 30min

R	Akcakaya[E16] (2000)	Turkey	1989-97	Depot Dust mite	88/5760	12 (13.6)	12 (0.2)	Most <30min
P	Bagg[E17] (2009)	US	2007-08	SPT ID testing	1456	6 (0.4) 46 (3.2)	Does not apply	
R	Valyasevi[E18] (1999)	US	Jan/92-Jun/97	SPT ID testing	16505 269	5 (0.03)	Does not apply	4 < 25min, 1 at 75min

* P/R = prospective or retrospective, ID = intradermal skin testing, ND = no data, SPT = skin puncture/prick test, SR = systemic reaction, US = United States of America

** Including 7 grade 0 reactions (=non-specific reactions).

*** The patient with the only grade 3 reaction was the only patient with an onset at 10min. All others started later.

Reprinted with permission from Elsevier Publishers

359

360 **Table E4. Example of a build-up schedule for weekly immunotherapy**

Dilution (vol/vol)	Volume (mL)
1:1000	0.05
	0.10
	0.20
	0.40
1:100	0.05
	0.10
	0.20
	0.30

	0.40
	0.50
1:10	0.05
	0.07
	0.10
	0.15
	0.25
	0.35
	0.40
	0.45
	0.50
Maintenance concentrate	0.05
	0.07

0.10

0.15

0.20

0.25

0.30

0.35

0.40

0.45

0.50

361 Dilutions are expressed as vol/vol from the maintenance concentrate.

362

363 **Table E5. Example of immunotherapy dose adjustment schedule for unscheduled gaps in allergen immunotherapy**

364 **injection intervals (modification of the AAAAI skin testing and immunotherapy consent and instruction forms:**

365 **immunotherapy administration instruction form, which can be found at http://www.aaaai.org)**

366 Build-up phase for weekly or biweekly injections (time intervals from missed injection)

367 - Up to 7 days, continue as scheduled (ie, if on weekly build-up, then it would be up to 14 days after administered

368 injection or 7 days after the missed scheduled injection).

369 • Eight to 13 days after missed scheduled injection; repeat previous dose.

370 • Fourteen to 21 days after missed scheduled injection; reduce dose 25%.

371 • Twenty-one to 28 days after missed scheduled injection; reduce previous dose

372 50%.

373 Then increase dose each injection visit as directed on the immunotherapy

374 schedule until therapeutic maintenance dose is reached.

375 This suggested approach to modification of doses of allergen immunotherapy

376 because of gaps between treatment during the build-up phase is not based on

377 retrospective or prospective published evidence, but it is presented as a

378 sample for your consideration. The individual physician should use this or a

379 similar protocol as a standard operating procedure for the specific clinical

380 setting. A similar dose-reduction protocol should be developed for gaps in

381 maintenance immunotherapy

382 **Table E6. Example of a cluster immunotherapy schedule**

Visit	Dose (mL)	Concentration as dilution of maintenance vial
1	0.10	1:1000 vol/vol
	0.40	1:1000 vol/vol
	0.10	1:100 vol/vol
2	0.20	1:100 vol/vol
	0.40	1:100 vol/vol
	0.07	1:10 vol/vol
3	0.10	1:10 vol/vol
	0.15	1:10 vol/vol
	0.25	1:10 vol/vol
4	0.35	1:10 vol/vol
	0.50	1:10 vol/vol
5	0.07	1:1 vol/vol
	0.10	1:1 vol/vol
6	0.15	1:1 vol/vol

	0.20	1:1 vol/vol
7	0.30	1:1 vol/vol
	0.40	1:1 vol/vol
8	0.50	1:1 vol/vol

383

384

385

386 **Table E7. Recommended documentation for allergen immunotherapy prescription**

387 **forms**

388 The purpose of the allergen immunotherapy prescription form is to define the contents

389 of the allergen immunotherapy extract in enough detail that it could be precisely

390 duplicated. The following information should be on an immunotherapy prescription

391 form:

392 Patient information:

393 Patient name, patient number (if applicable), birth date, telephone number, and

394 picture (if available) should be included.

395 Preparation information:

396 Name of person and signature preparing the allergen immunotherapy extract should

397 be included.

398 Date of preparation should be recorded.

399 Bottle name should be included (eg, trees and grass). If abbreviations are used, a

400 legend should be included to describe the meaning of the abbreviations.

Allergen immunotherapy extract content information:

The following information for each allergen should be included on the form in a separate column:

- Content of the allergen immunotherapy extract, including common name or genus and species of individual antigens and detail of all mixes, should be included..
- Concentration of available manufacturer's extract.
- Volume of manufacturer's extract addadded to achieve the projected effective concentration. This can be calculated by dividing the projected effective concentration by the concentration of available manufacturer's extract times the total volume.
- The type of diluent (if used).
- Extract manufacturer.
- Lot number should be included.
- Expiration date should be recorded and not exceed the expiration date of any of the individual components.

418

419 Figure E8a. Allergen immunotherapy extract blank and E8b completed prescription
420 form

Allergen Immunotherapy Extract Prescription Form

Patient Name:
Patient Number:
Birth Date:
Telephone:

Prescribing Physician:
Address:

Telephone:
Fax:

Allergen Extract Name:

Bottle Name Abbreviations	
Tree: T	Mold: M
Grass: G	Cat: C
Weed: W	Dog: D
Ragweed: R	Cockroach: Cr
Mixture: Mx	Dust Mite: Dm

Maintenance Concentrate Prescription Form

Prepared by: _____ **Date Prepared:**__/__/__

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial _____ from Vial _____ on __/__/__ Expiration date:__/__/__
Vial _____ from Vial _____ on __/__/__ Expiration date:__/__/__
Vial _____ from Vial _____ on __/__/__ Expiration date:__/__/__
Vial _____ from Vial _____ on __/__/__ Expiration date:__/__/__

Antigen Number	Extract Name Allergen or Diluent (Common name or Genus/species)*	Concentration and Type Manufacturer's Extract (AU, BAU, W/V, PNU)/ (50% G, Aq, Ly, AP)	Volume of Manufacturer's Extract to Add	Extract Manufacturer	Lot Number	Expiration Date
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
Diluent						
Total Volume						

*** Components of mixes listed on a separate sheet**

Volume to add = $\frac{\text{Maintenance Concentration}}{\text{Conc. Of Manufacturer's Extract}}$ x Total volume

Specific Instructions:

_____
_____
_____
_____
_____

Maintenance concentration and subsequent dilutions reported as volume/volume (v/v) dilutions with maintenance concentration=1:1 v/v

BAU = Bioeqivalent Allergy Unit, AU =Allergy Unit
PNU=Protein Nitrogen Unit
W/V=Weight per Volume Ratio
G= 50 % Glycerinated
Aq=Aqueous, Ly=Lyophilized
AP= Alum precipitated, AcP= Acetone precipitated

Updated 3/7/2010

421

Example of a Completed Allergen Immunotherapy Prescription

Patient Name: Jerry Cleanex
Patient Number: 23456
Birth Date: 05/05/90
Telephone: 645-345-0987

Prescribing Physician: Dr. Ah Choo
Address: 665 Rosebud Lane
Hollywood, Fl. 33424
Telephone: 645-123-4444
Fax: 645-123-4567

Vaccine Name: C, R, G, T, W

Maintenance Concentrate Prescription Form

Bottle Name Abbreviations

Tree: T	Mold: M
Grass: G	Cat: C
Weed: W	Dog: D
Ragweed: R	Cockroach: Cr
Mixture: Mx	Dust Mite: Dm

Prepared by: Mary Lancet Date Prepared: 6/10/09

*** Components of mixes listed on a separate sheet**

Antigen Number	Extract Name Allergen or Diluent (Common name or Genus/species)*	Concentration and Type Manufacturer's Extract (AU, BAU, W/V, PNU)/ (50% G, Aq, Ly, AP)	Volume of Manufacturer's Extract to Add*	Extract Manufacturer	Lot Number	Expiration Date
1	Short ragweed	1:10 w/v G (350 Amb a1)	0.25ml	Greer	12345	1/01/10
2	*D. farinae*	10,000 AU/ml G	0.5 ml	Allermed	5765	2/06/10
3	*D. Pteronyssinus*	10,000 AU/ml G	0.5ml	Antigen labs	4222	3/24/08
4	Cat	10,000 BAU/ml G	2.00ml	Hollister–Stier	9898	2/27/10
5	Timothy grass	100,000 BAU/ml G	0.2 ml	ALK	56789	7/09/09
6						
7						
8						
9						
10						
Diluent	HSA		0.6ml	ALK	68597	12/12/11
Total Volume			5.00 ml			6/09/09

**** Assumes 0.5 ml injection as target maintenance dose**

$$\text{Volume to add} = \frac{\text{Maintenance Concentration}}{\text{Conc. Of Manufacturer's Extract}} \times \text{Total volume}$$

Maintenance concentration and subsequent dilutions reported as volume/volume (v/v) dilutions with maintenance concentration=1:1 v/v

BAU = Bioeqivalent Allergy Unit, AU =Allergy Unit
PNU=Protein Nitrogen Unit
W/V=Weight per Volume Ratio
G= 50 % Glycerinated
Aq=Aqueous, Ly=Lyophilized
AP= Alum precipitated

423

424 **Table E9. Labels for allergen immunotherapy extracts**

425 Each vial of allergen immunotherapy extract should be labeled in a way that permits
426 easy identification. Each label should include the following information (example in
427 Figs 2 and 3):

428 - Appropriate patient identifiers might include the patient's name, patient's
429 number, patient's picture, and birth date.
430 - The contents of the allergen immunotherapy extract in a general way should be
431 included. The detail with which this can be identified depends on the size of the
432 label and the number of allergens in the vial. Ideally, allergens should be
433 identified as trees, grasses, weeds, mold, dust mite, cockroach, cat, and dog.
434 Because of space limitations, it might be necessary to abbreviate the antigens
435 (eg, T, G, W, M, DM, Cr, C, and D respectively [see Appendix 1). A full and
436 detailed description of vial contents should be recorded on the prescription/
437 content form.
438 - The dilution from the maintenance concentrate (vol/vol) should be recorded. If
439 colors, numbers, or letters are used to identify the dilution, they also should be
440 included.
441 - The expiration date should be included.

442

443

444

445 **Table E10. Examples of possible abbreviations for allergen immunotherapy extract**

446 **components**

Tree	T
Grass	G
Bermuda	B
Weeds	W
Ragweed	R
Mold	M
Alternaria	Alt
Cladosporium	Cla
Penicillium	Pcn
Cat	C
Dog	D
Cockroach	Cr
Dust mite	DM
D farinae	Df

D pteronyssinus	Dp
Mixture	Mx

449

450 **Table E11 Allergen immunotherapy administration form recommended documentation**

451 The purpose of the allergen immunotherapy administration form is to document the
452 administration of the allergen immunotherapy extract to a patient. Its design should be
453 clear enough so that the person administering an injection is unlikely to make an error
454 in administration. It also should provide documentation in enough detail to determine
455 what was done on each visit. The following recommendations on allergen
456 immunotherapy are taken from The Joint Task Force on Practice Parameters.

457 Patient information:

458 • Patient's name, date of birth, telephone number, and patient's picture (optional
459 but helpful).
460 • Allergen immunotherapy extract information:
461 • Allergen immunotherapy extract name and dilution from maintenance in vol/vol
462 bottle letter (eg, A and B), bottle color, or number, if used.
463 • Expiration date of all dilutions.

464 Administration information in separate columns:

465 Date of injection.

466 Arm administered injection, which might facilitate determination of exact cause of local
467 reaction.

468 Projected build-up schedule.

469 Delivered volume reported in milliliters.

470 Description of any reactions. The details of any treatment given in response to a
471 reaction would be documented elsewhere in the medical record and referenced on the
472 administration form.

473 Patient's health before injection. This can be performed through a verbal or written
474 interview of the patient before administering the immunotherapy injection. The patient
475 should be questioned about increased asthma symptoms, b-blocker use, change in
476 health status (including pregnancy and recent infections), or an adverse reaction to a
477 previous injection (including delayed large local reactions persisting through the next
478 day). Patients with significant systemic illness generally should not receive an
479 injection.

480 Antihistamine use. Antihistamines are frequently a component of an allergy
481 medication regimen, and it would be important to note whether a patient is taking an
482 antihistamine on the day he or she receives his or her immunotherapy injection. For

483 consistency in interpretation of reactions, it might be desirable for a patient to either
484 take or avoid antihistamines on a regular basis on the days he or she receives
485 immunotherapy. The physician should note on the form whether he or she
486 recommends the patient consistently take an antihistamine on immunotherapy
487 treatment days.

488 Peak flow reading. Consider obtaining a peak expiratory flow rate measurement
489 before administering an immunotherapy injection to asthmatic patients. Poorly
490 controlled asthma is considered a risk factor for immunotherapy. Obtaining a peak
491 expiratory flow rate measurement before the immunotherapy injection might help
492 identify patients with symptomatic asthma. The patient's baseline peak expiratory flow
493 rate should be provided on the form as a reference. Health care professionals
494 administering immunotherapy injections should be provided with specific guidelines
495 about the peak expiratory flow rate measurement for when an immunotherapy
496 injection should be withheld and the patient referred for clinical evaluation.

497 Baseline blood pressure. It might be useful to record the patient's blood pressure as a
498 baseline for future reference.

499 Figure E12. Allergen immunotherapy administration form for single extract

Allergen Immunotherapy Administration Form

Patient Name: **Date of Birth:** **Patient Number:** **Telephone Number:** **Diagnosis:**	**Prescribing Physician:** **Address:** **Telephone:** **Fax:**

Dilution Color	1:10,000 (v/v) Silver	1:1000 (v/v) Green	1:100 (v/v) Blue	1:10 (v/v) Yellow	Maintenance 1:1 (v/v) Red
Vial number	5	4	3	2	1
Expiration date(s)	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___

Immunotherapy	A	B
Date started		
Date maintenance dose reached		
Maintenance dose		
Maintenance interval		

Best Baseline Peak Flow: _____
Baseline Blood pressure: _____

Allergen extract: *contents*

	Date	Time	Health screen abnormal[1]	Anti-histamine taken?[2] or premed	Peak Flow	Arm	Vial Number or Dilution	Delivered Volume	Reaction[3]	Injector Initials
1.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
2.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
3.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
4.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
5.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
6.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
7.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
8.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
9.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
10.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
11.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
12.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
13.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
14.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
15.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
16.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
17.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
18.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
19.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
20.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
21.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
22.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
23.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____
24.	__/__/__	____	Y N	Y N	_____	R L	_____	_____	_____	_____

1. **Health screen** *refers to either a written or verbal interview of the patient prior to the administration of the allergy injection regarding: the presence of increased asthma symptoms or symptoms of respiratory tract infection, beta-blocker use, change in health status (including pregnancy) or adverse reaction to previous injection. A yes answer to this health screen may require further evaluation (see health screen record on back page).*
2. **Antihistamine use:** *to improve consistency in interpretation of reactions it should be noted if the patient has taken an antihistamine on injection days. Physician may also request that* ***antihistamines be taken consistently on injection days: recommended: Y N***
3. **Reaction**: *refers to either immediate or delayed systemic or local reactions. Local reactions (noted as LR) can be reported in millimeters as the longest diameter of wheal and erythema.. The details of the symptoms and treatment of a* ***systemic reaction*** *(noted as* ***SR****) would be recorded elsewhere in the medical record. Guidelines for dose reduction after a systemic reaction on a separate instruction sheet.*

Injector signature	Initials

Date to reorder: __/__/__

Projected Build-up Schedule						
Vial 5	Vial 4	Vial 3	Vial 2		Vial 1	

500

501 **Figure E13. Allergen immunotherapy administration form for two extracts**

502

Allergen Immunotherapy Administration Form

Patient Name: **Date of Birth:** **Patient Number:** **Telephone Number:** **Diagnosis:**	**Prescribing Physician:** **Address:** **Telephone:** **Fax:**

Dilution Color	1:10,000 (v/v) Silver	1:1000 (v/v) Green	1:100 (v/v) Blue	1:10 (v/v) Yellow	Maintenance 1:1 (v/v) Red
Vial number	5	4	3	2	1
Expiration date(s)	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___

Immunotherapy	A	B
Date started		
Date maintenance dose reached		
Maintenance dose		
Maintenance interval		

Best Baseline Peak Flow: _____
Baseline Blood pressure: _____

Allergen extract: *contents*

Allergen extract B: _____

	Date	Time	Health screen abnormal[1]	Anti-histamine taken?[2] or premed	Peak Flow	Arm	Vial Number or Dilution	Delivered Volume	Reaction[3]	Arm	Vial Number or Dilution	Delivered Volume	Reaction	Injector Initials
1.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
2.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
3.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
4.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
5.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
6.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
7.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
8.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
9.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
10.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
11.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
12.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
13.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
14.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
15.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
16.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
17.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
18.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
19.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
20.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
21.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
22.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
23.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____
24.	__/__/__	____	Y N	Y N	____	R L	____	____	____	R L	____	____	____	____

1. **Health screen** *refers to either a written or verbal interview of the patient prior to the administration of the allergy injection regarding: the presence of increased asthma symptoms or symptoms of respiratory tract infection, beta-blocker use, change in health status (including pregnancy) or adverse reaction to previous injection. A yes answer to this health screen may require further evaluation (see health screen record on back page).*

2. **Antihistamine use:** *to improve consistency in interpretation of reactions it should be noted if the patient has taken an antihistamine on injection days. Physician may also request that* ***antihistamines be taken consistently on injection days: recommended: Y N***

3. **Reaction**: *refers to either immediate or delayed systemic or local reactions. Local reactions (noted as LR) can be reported in millimeters as the longest diameter of wheal and erythema.. The details of the symptoms and treatment of a* ***systemic reaction*** *(noted as* ***SR****) would be recorded elsewhere in the medical record. Guidelines for dose reduction after a systemic reaction are on a separate instruction sheet.*

Injector signature	Initials

Date to reorder: __/__/__

Projected Build-up Schedule						
Vial 5	Vial 4	Vial 3	Vial 2		Vial 1	

Updated 3/7/2010

503

504

505 **Figure E14. Health screen record**

Patient name:_____ **Date of birth:**_____ **Patient number**_____

Health Screen Record

1. Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

2. Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

3. Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

4. Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

5. Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

6. Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

7.Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

8.Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

9.Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any) : _____

10. Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

11. Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
Staff action taken (if any): _____

12. Date of immunotherapy injection visit: _____/_____/_____
Patient's response to pre-injection screening questions: _____
_____
506 Staff action taken (if any): _____

507

508

509

510 **Figure E15. Allergen immunotherapy systemic reaction treatment record**

Allergen Immunotherapy Systemic Reaction/Anaphylaxis Treatment Record

Name:_____ **Date:**_____

Date of Birth:_____ **Prescribing Physician:**_____

Allergens: Tree-Grass-Weed-Mites-Cockroach-Animal Dander-Mold-Hymenoptera

Prior systemic rxn:_____ **Hx of asthma?**_____

Date/time of injection:_____ **Date/time of rxn:**_____

Dilution (Vial #): _____ **New? Yes No**

History of the systemic reaction (SR):

Immediate measures:
__Assess airway, breathing, circulation, and orientation
__EpinephrineIM into arm or when possible anterolateral thigh
__Activate EMS (call 911 or local rescue squad) Y/N Time called:_____AM/PM
__Management algorithm reviewed (as needed)

Signs and Symptoms

Respiratory:	**Skin:**	**Eye/Nasal:**	**Vascular:**	**Other:**
Shortness of Breath	Hives	Runny Nose	Hypotension	Difficulty Swallowing
Wheezing	Angioedema	Red Eyes	Chest Discomfort	Abdominal pain, nausea, diarrhea
Cough	Generalized Itch	Congestion	Dizziness	Diaphoresis
Stridor	Flushing	Sneezing		Headache
				Uterine cramps
				Impending doom

Time	**Resp. rate/ PEFR**	**Pulse/ O2 Saturation**	**BP**	**Intervention, Medications, Exam Comments**

Time of discharge from the office:_____ **Condition upon release:** _____
Patient instructions:
_____

Follow-up call to patient:
Time_____
Comments:
_____
_____
_____

WAO Subcutaneous Immunotherapy Systemic Reaction Grading System Final Report:
Grade a-d,or z _____First symptom _____ Time of onset of first symptom _____
Dosage adjustment? _____

Signatures_____ **RN**_____**ARNP/PA** _____ **MD/DO**

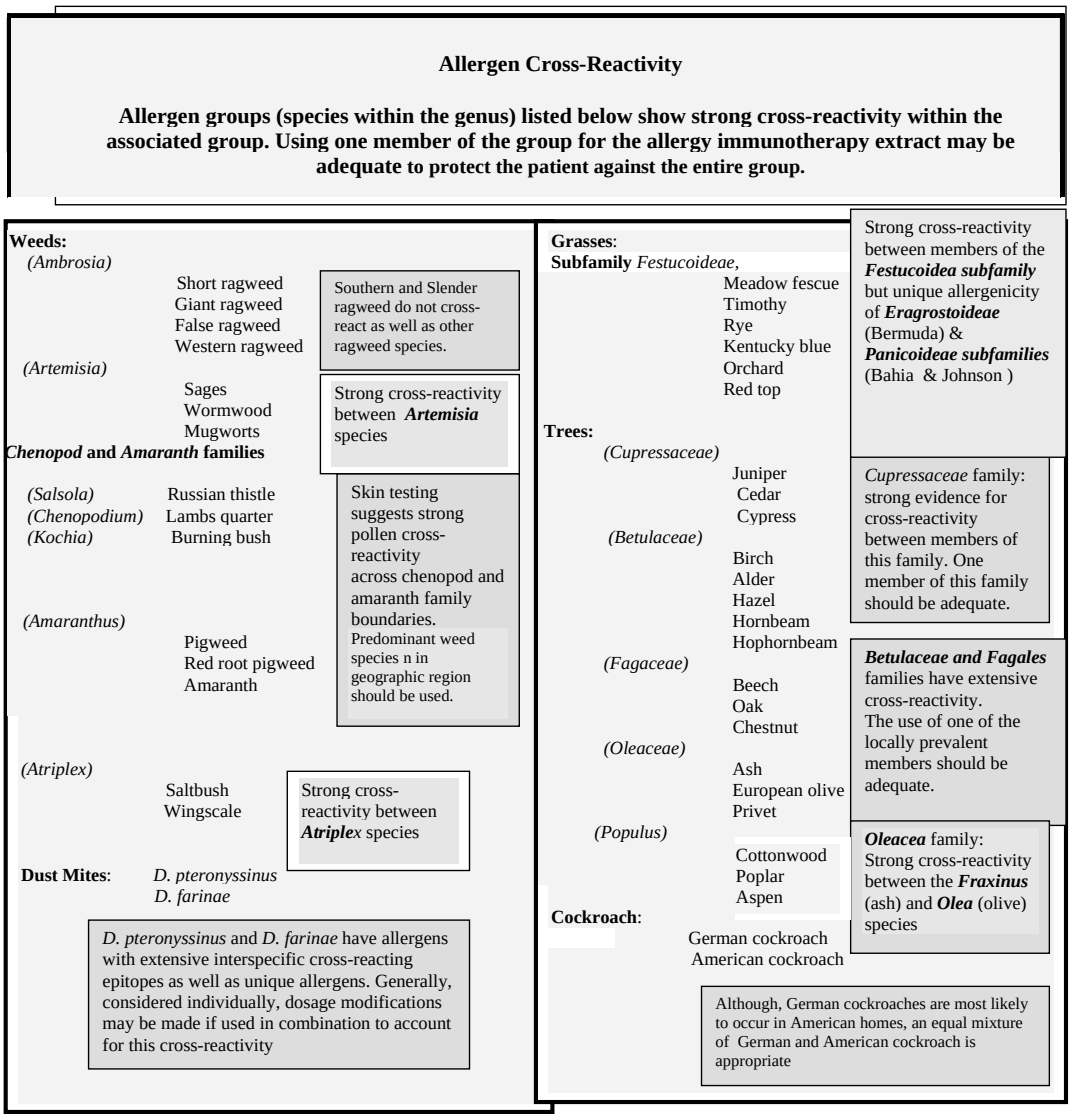
511

512

513

514 Figure E16. Patterns of allergen cross-

515 reactivity



516
517

518

519

520

521 **Table E17. Allergen immunotherapy informed consent**

Documentation that informed consent has been obtained.	Informed consent is a process by which a patient and physician discuss various aspects of a proposed treatment. Although many allergists use a written consent form before starting immunotherapy, a reasonable alternative is simply to document the consent process in the medical record. The consent process usually consists of the following: what the treatment is and alternatives to the treatment; potential benefits to be expected from the treatment; potential risks, including a fair description of how frequently they are likely to occur, if known, including the possibility of death; costs associated with immunotherapy and who pays for them; the anticipated duration of treatment; and any specific office policies that affect treatment.
Since the informed consent process is complex and details might vary from state	

to state, each allergist/immunologist should decide how they should document informed consent. Legal advice might be useful.

References for On-line Repository

E1 Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. J Allergy Clin Immunol 2010;125:569-74, 74 e1-74 e7. IV

E2. Phillips J, Bag A, Lockey R. Systemic Reactions to Subcutaneous Allergen Immunotherapy and the response to epinephrine. J Allergy Clin Immunol 2009; 123:S60.III

531 E3. DaVeiga S, Caruso K, Golubski S, Lang D. A Retrospective Survey of Systemic
532 Reaction from Allergen Immunotherapy. J Allergy Clin Immunol 2008:S124.III

533 E4. Rank MA, Oslie CL, Krogman JL, Park MA, Li JT. Allergen immunotherapy
534 safety: characterizing systemic reactions and identifying risk factors. Allergy Asthma
535 Proc 2008; 29:400-5.III

536 E5. Roy SR, Sigmon JR, Olivier J, Moffitt JE, Brown DA, Marshall GD. Increased
537 frequency of large local reactions among systemic reactors during subcutaneous
538 allergen immunotherapy. Ann Allergy Asthma Immunol 2007; 99:82-6.III

539 E6. Harvey SM, Laurie S, Hilton K, Khan DA. Safety of rush immunotherapy to
540 multiple aeroallergens in an adult population. Ann Allergy Asthma Immunol 2004;
541 92:414-9. III

542 E7. Tinkelman DG, Cole WQ, 3rd, Tunno J. Immunotherapy: a one-year prospective
543 study to evaluate risk factors of systemic reactions. J Allergy Clin Immunol 1995; 95:8-
544 14. III

545 E8. Brehler R, Wolf H, Kutting B, Schnitker J, Luger T. Safety of a two-day ultrarush
546 insect venom immunotherapy protocol in comparison with protocols of longer duration
547 and involving a larger number of injections. J Allergy Clin Immunol 2000; 105:1231-5.III

548 E9. Serrano P, Justicia J, Sanchez C, Cimarra M, Fernandez-Tavora L, Orovitg A, et
549 al. Systemic tolerability of specific subcutaneous immunotherapy with index-of-
550 reactivity–standardized allergen extracts administered using clustered regimens: a
551 retrospective, observational, multicenter study. Ann Allergy Asthma Immunol 2009;
552 102:247–52. III

553 E10. Schiappoli M, Ridolo E, Senna G, et al. A prospective Italian survey on the safety
554 of subcutaneous immunotherapy for respiratory allergy. Clin Exp Allergy 2009.

555 E11. Winther L, Arnved J, Malling HJ, Nolte H, Mosbech H. Side-effects of allergen-
556 specific immunotherapy: a prospective multi-centre study. Clin Exp Allergy 2006;36:254-
557 60. III

558 E12. Moreno C, Cuesta-Herranz J, Fernandez-Tavora L, Alvarez-Cuesta E.
559 Immunotherapy safety: a prospective multi-centric monitoring study of biologically
560 standardized therapeutic vaccines for allergic diseases. Clin Exp Allergy 2004; 34:527-
561 31.III

562 E13. Ragusa FV, Passalacqua G, Gambardella R, Campanari S, Barbieri MM,
563 Scordamaglia A, et al. Nonfatal systemic reactions to subcutaneous immunotherapy: a
564 10-year experience. J Investig Allergol Clin Immunol 1997; 7:151-4.III

565 E14. Ragusa VF, Massolo A. Non-fatal systemic reactions to subcutaneous
566 immunotherapy: a 20-year experience comparison of two 10-year periods. Allerg
567 Immunol (Paris) 2004; 36:52-5.

568 E15. Gastaminza G, Algorta J, Audicana M, Etxenagusia M, Fernandez E, Munoz D.
569 Systemic reactions to immunotherapy: influence of composition and manufacturer. Clin
570 Exp Allergy 2003; 33:470-4.

571 E16. Akcakaya N, Hassanzadeh A, Camcioglu Y, Cokugras H. Local and systemic
572 reactions during immunotherapy with adsorbed extracts of house dust mite in children.
573 Ann Allergy Asthma Immunol 2000; 85:317-21.

574 E17. Bagg AS, Chacko T, Lockey RF. Systemic Reactions to Prick and Intradermal
575 Skin Tests. J Allergy Clin Immunol 2009; 123.

576 E18. Valyasevi MA, Maddox DE, Li JT. Systemic reactions to allergy skin tests. Ann
577 Allergy Asthma Immunol 1999; 83:132-6.

578

579

580