Allergen immunotherapy: A practice parameter second update

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

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the "Allergen immunotherapy: a practice parameter second 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 and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
5. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
6. The diagnosis and management of anaphylaxis. J Allergy Clin Immunol 1998;101(suppl):S465-S528.
7. Algorithm for the diagnosis and management of asthma: a practice parameter update. Ann Allergy 1998;81:415-20.
8. Diagnosis and management of rhinitis: parameter documents of the Joint Task Force on Practice parameters in Allergy, Asthma and Immunology. Ann Allergy 1998;81(suppl):S463-S518.
9. Parameters for the diagnosis and management of sinusitis. J Allergy Clin Immunol 1998;102(suppl): S107-S144.
10. Stinging insect hypersensitivity: a practice parameter. J Allergy Clin Immunol 1999;103:963-80.
11. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999;83(suppl): S665–S700.
12. Diagnosis and management of urticaria: a practice parameter. Ann Allergy 2000;85(suppl):S521-S544.
13. Allergen immunotherapy: a practice parameter. Ann Allergy 2003;90(suppl):SI-S540.
14. Symptom severity assessment of allergic rhinitis: part I. Ann Allergy 2003;91:105-14.
15. Disease management of atopic dermatitis: an updated practice parameter. Ann Allergy 2004;93(suppl): S1-S21.
16. Stinging insect hypersensitivity: a practice parameter update. J Allergy Clin Immunol 2004;114:869-86.
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These parameters are also available on the internet at http://www.jcaai.org.

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PREFACE

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

The objective of ''Allergen immunotherapy: A practice parameter second update'' is to optimize the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. 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's ''Policy on development and use of practice parameters for medical quality decision-making'' (Appendix 1).[1]

This document builds on the previous Joint Task Force document, ''Allergen immunotherapy: a practice parameter'' published in the *Annals of Allergy, Asthma and Immunology* in 2003.[2] The updated practice parameters draft was prepared by Drs Linda Cox, James Li, Hal Nelson, and Richard Lockey. The Joint Task Force reworked the initial draft into a working draft of the document. The project was exclusively funded by the 3 allergy and immunology societies noted above.

In preparation for the 2003 ''Allergen immunotherapy: a practice parameter'' and the second update, a comprehensive search of the medical literature was conducted with various search engines, including PubMed; *immunotherapy*, *allergic rhinitis*, *asthma*, *stinging insect allergy*, and related search terms were used. 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 second update'' was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the ACAAI, AAAAI, and JCAAI. In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for review and comments from members of the sponsoring organizations. 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 allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. This document also contains recommendations for the safe practice of allergen immunotherapy, including specific recommendations on the prevention and management of 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 or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. Symptoms of allergic conjunctivitis (eg, itchy watery eyes) are often considered part of allergic rhinitis or are included in the diagnosis of rhinoconjunctivitis. Particularly good candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures, those in whom it is important to avoid the potential adverse effects of medications, and those who wish to reduce the long-term use of medications. Immunotherapy is recommended for patients with a history of systemic reaction to Hymenoptera stings and specific IgE antibodies to Hymenoptera venom.

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.[3]

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. 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 *maintenance concentrate* should be used to identify the allergen immunotherapy extract that contains a therapeutic effective dose for each of its individual constituents (see the Immunotherapy schedules and doses section).

The term *manufacturer's extract* refers to the allergy extract purchased from the manufacturer. The terms *stock*, *full-strength*, and *concentrate* are ambiguous and should not be used. 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).

Allergen immunotherapy is effective when appropriate doses of the allergens are administered. ''Allergen immunotherapy: A practice parameter'' recommends that vials of allergen immunotherapy extracts should be prepared individually for each patient to enhance the individualization of therapy, reduce the risk of allergen cross-contamination, and reduce the risk of error in administration.[4,5] This parameter recommends the use of standardized allergen immunotherapy prescription and administration forms to improve the safety, uniformity, and standardization of allergen immunotherapy practice.[4,5] The suggested forms are found in the Appendix (Appendices 7, 8, 11, 12, and 14) and in the members' section of the www.aaaai.org Web site. The routine use of these standardized forms should improve the quality of immunotherapy practice.

Members' feedback comments on the recommended allergen extract dilution dating in the 2003 ''Allergen immunotherapy: A practice parameter'' led to an allergen immunotherapy extract dilution stability study designed by the AAAAI Immunotherapy and Allergy Diagnostics Committee and funded by the AAAAI Board of Directors. The study was designed to investigate the effect of time, temperature, and dilution of standardized allergen extract potency, and the results of this study were considered in this update.

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 3 years after publication. Requests for information about or an interpretation of these practice parameters should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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. Allergen immunotherapy

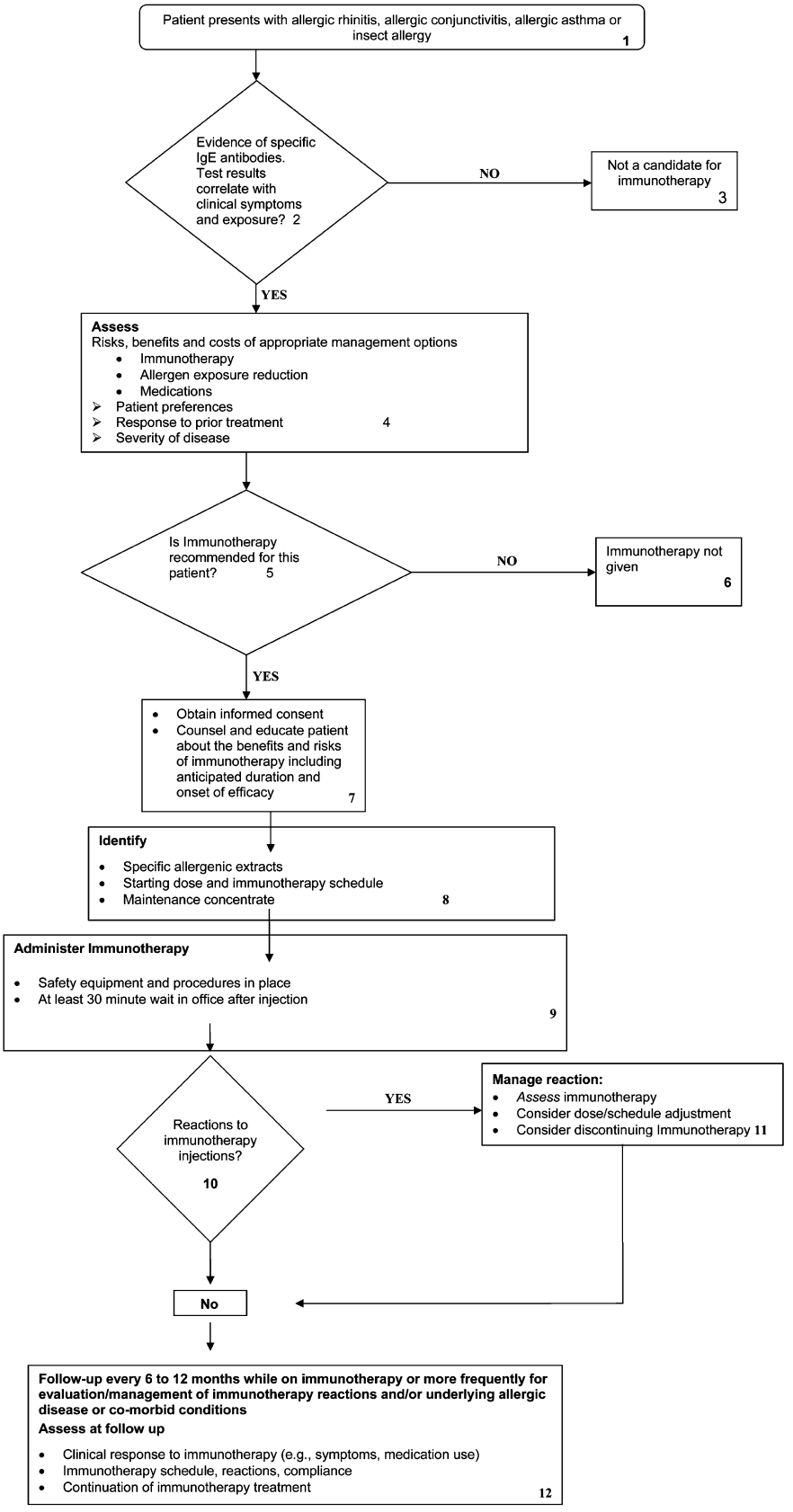


FIG 1. Algorithm for allergen immunotherapy.

might prevent the development of asthma in individuals with allergic rhinitis.[6-9] Evaluation of a patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic conjunctivitis, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for specific IgE antibody).[10]

Box 2

Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although *in vitro* testing for 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

Management of complex medical conditions, such as allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity, should include the careful evaluation of management 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 patient 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. On the basis of clinical considerations and patient 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 good candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy (VIT).

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 on the basis of 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 (see the Immunotherapy schedules and doses section). In general, the starting immunotherapy dose is 1000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 1000 to 4000 arbitrary units (AU; eg, for dust mite) or bioequivalent allergy units (BAU; eg, for grass) 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 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 referred to as *up-dosing*, *induction*, or the *dose-increase phase*) entails administration of gradually increasing doses during a period of approximately 14 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 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, in particular anaphylaxis. Patients should wait at the physician's office for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly, if they occur.

In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring 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. Some physicians recommend providing certain patients with epinephrine for self-administration in case of severe late reactions to immunotherapy injections.

Box 10

Injections of allergen immunotherapy extract can cause local or systemic reactions. Most severe reactions develop within 30 minutes after the immunotherapy injection, but reactions can occur after this time.

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 (anaphylaxis). Epinephrine is the treatment of choice in anaphylaxis, preferably when administered intramuscularly,[11] although subcutaneous administration is acceptable.[12]

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, see the practice parameters for anaphylaxis.[12]

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. After a severe systemic reaction, careful evaluation by the prescribing physician is recommended. For some patients, the immunotherapy maintenance dose might need to be reduced because of repeated systemic reactions to immunotherapy injections. The decision to continue immunotherapy should be re-evaluated after severe or repeated systemic reactions to allergen immunotherapy extracts.

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 doses, 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,[13] but others might experience a recurrence of their symptoms after discontinuation of allergen immunotherapy.[14] 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, and 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 on the basis of the patient's clinical response, disease severity, immunotherapy reaction history, and patient preference.

IMMUNOTHERAPY GLOSSARY

For more information on immunotherapy definitions, see the article by Kao.[15]

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 (pigments and salts; see the Allergen selection and handling section). Other terms used to describe the allergen immunotherapy extract include *allergen product*,[16] *allergy serum*, *allergen vaccine*,[17] 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.[18] Other terms that have been used for allergen immunotherapy include *hyposensitization*, *allergen-specific desensitization*, and the lay terms *allergy shots* or *allergy injections*.[15]

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

TABLE II. Allergen immunotherapy dose-calculation table

- Express weight per volume as a fraction: $\frac{1}{N}$ or 1:*N*.
- Calculate concentration of individual allergens in mixtures. If a mixture is made of equal amounts of N individual allergens to make a total concentration (C), the final concentration of an individual allergen (Ca) can be calculated by using the following equation:

$Ca = C \times \frac{1}{N} = \frac{C}{N}$ or *C*:*N*.

For example, if a mixture of equal amounts of 5 (N) allergens has a total concentration (C) of 100,000 BAU/mL, then the final concentration of each individual allergen (Ca) is: $Ca = \frac{C}{N} = \frac{100{,}000}{5} = 20{,}000\ BAU/mL$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{C}{N} = \frac{1/10}{5} = \frac{0.1}{5} = 0.02$ or $\frac{1}{50}$ or 1:50.

- Dilution of individual allergen: If an initial volume, Vi (in milliliters), of an individual antigen with concentration, Ci, is added to an allergen extract to make a final volume of Vf (in milliliters), the final allergen concentration (Ca) in the allergen extract mixture will be: $Ca = Ci \times \frac{Vi}{Vf}$.
- Final concentration of an allergen in a mixture of mixtures is determined by multiplying the initial concentration by the dilution factors from each mixing step.

For example, consider a mixture containing equal amounts of 5 (N) allergens with a total concentration (C) of 100,000 BAU/mL (first dilution). If an initial volume (Vi) of 0.5 mL of this mixture is further mixed with other components and diluent to make a final allergen extract mixture volume (Vf) of 5.0 mL (second dilution), the final concentration of an individual allergen (Ca) will be:

$$Ca = C \times \underbrace{\frac{1}{N}}_{\text{Mixture dilution}} \times \underbrace{\frac{Vi}{Vf}}_{\text{Allergen extract dilution}} = 100{,}000 \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{100{,}000}{50} = 2000\ BAU/mL$$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{1}{10} \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{1}{500}$ or 1:500.

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).

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 to 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-medicated 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 multiplied by volume of administered dose (see Table II for a dose-calculation table).

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, cat, 1000 BAU, [highest tolerated dose] vs 2000 BAU [projected effective dose]).

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 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 by a variety of immunologic transformations. Early definitions of the term immunotherapy included active and passive immunization for the purpose of improving 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 by means of induction of clonal deletion, anergy, immune tolerance, or immune deviation.

The *maintenance concentrate* is a preparation that contains individual 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 may not be the initially calculated projected effective dose.

The *maintenance goal* (or projected effective dose) is the allergen dose projected to provide therapeutic efficacy. The maintenance goal is based on published studies, but a projected effective dose has not been established for allergens. 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 the 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 large local reaction causing discomfort). The intervals between maintenance immunotherapy injections generally ranges 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 by means of immunoblotting or crossed allergoimmunoelectrophoresis.

For a definition of *projected effective dose*, see 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 test responses), and premedication with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similar high incidence of systemic reactions.

Off the board into one syringe is a phrase that describes a method of allergen immunotherapy preparation and administration that involves specifically mixing the patient's allergen immunotherapy injection in a single syringe, which is not recommended. This syringe might be inserted into more than one allergen extract vial, and this poses a risk of cross-contamination of the allergen extracts and might dull the needle with repeated penetration of the rubber stopper.

Shared specific patient vials is a method of allergen immunotherapy preparation and administration in which the allergy immunotherapy extract is withdrawn from a shared vial (eg, mixed vespids or dust mite mix). This is sometimes referred to as off the board, but it is distinct from the method of off the board into one syringe in that the syringe enters only one allergen extract vial.

INTRODUCTION

Immunity has been defined as protection against certain diseases. The initial immunotherapeutic interventions, which included the use of preventive vaccines and xenogenic 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 the field of allergen immunotherapy. From its humble empiric emergence in 1900, when ragweed injections were proposed as therapy for autumnal hay fever, allergen immunotherapy has progressed in both theory and practice from the passive immunologic approach to the active immunologic procedures pioneered by Noon[19] and Freeman.[20,21] 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 10 years. Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Some studies have suggested that allergen immunotherapy might prevent the development of asthma in individuals with allergic rhinitis.[6-9]

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,[22-26] and it should be differentiated from unproved methods, such as neutralization-provocation therapy and low-dose subcutaneous regimens based on the Rinkel technique, which have been found to ineffective in a double-blind placebo-controlled study.[27,28]

SUMMARY STATEMENTS

Mechanisms of immunotherapy

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, defined as a relative decrease in allergen-specific responsiveness and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

Allergen extracts

Summary Statement 6: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. **A**

Summary Statement 7: Nonstandardized extracts might vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Summary Statement 8: 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**

Cross-reactivity of allergen extract. Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

Efficacy of immunotherapy

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Summary Statement 10: Immunotherapy is effective for 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**

Food allergy, urticaria, and atopic dermatitis. Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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**

Measures of efficacy. Summary Statement 12: 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**

Safety of immunotherapy

Reaction rates. Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

Timing of anaphylactic reactions to immunotherapy injections. Summary Statement 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

β-*Adrenergic blocking agents.* Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

Contraindications. Summary Statement 18: 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**

Reducing the risk of anaphylaxis to immunotherapy injections. Summary Statement 19: 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**

Patient selection

Clinical indications. Summary Statement 20: 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 depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Special precautions in patients with asthma. Summary Statement 21: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. **C**

Clinical indications for VIT. Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Summary Statement 23: Patients selected for immunotherapy should be cooperative and compliant. **D**

Allergen selection and handling

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted in vitro tests for specific IgE antibodies can also be used. **A**

Specific allergens. Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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, supported by the presence of specific IgE antibodies. **A**

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Dose selection. Summary Statement 30: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. **A**

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens, is recommended. **B**

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extract handling

STORAGE

Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

STORING DILUTE EXTRACTS

Summary Statement 34a: More dilute concentrations of allergen immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: 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 a number of 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. **B**

Immunotherapy schedules and doses

Summary Statement 35: A customized individual 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 be based on single or multiple allergens. **D**

Maintenance concentrate. Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

Recommended doses. Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

Effect of dilution on dose. Summary Statement 38: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. **A**

Dilutions of the maintenance concentrate. Summary Statement 39: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. **D**

Labeling dilutions. Summary Statement 40: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. **D**

Individualized treatment vials. Summary Statement 41: 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. The mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. **C**

Starting doses. Summary Statement 42: The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. **D**

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

Dose adjustments for systemic reactions. Summary Statement 44: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. **D**

Reductions during periods of exacerbation of symptoms. Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Dose adjustments for late injections. Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

Cluster schedules. Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. **C**

Rush schedules. Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. **A**

Systemic reactions and rush schedules. Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

Premedication and weekly immunotherapy. Summary Statement 50: Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

Premedication with cluster and rush immunotherapy. Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

Maintenance schedules. Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. **A**

Continuing care

TIME COURSE OF IMPROVEMENT

Summary Statement 53: Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **A**

FOLLOW-UP VISITS

Summary Statement 54: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. **D**

DURATION OF TREATMENT

Summary Statement 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

DOCUMENTATION AND RECORD KEEPING

Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. **D**

INJECTION TECHNIQUES

Summary Statement 57: Allergen immunotherapy extract injections should be administered with a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **D**

Summary Statement 58: The injection should be administered subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Location of allergen immunotherapy administration

Physician's office. Summary Statement 59: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Summary Statement 60: 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**

Other locations. Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **D**

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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**

Summary Statement 63: 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for his or her immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extract might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Special considerations in immunotherapy

Allergen immunotherapy in children. Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Pregnancy. Summary Statement 71: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. **C**

Immunotherapy in the elderly patient. Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy in patients with immunodeficiency and autoimmune disorders. Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

Alternative routes of immunotherapy

Sublingual and oral immunotherapy. Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no US Food and Drug Administration (FDA)–approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **A**

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Immunotherapy techniques that are not recommended. Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

MECHANISMS OF IMMUNOTHERAPY

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, which is defined as a relative decrease in allergen-specific responsiveness, and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

The immunologic changes associated with immunotherapy are complex, and the exact mechanism or mechanisms responsible for its' clinical efficacy are continually being elucidated. Data support the concept that successful immunotherapy is associated with a change to a T_H1 $CD4^+$ cytokine profile.[29-34] Data indicate that increased production of IL-12, a strong inducer of T_H1 responses, contributes to this shift.[33] Clinically successful immunotherapy has been reported to be associated with immunologic tolerance, which is defined as a relative decrease in antigen-specific responsiveness, immune deviation, or anergy. For example, lymphoproliferative responses to allergen are reduced with immunotherapy.[32] Successful immunotherapy results in generation of a population of T regulatory cells, which are $CD4^+CD25^+$ T lymphocytes producing IL-10, TGF-β, or both.[35-39] Regulatory T-cell release has been described in allergen immunotherapy with Hymenoptera venom,[35] grass pollen extract,[37] and house dust mites.[38] IL-10 reduces B-cell antigen-specific IgE and increases IgG4 levels; reduces proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicits tolerance in T cells by means of selective inhibition of the CD28 costimulatory pathway.[36,37]

Allergen immunotherapy has been shown to block both the immediate and late-phase allergic response.[40] Allergen immunotherapy has been shown to decrease the recruitment of mast cells, basophils, and eosinophils in the skin, nose, eye, and bronchial mucosa after provocation or natural exposure to allergens.[41]

In patients receiving immunotherapy, initially there is an increase in specific IgE antibody levels, followed by a gradual decrease to a level that is still higher than that present before treatment. Clinical improvement in many patients develops before decreases in their IgE antibody levels occur or in other patients whose IgE antibody levels never decrease, thereby demonstrating that efficacy is not dependent on reductions in specific IgE levels.[42,43] Immunotherapy does diminish the seasonal increase in specific IgE levels.[44] Despite the persistence of significant levels of specific IgE antibody levels, immunotherapy usually causes a reduction in 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.[45-48]

An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, has also been associated with immunotherapy. The properties of allergen-specific IgA have yet to be determined, and there is a weak correlation between the increase in allergen-specific IgG levels and immunotherapy's clinical efficacy.[30,49,50]

Immunotherapy might alter the affinity and specificity of allergen-specific IgG.[51,52] During the initial phase of ultrarush VIT, a change in IgG specificity (ie, a change in the set of epitopes dominantly recognized by IgG on wasp venom antigens) occurred concomitantly with early clinical tolerance and was seen within 12 hours of ultrarush VIT ($P < .001$).[51] 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 individuals.[52] This change in IgG specificity preceded the increase in IgG titers and was sustained for up to 6 months.[52]

Allergen-specific IgG induced from immunotherapy can block IgE-dependent histamine release and subsequent IgE-mediated antigen presentation to T cells.[53] This effect might be dependent on IgE, allergen concentration, and CD23, the low-affinity receptor for IgE.

Whereas 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.[37,53]

The relationship between these immunologic changes and immunotherapy efficacy is not completely understood.

ALLERGEN EXTRACTS

Summary Statement 6: 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 has 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.[2,18,54-56] 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.

United States–licensed extracts can be obtained in aqueous, glycerinated, lyophilized, and acetone-precipitated and alum-precipitated formulations. Some commonly used allergens are standardized. These include extracts for cat hair, cat pelt, *Dermatophagoides pteronyssinus*, *Dermatophagoides 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.[57] 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.

Most standardized extracts are labeled in BAU. Short ragweed potency units were originally based on the content of the major allergen Amb a 1. Ragweed potency is reported in FDA units and BAU. One FDA unit of Amb a 1 equals 1 μg of Amb a 1, and 350 units of Amb a 1/mL is equivalent to 100,000 BAU/mL. Cat extracts were also originally standardized based on the content of major allergen (Fel d 1), with 100,000 arbitrary units (AU) per milliliter containing between 10 to 19.9 FDA units of Fel d 1 per milliliter (1 FDA unit of Fel d 1 equals 2 to 4 μg of Fel d 1).[55,58,59] Subsequently, $ID_{50}EAL$ testing suggested that 100,000 AU/mL was equal to 10,000 BAU/mL.[60] Approximately 22% of individuals with cat allergy have specific IgE antibodies to cat albumin.[61] Cat pelt extracts have a greater amount of albumin than cat hair extracts.[60]

Dust mites were originally standardized in AU by means of inhibition radioimmunoassay (RIA), and subsequent $ID_{50}EAL$ testing indicated that the AU was bioequivalent to the BAU, and the original AU nomenclature was kept. Dust mite extracts are still labeled in AU.

Summary Statement 7: Nonstandardized extracts can vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Nonstandardized extracts are labeled as wt/vol, which expresses weight in grams per volume in milliliters; that is, a potency of 1:100 indicates that 1 g 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 with a particular wt/vol or PNU potency can have widely varying biologic activities.[62-64] Therefore they should not be considered equipotent.

Summary Statement 8: 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**

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. The major clinically relevant aeroallergens of North America are listed in Table III. Furthermore, nonrelevant allergens in such mixtures could act as sensitizers rather than as tolerogens.[65,66] The physician must therefore select only those aeroallergens for testing and treatment that are clinically relevant in a particular geographic area.

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, dog), insect (cockroach), and Hymenoptera venom source materials.

Cross-reactivity of allergen extract

Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

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. A summary of cross-reactivity patterns of the clinically relevant North American aeroallergens can be found in Fig 2. 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,[67] inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[68-75] Grasses in other subfamilies (eg, Bermuda, Bahia, and Johnson) show greater diversity and should be evaluated separately.[76-78] Bermuda and Johnson grasses are increasingly important in the South,

TABLE III. The major clinically relevant aeroallergens of North America*

- Tree pollen
  - Chinese elm *(Ulmus parvifolia)*†‡; Siberian elm *(Ulmus pumila)*†‡; American elm *(Ulmus Americana)*†‡
  - Red oak *(Quercus rubra)*†; White oak *(Quercus alba)*†
  - Paper birch *(Betula papyrifera)*
  - Alder *(Alnus rubra)*
  - Box elder *(Acer negundo)*†; Red maple *(Acer rubra)*†
  - Eastern cottonwood *(Populus deltoides)*
  - Sycamore *(Platanus occidentalis)*
  - White ash *(Fraxinus americana)*†; Olive *(Olea europaea)*†‡
  - Black walnut *(Juglans nigra)*
  - Mulberry *(Morus rubra)*
  - Mountain cedar *(Juniperus ashei)*
  - Pecan *(Carya illinoensis)*
- Grass pollen
  - Rye *(Lolium perenne)*§‖
  - Timothy *(Phleum pratense)*§‖
  - Meadow fescue *(Festuca elatior)*§‖
  - Bermuda *(Cynodon dactylon)*‖
  - Johnson *(Holcus halepensis)*
  - Bahia *(Paspalum notatum)*
- Weed pollen
  - Short ragweed *(Ambrosia artemisiifolia)*‖
  - English (narrow leaf) plantain *(Plantago lanceolata)*
  - Mugwort *(Artemisia vulgaris)*
  - Russian thistle *(Salsola kali)*
  - Burning bush *(Kochia scoparia)*
  - Sheet (red) sorrel *(Rumex asetosella)*
  - Red root pigweed *(Amaranthus retroflexus)*
- Indoor aeroallergens
  - Cat epithelium *(Felis domesticus)*‖
  - Dog epithelium *(Canis familiaris)*
  - Arthropods (domestic mites: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*)‖
  - Insects (German cockroach: *Blattella germanica*)
- Fungi
  - *Alternaria alternata*¶
  - *Cladosporium* (*C cladosporioides*, *C herbarum*)¶
  - *Penicillium* (*P chrysogenum*, *P expansum*)¶
  - *Aspergillus fumigatus*¶
  - *Epicoccum nigrum*, *Drechslera* or *Bipolaris* type (eg, *Helminthosporium solani*)¶

*Compiled and selected in collaboration with the AAAAI Immunotherapy Committee Allergen Subcommittee for the identification of 35 key allergens of North America.
†Extensive cross-reaction of species within the genus.
‡Apart from regional prevalence, they are limited to local sites with substantial stands of these trees.
§Extensively cross-react with one another and bluegrass, orchard, red top, and sweet vernal.
‖Allergens for which standardized extracts are commercially available.
¶Species that are widely distributed and clinically important.

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.[79-82] 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.[83-85] Significant cross-reactivity between Betulaceae pollens and oak of the Fagaceae family has been demonstrated with percutaneous skin testing.[75] RAST inhibition studies have shown cross-inhibition between oaks and other *Fagales* species.[86] IgE immunoblot inhibition experiments have demonstrated that the *Fagales* species might be strongly inhibited by birch species.[87] The use of one of the locally prevalent members (eg, birch and alder) should be adequate.[88]

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.[89,90] Maple and box elder trees are found throughout the United States, except for the arid southwest. Although in the same genus as maple, *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,[91,92] and there are allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.[93]

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.[94] Similarly, Chenopod-Amaranth families have wide ranges in the western regions but are present throughout North America.[95] Current information on cross-reactivity of these families is limited.[96-98] 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.[99] The use of a single Amaranth extract should be sufficient to cover this family.[100,101] Similarly, *Atriplex* species (eg, saltbushes and scales) show near identity, and use of a single member is adequate. 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,

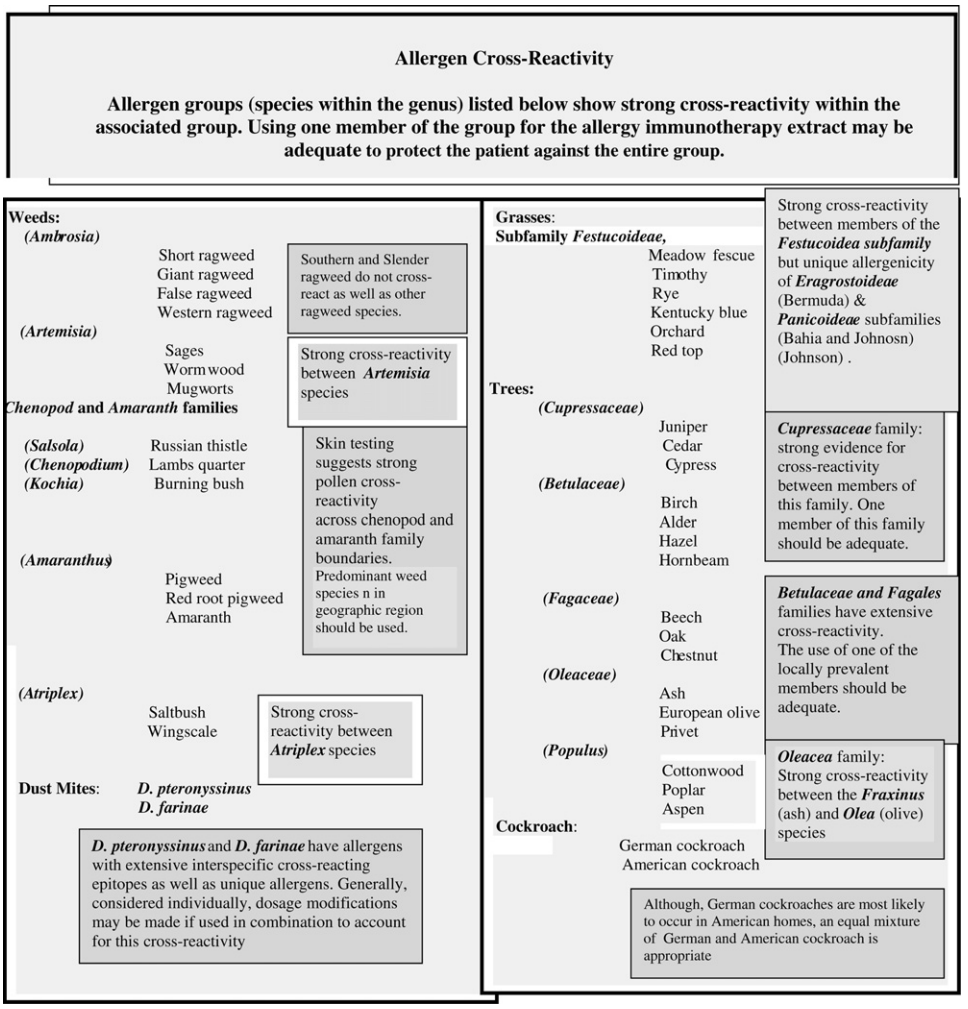


FIG 2. Patterns of allergen cross-reactivity.

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*).

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.[102,103] Stinging Hymenoptera insects occur throughout the United States; the fire ant is found only in Gulf Coast states, Texas, and some other southern and western states. Commercial venom extracts are available for some Hymenoptera species, except the fire ant, for which only whole-body extract is available.

EFFICACY OF IMMUNOTHERAPY

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity

Summary Statement 10: Immunotherapy is effective for 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.[104-111] Immunotherapy is effective for the treatment of allergic rhinitis[107] (including ocular symptoms[112,113]), allergic asthma,[104,109,111,114,115] and stinging insect hypersensitivity[108,116] and is effective in both adults and children.[117-124] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollens,[13,125-132] fungi,[133-138] animal allergens,[22,25,26,139-143] dust mite,[114,115,144-153] and cockroach.[154] There have been no controlled trials of fire ant whole-body extract, but it does appear to be effective in

TABLE IV. Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy

Outcome measure	House dust mite	Other allergens*†
Symptomatic improvement	2.7 (1.7-4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2-7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50)	5.5 (2.8-10.7)

Data are used with permission from Abramson et al.[104]
ND, Not done.
*Odds ratio (95% CI).
†Pollen, mold, or animal dander.

uncontrolled trials.[155-157] 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. A number of studies have also demonstrated a significant improvement in quality of life, as measured by using standardized questionnaires.[24,158-161] The magnitude of the effect depends on the outcome that is used (Table IV). For dust mite, the effect size ranges from a 2.7-fold improvement in symptoms to a 13.7-fold reduction in bronchial hyperresponsiveness. 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.[110] 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[107] and asthma[104,109,111] have been performed to deal with the issue of power. One review of 75 trials involving 3188 asthmatic patients found that, overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyperreactivity after immunotherapy, and it would have been necessary to treat 4 patients (95% CI, 3-5) with immunotherapy to avoid 1 deterioration in asthma symptoms and 5 (95% CI, 4-6) patients to avoid 1 requiring increased medication.[111] These meta-analyses strongly support the efficacy of allergen immunotherapy. Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued[13,162,163] and might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6,9,122,162-165] Allergen immunotherapy might also prevent the development of new allergen sensitivities in monosensitized patients.[120,166,167]

Food allergy, urticaria, and atopic dermatitis

Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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 use of allergen immunotherapy for individuals with the potential for IgE-mediated (anaphylaxis) reactions to foods should be regarded as investigational at this time.[168-171] There have been 2 investigational studies demonstrating efficacy in food hypersensitivity, the first using aqueous subcutaneous injections to peanut and the second using sublingual immunotherapy to hazelnut.[171-173]

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 a modified peanut extract is needed for clinical application of this method of treatment.[171] There is currently no FDA-approved formulation for sublingual immunotherapy, and this route of allergen immunotherapy is currently considered investigational at this time (see Summary Statement 73).

At the present time, there is not enough evidence to support food immunotherapy.

There is no evidence supporting the efficacy of immunotherapy for individuals with chronic urticaria, angioedema, or both.

There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[174-176] 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 ($P = .0379$) and topical corticosteroid use ($P = .0007$).[174]

The potential for benefit in symptoms related to oral allergy syndrome with the cross-reacting inhalant immunotherapy, which includes cross-reacting 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 subcutaneous immunotherapy directed against birch tree,[177] whereas another double-blind, double-dummy, placebo-controlled study comparing the effect of subcutaneous immunotherapy with sublingual immunotherapy 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, medication use, and decrease in IgE reactivity.[178] More investigation is required to substantiate the contention that benefits in oral symptoms will occur with immunotherapy.

Measures of efficacy

Summary Statement 12: 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. Objective measures, such as increase in allergen-specific IgG levels and decreased skin test reactivity, as measured by skin test titration, are changes generally associated with effective immunotherapy but, at present, are not practical for routine clinical use.[147] Nonquantitative skin testing or *in vitro* 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 are not very reliable given the strong placebo-like effect (Hawthorne effect) associated with any treatment. A more objective means for determining efficacy as validated in controlled clinical studies is the use of clinical symptom scores and the amount of medication required to control symptoms and maintain peak flow rates or pulmonary function tests within acceptable limits. Successful immunotherapy often results in a reduction in medication. Sequential measurement of disease-specific quality of life also might be helpful.

SAFETY OF IMMUNOTHERAPY

Reaction rates

Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Large local reactions associated with allergen immunotherapy are fairly common, with a frequency ranging from 26% to 86% of injections.[179] Two retrospective studies compared the effect of not adjusting immunotherapy dose based on large local reactions on the immunotherapy systemic reaction rate with dose-adjustment protocols.[179,180] There was a total of 12,464 injections administered with a dose-adjustment protocol in the 2 studies compared with 9542 injections administered with a no-dose-adjustment protocol. 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 for subsequent systemic reactions, 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 large local reactions, defined as 25 mm or larger, in patients who had experienced systemic reactions with age-, sex-, and allergen sensitivity–matched control subjects who had not had allergen immunotherapy systemic reactions found the rate of large local reactions was 4 times higher among the 258 patients who had subsequently experienced a systemic reaction compared with those who had never experienced a systemic reaction.[181] Patients who had experienced systemic reactions had 1573 large local reactions in 4460 visits (ie, 35.2% of visits) and 8081 injections (ie, 19.5% of injections) compared with the matched control group without systemic reactions who had 1388 large local reactions in 15,540 visits (8.9% per visit) and 26,259 injections (5.3% per injection; difference between groups, $P < .001$). Individual large local reactions were not predictive of future systemic reactions, but large local reactions preceded systemic reactions in approximately one third of the systemic reactions. These findings suggest that individuals with a greater frequency of large local reactions might be at greater risk for systemic reaction. Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy protocol modifications based on them are needed.

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

The prevalence of severe systemic reactions after allergen immunotherapy ranges from less than 1% of patients receiving conventional immunotherapy to greater than 36% of patients in some studies of patients receiving rush immunotherapy.[182,183]

In a recent survey of fatal and near-fatal reactions (NFRs) sent to physician members of the AAAAI, 273 of 646 respondents reported NFRs during the period of 1990-2001.[184]

The incidence of unconfirmed NFRs was 23 per year (5.4 events per million injections). Administration during the height of 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 angiotensin-converting enzyme 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 systemic reactions to subcutaneous immunotherapy over a 20-year period (1981-2000) during which 435,854 injections were administered to 4000 patients, 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.[185,186] In a prospective multicenter study there were 53 systemic reactions (0.3% of the doses) out of 17,526 administered doses in 18 (3.7%) of 423 patients.[187] 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 (21 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, there were 41 fatalities identified in the initial brief survey (20 directly reported and 17 with completed detailed questionnaire) from immunotherapy injections.[188] 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.[189,190] Therefore although severe systemic reactions to allergen immunotherapy are not common, serious systemic reactions (some fatal) can occur.

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

In the AAAAI survey of physician members on immunotherapy and skin testing, fatal reactions, and NFRs during the period of 1990-2001, 15 of the 17 fatalities had asthma, and in 9 patients asthma was considered the susceptibility factor that contributed to the fatal outcome.[188]

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.[184]

Administration during the peak pollen season (3 patients) and previous systemic reactions (4 patients) were cited as other contributing factors. Five fatalities occurred in outside medical facilities, and 2 fatalities occurred at home. No patients were receiving β-blockers; 1 patient was taking an angiotensin-converting enzyme inhibitor. In the most comprehensive evaluation of fatalities associated with allergen immunotherapy, from 1945-1987, there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[189] 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, with 73.3% of patients with an FEV_1 of less than 80% of predicted value experiencing 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 ($P < .0001$).[191] 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% of patients. These studies suggest that symptomatic asthma, severe asthma, or both might be a risk factor for immunotherapy.

In addition to symptomatic asthma and injections giving 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.[17] With the exception of dosing errors and 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 recent 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 or allergy symptom exacerbation, β-blocker use, change in health status (including pregnancy), or adverse reaction to previous allergen immunotherapy injection. The preinjection evaluation might also include a peak flow measurement to assess the airway function of asthmatic patients.

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 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

In a retrospective study the time to onset of a systemic reaction after an immunotherapy injection was less than 30 minutes in most cases.[189] A review of the literature indicates that 70% of systemic reactions occur within 30 minutes after an injection.[183] In the AAAAI 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.[184,188] 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.[190] 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 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.[192] In another prospective study 8% of systemic reactions occurred more than 2 hours after injection.[193]

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.[194]

Because most reactions that resulted from allergen immunotherapy occurred within 30 minutes after an injection, patients should remain in the physician's office for at least 30 minutes after receiving an injection, but longer waits are reasonable, as directed by the physician. In addition, patients who are at increased risk of a systemic reaction might need to carry injectable epinephrine. Such patients might also need to remain in the physician's office more than 30 minutes after an injection. 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.

β-Adrenergic blocking agents

Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

β-Blockade enhances pulmonary, cardiovascular, and dermatologic end-organ effects of mediators and increases mortality associated with experimental anaphylaxis induced by either immunologic or nonimmunologic mechanisms. Patients who are receiving β-adrenergic blocking medications might be at increased risk if they experience a systemic reaction to an allergen immunotherapy injection because the β-receptor blockade might attenuate the response to epinephrine.[195-202] Patients who are receiving β-blocking drugs were almost 9 times more likely to be hospitalized after an anaphylactoid reaction from radiocontrast media.[198] Although topical β-blockers have markedly less systemic β-antagonist effects than oral β-blockers, they still might exhibit some systemic β-antagonist effects. Whether topical β-blockers pose the same or a smaller risk than oral β-blockers in regard to the treatment of allergen immunotherapy–related systemic reactions is not known.

There have been very few studies that have examined the effect of β-blocker medications on allergen immunotherapy. A prospective 1-year study designed to determine whether patients taking β-blocker drugs were at increased risk of immunotherapy-induced systemic reactions found that there were 166 systemic reactions out of 56,105 injection visits in 3178 patients (68 were receiving a β-blocker).[203] The systemic reactions occurred in 144 (4.5%) patients, and only 1 of these patients was receiving a β-blocker medication. The authors calculated that by chance, 3.08 patients receiving the β-blocker medications drugs were expected to have had an systemic reaction and concluded that β-blocker medications did not increase the frequency of allergen immunotherapy systemic reactions ($P > .95$).

In another study of 1389 patients prescribed immunotherapy for Hymenoptera venom hypersensitivity who were followed for 34 months, there were 25 patients who received concomitant β-blocker medications.[204] Three (12%) of the 25 patients receiving β-blocker medications experienced systemic reactions during immunotherapy compared with 23 (16.7%) of 117 patients with cardiovascular disease not receiving β-blockers. Systemic reactions after a field sting or challenge occurred in 1 (14.3%) of 7 cardiovascular patients receiving β-blocker medications compared with 4 (13.8%) of 29 cardiovascular patients not receiving β-blocker medications. No severe reactions to immunotherapy or sting re-exposure were observed in patients receiving β-blockers medications.

Immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. In such cases, intravenous glucagon, which might reverse the refractory bronchospasm and hypotension by activating the adenyl cyclase directing and bypassing the β-adrenergic receptor, might be used if epinephrine has not been effective.[205,206] Prospective studies are necessary to clarify the magnitude of the risk of systemic reactions to allergens in patients who are receiving concomitant therapy with β-blockers, and a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy.

Contraindications

Summary Statement 18: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications

TABLE V. Actions to reduce the risk of anaphylaxis

- Assess the patient's general medical condition at the time of injection (eg, asthma exacerbation).
- Consider obtaining a PEFR before administration of the injection. If the PEFR is significantly less than the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.
- 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 with increased allergen sensitivity or those who have previously had a systemic reaction) might need to wait longer.
- Carefully evaluate any patient with a late reaction (eg, persistent large local reaction lasting >24 hours, systemic reaction occurring more than 30 minutes after the immunotherapy injection).
- 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.

PEFR, Peak expiratory flow rate measurement.

TABLE VI. Recommended equipment and medications to treat anaphylaxis

Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur. This should include at least the following equipment and medications:

- stethoscope and sphygmomanometer;
- tourniquet, syringes, hypodermic needles, and large-bore needles (14-gauge);
- aqueous epinephrine HCL 1:1000 wt/vol;
- equipment to administer oxygen by mask.
- intravenous fluid set-up;
- antihistamine for injection (second-line agents for anaphylaxis, but H_1 and H_2 antihistamines work better together than either one alone);
- corticosteroids for intravenous injection;
- vasopressor;
- equipment to maintain an airway appropriate for the supervising physician's expertise and skill.

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 venom hypersensitivity and cardiac disease being treated with β-blocker medications.

Reducing the risk of anaphylaxis to immunotherapy injections

Summary Statement 19: 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 extremely 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 or other health care professional appropriately trained in emergency treatment.

The 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. Epinephrine is the first-line treatment for anaphylaxis. 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.[12,207-213] It is important to administer epinephrine early in the management of anaphylaxis. 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 V and VI, respectively. Before allergen immunotherapy is chosen as a treatment, the physician should educate the patient about the benefits and risks of immunotherapy, as well as methods for minimizing risks. The patient also should be told that despite appropriate precautions, reactions might occur without warning signs or symptoms. Informed consent should include a discussion of the potential immunotherapy adverse reactions, and this discussion should be documented in the patient's medical record.

PATIENT SELECTION

Clinical indications

Summary Statement 20: Allergen immunotherapy should be considered for patients who have demonstrable

TABLE VII. Clinical indications for allergen immunotherapy

Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or both:
- symptoms of allergic rhinitis after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medications;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medication;
- coexisting allergic rhinitis and asthma;
- possible prevention of asthma in patients with allergic rhinitis

Symptoms of asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medication;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medications;
- coexisting allergic rhinitis and allergic asthma.

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);
- adults and children with a history of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.

evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic rhinitis.[107] Prospective, randomized, double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic asthma.[104,109,111]

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 proper identification and selection of component allergens on the basis of 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 (Table VII). The severity and duration of symptoms should also be considered in assessing the need for specific allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. In addition, specific allergen immunotherapy should be considered if the patient wishes to avoid long-term pharmacotherapy. Time lost from work, emergency department or physician's office visits, and responses to pharmacotherapy are important objective indicators of allergic disease severity.

Patients with allergic rhinitis who are unable to sleep because of symptoms or whose symptoms interfere with their work or school performance should be considered strong candidates for specific allergen immunotherapy. 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 considered. Unacceptable adverse effects of medications should also favor one's decision to initiate allergen immunotherapy. Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.[214]

Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued, and it might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6-9,122,162-165] These benefits of immunotherapy should be discussed with patients and might provide a clinical indication for immunotherapy for individual patients with allergic rhinitis.

Coexisting medical conditions should also be considered in the evaluation of a patient who might be a candidate for allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed with a combined aggressive regimen of allergen avoidance and pharmacotherapy and might also benefit from allergen immunotherapy.[215,216]

However, the patient's asthma must be stable before allergen immunotherapy is administered.[188,191]

Special precautions in patients with asthma

Summary Statement 21: 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 might be at increased risk for systemic reactions to immunotherapy injections.[182,188,191] Two surveys found that deaths from

immunotherapy were more common in symptomatic subjects with asthma.[188,189] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2,217]

Clinical indications for VIT

Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Systemic reactions to Hymenoptera stings, especially when associated with respiratory symptoms, cardiovascular symptoms, or both and positive skin test or *in vitro* test results for specific IgE antibodies, are a strong indication for allergen immunotherapy.[218] In the United States patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Several studies of patients with imported fire ant allergy have demonstrated the effectiveness of immunotherapy with whole-body extracts of fire ants.[155,156,219] 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. Patients younger than 16 years of age who present only with a cutaneous reaction to imported fire ant or Hymenoptera stings might not require immunotherapy.[218,220-222] In addition to allergen immunotherapy, patients with imported fire ant and Hymenoptera venom sensitivity should be instructed in how to best avoid insect stings, be prescribed epinephrine, and be taught how 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 the population that has not had a systemic reaction.[223] In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific IgE is recommended.[218] If the venom-specific IgE test result is also negative, it is recommended that the skin tests, venom-specific 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 IgE test result.[224] 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 re-stung. 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%).[225] 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 IgE test results who have had severe anaphylaxis to an insect sting.

Some patients who have negative venom skin test results and negative venom-specific IgE test results are reported to have had subsequent systemic reactions to stinging insects.[225-227] Controlled studies designed to evaluate the efficacy of immunotherapy in these patients have not been performed. There are very 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.[226] 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.

Summary Statement 23: 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.

ALLERGEN SELECTION AND HANDLING

Allergen selection

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

A careful history, noting environmental exposures and an understanding of the local and regional aerobiology of suspected allergens, such as pollen, fungi (mold), 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 skin or *in vitro* test results for specific IgE antibodies, provide good evidence that such exposures are relevant. Information concerning regional and local aerobiology is available on various Web sites or through the National Allergy Bureau at http://www.aaaai.org/nab. There are

no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma. 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 clinical history of an allergic disease.

There is no evidence to support the administration of immunotherapy based solely on results of specific *in vitro* 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.

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

The omission of clinically relevant allergens from an allergic patient's allergen immunotherapy extract contributes to decreased effectiveness of allergen immunotherapy. The 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 can make allergen immunotherapy less effective.

Knowledge of the total allergenic burden facing a patient and the realistic possibility of avoidance is important in determining whether allergen immunotherapy should be initiated. 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. Many individuals travel extensively for business or pleasure into different regions, and symptoms might worsen at these times. However, inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective. Determination of the significance of indoor allergens for a particular patient is harder because it is difficult to determine exposure in the home, school, and/or workplace. Historical factors, such as the presence of a furry animal in the home, a history of water damage and subsequent fungal exposure, or a history of insect infestation, might be helpful. However, such information is subjective and is often of uncertain reliability. In addition, some studies have demonstrated significant indoor levels of cat and dog allergen in households without pets[228] and significant levels of mouse allergen in suburban[229] and inner-city[230] homes 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 with increased asthma morbidity in inner-city children was found.[231] 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. Nevertheless, for most patients, determination of the clinical relevance of an allergen requires a strong correlation between the patient's history and evidence of allergen-specific IgE antibodies.

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted *in vitro* tests for specific IgE antibodies can also be used. **A**

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 the skin test results have demonstrated the efficacy of immunotherapy for relevant allergens.[25,26,112,130,134,135,140,141,149,154] 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 from skin testing in a highly sensitive individual.[232,233] In addition, skin tests might be difficult to perform in patients with dermatographism or atopic dermatitis. *In vitro* tests are particularly useful in such patients.

Studies indicate that skin testing is generally more sensitive than *in vitro* tests in detecting allergen-specific IgE.[234,235] Based on inhalation challenge test results, skin tests have shown specificity and sensitivity generally superior to those of *in vitro* tests. The comparability of skin tests and *in vitro* tests for specific IgE antibodies depends on the allergen being tested. For all of 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, prick testing is sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass[236] and cat,[237] are used. Intradermal/intracutaneous skin testing might be required for some allergen extracts. It is appropriate in some patients to use *in vitro* tests for specific IgE antibody as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. *In vitro* tests can also be used to define the allergens that should be used in allergen immunotherapy. If the allergy skin test result is negative and the *in vitro* test result is positive, a controlled challenge can be performed, and if the latter is positive, immunotherapy can be considered. 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 *in vitro* test results.

Specific allergens

Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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.[17,104,106,107,109] 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.[112,122] Because a particular pollen extract is a mixture of multiple glycoproteins, this suggests that mixing pollen allergens does not alter biologic activity.

Fungi (molds). Several studies with *Alternaria* and *Cladosporium* species suggest that allergen immunotherapy with fungi might be effective.[133-138] The allergen content of most mold extracts is highly variable.[238,239] However, there is evidence that proteolytic enzymes present in some mold extracts could digest other antigens, such as pollens, when combined in a mixture.[240] For this reason, it might be desirable to separate all pollen extracts from mold extracts when using mixtures.

Unfortunately, extracts for some potentially clinically important fungi are not available.[241] 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 distinguish 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.

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.

Because immunotherapy has been shown to be effective for cat[22,26,139-143,242] and dog,[25,141] the decision to include dog or cat allergen in an allergen immunotherapy extract should be considered in those circumstances in which there is exposure.

Dust mites and cockroach allergens. Crude house dust extract is generally an inappropriate substitute for house dust mite extract because the protein content measured is not restricted to dust mite allergens, nor does it necessarily guarantee inclusion of dust mite protein. Immunotherapy with standardized dust mite is generally more effective than that with crude house dust allergens. The house dust mites *D farinae* and *D 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, such as *Blomia tropicalis* and *Euroglyphus maynei*, partially cross-react with allergens from *Dermatophagoides* species. Only 50% of the projected amounts of each of the 2 house dust mites (*D pteronyssinus* and *D farinae*) need 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[144,147-149,151] 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. Dust mite hypersensitivity should particularly be considered in patients who have perennial symptoms exacerbated by a dusty environment at home, work, or both and periods of high humidity.

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. The major allergen of *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.[243] Immunotherapy with cockroach allergens is effective[154] and should 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.

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.[108,116,244] Efficacy has also been demonstrated with immunotherapy by using whole-body extracts of imported fire ants.[155,156]

Foods. Only a single clinical study accessing the efficacy and safety of subcutaneous immunotherapy with foods has been performed.[171,173] This study, which evaluated immunotherapy with peanut, found the incidence of systemic reactions, even during maintenance, was unacceptable. Thus there is no evidence to support the use of immunotherapy with food extracts. Currently, strict avoidance of the offending food is advisable, and subcutaneous immunotherapy for food allergy is not recommended.

Mixing of extracts

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Once the relevant allergens for each patient are identified, it is necessary to prepare a mixture that contains each of these allergens. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts. A number of 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 interactions between different types of allergens, when mixed, that could lead to degradation or unmasking of epitopes on exposure to proteolytic enzymes.

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Immunologic and 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.[71] 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 genera 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 the Allergen extract section, Fig 2, and the allergens and allergy diagnostic tests practice parameters).

Dose selection. Summary Statement 30: 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.[22-26,128,149,245] Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000 vol/vol).[28] A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy vaccine. Failure to do so might reduce the efficacy of immunotherapy. This occurs because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased (see the Immunotherapy schedules and doses section for further discussion and for recommended maintenance doses).

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as fungi (mold) and cockroach, from other extracts, such as pollens, is recommended. **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.[240,246,247] 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, and some weeds.[240,246,247] Cockroach had a similar deleterious effect on pollen extract potency.[246,248] Short ragweed appeared resistant to the effects of the proteolytic enzymes in one study,[240] 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.[247]

Dust mite extracts do not appear to have a deleterious effect on pollen extracts.[240,246,248] These studies suggest that pollen, dust mite, and cat extracts can be mixed together. 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. The evidence on mixing cockroach extract with other extracts is conflicting, and the clinical relevance of the changes is also unclear; therefore the clinician has the option of separating cockroach or not.

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 with lesser activities, such as pollen extracts.

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.

In this regard the number of separate injections that need to be given at each patient visit depends on whether all of the relevant extracts mixed into a single vial still deliver an optimal dose of each allergen. If mixing causes excessive dilution or if there are advantages to separating allergens into separate vials, then more than one vial might be necessary for successful immunotherapy.

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extracts are high-alert products that carry the risk for anaphylaxis. Policies, procedures, and processes intended for conventional drugs and medications might be highly 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 fatal anaphylactic reactions with allergenic products. 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. There are no reports of infection associated with allergen immunotherapy injections. Allergen vaccines are prepared by using sterile manufacturer's extracts and sterile diluents containing antibacterial constituents (usually phenol). A summary of the AAAAI/ACAAI/JCAAI proposed USP allergen immunotherapy extract preparation guidelines can be found in Table VIII.

TABLE VIII. AAAAI/ACAAI/JCAAI-proposed USP 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 below.*
   - 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.
2. **Physician responsibility**: A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in the preparation of immunotherapy using an aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files.
3. **Bacteriostasis**: Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if 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 the FDA-approved package insert 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 treatment with sanitizing agents containing alcohol and/or 70% isopropanol 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 the physical integrity of the vial.
10. **Labeling**: Immunotherapy vials are to be clearly labeled with the patient's name and 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.

*__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 media, such as from Valiteq (http://www.valiteq.com), 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.

Allergen immunotherapy extract handling

Storage. Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

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 a number of 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 extract, including reconstituted lyophilized extracts, should be stored at 4°C to minimize the rate of potency loss because storage at higher temperatures (eg, room temperature) can result in rapid deterioration.[249]

Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions (personal communication). These studies include actual shipments made by their carriers to places like

Phoenix in the summer and Alaska in the winter. 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.

Storing dilute extracts. Summary Statement 34a: More dilute concentrations of allergy immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than do more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: In determining the allergy vaccine expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of 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 allergen immunotherapy 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.[249,250]

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.[250] Phenol is a preservative added to extracts to prevent growth of microorganisms.

Phenol can denature proteins in allergen extracts.[251,252] Human serum albumin might protect against the deleterious effect of phenol on allergen extracts.[251] 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,[250,253] possibly through inhibition of the activity of proteolytic and glycosidic enzymes that are present in certain extracts. However, it is irritating when injected and should be diluted before beginning immunotherapy. Recommendations for extract stability are found in the manufacturers' product insert sheets. 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. The pain associated with glycerin increases in proportion to the glycerin concentration and injection volume, and the pain is proportional to the total injected dose of glycerin.[254] However, individual pain perception can vary substantially. Total glycerin doses of less than 0.05 mL rarely produce clinically important pain.

TABLE IX. Potency of selected manufacturer's extracts currently available

Extract	Potency
Cat hair and pelt	5000 and 10,000 BAU/mL
Dust mite	3000, 5000, 10,000, and 30,000 AU/mL
Bermuda grass	10,000 AU/mL
Short ragweed	1:10-1:20 wt/vol or 100,000 AU/mL
Other grasses*	10,000 and 100,000 BAU/mL
Other pollen	1:10 to 1:40 (wt/vol) or 10,000 PNU/mL
Molds	1:10 to 1:40 (wt/vol) or 20,000 to 100,000 PNU/mL

AU, Allergy unit; *BAU*, bioequivalent allergy unit; *PNU*, protein nitrogen unit.
*Perennial rye, Kentucky blue/June, timothy, sweet vernal, redtop, orchard, and meadow.

There have been few studies that have investigated the potency of dilutions of allergen extract mixture over time. Expiration dates for allergen extract dilutions are somewhat empiric and not strongly evidence based. A study undertaken by the AAAAI 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. Dust mite and cat at 1:10 and 1:100 vol/vol dilution were also stable in all conditions of storage over 12 months, as measured by an ELISA assay using 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.

IMMUNOTHERAPY SCHEDULES AND DOSES

Summary Statement 35: A customized individual 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 can be based on single or multiple allergens. **D**

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. Animal dander contains between 10 and 20 antigens,[255] house dust mites between 20 and 40 antigens,[256] and pollens between 30 and 50 antigens,[257,258] and fungal extract can contain as many as 80 antigens.[259]

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. This is designated as the patient's maintenance concentrate.

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. Standardized extracts are available with biologic potencies of 10,000 and 100,000 BAU for grasses; 5000 and 10,000 BAU for cat allergen; 5000, 10,000, or 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 wt/vol extracts (Table IX). 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.

Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

The highest concentration of an allergen extract mixture that is projected to be used as the therapeutically effective dose is called the maintenance concentrate. This should be prescribed individually for each patient by an allergist/immunologist. 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 individual manufacturer's extracts. Some patients might be unable to attain the projected therapeutically effective dose of the maintenance concentrate because of local reactions, systemic reactions, or both (eg, cat, 1000 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose]; see Table X for probable effective therapeutic dose range). Such patients might need weaker dilutions of their maintenance concentrate. Even so, 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 referred to as the maintenance dose. The consistent use of this nomenclature system is essential because errors in choosing the correct vial are a common cause of systemic reactions, especially when the patient transfers from one physician to another. Therefore it is important that standard terminology be adopted by all physicians who prescribe allergen immunotherapy.

Recommended doses

Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

The effective maintenance dose of immunotherapy for a particular patient must be individualized. To do this, the allergist/immunologist who prepares the allergen immunotherapy extract must balance the dose necessary to produce efficacy and the risk of reactions if such a dose is reached. The allergist/immunologist might need to prepare more than one maintenance concentrate to provide a therapeutic dose of each of the allergens for the polysensitized patient. Therapeutically effective doses for immunotherapy have been reported for some allergen extracts.[22,24,25,128,134,135,149,246,260,261] Effective doses have been determined for Hymenoptera venom, dust mite, cat allergen, dog, grass, and short ragweed (Table X).

Controlled studies demonstrate that the content of particular allergens in allergen immunotherapy extracts can be used to predict a therapeutic dose for those allergens, particularly when the extracts are standardized. For antigens 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. The therapeutically effective doses used in the most recent controlled clinical studies are the basis of the recommended dosage range of standardized extracts presented in Table X. 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 time that it is administered.[14]

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.[27] 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 risk of systemic reactions to immunotherapy injections with higher maintenance doses. The maintenance concentrate should be formulated to deliver a full therapeutic dose of each of its constituent components. However, some sensitive patients might not tolerate the targeted therapeutic dose, and their maintenance dose would be lower. Individuals 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 referred to as the maintenance dose.

Regardless of dose schedule, some patients are unable to progress to the predetermined maintenance dose because of large local or systemic reactions to the allergen

TABLE X. Probable effective dose range for allergen extracts US standardized units[a]

Antigen	Labeled potency or concentration[a,b]	Probable effective dose range
Dust mites: *D farinae* and *D pteronyssinus*[c]	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat[d]	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized[e]	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed[f]	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 μg of Amb a 1 1000-4000 AU Concentration of Amb a 1 is on the label of wt/vol extracts in FDA units[358]
Nonstandardized extract, dog[g]	1:10 to 1:100 wt/vol	15 μg of Can f 1
Nonstandardized extracts	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose

[a]Multiple studies have demonstrated that the efficacious dose for allergen immunotherapy is between 5 and 20 μg of the major allergen per injection. Only 2 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).

[b]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).

[c]There have been no dose-response studies with United States–licensed dust mite extracts, and dosing recommendations in AU value are extrapolated from published European studies that used aqueous[349] and alum-precipitated[149,151] extracts. 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.[149] The authors suggested the optimal maintenance dose was 7 μg of Der p 1. Corresponding doses were based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Extrapolating effective and safe doses in this manner might not be scientifically valid. *D farinae* and *D pteronyssinus* are similar in group 1 allergen content according to the FDA's current reference standards. 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*.

[d]The major cat allergen Fed d 1 is reported in FDA units, with 1 Fel d 1 unit equaling approximately 2 to 4 μg of Fel d 1.[55,58,59] The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 to 19.9 U/mL. One study demonstrated clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 dose in terms of decreased cat extract PD_{20}, titrated skin test results, and allergen-specific IgE and IgG levels.[350,351] In a recent study that investigated the efficacy in terms of immunologic changes of 3 doses of a United States–licensed cat extract (0.6, 3, and 15 μg) demonstrated that a significant effect on titrated skin prick test results, allergen-specific IgG4 levels, and $CD4^+$/IL-4 levels was only seen in the group treated with 15 μg of Fel d 1, although the 3-μg dose group did demonstrate a significant change in titrated skin test response and increase in cat-specific IgG4 levels.[22]

[e]There have been no dose-response studies with United States–licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,[130] alum-precipitated,[24,161] and calcium phosphate–precipitated grass pollen extracts.[352] One of these studies compared a dose of 2 μg with 20 μg of major timothy allergen (Phl p 5) and found clinical efficacy at both doses.[24] The efficacy was greater in the 20 μg of Phl p 5 dose, but the systemic reaction rate was also higher in the high-dose group. The package inserts for United States–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 BAU. Extrapolating effective and safe doses in this manner might not be scientifically valid. 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).

[f]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 suggested that 1 unit of Amb a 1 is equivalent to 1 μg of Amb a 1, and 350 Amb a 1 units/mL is equivalent to 100,000 BAU/mL.[60] The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2000 AU, with a range of 1000-4000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrated 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.[45] A ragweed dose-response study (0.6, 12.4, and 24.8 μg of Amb a 1) demonstrated efficacy, as measured by nasal challenge, at 12 and 24 μg of Amb a 1.[128] The efficacy of the 24-μg dose was not significantly better than the 12-μg dose, and the authors concluded that the optimal dose for ragweed extract was greater than 0.6 μg but not more than 12.4 μg of Amb a 1.

[g]Dog extracts are not standardized. However, one dose-response study with a United States–licensed acetone-precipitated dog extract investigated the efficacy of 3 doses (AP dog; Hollister-Stier, Spokane, Wash; 0.6, 3, and 15 μg) in terms of immunologic changes and found the dose of 15 μg of Can f 1 to be most efficacious.[25] 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 have assayed between 128 and 208 μg/mL (average Can f 1, 162 μg/mL [SD ± 26 μg/mL]; information provided by the extract manufacturer, Hollister-Stier).

immunotherapy extract. The evidence is not clear whether large local reactions are a potential risk for subsequent allergen immunotherapy systemic reactions.

Published studies do not indicate that an individual large local reaction is predictive of a subsequent systemic reaction.[179,180] However, one retrospective study found that individuals who have a history of repeated large local reactions (defined as >25 mm) might be at greater risk for a subsequent systemic reaction.[181]

The concept of highest tolerated dose does not apply for VIT, and all patients are expected to achieve the full recommended dose to achieve the necessary degree of protection. There are conflicting data over whether lower doses (50 μg) are less effective, but there are also data showing that 200 μg is more reliably effective.[245] In the case of VIT, patients are asked to tolerate more large local reactions to achieve the full dose, even though with inhalant immunotherapy the dose can be reduced for such large local reactions to minimize patient discomfort.

Effect of dilution on dose

Summary Statement 38: 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 vaccine, thereby limiting the ability to deliver a therapeutic effective dose for any given allergen.

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

Dilution from maintenance concentrate vaccine	Volume	Volume (mL)	Diluent volume (mL)	Final volume
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.

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 2000 BAU/mL, 2 mL of the manufacturer's extract (cat, 10,000 BAU/mL) can be added to 8 mL of diluent or 8 mL of other allergens, and the final concentration of cat will be 2000 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.

Dilutions of the maintenance concentrate

Summary Statement 39: 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 vol/vol 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, 1000 BAU or 100 BAU), but this system can be complicated if allergens with different potency units are used (eg, wt/vol, BAU, AU, or PNU) and make it difficult to easily interpret the vial label.

Instructions on how to prepare various allergen extracts 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.

Labeling dilutions

Summary Statement 40: 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, a number of 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 (vol/vol), a numbering system, a color-coding system, or an alphabetical system should be used. If this uniform labels 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.

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
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

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 3 and 4).

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 Appendix 2]).

Individualized treatment vials

Summary Statement 41: 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 (wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for 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). Labels on patient-specific vials can provide at least 2 patient identifiers (birth date and patient name), which would be consistent with the recommendations of the Joint Commission on Accreditation of Health Care Organizations National Patient Safety Goals: ''Goal 1: Improve the accuracy of patient identification by using at least two patient identifiers when providing care, treatment or services.''[5] 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 administration of the injection.[4,5]

In a survey of 1717 allergists endorsed by the AAAAI and JCAAI, 57% of the 476 respondents reported at least one wrong-patient injection, and 74% of the 473 respondents reported at least one wrong-dose injection.[4] 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 reasons why this might reduce incorrect injection errors. One reason was that patient-specific vials can be prepared in a quiet laboratory setting, which might provide substantially less distraction than the nurse in a room with a patient who is trying to concentrate only on drawing up the injection correctly. In addition, the specific components are mixed once with the preparation of individually prepared patient-labeled vials, whereas the mixing would be repeated on every injection visit if the allergen extract is withdrawn from different stock solutions, as it is in the off-the-board method. For safety reasons and to avoid cross-mixing of allergens removed from the manufacturer's extract, the mixing of antigens in the syringe (off the board) is not recommended.

Some allergists/immunologists prefer to administer immunotherapy doses drawn directly from a single stock dilution of individual allergens or common mixes (shared specific patient vials). In this way the immunotherapy dose is transferred to the patient without cross-contamination. If shared-patient (eg, mixed vespids and dust mite mix) vials are used, it is essential that policies and procedures are developed to verify that the correct dose from the correct vial is administered to the correct patient.

Starting doses

Summary Statement 42: The starting dose for build-up is usually a 1000- 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 slowly 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 1:1000 (vol/vol), although more diluted concentrations frequently are used for patients who are highly sensitive, as indicated by history or skin test reaction (see Appendix 3 for an example of a conventional immunotherapy schedule).

Frequency of build-up injections

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 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 2 times per week. 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 4 to 6 months, depending on the starting dilution and the occurrence of reactions. It is acceptable for patients to receive injections more frequently, provided there is adequate spacing between injections. The interval between injections is empiric but might be as short as 1 day without any increase in the occurrence of systemic reactions[262] if there is some urgency to achieve a maintenance dose (eg, allergy season is approaching) or for practical reasons (eg, patient's schedule). Alternatively, treatment schedules can be used that more rapidly achieve maintenance dosing. These cluster and rush dosing schedules are discussed in Summary Statements 47 through 49.

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 a number of 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).

Dose adjustments for systemic reactions

Summary Statement 44: 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 benefit/risk ratio justifies continuation of immunotherapy.

Reductions during periods of exacerbation of symptoms

Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Immunotherapy administered during periods of exacerbation of symptoms is considered a risk factor for immunotherapy.[17,184] Injections administered during periods when a patient is exposed to increased levels of allergen to which they are 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.[184] 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 sensitive, especially if their symptoms are poorly controlled.

Dose adjustments for late injections

Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

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 depends 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 Appendix 4 for an example of a dose-modification regimen for gaps in treatment).

Cluster schedules

Summary Statement 47: 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 (see Appendix 5).[22,26] 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. The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules.[145,263-266] The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.[267]

Rush schedules

Summary Statement 48: 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.[268] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.[191,269-272]

The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections over the course of 4 hours.[273] Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours.[274-276] 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 cluster[145,266] and rush[134,277] schedules.

Systemic reactions and rush schedules

Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

The advantages of rush immunotherapy come at a cost because there is an increased risk of local and systemic reactions. Systemic reaction rates have been reported to be

as high as 73% of patients, with the risk of such reactions reduced to 27% by premedication in one study.[272] Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing.[273]

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

Rush protocols for administration of Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions.[274-276,278,279]

Premedication and weekly immunotherapy

Summary Statement 50: Premedication can reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

There is concern that antihistamines taken before each injection with conventional immunotherapy might mask a minor reaction that would otherwise alert a physician to an impending systemic reaction. 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.[280] One study that compared terfenadine premedication with placebo premedication during rush VIT demonstrated greater clinical efficacy in the terfenadine-premedicated group in terms of subsequent responses to field stings or sting challenge.[281] There was also a significant difference in the systemic reaction rate between the 2 groups: 6 patients in the placebo-premedicated group had systemic reactions, whereas none of the patients in the terfenadine-premedicated group had systemic reactions ($P = .012$).

Unfortunately, patients might still have life-threatening anaphylaxis despite 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.

Premedication with cluster and rush immunotherapy

Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

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.[267] Premedication with a 3-day course of prednisone, an H_1 histamine receptor antagonist, and an H_2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.[272] In one study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on the safety and efficacy of rush immunotherapy, there was a 5-fold decrease in the risk of anaphylaxis in the group premedicated with omalizumab compared with the placebo premedication group.[282]

There are anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist, but there have been no published studies. Because the risk of a systemic reaction from rush VIT is relatively low, routine premedication before rush VIT is usually unnecessary.[274,276,278,279] In a study evaluating premedication with antihistamines and steroids for rush immunotherapy with imported fire ant venom, there was no statistically significant differences in the systemic reaction rates between the premedication and placebo premedication group (3.6% of the premedication group vs 6.7% of the placebo group, $P = .87$).[157]

Maintenance schedules

Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals 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 individuals might tolerate longer intervals between maintenance dose injections.

The interval between venom injections can be safely increased up to 8 weeks in some patients without loss of efficacy. 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.

Continuing care

Time course of improvement. Summary Statement 53: Clinical 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.[24,134,143,277] Improvement might not be observed for a number of reasons, including (1) failure to remove significant allergenic exposures (eg, a cat), (2) exposure to high levels of

allergen (eg, pollen or molds), (3) continued exposure to nonallergen triggers (eg, tobacco smoke), or (4) incomplete identification and treatment of clinically relevant allergens. 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 54: 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 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 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

The patient's response to immunotherapy should be evaluated on a regular basis. 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. 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.

There have been very 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 individuals.[283-285] However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported.[283,285] Nevertheless, systemic reactions to stings after discontinuing VIT were generally much milder than the pretreatment reactions and were rarely severe. Two studies did not find a difference in relapse rates between the patients treated for 3 years compared with those treated for 5 years,[283,286] but one of the studies noted that the small number of patients in the 3-year treatment group prevented them from making any conclusions about the risk of discontinuing treatment after 3 years.[283] However, one study found that patients who had experienced re-sting reactions after discontinuing VIT had received VIT for a significantly shorter duration (mean, 43.35 months) than those with continued protection (mean, 54.65 months; $P < .01$).[285] Another study reported that 5 years of VIT provided better immunologic and clinical outcomes than 2 to 4 years of treatment.[287]

Change in skin test reactivity did not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who experienced a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE.[286,288] Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment.[288] The relapse rate and the frequency of severe reactions were greater in patients who had a history of very severe reactions to stings before treatment, in patients who had systemic reactions during VIT (to a sting or a venom injection), in patients with honeybee allergy, and in those who had less than 5 years of treatment.

The duration of inhalant allergen immunotherapy efficacy has not been as extensively studied. Some studies have suggested 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 *(D pteronyssinus)* extract for 12 to 96 months.[14] 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.[13] There was a switch to placebo in half of 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. These studies demonstrate the uncertainty of the long-term benefit of inhalant immunotherapy after discontinuation.

Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained clinical remission after discontinuing inhalant immunotherapy, and 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 indication for continuation of immunotherapy can be found at http://www.aaaai.org or http://www.jcaai.org.

Documentation and record keeping. Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully 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 allergy immunotherapy and prescription forms can be found in the Appendix (Appendices 6-15), and these include examples of immunotherapy prescription and administration forms. These forms, along with examples of immunotherapy consent and instruction forms, can also be found at http://www.aaaai.org.

Injection techniques. Summary Statement 57: Allergen immunotherapy extract injections should be given using a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **C**

Immunotherapy should be given with a 26- to 27-gauge syringe with a half-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.[289-291]

If using shared specific patient vials (stock vials, such as mixed vespid or dust mite mix), a single dose should be drawn from each vial. Antigens from different vials should not be combined in a single syringe. Furthermore, extra care is needed to prevent using the wrong stock antigen.

Summary Statement 58: The injection should be given subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Each immunotherapy injection should be given in the posterior portion of the middle third of the upper 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.

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.

The syringe should be aspirated to check for blood return in the syringe before injecting. If blood is present, 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 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 syringe should be appropriately discarded. A fresh syringe and needle are necessary to determine whether a blood vessel has been entered.

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 could result in a local reaction.

LOCATION OF ALLERGEN IMMUNOTHERAPY ADMINISTRATION

Physician's office

Summary Statement 59: 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 to treat anaphylaxis should be in the immediate vicinity when immunotherapy injections are administered.

Summary Statement 60: 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.[292] 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.[184] 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 might be frequently necessary in the patient's immunotherapy schedule, as well as the patients total treatment program.

Other locations

Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **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.[292] The health care professional and staff 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, or allergy/asthma exacerbations at the time of allergen immunotherapy extract injection or poorly controlled asthma).

Appropriate adjustment of dose should be made as clinically indicated. The physician who prepared the patient's allergen immunotherapy extract should provide adequately labeled allergen immunotherapy extract vials, detailed directions regarding dosage schedule for build-up and maintenance, and instructions on adjustments that might be necessary under the following circumstances:

1. when providing patients with new vials;
2. during seasonal exposure to allergens that are in the patient's allergen vaccine, to which the patient is very sensitive, or both;
3. if the patient has missed injections; and
4. when reactions occur to the allergen immunotherapy extract.

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

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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 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 very 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 fully trained to administer the injection and to treat anaphylaxis if this should 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 supports (personnel, medications, supplies, and equipment) are more optimal for encouraging prompt recognition and treatment of anaphylaxis (Table V). 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.

Summary Statement 63: If a patient on 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for their immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extracts might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Patients often 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 brought from the previous physician (ie, an unchanged immunotherapy program) or one to be prepared by the current physician (ie, a new immunotherapy program).

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 full, clear, and detailed documentation of the patient's previous schedule and the contents of the allergen immunotherapy extract (see Appendices 7, 8, 11, 12, and 14 for examples of allergen immunotherapy prescription and administration forms and documentation guidelines for allergen immunotherapy forms). In addition, the patient's previous response to and compliance with this program 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 a schedule and the allergen immunotherapy extract, (2) the patient has shown significant improvement on this immunotherapy program, and (3) the contents of the allergen immunotherapy extract are appropriate for the area in which the patient is now living.

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, vaccine type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient's dose is not modified. This increased risk is due to the significant variability in content and potency of extracts and the variability in methods used by physicians to prepare the patient's maintenance concentrate and its dilutions. For example, the strength of a given concentration of nonstandardized extracts might vary significantly from vial to vial. The risk of systemic reactions in such a situation might be greater with nonstandardized extracts and allergen immunotherapy extracts that contain mixtures of allergens.

Therefore if the allergen immunotherapy extract is to be changed, the patient might need to be retested for specific IgE to the appropriate allergens 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 provided the interval of time since the last injection has not been too long. For lot changes from the same manufacturer, the physician can consider decreasing the dose by 50% to 90%. For changes in manufacturer and nonstandardized extracts, a greater decrease in dose might be necessary.

SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

Allergen immunotherapy in children

Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children

with allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Immunotherapy for children has been shown to be effective and often well tolerated,[137,242] although at least one study did not show efficacy.[293] 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.[294] In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (see the Patient selection section and Table VII). In recent studies children receiving allergen immunotherapy have demonstrated:

1. improvement in symptom control for asthma[117,119,121,122] and allergic rhinitis[118];
2. increased PC_{20} to histamine[121];
3. increased PC_{20} to cat and house dust mite allergens[121,149];
4. decreased risk of development of asthma[6,9,163-165];
5. decreased development of new sensitivities[120,166]; and
6. modification in release of mediators in children receiving immunotherapy that correlates with decreased clinical symptoms.[123]

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Although there is some disagreement about the role of allergen immunotherapy in children under the age of 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.[117,122] In children with allergic rhinitis, allergen immunotherapy might prevent the development of asthma.[6,9,163-165] However, allergen immunotherapy for inhalant allergens is usually not considered necessary in infants and toddlers because (1) there is 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 in pregnancy

Summary Statement 71: Allergen immunotherapy might be continued but is usually not initiated in the pregnant patient. **C**

The physician must be aware of the benefits and risks of immunotherapy in pregnant patients. The recommended precautions for prevention of adverse reactions are especially important in the pregnant patient. Allergen immunotherapy is effective in the pregnant patient. Thus allergen immunotherapy maintenance doses can be continued during pregnancy. Allergen immunotherapy is usually not initiated during pregnancy because of risks associated with systemic reactions and their treatment (ie, spontaneous abortion, premature labor, or fetal hypoxia). 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, and the patient is maintained on the dose that she is receiving at that time.

Immunotherapy in the elderly patient

Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy might be considered in the treatment of the elderly patient, but the benefit/risk assessment must be evaluated carefully in this population. Older 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. However, elderly patients may also benefit from allergen immunotherapy and age alone should not preclude the consideration of allergen immunotherapy.[295]

Immunotherapy in patients with immunodeficiency and autoimmune disorders

Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with immunodeficiency or autoimmune disorders. Therefore the decision to begin immunotherapy in patients with major humoral or cellular immune defects must be individualized. Concern about the increased risk of immunotherapy in such patients is largely hypothetical.

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

ALTERNATIVE ROUTES OF IMMUNOTHERAPY

Sublingual and oral immunotherapy

Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be

effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no FDA-approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **B**

Alternative routes of administration of allergen immunotherapy are ''a viable alternative to parenteral injection therapy'' in some cases.[106,296] Studies of oral immunotherapy have provided conflicting results for ragweed,[297] birch,[298] and cat[299] immunotherapy. The present dosage of oral immunotherapy extract is 20 to 200 times the parenteral injected dosage, which requires a cost assessment for this type of therapy. Furthermore, adverse effects have included gastrointestinal and oral reactions (50% in 1 study) that might preclude home therapy. Oral immunotherapy should be considered investigational at this time.

Optimal-dose (high-dose) sublingual swallow immunotherapy is effective in adults and children.[300-304] In a study of 855 patients with grass pollen allergy and allergic rhinitis randomized to placebo or one of 3 grass tablet doses, there was a significant reduction in symptom and medication scores in the highest-dose subgroup, who were treated for at least 8 weeks before the grass pollen season, compared with the placebo group (symptoms, 21%, $P = .0020$; medication use, 29%, $P = .0120$).[303]

Sublingual allergen studies have evaluated house dust, olive pollen, grass pollen, ragweed, birch, cat, latex, *Alternaria* species, and *Parietaria judaica*.[305-313] Sublingual immunotherapy has been shown to be effective in patients sensitized to 2 non–cross-reacting allergens, grass and birch.[314] It has been noted that the allergen is not degraded by saliva and that there is no direct sublingual absorption of allergen. Radiolabeled allergen has been detected after 48 hours in the sublingual region.[315,316] Alternative protocols, such as rush and ultra-rush (20 minutes) sublingual swallow[307,316,318] and no induction (build-up) phase,[301,303,317,319,320] have been studied. Several studies have suggested a relationship between dose and efficacy with sublingual immunotherapy,[303,310,321] but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. The majority of sublingual studies have demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both, but approximately 35% of the randomized, double-blind, placebo-controlled studies did not demonstrate efficacy in either parameter during the first year of treatment.[322] Further studies are needed to confirm the optimal dose for sublingual immunotherapy.

One of the potential advantages of sublingual immunotherapy is that it appears to be safe, even at very high doses (up to 500 times the usual monthly subcutaneous dose), and to be associated with a lower incidence of serious side effects.[310,320,323] This appears to apply to young children (<5 years), for whom there are prospective safety data[324,325] and a postmarketing survey.[326]



FIG 3. Sample of labels for allergen immunotherapy extract vials.

There have been no SLIT-related fatalities, but there have been 3 case reports of anaphylaxis caused by sublingual immunotherapy. One patient with latex hypersensitivity had anaphylactic shock 20 minutes after reaching the maximal dose on the fourth day of latex rush sublingual rush immunotherapy.[327]

The other 2 reported cases of SLIT anaphylaxis involved patients treated with multiple inhalant allergens. In one case a patient with allergic rhinitis and asthma who was prescribed a sublingual immunotherapy extract composed of multiple non–cross-reacting allergens (*Alternaria* species, dog, cat, ragweed mix, weed mix, and grass mix)[328] had generalized pruritis, followed by angioedema, shortness of breath, and dizziness, within a few minutes of administering 6 drops of the 1:100 vol/vol dilution on the third day of treatment. This episode was preceded by a milder systemic reaction the previous day (generalized pruritis). In the other case, a 13-year-old girl with allergic rhinitis and asthma had swelling of her lower lip 3 minutes after pollen drops, high fever, chest pain, nausea, and abdominal pain.[329] She was treated in the emergency department for anaphylaxis and hospitalized for observation. The reaction occurred 1 month after she had reached the maintenance dose during the peak of the spring season.

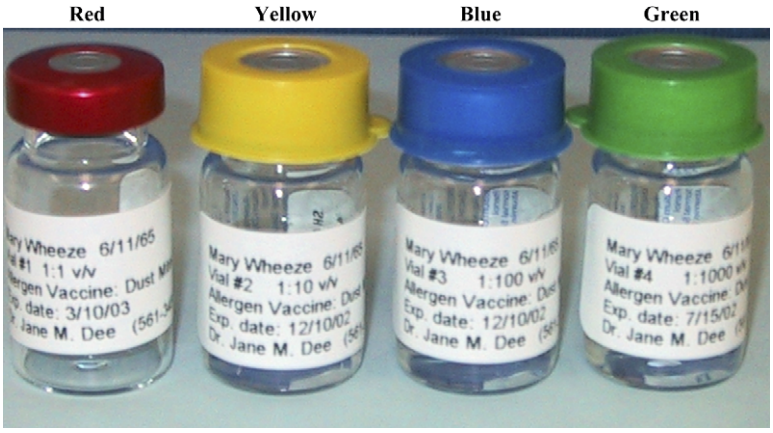


FIG 4. Sample set of color-coded vials of allergen vaccine.

There is currently no FDA-approved formulation for sublingual immunotherapy in the United States at this time, and this modality should be considered investigational. Current investigation of sublingual immunotherapy should not be confused with low-dose sublingual immunotherapy based on provocation neutralization testing or Rinkel-type skin testing.

Intranasal immunotherapy

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Based on controlled, well-designed studies, intranasal immunotherapy has been shown to improve the nasal symptoms of rhinitis.[330] Intranasal dry powder extract immunotherapy has been studied in grass,[330] birch,[331] *P judaica*,[332-334] and house dust mite[335] allergy. Clinical efficacy was noted in all of these studies. Nasal reactivity to allergen challenge was reduced, and only minor side effects were noted in 2 of the above studies. A 3-year study with *P judaica* reported to provide persistent benefits for up to 12 months after conclusion of allergen immunotherapy.[333] Local administration of nasal allergen in an aqueous solution for immunotherapy might be limited by the local side effects. Further studies in both pediatric and adult groups are needed. In human studies the antigen has been noted to appear in the serum within 15 to 30 minutes of administration, with a peak level occurring within 2 to 3 hours.[315] Some allergens have been reported to be retained in the nasal mucosa for up to 48 hours after administration. Intranasal immunotherapy is not currently available in the United States but has gained some acceptance in other parts of the world.

Immunotherapy techniques that are not recommended

Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

Low-dose regimens, including coseasonal low-dose immunotherapy for aeroallergens and the Rinkel low-dose titration techniques, are not effective.[27,28] Immunotherapy based on provocation–neutralization testing with food and aeroallergens and enzyme-potentiated desensitization is not effective.[336]

FUTURE TRENDS IN IMMUNOTHERAPY

Therapy with aeroallergen extracts will become more uniform (as is the current practice for insect venoms) as greater numbers of biologically standardized allergen extracts become available. The actual number of commercially available allergen extracts will be reduced based on consensus agreements about the regional prevalence of aeroallergens, their cross-allergenicity, and the relevance of their effect on human health in specific locales. Novel routes for more effective, convenient, and safer allergen immunotherapy are being investigated throughout the world.

For example, the sublingual route of administering allergen immunotherapy has been studied extensively in Europe. A meta-analysis confirmed its clinical effectiveness in allergic rhinitis,[302] and it has been reported to be effective in asthma as well.[337] Sublingual immunotherapy appears to have a very low risk of serious life-threatening systemic side effects, which might allow for home administration.[324,338] In some studies the clinical benefits of sublingual immunotherapy were not significant until the second year of treatment,[306,339] and comparisons suggest that the magnitude of the clinical benefit of sublingual immunotherapy might not be as great as that of subcutaneous immunotherapy.[311]

Trials with non–IgE-binding peptides containing T-cell stimulating peptides have been reported.[340] Site-directed mutagenesis has produced allergens with decreased IgE-binding capacity without decreased T-cell responses.[341,342]

Immunostimulatory sequences mimicking bacterial and viral DNA have been prepared that stimulate the innate immune system to direct T-cell responses toward

T_H1 rather than T_H2 phenotypes.[343] The results of clinical trials with a conjugate of the immunostimulatory sequence to the major allergen of ragweed, Amb a 1 (AIC), have been reported.[34,343] In a double-blind, placebo-controlled study of 25 adults who received 6 weekly injections of the AIC or placebo vaccine before ragweed season, the AIC group had better peak-season rhinitis scores on the visual analog scale ($P = .006$), peak-season daily nasal symptom diary scores ($P = .02$), and midseason overall quality-of-life scores ($P = .05$) than the placebo group during the first ragweed season, and this effect was observed in the subsequent ragweed season.[344]

Humanized anti-IgE mAb has been shown to have clinical effects in both allergic rhinitis and asthma.[345-348] Theoretically, this new therapeutic modality could be used as protective cover for clinical applications of rapid forms of immunotherapy. It is possible that preadministration of anti-IgE could provide a more effective protective effect than premedication with antihistamines and therefore permit a rush allergen immunotherapeutic regimen with reduced risk of serious systemic reactions.[282]

AUTHOR'S 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 2 systemic reaction grading systems (the European Academy of Allergy and Clinical Immunology's grading of severity for systemic side effects and the Portnoy method for numeric grading of reactions to allergen immunotherapy) can be found in the Appendix section. These forms can also be found along with examples of immunotherapy instruction and consent forms, preinjection health questionnaires, and indications for beginning and continuing immunotherapy forms at www.aaaai.org.

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APPENDIX 1. American College of Medical Quality's policy on the development and use of practice parameters for medical quality decision-making[1]

Practice parameters are strategies for patient management developed to assist health care professionals in clinical decision making. Practice parameters include standards, guidelines, and other patient management strategies. Standards are accepted principles for patient management. Guidelines are recommendations for patient management that identify a particular management strategy or a range of management strategies. Other strategies for patient management include practice policies and practice options. Practice parameters are to be used as screening tools to identify possible deviations from the applicable standards of care. Such parameters are not to be used as absolute standards or to profile or report on health care personnel. Parameters are designed to trigger a process in which possible deviations from the standard of care are identified as outlier practice patterns. Once a deviation from the parameter is identified, such a deviation should be referred to the appropriate qualified physician advisor or reviewer for a determination of medical necessity that conforms to the applicable standard of care. Parameters used in the day-to-day practice of clinical medicine should be clinically relevant. They should not be considered as substitutes for the standard of care but might contribute to its formulation.

Practice parameters must be developed, designed, and implemented only by board-certified, clinically practicing, specialty-matched physician advisors/reviewers with unrestricted medical licenses. Qualified nonphysicians might participate in the development of these parameters only in the areas in which their clinical expertise based on the standard of care is applicable. The health care personnel who develop these parameters should sign their names and date the final version as evidence of their participation and support. Practice parameters must be based on sound scientific research findings, professional literature, clinical experience and appropriate well-recognized methodologies and reflect professionally recognized national standards of care practiced in the clinical community of medicine. The development procedures followed, the participants involved, the evidence used, the assumptions and rationales accepted, and the analytic methods used should be meticulously documented, described, and made publicly available for national peer review. Parameters should be updated as needed.

Practice parameters are used as tools to enhance medical decision making but not as replacements for physicians' clinical judgment. They can be considered as means to enhance the performance of clinical and review personnel but not to replace them. It is below the standard of care of the medical review process to substitute qualified physician reviewer experts with unqualified reviewers who are using parameters.

APPENDIX 2. Examples of possible abbreviations for allergen immunotherapy extract 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

APPENDIX 3. 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

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

APPENDIX 4. Example of immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals (modification of the AAAAI skin testing and immunotherapy consent and instruction forms: immunotherapy administration instruction form, which can be found at http://www.aaaai.org)

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

- Up to 7 days, continue as scheduled (ie, if on weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection).
- Eight to 13 days after missed scheduled injection; repeat previous dose.
- Fourteen to 21 days after missed scheduled injection; reduce dose 25%.
- Twenty-one to 28 days after missed scheduled injection; reduce previous dose 50%.

Then increase dose each injection visit as directed on the immunotherapy schedule until therapeutic maintenance dose is reached.

This suggested approach to modification of doses of allergen immunotherapy because of gaps between treatment during the build-up phase is not based on retrospective or prospective published evidence, but it is presented as a sample for your consideration. The individual physician should use this or a similar protocol as a standard operating procedure for the specific clinical setting. A similar dose-reduction protocol should be developed for gaps in maintenance immunotherapy.

APPENDIX 5. Example of a cluster immunotherapy schedule[22,26]

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

APPENDIX 6. Recommended documentation for allergen immunotherapy prescription forms

The purpose of the allergen immunotherapy prescription form is to define the contents of the allergen immunotherapy extract in enough detail that it could be precisely duplicated. The following information should be on an immunotherapy prescription form:

Patient information:

- Patient name, patient number (if applicable), birth date, telephone number, and picture (if available) should be included.

Preparation information:

- Name of person and signature preparing the allergen immunotherapy extract should be included.
- Date of preparation should be recorded.
- Bottle name should be included (eg, trees and grass). If abbreviations are used, a 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 should be included.
- Volume of manufacturer's extract to add to achieve the projected effective concentration should be included. 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) should be included.
- Extract manufacturer should be included.
- Lot number should be included.
- Expiration date should be recorded and should not exceed the expiration date of any of the individual components.

APPENDIX 7. Allergen immunotherapy extract prescription 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:

_____
_____
_____
_____

_____ ____/____/____
Prescribing Physician Signature Date

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

APPENDIX 8. Maintenance concentrate prescription form

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: 6/10/06

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial **4** from Vial **1** on **8/30/06** Expiration date: **10/15/06**
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	Short ragweed	1:20 w/v G (150 Amb a1)	0.5ml	Greer	12345	1/01/08
2	Amaranthus Retroflexus	1:10 w/v G	0.5ml	H-S	6789	2/07/08
3	Ash	1:10 w/v G	0.5ml	Center	3333	3/17/08
4	Cat	10,000 BAU/ml G	2.00ml	ALO	9898	2/27/08
5	Timothy Grass	100,000 BAU/ml G	0.4ml	ALK	56789	7/09/08
6	Johnson Grass	1:10 w/v G	0.5ml	Greer	2434	7/20/08
7						
8						
9						
10						
Diluent	HSA		0.6ml	ALK	68597	12/08
Total Volume			5.00 ml			6/10/07

*** Components of mixes listed on a separate sheet**
**** Assumes 0.5 ml injection as target maintenance dose**

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

Specific Instructions:

_____

_____

Prescribing Physician Signature

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

APPENDIX 9. Labels for allergen immunotherapy extracts

Each vial of allergen immunotherapy extract should be labeled in a way that permits easy identification. Each label should include the following information (example in Figs 3 and 4):

- Appropriate patient identifiers might include the patient's name, patient's number, patient's picture, and birth date.
- The contents of the allergen immunotherapy extract in a general way should be included. The detail with which this can be identified depends on the size of the label and the number of allergens in the vial. Ideally, allergens should be identified as trees, grasses, weeds, mold, dust mite, cockroach, cat, and dog. Because of space limitations, it might be necessary to abbreviate the antigens (eg, T, G, W, M, DM, Cr, C, and D respectively [see Appendix 2]). A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate (vol/vol) should be recorded. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- The expiration date should be included.

APPENDIX 10. Allergen immunotherapy administration form recommended documentation

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

Patient information:

- Patient's name, date of birth, telephone number, and patient's picture (optional but helpful).

Allergen immunotherapy extract information:

- Allergen immunotherapy extract name and dilution from maintenance in vol/vol bottle letter (eg, A and B), bottle color, or number, if used.
- Expiration date of all dilutions.

Administration information in separate columns:

- Date of injection.
- Arm administered injection, which might facilitate determination of exact cause of local reaction.
- Projected build-up schedule.
- Delivered volume reported in milliliters.
- Description of any reactions. The details of any treatment given in response to a reaction would be documented elsewhere in the medical record and referenced on the administration form.
- *Patient's health before injection*. This can be performed through a verbal or written interview of the patient before administering the immunotherapy injection. The patient should be questioned about increased asthma or allergy symptoms, β-blocker use, change in health status (including pregnancy and recent infections), or an adverse reaction to a previous injection (including delayed large local reactions persisting through the next day). Patients with significant systemic illness generally should not receive an injection.
- *Antihistamine use*. Antihistamines are frequently a component of an allergy medication regimen, and it would be important to note whether a patient is taking an antihistamine on the day he or she receives his or her immunotherapy injection. For consistency in interpretation of reactions, it might be desirable for a patient to either take or avoid antihistamines on a regular basis on the days he or she receives immunotherapy. The physician should note on the form whether he or she recommends the patient consistently take an antihistamine on immunotherapy treatment days.
- *Peak flow reading*. Consider obtaining a peak expiratory flow rate measurement before administering an immunotherapy injection to asthmatic patients. Poorly controlled asthma is considered a risk factor for immunotherapy. Obtaining a peak expiratory flow rate measurement before the immunotherapy injection might help identify patients with symptomatic asthma. The patient's baseline peak expiratory flow rate should be provided on the form as a reference. Health care professionals administering immunotherapy injections should be provided with specific guidelines about the peak expiratory flow rate measurement for when an immunotherapy injection should be withheld and the patient referred for clinical evaluation.
- **Baseline blood pressure**. It might be useful to record the patient's blood pressure as a baseline for future reference.

APPENDIX 11. Allergen immunotherapy administration form

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 allergy or 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

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

Date to reorder: __/__/__

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 allergy or 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**	

APPENDIX 12. 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: _____
_____
Staff action taken (if any): _____

APPENDIX 13. 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.

APPENDIX 14. Allergen immunotherapy systemic reaction/anaphylaxis 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
__Epinephrine IM into 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	

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:
_____
_____
_____
_____

Clinical impression: True SR Questionable SR No SR

Systemic reaction severity classification: EAACI_____ **Portnoy** _____

Dosage adjustment? _____

Signatures_____ **RN** _____**MD/DO**

APPENDIX 15. Grading severity of allergen immunotherapy reactions: Two methods

1. **The European Academy of Allergy and Clinical Immunology grading of severity for systemic side effects***

Classification of systemic reactions

0 = No symptoms or nonspecific symptoms

I = Mild systemic reactions: symptoms—localized urticaria, rhinitis, or mild asthma (PF <20% decrease from baseline).

II = Moderate systemic reaction: symptoms—slow onset (>15 minutes) of generalized urticaria, moderate asthma, or both (PF < 40% decrease from baseline).

III = Severe (non–life-threatening) systemic reactions: symptoms—rapid onset (<15 minutes) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).

IV = Anaphylactic shock: symptoms—immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, and hypotension, for example.

2. **Portnoy method for numeric grading of reactions to allergen immunotherapy†**

Local

0+ = No significant reaction or small area of erythema less than the size of a half dollar without swelling or wheal formation

1+ = Erythema greater than the size of a half dollar, swelling or wheal formation, or both

Systemic

2+ = Systemic reactions: cutaneous only—might consist of a cutaneous eruption, such as urticaria

3+ = Systemic reaction: generalized pruritus, sneezing, or both—might consist of increased allergy symptoms, such as nasal congestion, sneezing, or pruritus, especially in the mouth or throat

4+ = Systemic reaction: pulmonary—consists of wheezing, shortness of breath, and tightness. Might be associated with decreased pulmonary function tests

5+ = Systemic reaction: anaphylaxis—a sensation of not feeling right is a frequent prelude; might consist of hypotension, laryngeal edema, severe wheezing, and cramping

6+ = Cardiopulmonary arrest

PF, Peak expiratory flow.

*Subcutaneous immunotherapy. Allergy 2006;61(suppl 82):5-13.

†Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80.

Allergen immunotherapy: A practice parameter second update

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

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the "Allergen immunotherapy: a practice parameter second 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 and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
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These parameters are also available on the internet at http://www.jcaai.org.

CONTRIBUTORS

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Allergen immunotherapy: A practice parameter second update

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PREFACE

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

The objective of ''Allergen immunotherapy: A practice parameter second update'' is to optimize the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. 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's ''Policy on development and use of practice parameters for medical quality decision-making'' (Appendix 1).[1]

This document builds on the previous Joint Task Force document, ''Allergen immunotherapy: a practice parameter'' published in the *Annals of Allergy, Asthma and Immunology* in 2003.[2] The updated practice parameters draft was prepared by Drs Linda Cox, James Li, Hal Nelson, and Richard Lockey. The Joint Task Force reworked the initial draft into a working draft of the document. The project was exclusively funded by the 3 allergy and immunology societies noted above.

In preparation for the 2003 ''Allergen immunotherapy: a practice parameter'' and the second update, a comprehensive search of the medical literature was conducted with various search engines, including PubMed; *immunotherapy*, *allergic rhinitis*, *asthma*, *stinging insect allergy*, and related search terms were used. 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 second update'' was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the ACAAI, AAAAI, and JCAAI. In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for review and comments from members of the sponsoring organizations. 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 allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. This document also contains recommendations for the safe practice of allergen immunotherapy, including specific recommendations on the prevention and management of 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 or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. Symptoms of allergic conjunctivitis (eg, itchy watery eyes) are often considered part of allergic rhinitis or are included in the diagnosis of rhinoconjunctivitis. Particularly good candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures, those in whom it is important to avoid the potential adverse effects of medications, and those who wish to reduce the long-term use of medications. Immunotherapy is recommended for patients with a history of systemic reaction to Hymenoptera stings and specific IgE antibodies to Hymenoptera venom.

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.[3]

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. 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 *maintenance concentrate* should be used to identify the allergen immunotherapy extract that contains a therapeutic effective dose for each of its individual constituents (see the Immunotherapy schedules and doses section).

The term *manufacturer's extract* refers to the allergy extract purchased from the manufacturer. The terms *stock*, *full-strength*, and *concentrate* are ambiguous and should not be used. 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).

Allergen immunotherapy is effective when appropriate doses of the allergens are administered. ''Allergen immunotherapy: A practice parameter'' recommends that vials of allergen immunotherapy extracts should be prepared individually for each patient to enhance the individualization of therapy, reduce the risk of allergen cross-contamination, and reduce the risk of error in administration.[4,5] This parameter recommends the use of standardized allergen immunotherapy prescription and administration forms to improve the safety, uniformity, and standardization of allergen immunotherapy practice.[4,5] The suggested forms are found in the Appendix (Appendices 7, 8, 11, 12, and 14) and in the members' section of the www.aaaai.org Web site. The routine use of these standardized forms should improve the quality of immunotherapy practice.

Members' feedback comments on the recommended allergen extract dilution dating in the 2003 ''Allergen immunotherapy: A practice parameter'' led to an allergen immunotherapy extract dilution stability study designed by the AAAAI Immunotherapy and Allergy Diagnostics Committee and funded by the AAAAI Board of Directors. The study was designed to investigate the effect of time, temperature, and dilution of standardized allergen extract potency, and the results of this study were considered in this update.

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 3 years after publication. Requests for information about or an interpretation of these practice parameters should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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. Allergen immunotherapy

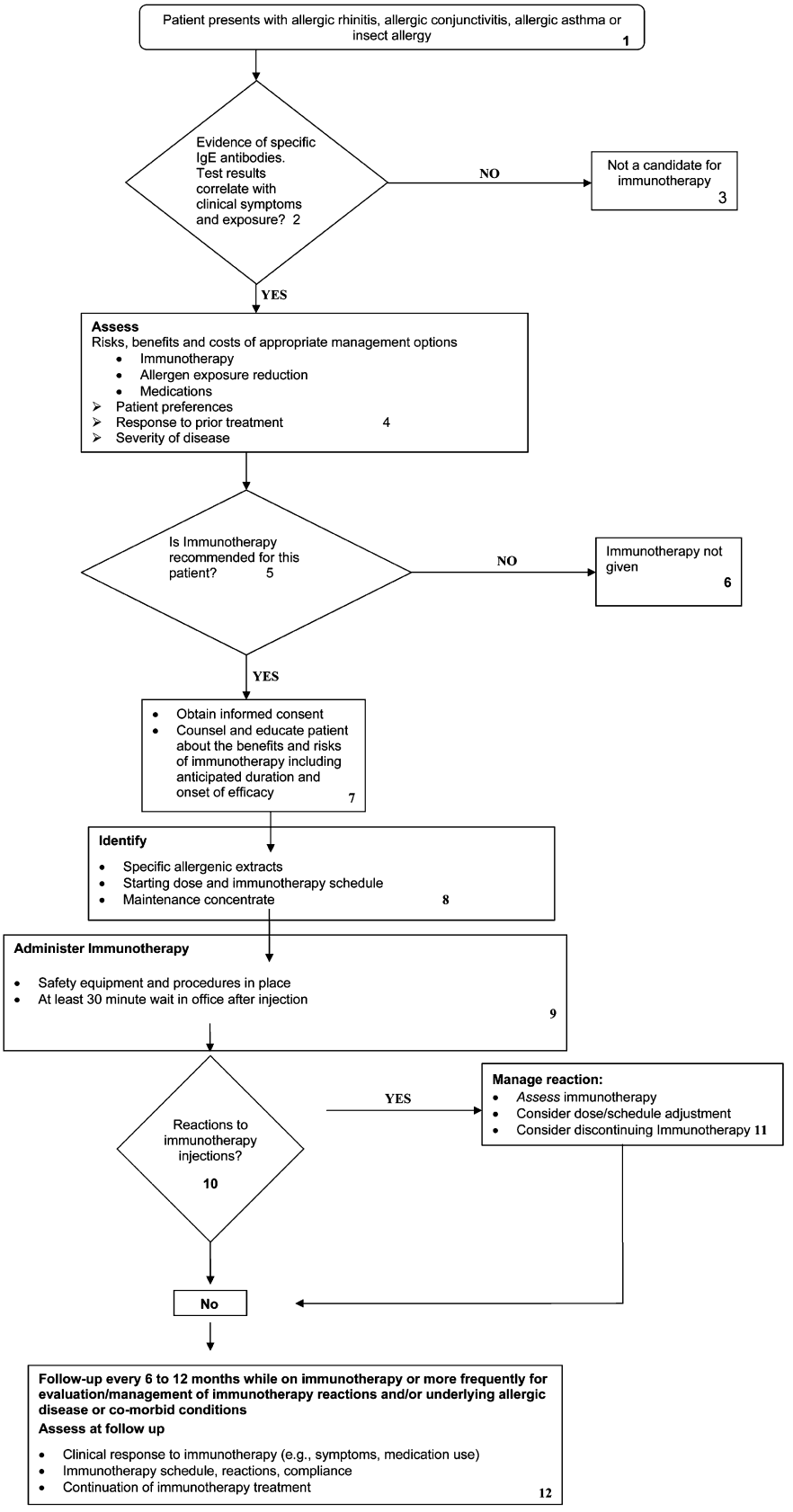


FIG 1. Algorithm for allergen immunotherapy.

might prevent the development of asthma in individuals with allergic rhinitis.[6-9] Evaluation of a patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic conjunctivitis, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for specific IgE antibody).[10]

Box 2

Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although *in vitro* testing for 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

Management of complex medical conditions, such as allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity, should include the careful evaluation of management 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 patient 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. On the basis of clinical considerations and patient 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 good candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy (VIT).

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 on the basis of 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 (see the Immunotherapy schedules and doses section). In general, the starting immunotherapy dose is 1000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 1000 to 4000 arbitrary units (AU; eg, for dust mite) or bioequivalent allergy units (BAU; eg, for grass) 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 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 referred to as *up-dosing*, *induction*, or the *dose-increase phase*) entails administration of gradually increasing doses during a period of approximately 14 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 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, in particular anaphylaxis. Patients should wait at the physician's office for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly, if they occur.

In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring 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. Some physicians recommend providing certain patients with epinephrine for self-administration in case of severe late reactions to immunotherapy injections.

Box 10

Injections of allergen immunotherapy extract can cause local or systemic reactions. Most severe reactions develop within 30 minutes after the immunotherapy injection, but reactions can occur after this time.

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 (anaphylaxis). Epinephrine is the treatment of choice in anaphylaxis, preferably when administered intramuscularly,[11] although subcutaneous administration is acceptable.[12]

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, see the practice parameters for anaphylaxis.[12]

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. After a severe systemic reaction, careful evaluation by the prescribing physician is recommended. For some patients, the immunotherapy maintenance dose might need to be reduced because of repeated systemic reactions to immunotherapy injections. The decision to continue immunotherapy should be re-evaluated after severe or repeated systemic reactions to allergen immunotherapy extracts.

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 doses, 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,[13] but others might experience a recurrence of their symptoms after discontinuation of allergen immunotherapy.[14] 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, and 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 on the basis of the patient's clinical response, disease severity, immunotherapy reaction history, and patient preference.

IMMUNOTHERAPY GLOSSARY

For more information on immunotherapy definitions, see the article by Kao.[15]

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 (pigments and salts; see the Allergen selection and handling section). Other terms used to describe the allergen immunotherapy extract include *allergen product*,[16] *allergy serum*, *allergen vaccine*,[17] 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.[18] Other terms that have been used for allergen immunotherapy include *hyposensitization*, *allergen-specific desensitization*, and the lay terms *allergy shots* or *allergy injections*.[15]

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

TABLE II. Allergen immunotherapy dose-calculation table

- Express weight per volume as a fraction: $\frac{1}{N}$ or 1:*N*.
- Calculate concentration of individual allergens in mixtures. If a mixture is made of equal amounts of N individual allergens to make a total concentration (C), the final concentration of an individual allergen (Ca) can be calculated by using the following equation:

$Ca = C \times \frac{1}{N} = \frac{C}{N}$ or *C*:*N*.

For example, if a mixture of equal amounts of 5 (N) allergens has a total concentration (C) of 100,000 BAU/mL, then the final concentration of each individual allergen (Ca) is: $Ca = \frac{C}{N} = \frac{100{,}000}{5} = 20{,}000\ BAU/mL$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{C}{N} = \frac{1/10}{5} = \frac{0.1}{5} = 0.02$ or $\frac{1}{50}$ or 1:50.

- Dilution of individual allergen: If an initial volume, Vi (in milliliters), of an individual antigen with concentration, Ci, is added to an allergen extract to make a final volume of Vf (in milliliters), the final allergen concentration (Ca) in the allergen extract mixture will be: $Ca = Ci \times \frac{Vi}{Vf}$.
- Final concentration of an allergen in a mixture of mixtures is determined by multiplying the initial concentration by the dilution factors from each mixing step.

For example, consider a mixture containing equal amounts of 5 (N) allergens with a total concentration (C) of 100,000 BAU/mL (first dilution). If an initial volume (Vi) of 0.5 mL of this mixture is further mixed with other components and diluent to make a final allergen extract mixture volume (Vf) of 5.0 mL (second dilution), the final concentration of an individual allergen (Ca) will be:

$$Ca = C \times \underbrace{\frac{1}{N}}_{\text{Mixture dilution}} \times \underbrace{\frac{Vi}{Vf}}_{\text{Allergen extract dilution}} = 100{,}000 \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{100{,}000}{50} = 2000\ BAU/mL$$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{1}{10} \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{1}{500}$ or 1:500.

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).

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 to 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-medicated 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 multiplied by volume of administered dose (see Table II for a dose-calculation table).

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, cat, 1000 BAU, [highest tolerated dose] vs 2000 BAU [projected effective dose]).

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 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 by a variety of immunologic transformations. Early definitions of the term immunotherapy included active and passive immunization for the purpose of improving 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 by means of induction of clonal deletion, anergy, immune tolerance, or immune deviation.

The *maintenance concentrate* is a preparation that contains individual 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 may not be the initially calculated projected effective dose.

The *maintenance goal* (or projected effective dose) is the allergen dose projected to provide therapeutic efficacy. The maintenance goal is based on published studies, but a projected effective dose has not been established for allergens. 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 the 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 large local reaction causing discomfort). The intervals between maintenance immunotherapy injections generally ranges 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 by means of immunoblotting or crossed allergoimmunoelectrophoresis.

For a definition of *projected effective dose*, see 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 test responses), and premedication with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similar high incidence of systemic reactions.

Off the board into one syringe is a phrase that describes a method of allergen immunotherapy preparation and administration that involves specifically mixing the patient's allergen immunotherapy injection in a single syringe, which is not recommended. This syringe might be inserted into more than one allergen extract vial, and this poses a risk of cross-contamination of the allergen extracts and might dull the needle with repeated penetration of the rubber stopper.

Shared specific patient vials is a method of allergen immunotherapy preparation and administration in which the allergy immunotherapy extract is withdrawn from a shared vial (eg, mixed vespids or dust mite mix). This is sometimes referred to as off the board, but it is distinct from the method of off the board into one syringe in that the syringe enters only one allergen extract vial.

INTRODUCTION

Immunity has been defined as protection against certain diseases. The initial immunotherapeutic interventions, which included the use of preventive vaccines and xenogenic 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 the field of allergen immunotherapy. From its humble empiric emergence in 1900, when ragweed injections were proposed as therapy for autumnal hay fever, allergen immunotherapy has progressed in both theory and practice from the passive immunologic approach to the active immunologic procedures pioneered by Noon[19] and Freeman.[20,21] 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 10 years. Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Some studies have suggested that allergen immunotherapy might prevent the development of asthma in individuals with allergic rhinitis.[6-9]

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,[22-26] and it should be differentiated from unproved methods, such as neutralization-provocation therapy and low-dose subcutaneous regimens based on the Rinkel technique, which have been found to ineffective in a double-blind placebo-controlled study.[27,28]

SUMMARY STATEMENTS

Mechanisms of immunotherapy

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, defined as a relative decrease in allergen-specific responsiveness and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

Allergen extracts

Summary Statement 6: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. **A**

Summary Statement 7: Nonstandardized extracts might vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Summary Statement 8: 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**

Cross-reactivity of allergen extract. Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

Efficacy of immunotherapy

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Summary Statement 10: Immunotherapy is effective for 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**

Food allergy, urticaria, and atopic dermatitis. Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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**

Measures of efficacy. Summary Statement 12: 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**

Safety of immunotherapy

Reaction rates. Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

Timing of anaphylactic reactions to immunotherapy injections. Summary Statement 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

β-*Adrenergic blocking agents.* Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

Contraindications. Summary Statement 18: 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**

Reducing the risk of anaphylaxis to immunotherapy injections. Summary Statement 19: 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**

Patient selection

Clinical indications. Summary Statement 20: 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 depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Special precautions in patients with asthma. Summary Statement 21: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. **C**

Clinical indications for VIT. Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Summary Statement 23: Patients selected for immunotherapy should be cooperative and compliant. **D**

Allergen selection and handling

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted in vitro tests for specific IgE antibodies can also be used. **A**

Specific allergens. Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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, supported by the presence of specific IgE antibodies. **A**

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Dose selection. Summary Statement 30: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. **A**

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens, is recommended. **B**

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extract handling

STORAGE

Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

STORING DILUTE EXTRACTS

Summary Statement 34a: More dilute concentrations of allergen immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: 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 a number of 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. **B**

Immunotherapy schedules and doses

Summary Statement 35: A customized individual 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 be based on single or multiple allergens. **D**

Maintenance concentrate. Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

Recommended doses. Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

Effect of dilution on dose. Summary Statement 38: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. **A**

Dilutions of the maintenance concentrate. Summary Statement 39: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. **D**

Labeling dilutions. Summary Statement 40: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. **D**

Individualized treatment vials. Summary Statement 41: 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. The mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. **C**

Starting doses. Summary Statement 42: The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. **D**

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

Dose adjustments for systemic reactions. Summary Statement 44: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. **D**

Reductions during periods of exacerbation of symptoms. Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Dose adjustments for late injections. Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

Cluster schedules. Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. **C**

Rush schedules. Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. **A**

Systemic reactions and rush schedules. Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

Premedication and weekly immunotherapy. Summary Statement 50: Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

Premedication with cluster and rush immunotherapy. Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

Maintenance schedules. Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. **A**

Continuing care

TIME COURSE OF IMPROVEMENT

Summary Statement 53: Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **A**

FOLLOW-UP VISITS

Summary Statement 54: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. **D**

DURATION OF TREATMENT

Summary Statement 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

DOCUMENTATION AND RECORD KEEPING

Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. **D**

INJECTION TECHNIQUES

Summary Statement 57: Allergen immunotherapy extract injections should be administered with a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **D**

Summary Statement 58: The injection should be administered subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Location of allergen immunotherapy administration

Physician's office. Summary Statement 59: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Summary Statement 60: 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**

Other locations. Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **D**

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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**

Summary Statement 63: 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for his or her immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extract might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Special considerations in immunotherapy

Allergen immunotherapy in children. Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Pregnancy. Summary Statement 71: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. **C**

Immunotherapy in the elderly patient. Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy in patients with immunodeficiency and autoimmune disorders. Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

Alternative routes of immunotherapy

Sublingual and oral immunotherapy. Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no US Food and Drug Administration (FDA)–approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **A**

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Immunotherapy techniques that are not recommended. Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

MECHANISMS OF IMMUNOTHERAPY

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, which is defined as a relative decrease in allergen-specific responsiveness, and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

The immunologic changes associated with immunotherapy are complex, and the exact mechanism or mechanisms responsible for its' clinical efficacy are continually being elucidated. Data support the concept that successful immunotherapy is associated with a change to a T_H1 $CD4^+$ cytokine profile.[29-34] Data indicate that increased production of IL-12, a strong inducer of T_H1 responses, contributes to this shift.[33] Clinically successful immunotherapy has been reported to be associated with immunologic tolerance, which is defined as a relative decrease in antigen-specific responsiveness, immune deviation, or anergy. For example, lymphoproliferative responses to allergen are reduced with immunotherapy.[32] Successful immunotherapy results in generation of a population of T regulatory cells, which are $CD4^+CD25^+$ T lymphocytes producing IL-10, TGF-β, or both.[35-39] Regulatory T-cell release has been described in allergen immunotherapy with Hymenoptera venom,[35] grass pollen extract,[37] and house dust mites.[38] IL-10 reduces B-cell antigen-specific IgE and increases IgG4 levels; reduces proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicits tolerance in T cells by means of selective inhibition of the CD28 costimulatory pathway.[36,37]

Allergen immunotherapy has been shown to block both the immediate and late-phase allergic response.[40] Allergen immunotherapy has been shown to decrease the recruitment of mast cells, basophils, and eosinophils in the skin, nose, eye, and bronchial mucosa after provocation or natural exposure to allergens.[41]

In patients receiving immunotherapy, initially there is an increase in specific IgE antibody levels, followed by a gradual decrease to a level that is still higher than that present before treatment. Clinical improvement in many patients develops before decreases in their IgE antibody levels occur or in other patients whose IgE antibody levels never decrease, thereby demonstrating that efficacy is not dependent on reductions in specific IgE levels.[42,43] Immunotherapy does diminish the seasonal increase in specific IgE levels.[44] Despite the persistence of significant levels of specific IgE antibody levels, immunotherapy usually causes a reduction in 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.[45-48]

An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, has also been associated with immunotherapy. The properties of allergen-specific IgA have yet to be determined, and there is a weak correlation between the increase in allergen-specific IgG levels and immunotherapy's clinical efficacy.[30,49,50]

Immunotherapy might alter the affinity and specificity of allergen-specific IgG.[51,52] During the initial phase of ultrarush VIT, a change in IgG specificity (ie, a change in the set of epitopes dominantly recognized by IgG on wasp venom antigens) occurred concomitantly with early clinical tolerance and was seen within 12 hours of ultrarush VIT ($P < .001$).[51] 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 individuals.[52] This change in IgG specificity preceded the increase in IgG titers and was sustained for up to 6 months.[52]

Allergen-specific IgG induced from immunotherapy can block IgE-dependent histamine release and subsequent IgE-mediated antigen presentation to T cells.[53] This effect might be dependent on IgE, allergen concentration, and CD23, the low-affinity receptor for IgE.

Whereas 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.[37,53]

The relationship between these immunologic changes and immunotherapy efficacy is not completely understood.

ALLERGEN EXTRACTS

Summary Statement 6: 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 has 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.[2,18,54-56] 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.

United States–licensed extracts can be obtained in aqueous, glycerinated, lyophilized, and acetone-precipitated and alum-precipitated formulations. Some commonly used allergens are standardized. These include extracts for cat hair, cat pelt, *Dermatophagoides pteronyssinus*, *Dermatophagoides 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.[57] 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.

Most standardized extracts are labeled in BAU. Short ragweed potency units were originally based on the content of the major allergen Amb a 1. Ragweed potency is reported in FDA units and BAU. One FDA unit of Amb a 1 equals 1 μg of Amb a 1, and 350 units of Amb a 1/mL is equivalent to 100,000 BAU/mL. Cat extracts were also originally standardized based on the content of major allergen (Fel d 1), with 100,000 arbitrary units (AU) per milliliter containing between 10 to 19.9 FDA units of Fel d 1 per milliliter (1 FDA unit of Fel d 1 equals 2 to 4 μg of Fel d 1).[55,58,59] Subsequently, $ID_{50}EAL$ testing suggested that 100,000 AU/mL was equal to 10,000 BAU/mL.[60] Approximately 22% of individuals with cat allergy have specific IgE antibodies to cat albumin.[61] Cat pelt extracts have a greater amount of albumin than cat hair extracts.[60]

Dust mites were originally standardized in AU by means of inhibition radioimmunoassay (RIA), and subsequent $ID_{50}EAL$ testing indicated that the AU was bioequivalent to the BAU, and the original AU nomenclature was kept. Dust mite extracts are still labeled in AU.

Summary Statement 7: Nonstandardized extracts can vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Nonstandardized extracts are labeled as wt/vol, which expresses weight in grams per volume in milliliters; that is, a potency of 1:100 indicates that 1 g 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 with a particular wt/vol or PNU potency can have widely varying biologic activities.[62-64] Therefore they should not be considered equipotent.

Summary Statement 8: 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**

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. The major clinically relevant aeroallergens of North America are listed in Table III. Furthermore, nonrelevant allergens in such mixtures could act as sensitizers rather than as tolerogens.[65,66] The physician must therefore select only those aeroallergens for testing and treatment that are clinically relevant in a particular geographic area.

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, dog), insect (cockroach), and Hymenoptera venom source materials.

Cross-reactivity of allergen extract

Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

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. A summary of cross-reactivity patterns of the clinically relevant North American aeroallergens can be found in Fig 2. 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,[67] inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[68-75] Grasses in other subfamilies (eg, Bermuda, Bahia, and Johnson) show greater diversity and should be evaluated separately.[76-78] Bermuda and Johnson grasses are increasingly important in the South,

TABLE III. The major clinically relevant aeroallergens of North America*

- Tree pollen
  - Chinese elm *(Ulmus parvifolia)*†‡; Siberian elm *(Ulmus pumila)*†‡; American elm *(Ulmus Americana)*†‡
  - Red oak *(Quercus rubra)*†; White oak *(Quercus alba)*†
  - Paper birch *(Betula papyrifera)*
  - Alder *(Alnus rubra)*
  - Box elder *(Acer negundo)*†; Red maple *(Acer rubra)*†
  - Eastern cottonwood *(Populus deltoides)*
  - Sycamore *(Platanus occidentalis)*
  - White ash *(Fraxinus americana)*†; Olive *(Olea europaea)*†‡
  - Black walnut *(Juglans nigra)*
  - Mulberry *(Morus rubra)*
  - Mountain cedar *(Juniperus ashei)*
  - Pecan *(Carya illinoensis)*
- Grass pollen
  - Rye *(Lolium perenne)*§‖
  - Timothy *(Phleum pratense)*§‖
  - Meadow fescue *(Festuca elatior)*§‖
  - Bermuda *(Cynodon dactylon)*‖
  - Johnson *(Holcus halepensis)*
  - Bahia *(Paspalum notatum)*
- Weed pollen
  - Short ragweed *(Ambrosia artemisiifolia)*‖
  - English (narrow leaf) plantain *(Plantago lanceolata)*
  - Mugwort *(Artemisia vulgaris)*
  - Russian thistle *(Salsola kali)*
  - Burning bush *(Kochia scoparia)*
  - Sheet (red) sorrel *(Rumex asetosella)*
  - Red root pigweed *(Amaranthus retroflexus)*
- Indoor aeroallergens
  - Cat epithelium *(Felis domesticus)*‖
  - Dog epithelium *(Canis familiaris)*
  - Arthropods (domestic mites: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*)‖
  - Insects (German cockroach: *Blattella germanica*)
- Fungi
  - *Alternaria alternata*¶
  - *Cladosporium* (*C cladosporioides*, *C herbarum*)¶
  - *Penicillium* (*P chrysogenum*, *P expansum*)¶
  - *Aspergillus fumigatus*¶
  - *Epicoccum nigrum*, *Drechslera* or *Bipolaris* type (eg, *Helminthosporium solani*)¶

*Compiled and selected in collaboration with the AAAAI Immunotherapy Committee Allergen Subcommittee for the identification of 35 key allergens of North America.
†Extensive cross-reaction of species within the genus.
‡Apart from regional prevalence, they are limited to local sites with substantial stands of these trees.
§Extensively cross-react with one another and bluegrass, orchard, red top, and sweet vernal.
‖Allergens for which standardized extracts are commercially available.
¶Species that are widely distributed and clinically important.

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.[79-82] 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.[83-85] Significant cross-reactivity between Betulaceae pollens and oak of the Fagaceae family has been demonstrated with percutaneous skin testing.[75] RAST inhibition studies have shown cross-inhibition between oaks and other *Fagales* species.[86] IgE immunoblot inhibition experiments have demonstrated that the *Fagales* species might be strongly inhibited by birch species.[87] The use of one of the locally prevalent members (eg, birch and alder) should be adequate.[88]

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.[89,90] Maple and box elder trees are found throughout the United States, except for the arid southwest. Although in the same genus as maple, *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,[91,92] and there are allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.[93]

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.[94] Similarly, Chenopod-Amaranth families have wide ranges in the western regions but are present throughout North America.[95] Current information on cross-reactivity of these families is limited.[96-98] 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.[99] The use of a single Amaranth extract should be sufficient to cover this family.[100,101] Similarly, *Atriplex* species (eg, saltbushes and scales) show near identity, and use of a single member is adequate. 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,

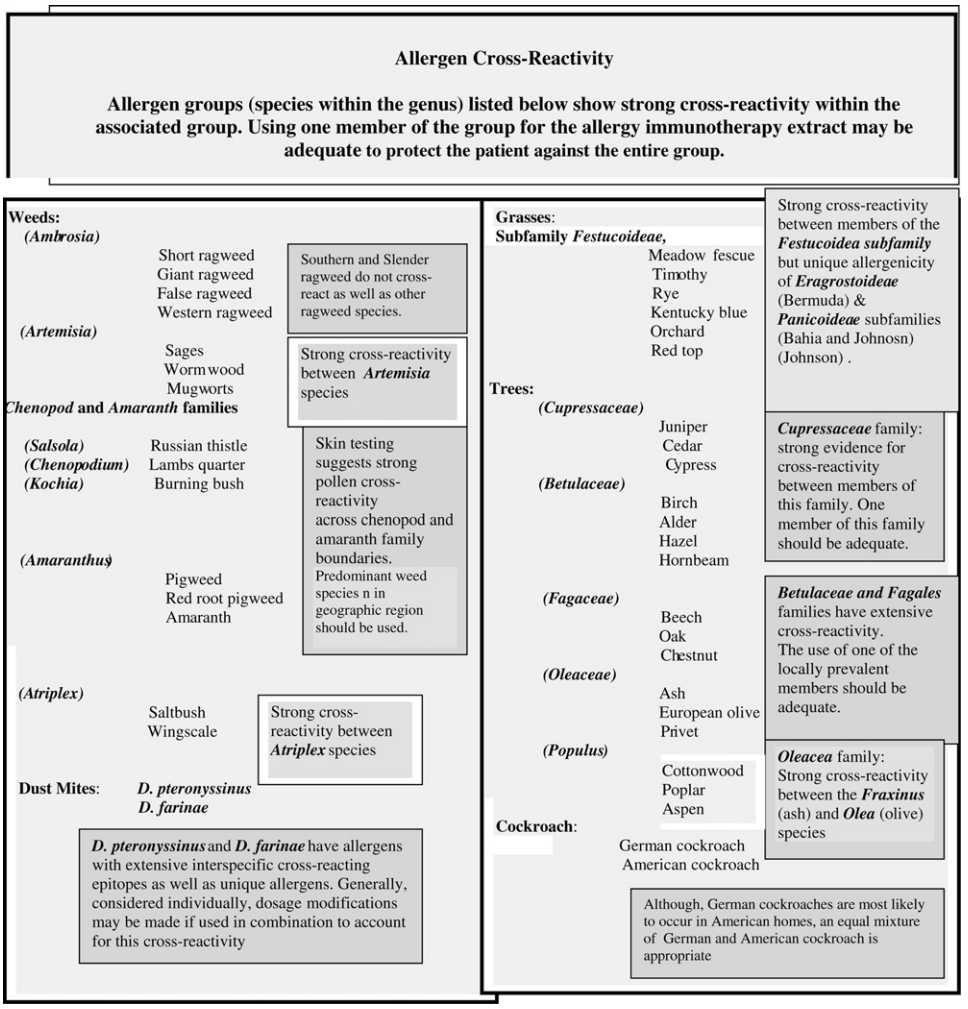


FIG 2. Patterns of allergen cross-reactivity.

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*).

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.[102,103] Stinging Hymenoptera insects occur throughout the United States; the fire ant is found only in Gulf Coast states, Texas, and some other southern and western states. Commercial venom extracts are available for some Hymenoptera species, except the fire ant, for which only whole-body extract is available.

EFFICACY OF IMMUNOTHERAPY

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity

Summary Statement 10: Immunotherapy is effective for 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.[104-111] Immunotherapy is effective for the treatment of allergic rhinitis[107] (including ocular symptoms[112,113]), allergic asthma,[104,109,111,114,115] and stinging insect hypersensitivity[108,116] and is effective in both adults and children.[117-124] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollens,[13,125-132] fungi,[133-138] animal allergens,[22,25,26,139-143] dust mite,[114,115,144-153] and cockroach.[154] There have been no controlled trials of fire ant whole-body extract, but it does appear to be effective in

TABLE IV. Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy

Outcome measure	House dust mite	Other allergens*†
Symptomatic improvement	2.7 (1.7-4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2-7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50)	5.5 (2.8-10.7)

Data are used with permission from Abramson et al.[104]
ND, Not done.
*Odds ratio (95% CI).
†Pollen, mold, or animal dander.

uncontrolled trials.[155-157] 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. A number of studies have also demonstrated a significant improvement in quality of life, as measured by using standardized questionnaires.[24,158-161] The magnitude of the effect depends on the outcome that is used (Table IV). For dust mite, the effect size ranges from a 2.7-fold improvement in symptoms to a 13.7-fold reduction in bronchial hyperresponsiveness. 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.[110] 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[107] and asthma[104,109,111] have been performed to deal with the issue of power. One review of 75 trials involving 3188 asthmatic patients found that, overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyperreactivity after immunotherapy, and it would have been necessary to treat 4 patients (95% CI, 3-5) with immunotherapy to avoid 1 deterioration in asthma symptoms and 5 (95% CI, 4-6) patients to avoid 1 requiring increased medication.[111] These meta-analyses strongly support the efficacy of allergen immunotherapy. Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued[13,162,163] and might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6,9,122,162-165] Allergen immunotherapy might also prevent the development of new allergen sensitivities in monosensitized patients.[120,166,167]

Food allergy, urticaria, and atopic dermatitis

Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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 use of allergen immunotherapy for individuals with the potential for IgE-mediated (anaphylaxis) reactions to foods should be regarded as investigational at this time.[168-171] There have been 2 investigational studies demonstrating efficacy in food hypersensitivity, the first using aqueous subcutaneous injections to peanut and the second using sublingual immunotherapy to hazelnut.[171-173]

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 a modified peanut extract is needed for clinical application of this method of treatment.[171] There is currently no FDA-approved formulation for sublingual immunotherapy, and this route of allergen immunotherapy is currently considered investigational at this time (see Summary Statement 73).

At the present time, there is not enough evidence to support food immunotherapy.

There is no evidence supporting the efficacy of immunotherapy for individuals with chronic urticaria, angioedema, or both.

There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[174-176] 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 ($P = .0379$) and topical corticosteroid use ($P = .0007$).[174]

The potential for benefit in symptoms related to oral allergy syndrome with the cross-reacting inhalant immunotherapy, which includes cross-reacting 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 subcutaneous immunotherapy directed against birch tree,[177] whereas another double-blind, double-dummy, placebo-controlled study comparing the effect of subcutaneous immunotherapy with sublingual immunotherapy 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, medication use, and decrease in IgE reactivity.[178] More investigation is required to substantiate the contention that benefits in oral symptoms will occur with immunotherapy.

Measures of efficacy

Summary Statement 12: 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. Objective measures, such as increase in allergen-specific IgG levels and decreased skin test reactivity, as measured by skin test titration, are changes generally associated with effective immunotherapy but, at present, are not practical for routine clinical use.[147] Nonquantitative skin testing or *in vitro* 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 are not very reliable given the strong placebo-like effect (Hawthorne effect) associated with any treatment. A more objective means for determining efficacy as validated in controlled clinical studies is the use of clinical symptom scores and the amount of medication required to control symptoms and maintain peak flow rates or pulmonary function tests within acceptable limits. Successful immunotherapy often results in a reduction in medication. Sequential measurement of disease-specific quality of life also might be helpful.

SAFETY OF IMMUNOTHERAPY

Reaction rates

Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Large local reactions associated with allergen immunotherapy are fairly common, with a frequency ranging from 26% to 86% of injections.[179] Two retrospective studies compared the effect of not adjusting immunotherapy dose based on large local reactions on the immunotherapy systemic reaction rate with dose-adjustment protocols.[179,180] There was a total of 12,464 injections administered with a dose-adjustment protocol in the 2 studies compared with 9542 injections administered with a no-dose-adjustment protocol. 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 for subsequent systemic reactions, 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 large local reactions, defined as 25 mm or larger, in patients who had experienced systemic reactions with age-, sex-, and allergen sensitivity–matched control subjects who had not had allergen immunotherapy systemic reactions found the rate of large local reactions was 4 times higher among the 258 patients who had subsequently experienced a systemic reaction compared with those who had never experienced a systemic reaction.[181] Patients who had experienced systemic reactions had 1573 large local reactions in 4460 visits (ie, 35.2% of visits) and 8081 injections (ie, 19.5% of injections) compared with the matched control group without systemic reactions who had 1388 large local reactions in 15,540 visits (8.9% per visit) and 26,259 injections (5.3% per injection; difference between groups, $P < .001$). Individual large local reactions were not predictive of future systemic reactions, but large local reactions preceded systemic reactions in approximately one third of the systemic reactions. These findings suggest that individuals with a greater frequency of large local reactions might be at greater risk for systemic reaction. Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy protocol modifications based on them are needed.

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

The prevalence of severe systemic reactions after allergen immunotherapy ranges from less than 1% of patients receiving conventional immunotherapy to greater than 36% of patients in some studies of patients receiving rush immunotherapy.[182,183]

In a recent survey of fatal and near-fatal reactions (NFRs) sent to physician members of the AAAAI, 273 of 646 respondents reported NFRs during the period of 1990-2001.[184]

The incidence of unconfirmed NFRs was 23 per year (5.4 events per million injections). Administration during the height of 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 angiotensin-converting enzyme 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 systemic reactions to subcutaneous immunotherapy over a 20-year period (1981-2000) during which 435,854 injections were administered to 4000 patients, 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.[185,186] In a prospective multicenter study there were 53 systemic reactions (0.3% of the doses) out of 17,526 administered doses in 18 (3.7%) of 423 patients.[187] 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 (21 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, there were 41 fatalities identified in the initial brief survey (20 directly reported and 17 with completed detailed questionnaire) from immunotherapy injections.[188] 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.[189,190] Therefore although severe systemic reactions to allergen immunotherapy are not common, serious systemic reactions (some fatal) can occur.

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

In the AAAAI survey of physician members on immunotherapy and skin testing, fatal reactions, and NFRs during the period of 1990-2001, 15 of the 17 fatalities had asthma, and in 9 patients asthma was considered the susceptibility factor that contributed to the fatal outcome.[188]

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.[184]

Administration during the peak pollen season (3 patients) and previous systemic reactions (4 patients) were cited as other contributing factors. Five fatalities occurred in outside medical facilities, and 2 fatalities occurred at home. No patients were receiving β-blockers; 1 patient was taking an angiotensin-converting enzyme inhibitor. In the most comprehensive evaluation of fatalities associated with allergen immunotherapy, from 1945-1987, there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[189] 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, with 73.3% of patients with an FEV_1 of less than 80% of predicted value experiencing 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 ($P < .0001$).[191] 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% of patients. These studies suggest that symptomatic asthma, severe asthma, or both might be a risk factor for immunotherapy.

In addition to symptomatic asthma and injections giving 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.[17] With the exception of dosing errors and 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 recent 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 or allergy symptom exacerbation, β-blocker use, change in health status (including pregnancy), or adverse reaction to previous allergen immunotherapy injection. The preinjection evaluation might also include a peak flow measurement to assess the airway function of asthmatic patients.

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 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

In a retrospective study the time to onset of a systemic reaction after an immunotherapy injection was less than 30 minutes in most cases.[189] A review of the literature indicates that 70% of systemic reactions occur within 30 minutes after an injection.[183] In the AAAAI 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.[184,188] 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.[190] 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 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.[192] In another prospective study 8% of systemic reactions occurred more than 2 hours after injection.[193]

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.[194]

Because most reactions that resulted from allergen immunotherapy occurred within 30 minutes after an injection, patients should remain in the physician's office for at least 30 minutes after receiving an injection, but longer waits are reasonable, as directed by the physician. In addition, patients who are at increased risk of a systemic reaction might need to carry injectable epinephrine. Such patients might also need to remain in the physician's office more than 30 minutes after an injection. 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.

β-Adrenergic blocking agents

Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

β-Blockade enhances pulmonary, cardiovascular, and dermatologic end-organ effects of mediators and increases mortality associated with experimental anaphylaxis induced by either immunologic or nonimmunologic mechanisms. Patients who are receiving β-adrenergic blocking medications might be at increased risk if they experience a systemic reaction to an allergen immunotherapy injection because the β-receptor blockade might attenuate the response to epinephrine.[195-202] Patients who are receiving β-blocking drugs were almost 9 times more likely to be hospitalized after an anaphylactoid reaction from radiocontrast media.[198] Although topical β-blockers have markedly less systemic β-antagonist effects than oral β-blockers, they still might exhibit some systemic β-antagonist effects. Whether topical β-blockers pose the same or a smaller risk than oral β-blockers in regard to the treatment of allergen immunotherapy–related systemic reactions is not known.

There have been very few studies that have examined the effect of β-blocker medications on allergen immunotherapy. A prospective 1-year study designed to determine whether patients taking β-blocker drugs were at increased risk of immunotherapy-induced systemic reactions found that there were 166 systemic reactions out of 56,105 injection visits in 3178 patients (68 were receiving a β-blocker).[203] The systemic reactions occurred in 144 (4.5%) patients, and only 1 of these patients was receiving a β-blocker medication. The authors calculated that by chance, 3.08 patients receiving the β-blocker medications drugs were expected to have had an systemic reaction and concluded that β-blocker medications did not increase the frequency of allergen immunotherapy systemic reactions ($P > .95$).

In another study of 1389 patients prescribed immunotherapy for Hymenoptera venom hypersensitivity who were followed for 34 months, there were 25 patients who received concomitant β-blocker medications.[204] Three (12%) of the 25 patients receiving β-blocker medications experienced systemic reactions during immunotherapy compared with 23 (16.7%) of 117 patients with cardiovascular disease not receiving β-blockers. Systemic reactions after a field sting or challenge occurred in 1 (14.3%) of 7 cardiovascular patients receiving β-blocker medications compared with 4 (13.8%) of 29 cardiovascular patients not receiving β-blocker medications. No severe reactions to immunotherapy or sting re-exposure were observed in patients receiving β-blockers medications.

Immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. In such cases, intravenous glucagon, which might reverse the refractory bronchospasm and hypotension by activating the adenyl cyclase directing and bypassing the β-adrenergic receptor, might be used if epinephrine has not been effective.[205,206] Prospective studies are necessary to clarify the magnitude of the risk of systemic reactions to allergens in patients who are receiving concomitant therapy with β-blockers, and a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy.

Contraindications

Summary Statement 18: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications

TABLE V. Actions to reduce the risk of anaphylaxis

- Assess the patient's general medical condition at the time of injection (eg, asthma exacerbation).
- Consider obtaining a PEFR before administration of the injection. If the PEFR is significantly less than the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.
- 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 with increased allergen sensitivity or those who have previously had a systemic reaction) might need to wait longer.
- Carefully evaluate any patient with a late reaction (eg, persistent large local reaction lasting >24 hours, systemic reaction occurring more than 30 minutes after the immunotherapy injection).
- 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.

PEFR, Peak expiratory flow rate measurement.

TABLE VI. Recommended equipment and medications to treat anaphylaxis

Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur. This should include at least the following equipment and medications:

- stethoscope and sphygmomanometer;
- tourniquet, syringes, hypodermic needles, and large-bore needles (14-gauge);
- aqueous epinephrine HCL 1:1000 wt/vol;
- equipment to administer oxygen by mask.
- intravenous fluid set-up;
- antihistamine for injection (second-line agents for anaphylaxis, but H_1 and H_2 antihistamines work better together than either one alone);
- corticosteroids for intravenous injection;
- vasopressor;
- equipment to maintain an airway appropriate for the supervising physician's expertise and skill.

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 venom hypersensitivity and cardiac disease being treated with β-blocker medications.

Reducing the risk of anaphylaxis to immunotherapy injections

Summary Statement 19: 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 extremely 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 or other health care professional appropriately trained in emergency treatment.

The 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. Epinephrine is the first-line treatment for anaphylaxis. 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.[12,207-213] It is important to administer epinephrine early in the management of anaphylaxis. 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 V and VI, respectively. Before allergen immunotherapy is chosen as a treatment, the physician should educate the patient about the benefits and risks of immunotherapy, as well as methods for minimizing risks. The patient also should be told that despite appropriate precautions, reactions might occur without warning signs or symptoms. Informed consent should include a discussion of the potential immunotherapy adverse reactions, and this discussion should be documented in the patient's medical record.

PATIENT SELECTION

Clinical indications

Summary Statement 20: Allergen immunotherapy should be considered for patients who have demonstrable

TABLE VII. Clinical indications for allergen immunotherapy

Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or both:
- symptoms of allergic rhinitis after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medications;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medication;
- coexisting allergic rhinitis and asthma;
- possible prevention of asthma in patients with allergic rhinitis

Symptoms of asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medication;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medications;
- coexisting allergic rhinitis and allergic asthma.

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);
- adults and children with a history of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.

evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic rhinitis.[107] Prospective, randomized, double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic asthma.[104,109,111]

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 proper identification and selection of component allergens on the basis of 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 (Table VII). The severity and duration of symptoms should also be considered in assessing the need for specific allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. In addition, specific allergen immunotherapy should be considered if the patient wishes to avoid long-term pharmacotherapy. Time lost from work, emergency department or physician's office visits, and responses to pharmacotherapy are important objective indicators of allergic disease severity.

Patients with allergic rhinitis who are unable to sleep because of symptoms or whose symptoms interfere with their work or school performance should be considered strong candidates for specific allergen immunotherapy. 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 considered. Unacceptable adverse effects of medications should also favor one's decision to initiate allergen immunotherapy. Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.[214]

Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued, and it might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6-9,122,162-165] These benefits of immunotherapy should be discussed with patients and might provide a clinical indication for immunotherapy for individual patients with allergic rhinitis.

Coexisting medical conditions should also be considered in the evaluation of a patient who might be a candidate for allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed with a combined aggressive regimen of allergen avoidance and pharmacotherapy and might also benefit from allergen immunotherapy.[215,216]

However, the patient's asthma must be stable before allergen immunotherapy is administered.[188,191]

Special precautions in patients with asthma

Summary Statement 21: 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 might be at increased risk for systemic reactions to immunotherapy injections.[182,188,191] Two surveys found that deaths from

immunotherapy were more common in symptomatic subjects with asthma.[188,189] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2,217]

Clinical indications for VIT

Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Systemic reactions to Hymenoptera stings, especially when associated with respiratory symptoms, cardiovascular symptoms, or both and positive skin test or *in vitro* test results for specific IgE antibodies, are a strong indication for allergen immunotherapy.[218] In the United States patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Several studies of patients with imported fire ant allergy have demonstrated the effectiveness of immunotherapy with whole-body extracts of fire ants.[155,156,219] 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. Patients younger than 16 years of age who present only with a cutaneous reaction to imported fire ant or Hymenoptera stings might not require immunotherapy.[218,220-222] In addition to allergen immunotherapy, patients with imported fire ant and Hymenoptera venom sensitivity should be instructed in how to best avoid insect stings, be prescribed epinephrine, and be taught how 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 the population that has not had a systemic reaction.[223] In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific IgE is recommended.[218] If the venom-specific IgE test result is also negative, it is recommended that the skin tests, venom-specific 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 IgE test result.[224] 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 re-stung. 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%).[225] 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 IgE test results who have had severe anaphylaxis to an insect sting.

Some patients who have negative venom skin test results and negative venom-specific IgE test results are reported to have had subsequent systemic reactions to stinging insects.[225-227] Controlled studies designed to evaluate the efficacy of immunotherapy in these patients have not been performed. There are very 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.[226] 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.

Summary Statement 23: 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.

ALLERGEN SELECTION AND HANDLING

Allergen selection

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

A careful history, noting environmental exposures and an understanding of the local and regional aerobiology of suspected allergens, such as pollen, fungi (mold), 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 skin or *in vitro* test results for specific IgE antibodies, provide good evidence that such exposures are relevant. Information concerning regional and local aerobiology is available on various Web sites or through the National Allergy Bureau at http://www.aaaai.org/nab. There are

no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma. 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 clinical history of an allergic disease.

There is no evidence to support the administration of immunotherapy based solely on results of specific *in vitro* 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.

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

The omission of clinically relevant allergens from an allergic patient's allergen immunotherapy extract contributes to decreased effectiveness of allergen immunotherapy. The 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 can make allergen immunotherapy less effective.

Knowledge of the total allergenic burden facing a patient and the realistic possibility of avoidance is important in determining whether allergen immunotherapy should be initiated. 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. Many individuals travel extensively for business or pleasure into different regions, and symptoms might worsen at these times. However, inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective. Determination of the significance of indoor allergens for a particular patient is harder because it is difficult to determine exposure in the home, school, and/or workplace. Historical factors, such as the presence of a furry animal in the home, a history of water damage and subsequent fungal exposure, or a history of insect infestation, might be helpful. However, such information is subjective and is often of uncertain reliability. In addition, some studies have demonstrated significant indoor levels of cat and dog allergen in households without pets[228] and significant levels of mouse allergen in suburban[229] and inner-city[230] homes 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 with increased asthma morbidity in inner-city children was found.[231] 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. Nevertheless, for most patients, determination of the clinical relevance of an allergen requires a strong correlation between the patient's history and evidence of allergen-specific IgE antibodies.

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted *in vitro* tests for specific IgE antibodies can also be used. **A**

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 the skin test results have demonstrated the efficacy of immunotherapy for relevant allergens.[25,26,112,130,134,135,140,141,149,154] 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 from skin testing in a highly sensitive individual.[232,233] In addition, skin tests might be difficult to perform in patients with dermatographism or atopic dermatitis. *In vitro* tests are particularly useful in such patients.

Studies indicate that skin testing is generally more sensitive than *in vitro* tests in detecting allergen-specific IgE.[234,235] Based on inhalation challenge test results, skin tests have shown specificity and sensitivity generally superior to those of *in vitro* tests. The comparability of skin tests and *in vitro* tests for specific IgE antibodies depends on the allergen being tested. For all of 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, prick testing is sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass[236] and cat,[237] are used. Intradermal/intracutaneous skin testing might be required for some allergen extracts. It is appropriate in some patients to use *in vitro* tests for specific IgE antibody as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. *In vitro* tests can also be used to define the allergens that should be used in allergen immunotherapy. If the allergy skin test result is negative and the *in vitro* test result is positive, a controlled challenge can be performed, and if the latter is positive, immunotherapy can be considered. 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 *in vitro* test results.

Specific allergens

Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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.[17,104,106,107,109] 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.[112,122] Because a particular pollen extract is a mixture of multiple glycoproteins, this suggests that mixing pollen allergens does not alter biologic activity.

Fungi (molds). Several studies with *Alternaria* and *Cladosporium* species suggest that allergen immunotherapy with fungi might be effective.[133-138] The allergen content of most mold extracts is highly variable.[238,239] However, there is evidence that proteolytic enzymes present in some mold extracts could digest other antigens, such as pollens, when combined in a mixture.[240] For this reason, it might be desirable to separate all pollen extracts from mold extracts when using mixtures.

Unfortunately, extracts for some potentially clinically important fungi are not available.[241] 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 distinguish 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.

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.

Because immunotherapy has been shown to be effective for cat[22,26,139-143,242] and dog,[25,141] the decision to include dog or cat allergen in an allergen immunotherapy extract should be considered in those circumstances in which there is exposure.

Dust mites and cockroach allergens. Crude house dust extract is generally an inappropriate substitute for house dust mite extract because the protein content measured is not restricted to dust mite allergens, nor does it necessarily guarantee inclusion of dust mite protein. Immunotherapy with standardized dust mite is generally more effective than that with crude house dust allergens. The house dust mites *D farinae* and *D 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, such as *Blomia tropicalis* and *Euroglyphus maynei*, partially cross-react with allergens from *Dermatophagoides* species. Only 50% of the projected amounts of each of the 2 house dust mites (*D pteronyssinus* and *D farinae*) need 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[144,147-149,151] 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. Dust mite hypersensitivity should particularly be considered in patients who have perennial symptoms exacerbated by a dusty environment at home, work, or both and periods of high humidity.

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. The major allergen of *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.[243] Immunotherapy with cockroach allergens is effective[154] and should 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.

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.[108,116,244] Efficacy has also been demonstrated with immunotherapy by using whole-body extracts of imported fire ants.[155,156]

Foods. Only a single clinical study accessing the efficacy and safety of subcutaneous immunotherapy with foods has been performed.[171,173] This study, which evaluated immunotherapy with peanut, found the incidence of systemic reactions, even during maintenance, was unacceptable. Thus there is no evidence to support the use of immunotherapy with food extracts. Currently, strict avoidance of the offending food is advisable, and subcutaneous immunotherapy for food allergy is not recommended.

Mixing of extracts

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Once the relevant allergens for each patient are identified, it is necessary to prepare a mixture that contains each of these allergens. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts. A number of 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 interactions between different types of allergens, when mixed, that could lead to degradation or unmasking of epitopes on exposure to proteolytic enzymes.

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Immunologic and 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.[71] 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 genera 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 the Allergen extract section, Fig 2, and the allergens and allergy diagnostic tests practice parameters).

Dose selection. Summary Statement 30: 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.[22-26,128,149,245] Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000 vol/vol).[28] A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy vaccine. Failure to do so might reduce the efficacy of immunotherapy. This occurs because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased (see the Immunotherapy schedules and doses section for further discussion and for recommended maintenance doses).

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as fungi (mold) and cockroach, from other extracts, such as pollens, is recommended. **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.[240,246,247] 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, and some weeds.[240,246,247] Cockroach had a similar deleterious effect on pollen extract potency.[246,248] Short ragweed appeared resistant to the effects of the proteolytic enzymes in one study,[240] 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.[247]

Dust mite extracts do not appear to have a deleterious effect on pollen extracts.[240,246,248] These studies suggest that pollen, dust mite, and cat extracts can be mixed together. 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. The evidence on mixing cockroach extract with other extracts is conflicting, and the clinical relevance of the changes is also unclear; therefore the clinician has the option of separating cockroach or not.

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 with lesser activities, such as pollen extracts.

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.

In this regard the number of separate injections that need to be given at each patient visit depends on whether all of the relevant extracts mixed into a single vial still deliver an optimal dose of each allergen. If mixing causes excessive dilution or if there are advantages to separating allergens into separate vials, then more than one vial might be necessary for successful immunotherapy.

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extracts are high-alert products that carry the risk for anaphylaxis. Policies, procedures, and processes intended for conventional drugs and medications might be highly 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 fatal anaphylactic reactions with allergenic products. 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. There are no reports of infection associated with allergen immunotherapy injections. Allergen vaccines are prepared by using sterile manufacturer's extracts and sterile diluents containing antibacterial constituents (usually phenol). A summary of the AAAAI/ACAAI/JCAAI proposed USP allergen immunotherapy extract preparation guidelines can be found in Table VIII.

TABLE VIII. AAAAI/ACAAI/JCAAI-proposed USP 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 below.*
   - 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.
2. **Physician responsibility**: A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in the preparation of immunotherapy using an aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files.
3. **Bacteriostasis**: Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if 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 the FDA-approved package insert 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 treatment with sanitizing agents containing alcohol and/or 70% isopropanol 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 the physical integrity of the vial.
10. **Labeling**: Immunotherapy vials are to be clearly labeled with the patient's name and 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.

*__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 media, such as from Valiteq (http://www.valiteq.com), 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.

Allergen immunotherapy extract handling

Storage. Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

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 a number of 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 extract, including reconstituted lyophilized extracts, should be stored at 4°C to minimize the rate of potency loss because storage at higher temperatures (eg, room temperature) can result in rapid deterioration.[249]

Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions (personal communication). These studies include actual shipments made by their carriers to places like

Phoenix in the summer and Alaska in the winter. 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.

Storing dilute extracts. Summary Statement 34a: More dilute concentrations of allergy immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than do more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: In determining the allergy vaccine expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of 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 allergen immunotherapy 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.[249,250]

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.[250] Phenol is a preservative added to extracts to prevent growth of microorganisms.

Phenol can denature proteins in allergen extracts.[251,252] Human serum albumin might protect against the deleterious effect of phenol on allergen extracts.[251] 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,[250,253] possibly through inhibition of the activity of proteolytic and glycosidic enzymes that are present in certain extracts. However, it is irritating when injected and should be diluted before beginning immunotherapy. Recommendations for extract stability are found in the manufacturers' product insert sheets. 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. The pain associated with glycerin increases in proportion to the glycerin concentration and injection volume, and the pain is proportional to the total injected dose of glycerin.[254] However, individual pain perception can vary substantially. Total glycerin doses of less than 0.05 mL rarely produce clinically important pain.

TABLE IX. Potency of selected manufacturer's extracts currently available

Extract	Potency
Cat hair and pelt	5000 and 10,000 BAU/mL
Dust mite	3000, 5000, 10,000, and 30,000 AU/mL
Bermuda grass	10,000 AU/mL
Short ragweed	1:10-1:20 wt/vol or 100,000 AU/mL
Other grasses*	10,000 and 100,000 BAU/mL
Other pollen	1:10 to 1:40 (wt/vol) or 10,000 PNU/mL
Molds	1:10 to 1:40 (wt/vol) or 20,000 to 100,000 PNU/mL

AU, Allergy unit; *BAU*, bioequivalent allergy unit; *PNU*, protein nitrogen unit.
*Perennial rye, Kentucky blue/June, timothy, sweet vernal, redtop, orchard, and meadow.

There have been few studies that have investigated the potency of dilutions of allergen extract mixture over time. Expiration dates for allergen extract dilutions are somewhat empiric and not strongly evidence based. A study undertaken by the AAAAI 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. Dust mite and cat at 1:10 and 1:100 vol/vol dilution were also stable in all conditions of storage over 12 months, as measured by an ELISA assay using 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.

IMMUNOTHERAPY SCHEDULES AND DOSES

Summary Statement 35: A customized individual 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 can be based on single or multiple allergens. **D**

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. Animal dander contains between 10 and 20 antigens,[255] house dust mites between 20 and 40 antigens,[256] and pollens between 30 and 50 antigens,[257,258] and fungal extract can contain as many as 80 antigens.[259]

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. This is designated as the patient's maintenance concentrate.

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. Standardized extracts are available with biologic potencies of 10,000 and 100,000 BAU for grasses; 5000 and 10,000 BAU for cat allergen; 5000, 10,000, or 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 wt/vol extracts (Table IX). 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.

Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

The highest concentration of an allergen extract mixture that is projected to be used as the therapeutically effective dose is called the maintenance concentrate. This should be prescribed individually for each patient by an allergist/immunologist. 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 individual manufacturer's extracts. Some patients might be unable to attain the projected therapeutically effective dose of the maintenance concentrate because of local reactions, systemic reactions, or both (eg, cat, 1000 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose]; see Table X for probable effective therapeutic dose range). Such patients might need weaker dilutions of their maintenance concentrate. Even so, 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 referred to as the maintenance dose. The consistent use of this nomenclature system is essential because errors in choosing the correct vial are a common cause of systemic reactions, especially when the patient transfers from one physician to another. Therefore it is important that standard terminology be adopted by all physicians who prescribe allergen immunotherapy.

Recommended doses

Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

The effective maintenance dose of immunotherapy for a particular patient must be individualized. To do this, the allergist/immunologist who prepares the allergen immunotherapy extract must balance the dose necessary to produce efficacy and the risk of reactions if such a dose is reached. The allergist/immunologist might need to prepare more than one maintenance concentrate to provide a therapeutic dose of each of the allergens for the polysensitized patient. Therapeutically effective doses for immunotherapy have been reported for some allergen extracts.[22,24,25,128,134,135,149,246,260,261] Effective doses have been determined for Hymenoptera venom, dust mite, cat allergen, dog, grass, and short ragweed (Table X).

Controlled studies demonstrate that the content of particular allergens in allergen immunotherapy extracts can be used to predict a therapeutic dose for those allergens, particularly when the extracts are standardized. For antigens 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. The therapeutically effective doses used in the most recent controlled clinical studies are the basis of the recommended dosage range of standardized extracts presented in Table X. 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 time that it is administered.[14]

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.[27] 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 risk of systemic reactions to immunotherapy injections with higher maintenance doses. The maintenance concentrate should be formulated to deliver a full therapeutic dose of each of its constituent components. However, some sensitive patients might not tolerate the targeted therapeutic dose, and their maintenance dose would be lower. Individuals 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 referred to as the maintenance dose.

Regardless of dose schedule, some patients are unable to progress to the predetermined maintenance dose because of large local or systemic reactions to the allergen

TABLE X. Probable effective dose range for allergen extracts US standardized units[a]

Antigen	Labeled potency or concentration[a,b]	Probable effective dose range
Dust mites: *D farinae* and *D pteronyssinus*[c]	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat[d]	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized[e]	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed[f]	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 μg of Amb a 1 1000-4000 AU Concentration of Amb a 1 is on the label of wt/vol extracts in FDA units[358]
Nonstandardized extract, dog[g]	1:10 to 1:100 wt/vol	15 μg of Can f 1
Nonstandardized extracts	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose

[a]Multiple studies have demonstrated that the efficacious dose for allergen immunotherapy is between 5 and 20 μg of the major allergen per injection. Only 2 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).

[b]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).

[c]There have been no dose-response studies with United States–licensed dust mite extracts, and dosing recommendations in AU value are extrapolated from published European studies that used aqueous[349] and alum-precipitated[149,151] extracts. 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.[149] The authors suggested the optimal maintenance dose was 7 μg of Der p 1. Corresponding doses were based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Extrapolating effective and safe doses in this manner might not be scientifically valid. *D farinae* and *D pteronyssinus* are similar in group 1 allergen content according to the FDA's current reference standards. 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*.

[d]The major cat allergen Fed d 1 is reported in FDA units, with 1 Fel d 1 unit equaling approximately 2 to 4 μg of Fel d 1.[55,58,59] The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 to 19.9 U/mL. One study demonstrated clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 dose in terms of decreased cat extract PD_{20}, titrated skin test results, and allergen-specific IgE and IgG levels.[350,351] In a recent study that investigated the efficacy in terms of immunologic changes of 3 doses of a United States–licensed cat extract (0.6, 3, and 15 μg) demonstrated that a significant effect on titrated skin prick test results, allergen-specific IgG4 levels, and $CD4^+$/IL-4 levels was only seen in the group treated with 15 μg of Fel d 1, although the 3-μg dose group did demonstrate a significant change in titrated skin test response and increase in cat-specific IgG4 levels.[22]

[e]There have been no dose-response studies with United States–licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,[130] alum-precipitated,[24,161] and calcium phosphate–precipitated grass pollen extracts.[352] One of these studies compared a dose of 2 μg with 20 μg of major timothy allergen (Phl p 5) and found clinical efficacy at both doses.[24] The efficacy was greater in the 20 μg of Phl p 5 dose, but the systemic reaction rate was also higher in the high-dose group. The package inserts for United States–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 BAU. Extrapolating effective and safe doses in this manner might not be scientifically valid. 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).

[f]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 suggested that 1 unit of Amb a 1 is equivalent to 1 μg of Amb a 1, and 350 Amb a 1 units/mL is equivalent to 100,000 BAU/mL.[60] The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2000 AU, with a range of 1000-4000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrated 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.[45] A ragweed dose-response study (0.6, 12.4, and 24.8 μg of Amb a 1) demonstrated efficacy, as measured by nasal challenge, at 12 and 24 μg of Amb a 1.[128] The efficacy of the 24-μg dose was not significantly better than the 12-μg dose, and the authors concluded that the optimal dose for ragweed extract was greater than 0.6 μg but not more than 12.4 μg of Amb a 1.

[g]Dog extracts are not standardized. However, one dose-response study with a United States–licensed acetone-precipitated dog extract investigated the efficacy of 3 doses (AP dog; Hollister-Stier, Spokane, Wash; 0.6, 3, and 15 μg) in terms of immunologic changes and found the dose of 15 μg of Can f 1 to be most efficacious.[25] 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 have assayed between 128 and 208 μg/mL (average Can f 1, 162 μg/mL [SD ± 26 μg/mL]; information provided by the extract manufacturer, Hollister-Stier).

immunotherapy extract. The evidence is not clear whether large local reactions are a potential risk for subsequent allergen immunotherapy systemic reactions.

Published studies do not indicate that an individual large local reaction is predictive of a subsequent systemic reaction.[179,180] However, one retrospective study found that individuals who have a history of repeated large local reactions (defined as >25 mm) might be at greater risk for a subsequent systemic reaction.[181]

The concept of highest tolerated dose does not apply for VIT, and all patients are expected to achieve the full recommended dose to achieve the necessary degree of protection. There are conflicting data over whether lower doses (50 μg) are less effective, but there are also data showing that 200 μg is more reliably effective.[245] In the case of VIT, patients are asked to tolerate more large local reactions to achieve the full dose, even though with inhalant immunotherapy the dose can be reduced for such large local reactions to minimize patient discomfort.

Effect of dilution on dose

Summary Statement 38: 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 vaccine, thereby limiting the ability to deliver a therapeutic effective dose for any given allergen.

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

Dilution from maintenance concentrate vaccine	Volume	Volume (mL)	Diluent volume (mL)	Final volume
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.

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 2000 BAU/mL, 2 mL of the manufacturer's extract (cat, 10,000 BAU/mL) can be added to 8 mL of diluent or 8 mL of other allergens, and the final concentration of cat will be 2000 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.

Dilutions of the maintenance concentrate

Summary Statement 39: 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 vol/vol 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, 1000 BAU or 100 BAU), but this system can be complicated if allergens with different potency units are used (eg, wt/vol, BAU, AU, or PNU) and make it difficult to easily interpret the vial label.

Instructions on how to prepare various allergen extracts 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.

Labeling dilutions

Summary Statement 40: 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, a number of 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 (vol/vol), a numbering system, a color-coding system, or an alphabetical system should be used. If this uniform labels 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.

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
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

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 3 and 4).

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 Appendix 2]).

Individualized treatment vials

Summary Statement 41: 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 (wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for 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). Labels on patient-specific vials can provide at least 2 patient identifiers (birth date and patient name), which would be consistent with the recommendations of the Joint Commission on Accreditation of Health Care Organizations National Patient Safety Goals: ''Goal 1: Improve the accuracy of patient identification by using at least two patient identifiers when providing care, treatment or services.''[5] 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 administration of the injection.[4,5]

In a survey of 1717 allergists endorsed by the AAAAI and JCAAI, 57% of the 476 respondents reported at least one wrong-patient injection, and 74% of the 473 respondents reported at least one wrong-dose injection.[4] 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 reasons why this might reduce incorrect injection errors. One reason was that patient-specific vials can be prepared in a quiet laboratory setting, which might provide substantially less distraction than the nurse in a room with a patient who is trying to concentrate only on drawing up the injection correctly. In addition, the specific components are mixed once with the preparation of individually prepared patient-labeled vials, whereas the mixing would be repeated on every injection visit if the allergen extract is withdrawn from different stock solutions, as it is in the off-the-board method. For safety reasons and to avoid cross-mixing of allergens removed from the manufacturer's extract, the mixing of antigens in the syringe (off the board) is not recommended.

Some allergists/immunologists prefer to administer immunotherapy doses drawn directly from a single stock dilution of individual allergens or common mixes (shared specific patient vials). In this way the immunotherapy dose is transferred to the patient without cross-contamination. If shared-patient (eg, mixed vespids and dust mite mix) vials are used, it is essential that policies and procedures are developed to verify that the correct dose from the correct vial is administered to the correct patient.

Starting doses

Summary Statement 42: The starting dose for build-up is usually a 1000- 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 slowly 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 1:1000 (vol/vol), although more diluted concentrations frequently are used for patients who are highly sensitive, as indicated by history or skin test reaction (see Appendix 3 for an example of a conventional immunotherapy schedule).

Frequency of build-up injections

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 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 2 times per week. 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 4 to 6 months, depending on the starting dilution and the occurrence of reactions. It is acceptable for patients to receive injections more frequently, provided there is adequate spacing between injections. The interval between injections is empiric but might be as short as 1 day without any increase in the occurrence of systemic reactions[262] if there is some urgency to achieve a maintenance dose (eg, allergy season is approaching) or for practical reasons (eg, patient's schedule). Alternatively, treatment schedules can be used that more rapidly achieve maintenance dosing. These cluster and rush dosing schedules are discussed in Summary Statements 47 through 49.

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 a number of 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).

Dose adjustments for systemic reactions

Summary Statement 44: 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 benefit/risk ratio justifies continuation of immunotherapy.

Reductions during periods of exacerbation of symptoms

Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Immunotherapy administered during periods of exacerbation of symptoms is considered a risk factor for immunotherapy.[17,184] Injections administered during periods when a patient is exposed to increased levels of allergen to which they are 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.[184] 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 sensitive, especially if their symptoms are poorly controlled.

Dose adjustments for late injections

Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

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 depends 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 Appendix 4 for an example of a dose-modification regimen for gaps in treatment).

Cluster schedules

Summary Statement 47: 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 (see Appendix 5).[22,26] 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. The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules.[145,263-266] The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.[267]

Rush schedules

Summary Statement 48: 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.[268] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.[191,269-272]

The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections over the course of 4 hours.[273] Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours.[274-276] 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 cluster[145,266] and rush[134,277] schedules.

Systemic reactions and rush schedules

Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

The advantages of rush immunotherapy come at a cost because there is an increased risk of local and systemic reactions. Systemic reaction rates have been reported to be

as high as 73% of patients, with the risk of such reactions reduced to 27% by premedication in one study.[272] Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing.[273]

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

Rush protocols for administration of Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions.[274-276,278,279]

Premedication and weekly immunotherapy

Summary Statement 50: Premedication can reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

There is concern that antihistamines taken before each injection with conventional immunotherapy might mask a minor reaction that would otherwise alert a physician to an impending systemic reaction. 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.[280] One study that compared terfenadine premedication with placebo premedication during rush VIT demonstrated greater clinical efficacy in the terfenadine-premedicated group in terms of subsequent responses to field stings or sting challenge.[281] There was also a significant difference in the systemic reaction rate between the 2 groups: 6 patients in the placebo-premedicated group had systemic reactions, whereas none of the patients in the terfenadine-premedicated group had systemic reactions ($P = .012$).

Unfortunately, patients might still have life-threatening anaphylaxis despite 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.

Premedication with cluster and rush immunotherapy

Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

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.[267] Premedication with a 3-day course of prednisone, an H_1 histamine receptor antagonist, and an H_2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.[272] In one study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on the safety and efficacy of rush immunotherapy, there was a 5-fold decrease in the risk of anaphylaxis in the group premedicated with omalizumab compared with the placebo premedication group.[282]

There are anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist, but there have been no published studies. Because the risk of a systemic reaction from rush VIT is relatively low, routine premedication before rush VIT is usually unnecessary.[274,276,278,279] In a study evaluating premedication with antihistamines and steroids for rush immunotherapy with imported fire ant venom, there was no statistically significant differences in the systemic reaction rates between the premedication and placebo premedication group (3.6% of the premedication group vs 6.7% of the placebo group, $P = .87$).[157]

Maintenance schedules

Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals 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 individuals might tolerate longer intervals between maintenance dose injections.

The interval between venom injections can be safely increased up to 8 weeks in some patients without loss of efficacy. 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.

Continuing care

Time course of improvement. Summary Statement 53: Clinical 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.[24,134,143,277] Improvement might not be observed for a number of reasons, including (1) failure to remove significant allergenic exposures (eg, a cat), (2) exposure to high levels of

allergen (eg, pollen or molds), (3) continued exposure to nonallergen triggers (eg, tobacco smoke), or (4) incomplete identification and treatment of clinically relevant allergens. 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 54: 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 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 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

The patient's response to immunotherapy should be evaluated on a regular basis. 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. 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.

There have been very 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 individuals.[283-285] However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported.[283,285] Nevertheless, systemic reactions to stings after discontinuing VIT were generally much milder than the pretreatment reactions and were rarely severe. Two studies did not find a difference in relapse rates between the patients treated for 3 years compared with those treated for 5 years,[283,286] but one of the studies noted that the small number of patients in the 3-year treatment group prevented them from making any conclusions about the risk of discontinuing treatment after 3 years.[283] However, one study found that patients who had experienced re-sting reactions after discontinuing VIT had received VIT for a significantly shorter duration (mean, 43.35 months) than those with continued protection (mean, 54.65 months; $P < .01$).[285] Another study reported that 5 years of VIT provided better immunologic and clinical outcomes than 2 to 4 years of treatment.[287]

Change in skin test reactivity did not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who experienced a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE.[286,288] Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment.[288] The relapse rate and the frequency of severe reactions were greater in patients who had a history of very severe reactions to stings before treatment, in patients who had systemic reactions during VIT (to a sting or a venom injection), in patients with honeybee allergy, and in those who had less than 5 years of treatment.

The duration of inhalant allergen immunotherapy efficacy has not been as extensively studied. Some studies have suggested 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 *(D pteronyssinus)* extract for 12 to 96 months.[14] 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.[13] There was a switch to placebo in half of 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. These studies demonstrate the uncertainty of the long-term benefit of inhalant immunotherapy after discontinuation.

Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained clinical remission after discontinuing inhalant immunotherapy, and 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 indication for continuation of immunotherapy can be found at http://www.aaaai.org or http://www.jcaai.org.

Documentation and record keeping. Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully 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 allergy immunotherapy and prescription forms can be found in the Appendix (Appendices 6-15), and these include examples of immunotherapy prescription and administration forms. These forms, along with examples of immunotherapy consent and instruction forms, can also be found at http://www.aaaai.org.

Injection techniques. Summary Statement 57: Allergen immunotherapy extract injections should be given using a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **C**

Immunotherapy should be given with a 26- to 27-gauge syringe with a half-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.[289-291]

If using shared specific patient vials (stock vials, such as mixed vespid or dust mite mix), a single dose should be drawn from each vial. Antigens from different vials should not be combined in a single syringe. Furthermore, extra care is needed to prevent using the wrong stock antigen.

Summary Statement 58: The injection should be given subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Each immunotherapy injection should be given in the posterior portion of the middle third of the upper 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.

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.

The syringe should be aspirated to check for blood return in the syringe before injecting. If blood is present, 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 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 syringe should be appropriately discarded. A fresh syringe and needle are necessary to determine whether a blood vessel has been entered.

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 could result in a local reaction.

LOCATION OF ALLERGEN IMMUNOTHERAPY ADMINISTRATION

Physician's office

Summary Statement 59: 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 to treat anaphylaxis should be in the immediate vicinity when immunotherapy injections are administered.

Summary Statement 60: 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.[292] 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.[184] 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 might be frequently necessary in the patient's immunotherapy schedule, as well as the patients total treatment program.

Other locations

Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **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.[292] The health care professional and staff 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, or allergy/asthma exacerbations at the time of allergen immunotherapy extract injection or poorly controlled asthma).

Appropriate adjustment of dose should be made as clinically indicated. The physician who prepared the patient's allergen immunotherapy extract should provide adequately labeled allergen immunotherapy extract vials, detailed directions regarding dosage schedule for build-up and maintenance, and instructions on adjustments that might be necessary under the following circumstances:

1. when providing patients with new vials;
2. during seasonal exposure to allergens that are in the patient's allergen vaccine, to which the patient is very sensitive, or both;
3. if the patient has missed injections; and
4. when reactions occur to the allergen immunotherapy extract.

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

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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 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 very 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 fully trained to administer the injection and to treat anaphylaxis if this should 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 supports (personnel, medications, supplies, and equipment) are more optimal for encouraging prompt recognition and treatment of anaphylaxis (Table V). 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.

Summary Statement 63: If a patient on 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for their immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extracts might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Patients often 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 brought from the previous physician (ie, an unchanged immunotherapy program) or one to be prepared by the current physician (ie, a new immunotherapy program).

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 full, clear, and detailed documentation of the patient's previous schedule and the contents of the allergen immunotherapy extract (see Appendices 7, 8, 11, 12, and 14 for examples of allergen immunotherapy prescription and administration forms and documentation guidelines for allergen immunotherapy forms). In addition, the patient's previous response to and compliance with this program 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 a schedule and the allergen immunotherapy extract, (2) the patient has shown significant improvement on this immunotherapy program, and (3) the contents of the allergen immunotherapy extract are appropriate for the area in which the patient is now living.

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, vaccine type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient's dose is not modified. This increased risk is due to the significant variability in content and potency of extracts and the variability in methods used by physicians to prepare the patient's maintenance concentrate and its dilutions. For example, the strength of a given concentration of nonstandardized extracts might vary significantly from vial to vial. The risk of systemic reactions in such a situation might be greater with nonstandardized extracts and allergen immunotherapy extracts that contain mixtures of allergens.

Therefore if the allergen immunotherapy extract is to be changed, the patient might need to be retested for specific IgE to the appropriate allergens 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 provided the interval of time since the last injection has not been too long. For lot changes from the same manufacturer, the physician can consider decreasing the dose by 50% to 90%. For changes in manufacturer and nonstandardized extracts, a greater decrease in dose might be necessary.

SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

Allergen immunotherapy in children

Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children

with allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Immunotherapy for children has been shown to be effective and often well tolerated,[137,242] although at least one study did not show efficacy.[293] 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.[294] In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (see the Patient selection section and Table VII). In recent studies children receiving allergen immunotherapy have demonstrated:

1. improvement in symptom control for asthma[117,119,121,122] and allergic rhinitis[118];
2. increased PC_{20} to histamine[121];
3. increased PC_{20} to cat and house dust mite allergens[121,149];
4. decreased risk of development of asthma[6,9,163-165];
5. decreased development of new sensitivities[120,166]; and
6. modification in release of mediators in children receiving immunotherapy that correlates with decreased clinical symptoms.[123]

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Although there is some disagreement about the role of allergen immunotherapy in children under the age of 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.[117,122] In children with allergic rhinitis, allergen immunotherapy might prevent the development of asthma.[6,9,163-165] However, allergen immunotherapy for inhalant allergens is usually not considered necessary in infants and toddlers because (1) there is 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 in pregnancy

Summary Statement 71: Allergen immunotherapy might be continued but is usually not initiated in the pregnant patient. **C**

The physician must be aware of the benefits and risks of immunotherapy in pregnant patients. The recommended precautions for prevention of adverse reactions are especially important in the pregnant patient. Allergen immunotherapy is effective in the pregnant patient. Thus allergen immunotherapy maintenance doses can be continued during pregnancy. Allergen immunotherapy is usually not initiated during pregnancy because of risks associated with systemic reactions and their treatment (ie, spontaneous abortion, premature labor, or fetal hypoxia). 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, and the patient is maintained on the dose that she is receiving at that time.

Immunotherapy in the elderly patient

Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy might be considered in the treatment of the elderly patient, but the benefit/risk assessment must be evaluated carefully in this population. Older 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. However, elderly patients may also benefit from allergen immunotherapy and age alone should not preclude the consideration of allergen immunotherapy.[295]

Immunotherapy in patients with immunodeficiency and autoimmune disorders

Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with immunodeficiency or autoimmune disorders. Therefore the decision to begin immunotherapy in patients with major humoral or cellular immune defects must be individualized. Concern about the increased risk of immunotherapy in such patients is largely hypothetical.

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

ALTERNATIVE ROUTES OF IMMUNOTHERAPY

Sublingual and oral immunotherapy

Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be

effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no FDA-approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **B**

Alternative routes of administration of allergen immunotherapy are ''a viable alternative to parenteral injection therapy'' in some cases.[106,296] Studies of oral immunotherapy have provided conflicting results for ragweed,[297] birch,[298] and cat[299] immunotherapy. The present dosage of oral immunotherapy extract is 20 to 200 times the parenteral injected dosage, which requires a cost assessment for this type of therapy. Furthermore, adverse effects have included gastrointestinal and oral reactions (50% in 1 study) that might preclude home therapy. Oral immunotherapy should be considered investigational at this time.

Optimal-dose (high-dose) sublingual swallow immunotherapy is effective in adults and children.[300-304] In a study of 855 patients with grass pollen allergy and allergic rhinitis randomized to placebo or one of 3 grass tablet doses, there was a significant reduction in symptom and medication scores in the highest-dose subgroup, who were treated for at least 8 weeks before the grass pollen season, compared with the placebo group (symptoms, 21%, $P = .0020$; medication use, 29%, $P = .0120$).[303]

Sublingual allergen studies have evaluated house dust, olive pollen, grass pollen, ragweed, birch, cat, latex, *Alternaria* species, and *Parietaria judaica*.[305-313] Sublingual immunotherapy has been shown to be effective in patients sensitized to 2 non–cross-reacting allergens, grass and birch.[314] It has been noted that the allergen is not degraded by saliva and that there is no direct sublingual absorption of allergen. Radiolabeled allergen has been detected after 48 hours in the sublingual region.[315,316] Alternative protocols, such as rush and ultra-rush (20 minutes) sublingual swallow[307,316,318] and no induction (build-up) phase,[301,303,317,319,320] have been studied. Several studies have suggested a relationship between dose and efficacy with sublingual immunotherapy,[303,310,321] but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. The majority of sublingual studies have demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both, but approximately 35% of the randomized, double-blind, placebo-controlled studies did not demonstrate efficacy in either parameter during the first year of treatment.[322] Further studies are needed to confirm the optimal dose for sublingual immunotherapy.

One of the potential advantages of sublingual immunotherapy is that it appears to be safe, even at very high doses (up to 500 times the usual monthly subcutaneous dose), and to be associated with a lower incidence of serious side effects.[310,320,323] This appears to apply to young children (<5 years), for whom there are prospective safety data[324,325] and a postmarketing survey.[326]



FIG 3. Sample of labels for allergen immunotherapy extract vials.

There have been no SLIT-related fatalities, but there have been 3 case reports of anaphylaxis caused by sublingual immunotherapy. One patient with latex hypersensitivity had anaphylactic shock 20 minutes after reaching the maximal dose on the fourth day of latex rush sublingual rush immunotherapy.[327]

The other 2 reported cases of SLIT anaphylaxis involved patients treated with multiple inhalant allergens. In one case a patient with allergic rhinitis and asthma who was prescribed a sublingual immunotherapy extract composed of multiple non–cross-reacting allergens (*Alternaria* species, dog, cat, ragweed mix, weed mix, and grass mix)[328] had generalized pruritis, followed by angioedema, shortness of breath, and dizziness, within a few minutes of administering 6 drops of the 1:100 vol/vol dilution on the third day of treatment. This episode was preceded by a milder systemic reaction the previous day (generalized pruritis). In the other case, a 13-year-old girl with allergic rhinitis and asthma had swelling of her lower lip 3 minutes after pollen drops, high fever, chest pain, nausea, and abdominal pain.[329] She was treated in the emergency department for anaphylaxis and hospitalized for observation. The reaction occurred 1 month after she had reached the maintenance dose during the peak of the spring season.

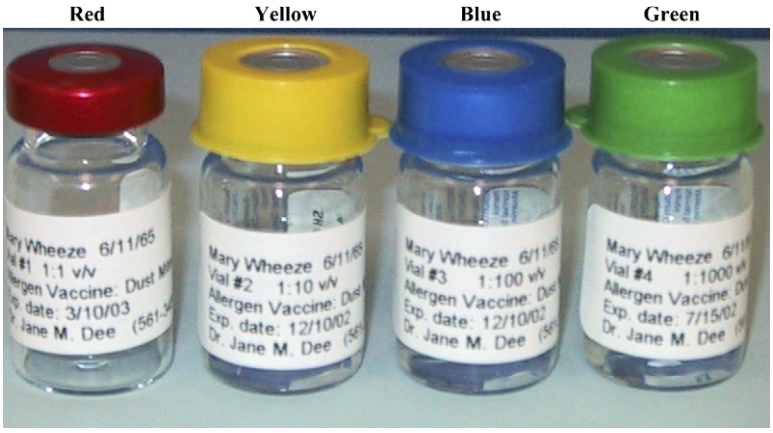


FIG 4. Sample set of color-coded vials of allergen vaccine.

There is currently no FDA-approved formulation for sublingual immunotherapy in the United States at this time, and this modality should be considered investigational. Current investigation of sublingual immunotherapy should not be confused with low-dose sublingual immunotherapy based on provocation neutralization testing or Rinkel-type skin testing.

Intranasal immunotherapy

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Based on controlled, well-designed studies, intranasal immunotherapy has been shown to improve the nasal symptoms of rhinitis.[330] Intranasal dry powder extract immunotherapy has been studied in grass,[330] birch,[331] *P judaica*,[332-334] and house dust mite[335] allergy. Clinical efficacy was noted in all of these studies. Nasal reactivity to allergen challenge was reduced, and only minor side effects were noted in 2 of the above studies. A 3-year study with *P judaica* reported to provide persistent benefits for up to 12 months after conclusion of allergen immunotherapy.[333] Local administration of nasal allergen in an aqueous solution for immunotherapy might be limited by the local side effects. Further studies in both pediatric and adult groups are needed. In human studies the antigen has been noted to appear in the serum within 15 to 30 minutes of administration, with a peak level occurring within 2 to 3 hours.[315] Some allergens have been reported to be retained in the nasal mucosa for up to 48 hours after administration. Intranasal immunotherapy is not currently available in the United States but has gained some acceptance in other parts of the world.

Immunotherapy techniques that are not recommended

Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

Low-dose regimens, including coseasonal low-dose immunotherapy for aeroallergens and the Rinkel low-dose titration techniques, are not effective.[27,28] Immunotherapy based on provocation–neutralization testing with food and aeroallergens and enzyme-potentiated desensitization is not effective.[336]

FUTURE TRENDS IN IMMUNOTHERAPY

Therapy with aeroallergen extracts will become more uniform (as is the current practice for insect venoms) as greater numbers of biologically standardized allergen extracts become available. The actual number of commercially available allergen extracts will be reduced based on consensus agreements about the regional prevalence of aeroallergens, their cross-allergenicity, and the relevance of their effect on human health in specific locales. Novel routes for more effective, convenient, and safer allergen immunotherapy are being investigated throughout the world.

For example, the sublingual route of administering allergen immunotherapy has been studied extensively in Europe. A meta-analysis confirmed its clinical effectiveness in allergic rhinitis,[302] and it has been reported to be effective in asthma as well.[337] Sublingual immunotherapy appears to have a very low risk of serious life-threatening systemic side effects, which might allow for home administration.[324,338] In some studies the clinical benefits of sublingual immunotherapy were not significant until the second year of treatment,[306,339] and comparisons suggest that the magnitude of the clinical benefit of sublingual immunotherapy might not be as great as that of subcutaneous immunotherapy.[311]

Trials with non–IgE-binding peptides containing T-cell stimulating peptides have been reported.[340] Site-directed mutagenesis has produced allergens with decreased IgE-binding capacity without decreased T-cell responses.[341,342]

Immunostimulatory sequences mimicking bacterial and viral DNA have been prepared that stimulate the innate immune system to direct T-cell responses toward

T_H1 rather than T_H2 phenotypes.[343] The results of clinical trials with a conjugate of the immunostimulatory sequence to the major allergen of ragweed, Amb a 1 (AIC), have been reported.[34,343] In a double-blind, placebo-controlled study of 25 adults who received 6 weekly injections of the AIC or placebo vaccine before ragweed season, the AIC group had better peak-season rhinitis scores on the visual analog scale ($P = .006$), peak-season daily nasal symptom diary scores ($P = .02$), and midseason overall quality-of-life scores ($P = .05$) than the placebo group during the first ragweed season, and this effect was observed in the subsequent ragweed season.[344]

Humanized anti-IgE mAb has been shown to have clinical effects in both allergic rhinitis and asthma.[345-348] Theoretically, this new therapeutic modality could be used as protective cover for clinical applications of rapid forms of immunotherapy. It is possible that preadministration of anti-IgE could provide a more effective protective effect than premedication with antihistamines and therefore permit a rush allergen immunotherapeutic regimen with reduced risk of serious systemic reactions.[282]

AUTHOR'S 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 2 systemic reaction grading systems (the European Academy of Allergy and Clinical Immunology's grading of severity for systemic side effects and the Portnoy method for numeric grading of reactions to allergen immunotherapy) can be found in the Appendix section. These forms can also be found along with examples of immunotherapy instruction and consent forms, preinjection health questionnaires, and indications for beginning and continuing immunotherapy forms at www.aaaai.org.

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APPENDIX 1. American College of Medical Quality's policy on the development and use of practice parameters for medical quality decision-making[1]

Practice parameters are strategies for patient management developed to assist health care professionals in clinical decision making. Practice parameters include standards, guidelines, and other patient management strategies. Standards are accepted principles for patient management. Guidelines are recommendations for patient management that identify a particular management strategy or a range of management strategies. Other strategies for patient management include practice policies and practice options. Practice parameters are to be used as screening tools to identify possible deviations from the applicable standards of care. Such parameters are not to be used as absolute standards or to profile or report on health care personnel. Parameters are designed to trigger a process in which possible deviations from the standard of care are identified as outlier practice patterns. Once a deviation from the parameter is identified, such a deviation should be referred to the appropriate qualified physician advisor or reviewer for a determination of medical necessity that conforms to the applicable standard of care. Parameters used in the day-to-day practice of clinical medicine should be clinically relevant. They should not be considered as substitutes for the standard of care but might contribute to its formulation.

Practice parameters must be developed, designed, and implemented only by board-certified, clinically practicing, specialty-matched physician advisors/reviewers with unrestricted medical licenses. Qualified nonphysicians might participate in the development of these parameters only in the areas in which their clinical expertise based on the standard of care is applicable. The health care personnel who develop these parameters should sign their names and date the final version as evidence of their participation and support. Practice parameters must be based on sound scientific research findings, professional literature, clinical experience and appropriate well-recognized methodologies and reflect professionally recognized national standards of care practiced in the clinical community of medicine. The development procedures followed, the participants involved, the evidence used, the assumptions and rationales accepted, and the analytic methods used should be meticulously documented, described, and made publicly available for national peer review. Parameters should be updated as needed.

Practice parameters are used as tools to enhance medical decision making but not as replacements for physicians' clinical judgment. They can be considered as means to enhance the performance of clinical and review personnel but not to replace them. It is below the standard of care of the medical review process to substitute qualified physician reviewer experts with unqualified reviewers who are using parameters.

APPENDIX 2. Examples of possible abbreviations for allergen immunotherapy extract 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

APPENDIX 3. 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

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

APPENDIX 4. Example of immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals (modification of the AAAAI skin testing and immunotherapy consent and instruction forms: immunotherapy administration instruction form, which can be found at http://www.aaaai.org)

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

- Up to 7 days, continue as scheduled (ie, if on weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection).
- Eight to 13 days after missed scheduled injection; repeat previous dose.
- Fourteen to 21 days after missed scheduled injection; reduce dose 25%.
- Twenty-one to 28 days after missed scheduled injection; reduce previous dose 50%.

Then increase dose each injection visit as directed on the immunotherapy schedule until therapeutic maintenance dose is reached.

This suggested approach to modification of doses of allergen immunotherapy because of gaps between treatment during the build-up phase is not based on retrospective or prospective published evidence, but it is presented as a sample for your consideration. The individual physician should use this or a similar protocol as a standard operating procedure for the specific clinical setting. A similar dose-reduction protocol should be developed for gaps in maintenance immunotherapy.

APPENDIX 5. Example of a cluster immunotherapy schedule[22,26]

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

APPENDIX 6. Recommended documentation for allergen immunotherapy prescription forms

The purpose of the allergen immunotherapy prescription form is to define the contents of the allergen immunotherapy extract in enough detail that it could be precisely duplicated. The following information should be on an immunotherapy prescription form:

Patient information:

- Patient name, patient number (if applicable), birth date, telephone number, and picture (if available) should be included.

Preparation information:

- Name of person and signature preparing the allergen immunotherapy extract should be included.
- Date of preparation should be recorded.
- Bottle name should be included (eg, trees and grass). If abbreviations are used, a 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 should be included.
- Volume of manufacturer's extract to add to achieve the projected effective concentration should be included. 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) should be included.
- Extract manufacturer should be included.
- Lot number should be included.
- Expiration date should be recorded and should not exceed the expiration date of any of the individual components.

APPENDIX 7. Allergen immunotherapy extract prescription 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:

_____
_____
_____
_____

_____ ____/____/____
Prescribing Physician Signature Date

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

APPENDIX 8. Maintenance concentrate prescription form

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: 6/10/06

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial **4** from Vial **1** on **8/30/06** Expiration date: **10/15/06**
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	Short ragweed	1:20 w/v G (150 Amb a1)	0.5ml	Greer	12345	1/01/08
2	Amaranthus Retroflexus	1:10 w/v G	0.5ml	H-S	6789	2/07/08
3	Ash	1:10 w/v G	0.5ml	Center	3333	3/17/08
4	Cat	10,000 BAU/ml G	2.00ml	ALO	9898	2/27/08
5	Timothy Grass	100,000 BAU/ml G	0.4ml	ALK	56789	7/09/08
6	Johnson Grass	1:10 w/v G	0.5ml	Greer	2434	7/20/08
7						
8						
9						
10						
Diluent	HSA		0.6ml	ALK	68597	12/08
Total Volume			5.00 ml			6/10/07

*** Components of mixes listed on a separate sheet**
**** Assumes 0.5 ml injection as target maintenance dose**

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

Specific Instructions:

_____

_____

Prescribing Physician Signature

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

APPENDIX 9. Labels for allergen immunotherapy extracts

Each vial of allergen immunotherapy extract should be labeled in a way that permits easy identification. Each label should include the following information (example in Figs 3 and 4):

- Appropriate patient identifiers might include the patient's name, patient's number, patient's picture, and birth date.
- The contents of the allergen immunotherapy extract in a general way should be included. The detail with which this can be identified depends on the size of the label and the number of allergens in the vial. Ideally, allergens should be identified as trees, grasses, weeds, mold, dust mite, cockroach, cat, and dog. Because of space limitations, it might be necessary to abbreviate the antigens (eg, T, G, W, M, DM, Cr, C, and D respectively [see Appendix 2]). A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate (vol/vol) should be recorded. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- The expiration date should be included.

APPENDIX 10. Allergen immunotherapy administration form recommended documentation

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

Patient information:

- Patient's name, date of birth, telephone number, and patient's picture (optional but helpful).

Allergen immunotherapy extract information:

- Allergen immunotherapy extract name and dilution from maintenance in vol/vol bottle letter (eg, A and B), bottle color, or number, if used.
- Expiration date of all dilutions.

Administration information in separate columns:

- Date of injection.
- Arm administered injection, which might facilitate determination of exact cause of local reaction.
- Projected build-up schedule.
- Delivered volume reported in milliliters.
- Description of any reactions. The details of any treatment given in response to a reaction would be documented elsewhere in the medical record and referenced on the administration form.
- *Patient's health before injection*. This can be performed through a verbal or written interview of the patient before administering the immunotherapy injection. The patient should be questioned about increased asthma or allergy symptoms, β-blocker use, change in health status (including pregnancy and recent infections), or an adverse reaction to a previous injection (including delayed large local reactions persisting through the next day). Patients with significant systemic illness generally should not receive an injection.
- *Antihistamine use*. Antihistamines are frequently a component of an allergy medication regimen, and it would be important to note whether a patient is taking an antihistamine on the day he or she receives his or her immunotherapy injection. For consistency in interpretation of reactions, it might be desirable for a patient to either take or avoid antihistamines on a regular basis on the days he or she receives immunotherapy. The physician should note on the form whether he or she recommends the patient consistently take an antihistamine on immunotherapy treatment days.
- *Peak flow reading*. Consider obtaining a peak expiratory flow rate measurement before administering an immunotherapy injection to asthmatic patients. Poorly controlled asthma is considered a risk factor for immunotherapy. Obtaining a peak expiratory flow rate measurement before the immunotherapy injection might help identify patients with symptomatic asthma. The patient's baseline peak expiratory flow rate should be provided on the form as a reference. Health care professionals administering immunotherapy injections should be provided with specific guidelines about the peak expiratory flow rate measurement for when an immunotherapy injection should be withheld and the patient referred for clinical evaluation.
- **Baseline blood pressure**. It might be useful to record the patient's blood pressure as a baseline for future reference.

APPENDIX 11. Allergen immunotherapy administration form

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 allergy or 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

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

Date to reorder: __/__/__

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 allergy or 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**	

APPENDIX 12. 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: _____
_____
Staff action taken (if any): _____

APPENDIX 13. 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.

APPENDIX 14. Allergen immunotherapy systemic reaction/anaphylaxis 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
__Epinephrine IM into 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	

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:
_____
_____
_____
_____

Clinical impression: True SR Questionable SR No SR

Systemic reaction severity classification: EAACI_____ **Portnoy** _____

Dosage adjustment? _____

Signatures_____ **RN** _____**MD/DO**

APPENDIX 15. Grading severity of allergen immunotherapy reactions: Two methods

1. **The European Academy of Allergy and Clinical Immunology grading of severity for systemic side effects***

Classification of systemic reactions

0 = No symptoms or nonspecific symptoms

I = Mild systemic reactions: symptoms—localized urticaria, rhinitis, or mild asthma (PF <20% decrease from baseline).

II = Moderate systemic reaction: symptoms—slow onset (>15 minutes) of generalized urticaria, moderate asthma, or both (PF < 40% decrease from baseline).

III = Severe (non–life-threatening) systemic reactions: symptoms—rapid onset (<15 minutes) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).

IV = Anaphylactic shock: symptoms—immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, and hypotension, for example.

2. **Portnoy method for numeric grading of reactions to allergen immunotherapy†**

Local

0+ = No significant reaction or small area of erythema less than the size of a half dollar without swelling or wheal formation

1+ = Erythema greater than the size of a half dollar, swelling or wheal formation, or both

Systemic

2+ = Systemic reactions: cutaneous only—might consist of a cutaneous eruption, such as urticaria

3+ = Systemic reaction: generalized pruritus, sneezing, or both—might consist of increased allergy symptoms, such as nasal congestion, sneezing, or pruritus, especially in the mouth or throat

4+ = Systemic reaction: pulmonary—consists of wheezing, shortness of breath, and tightness. Might be associated with decreased pulmonary function tests

5+ = Systemic reaction: anaphylaxis—a sensation of not feeling right is a frequent prelude; might consist of hypotension, laryngeal edema, severe wheezing, and cramping

6+ = Cardiopulmonary arrest

PF, Peak expiratory flow.

*Subcutaneous immunotherapy. Allergy 2006;61(suppl 82):5-13.

†Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80.

Allergen immunotherapy: A practice parameter second update

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

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the "Allergen immunotherapy: a practice parameter second 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 and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
5. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
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13. Allergen immunotherapy: a practice parameter. Ann Allergy 2003;90(suppl):SI-S540.
14. Symptom severity assessment of allergic rhinitis: part I. Ann Allergy 2003;91:105-14.
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17. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol 2005;115(suppl):S483-S523.

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

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Allergen immunotherapy: A practice parameter second update

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PREFACE

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

The objective of ''Allergen immunotherapy: A practice parameter second update'' is to optimize the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. 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's ''Policy on development and use of practice parameters for medical quality decision-making'' (Appendix 1).[1]

This document builds on the previous Joint Task Force document, ''Allergen immunotherapy: a practice parameter'' published in the *Annals of Allergy, Asthma and Immunology* in 2003.[2] The updated practice parameters draft was prepared by Drs Linda Cox, James Li, Hal Nelson, and Richard Lockey. The Joint Task Force reworked the initial draft into a working draft of the document. The project was exclusively funded by the 3 allergy and immunology societies noted above.

In preparation for the 2003 ''Allergen immunotherapy: a practice parameter'' and the second update, a comprehensive search of the medical literature was conducted with various search engines, including PubMed; *immunotherapy*, *allergic rhinitis*, *asthma*, *stinging insect allergy*, and related search terms were used. 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 second update'' was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the ACAAI, AAAAI, and JCAAI. In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for review and comments from members of the sponsoring organizations. 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 allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. This document also contains recommendations for the safe practice of allergen immunotherapy, including specific recommendations on the prevention and management of 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 or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. Symptoms of allergic conjunctivitis (eg, itchy watery eyes) are often considered part of allergic rhinitis or are included in the diagnosis of rhinoconjunctivitis. Particularly good candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures, those in whom it is important to avoid the potential adverse effects of medications, and those who wish to reduce the long-term use of medications. Immunotherapy is recommended for patients with a history of systemic reaction to Hymenoptera stings and specific IgE antibodies to Hymenoptera venom.

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.[3]

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. 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 *maintenance concentrate* should be used to identify the allergen immunotherapy extract that contains a therapeutic effective dose for each of its individual constituents (see the Immunotherapy schedules and doses section).

The term *manufacturer's extract* refers to the allergy extract purchased from the manufacturer. The terms *stock*, *full-strength*, and *concentrate* are ambiguous and should not be used. 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).

Allergen immunotherapy is effective when appropriate doses of the allergens are administered. ''Allergen immunotherapy: A practice parameter'' recommends that vials of allergen immunotherapy extracts should be prepared individually for each patient to enhance the individualization of therapy, reduce the risk of allergen cross-contamination, and reduce the risk of error in administration.[4,5] This parameter recommends the use of standardized allergen immunotherapy prescription and administration forms to improve the safety, uniformity, and standardization of allergen immunotherapy practice.[4,5] The suggested forms are found in the Appendix (Appendices 7, 8, 11, 12, and 14) and in the members' section of the www.aaaai.org Web site. The routine use of these standardized forms should improve the quality of immunotherapy practice.

Members' feedback comments on the recommended allergen extract dilution dating in the 2003 ''Allergen immunotherapy: A practice parameter'' led to an allergen immunotherapy extract dilution stability study designed by the AAAAI Immunotherapy and Allergy Diagnostics Committee and funded by the AAAAI Board of Directors. The study was designed to investigate the effect of time, temperature, and dilution of standardized allergen extract potency, and the results of this study were considered in this update.

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 3 years after publication. Requests for information about or an interpretation of these practice parameters should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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. Allergen immunotherapy

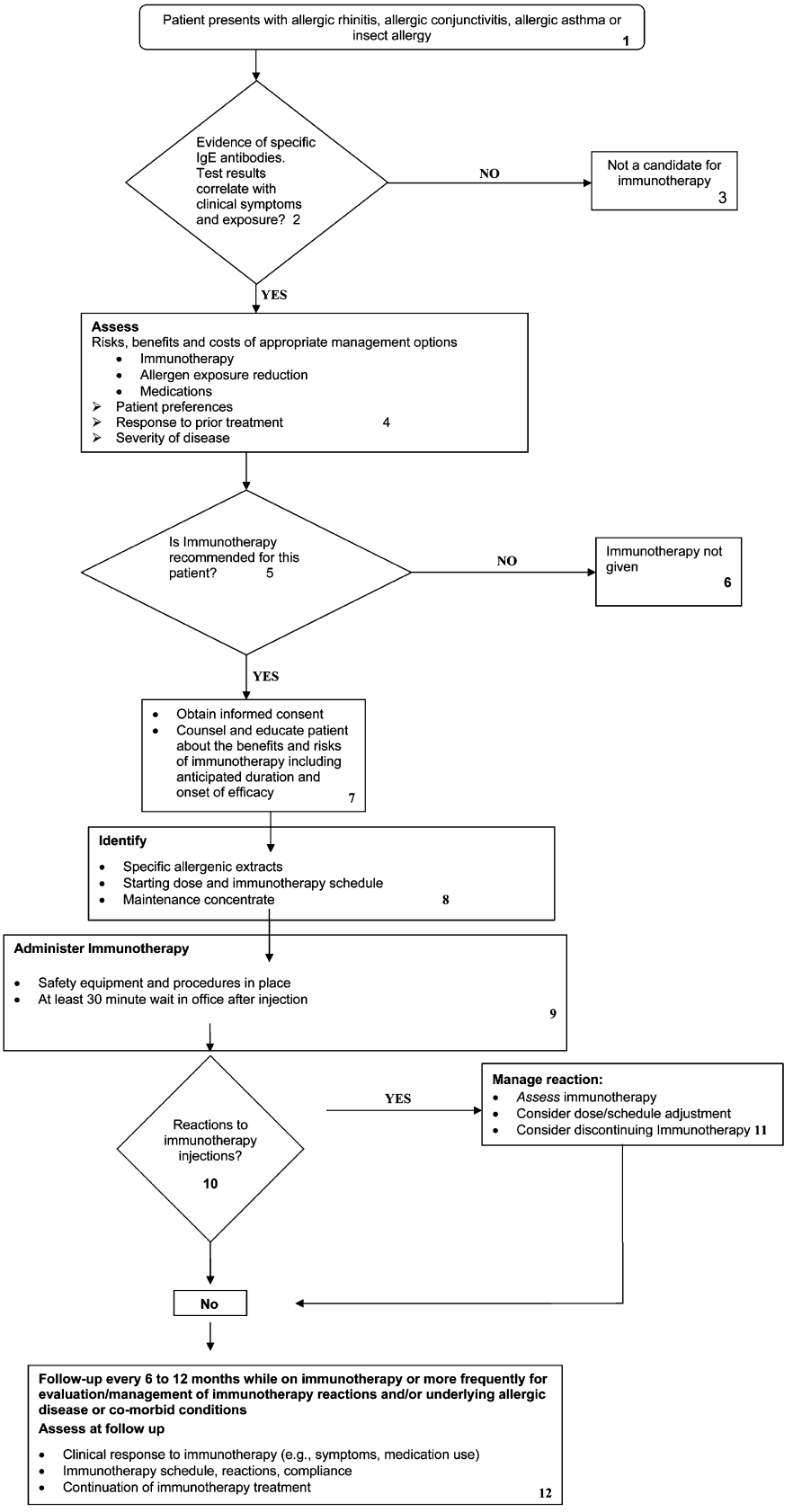


FIG 1. Algorithm for allergen immunotherapy.

might prevent the development of asthma in individuals with allergic rhinitis.[6-9] Evaluation of a patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic conjunctivitis, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for specific IgE antibody).[10]

Box 2

Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although *in vitro* testing for 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

Management of complex medical conditions, such as allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity, should include the careful evaluation of management 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 patient 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. On the basis of clinical considerations and patient 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 good candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy (VIT).

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 on the basis of 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 (see the Immunotherapy schedules and doses section). In general, the starting immunotherapy dose is 1000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 1000 to 4000 arbitrary units (AU; eg, for dust mite) or bioequivalent allergy units (BAU; eg, for grass) 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 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 referred to as *up-dosing*, *induction*, or the *dose-increase phase*) entails administration of gradually increasing doses during a period of approximately 14 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 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, in particular anaphylaxis. Patients should wait at the physician's office for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly, if they occur.

In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring 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. Some physicians recommend providing certain patients with epinephrine for self-administration in case of severe late reactions to immunotherapy injections.

Box 10

Injections of allergen immunotherapy extract can cause local or systemic reactions. Most severe reactions develop within 30 minutes after the immunotherapy injection, but reactions can occur after this time.

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 (anaphylaxis). Epinephrine is the treatment of choice in anaphylaxis, preferably when administered intramuscularly,[11] although subcutaneous administration is acceptable.[12]

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, see the practice parameters for anaphylaxis.[12]

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. After a severe systemic reaction, careful evaluation by the prescribing physician is recommended. For some patients, the immunotherapy maintenance dose might need to be reduced because of repeated systemic reactions to immunotherapy injections. The decision to continue immunotherapy should be re-evaluated after severe or repeated systemic reactions to allergen immunotherapy extracts.

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 doses, 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,[13] but others might experience a recurrence of their symptoms after discontinuation of allergen immunotherapy.[14] 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, and 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 on the basis of the patient's clinical response, disease severity, immunotherapy reaction history, and patient preference.

IMMUNOTHERAPY GLOSSARY

For more information on immunotherapy definitions, see the article by Kao.[15]

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 (pigments and salts; see the Allergen selection and handling section). Other terms used to describe the allergen immunotherapy extract include *allergen product*,[16] *allergy serum*, *allergen vaccine*,[17] 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.[18] Other terms that have been used for allergen immunotherapy include *hyposensitization*, *allergen-specific desensitization*, and the lay terms *allergy shots* or *allergy injections*.[15]

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

TABLE II. Allergen immunotherapy dose-calculation table

- Express weight per volume as a fraction: $\frac{1}{N}$ or 1:*N*.
- Calculate concentration of individual allergens in mixtures. If a mixture is made of equal amounts of N individual allergens to make a total concentration (C), the final concentration of an individual allergen (Ca) can be calculated by using the following equation:

$Ca = C \times \frac{1}{N} = \frac{C}{N}$ or *C*:*N*.

For example, if a mixture of equal amounts of 5 (N) allergens has a total concentration (C) of 100,000 BAU/mL, then the final concentration of each individual allergen (Ca) is: $Ca = \frac{C}{N} = \frac{100{,}000}{5} = 20{,}000\ BAU/mL$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{C}{N} = \frac{1/10}{5} = \frac{0.1}{5} = 0.02$ or $\frac{1}{50}$ or 1:50.

- Dilution of individual allergen: If an initial volume, Vi (in milliliters), of an individual antigen with concentration, Ci, is added to an allergen extract to make a final volume of Vf (in milliliters), the final allergen concentration (Ca) in the allergen extract mixture will be: $Ca = Ci \times \frac{Vi}{Vf}$.
- Final concentration of an allergen in a mixture of mixtures is determined by multiplying the initial concentration by the dilution factors from each mixing step.

For example, consider a mixture containing equal amounts of 5 (N) allergens with a total concentration (C) of 100,000 BAU/mL (first dilution). If an initial volume (Vi) of 0.5 mL of this mixture is further mixed with other components and diluent to make a final allergen extract mixture volume (Vf) of 5.0 mL (second dilution), the final concentration of an individual allergen (Ca) will be:

$$Ca = C \times \underbrace{\frac{1}{N}}_{\text{Mixture dilution}} \times \underbrace{\frac{Vi}{Vf}}_{\text{Allergen extract dilution}} = 100{,}000 \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{100{,}000}{50} = 2000\ BAU/mL$$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{1}{10} \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{1}{500}$ or 1:500.

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).

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 to 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-medicated 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 multiplied by volume of administered dose (see Table II for a dose-calculation table).

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, cat, 1000 BAU, [highest tolerated dose] vs 2000 BAU [projected effective dose]).

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 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 by a variety of immunologic transformations. Early definitions of the term immunotherapy included active and passive immunization for the purpose of improving 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 by means of induction of clonal deletion, anergy, immune tolerance, or immune deviation.

The *maintenance concentrate* is a preparation that contains individual 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 may not be the initially calculated projected effective dose.

The *maintenance goal* (or projected effective dose) is the allergen dose projected to provide therapeutic efficacy. The maintenance goal is based on published studies, but a projected effective dose has not been established for allergens. 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 the 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 large local reaction causing discomfort). The intervals between maintenance immunotherapy injections generally ranges 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 by means of immunoblotting or crossed allergoimmunoelectrophoresis.

For a definition of *projected effective dose*, see 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 test responses), and premedication with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similar high incidence of systemic reactions.

Off the board into one syringe is a phrase that describes a method of allergen immunotherapy preparation and administration that involves specifically mixing the patient's allergen immunotherapy injection in a single syringe, which is not recommended. This syringe might be inserted into more than one allergen extract vial, and this poses a risk of cross-contamination of the allergen extracts and might dull the needle with repeated penetration of the rubber stopper.

Shared specific patient vials is a method of allergen immunotherapy preparation and administration in which the allergy immunotherapy extract is withdrawn from a shared vial (eg, mixed vespids or dust mite mix). This is sometimes referred to as off the board, but it is distinct from the method of off the board into one syringe in that the syringe enters only one allergen extract vial.

INTRODUCTION

Immunity has been defined as protection against certain diseases. The initial immunotherapeutic interventions, which included the use of preventive vaccines and xenogenic 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 the field of allergen immunotherapy. From its humble empiric emergence in 1900, when ragweed injections were proposed as therapy for autumnal hay fever, allergen immunotherapy has progressed in both theory and practice from the passive immunologic approach to the active immunologic procedures pioneered by Noon[19] and Freeman.[20,21] 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 10 years. Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Some studies have suggested that allergen immunotherapy might prevent the development of asthma in individuals with allergic rhinitis.[6-9]

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,[22-26] and it should be differentiated from unproved methods, such as neutralization-provocation therapy and low-dose subcutaneous regimens based on the Rinkel technique, which have been found to ineffective in a double-blind placebo-controlled study.[27,28]

SUMMARY STATEMENTS

Mechanisms of immunotherapy

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, defined as a relative decrease in allergen-specific responsiveness and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

Allergen extracts

Summary Statement 6: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. **A**

Summary Statement 7: Nonstandardized extracts might vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Summary Statement 8: 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**

Cross-reactivity of allergen extract. Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

Efficacy of immunotherapy

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Summary Statement 10: Immunotherapy is effective for 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**

Food allergy, urticaria, and atopic dermatitis. Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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**

Measures of efficacy. Summary Statement 12: 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**

Safety of immunotherapy

Reaction rates. Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

Timing of anaphylactic reactions to immunotherapy injections. Summary Statement 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

β-*Adrenergic blocking agents.* Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

Contraindications. Summary Statement 18: 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**

Reducing the risk of anaphylaxis to immunotherapy injections. Summary Statement 19: 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**

Patient selection

Clinical indications. Summary Statement 20: 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 depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Special precautions in patients with asthma. Summary Statement 21: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. **C**

Clinical indications for VIT. Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Summary Statement 23: Patients selected for immunotherapy should be cooperative and compliant. **D**

Allergen selection and handling

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted in vitro tests for specific IgE antibodies can also be used. **A**

Specific allergens. Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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, supported by the presence of specific IgE antibodies. **A**

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Dose selection. Summary Statement 30: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. **A**

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens, is recommended. **B**

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extract handling

STORAGE

Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

STORING DILUTE EXTRACTS

Summary Statement 34a: More dilute concentrations of allergen immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: 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 a number of 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. **B**

Immunotherapy schedules and doses

Summary Statement 35: A customized individual 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 be based on single or multiple allergens. **D**

Maintenance concentrate. Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

Recommended doses. Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

Effect of dilution on dose. Summary Statement 38: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. **A**

Dilutions of the maintenance concentrate. Summary Statement 39: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. **D**

Labeling dilutions. Summary Statement 40: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. **D**

Individualized treatment vials. Summary Statement 41: 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. The mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. **C**

Starting doses. Summary Statement 42: The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. **D**

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

Dose adjustments for systemic reactions. Summary Statement 44: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. **D**

Reductions during periods of exacerbation of symptoms. Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Dose adjustments for late injections. Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

Cluster schedules. Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. **C**

Rush schedules. Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. **A**

Systemic reactions and rush schedules. Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

Premedication and weekly immunotherapy. Summary Statement 50: Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

Premedication with cluster and rush immunotherapy. Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

Maintenance schedules. Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. **A**

Continuing care

TIME COURSE OF IMPROVEMENT

Summary Statement 53: Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **A**

FOLLOW-UP VISITS

Summary Statement 54: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. **D**

DURATION OF TREATMENT

Summary Statement 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

DOCUMENTATION AND RECORD KEEPING

Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. **D**

INJECTION TECHNIQUES

Summary Statement 57: Allergen immunotherapy extract injections should be administered with a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **D**

Summary Statement 58: The injection should be administered subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Location of allergen immunotherapy administration

Physician's office. Summary Statement 59: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Summary Statement 60: 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**

Other locations. Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **D**

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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**

Summary Statement 63: 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for his or her immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extract might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Special considerations in immunotherapy

Allergen immunotherapy in children. Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Pregnancy. Summary Statement 71: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. **C**

Immunotherapy in the elderly patient. Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy in patients with immunodeficiency and autoimmune disorders. Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

Alternative routes of immunotherapy

Sublingual and oral immunotherapy. Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no US Food and Drug Administration (FDA)–approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **A**

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Immunotherapy techniques that are not recommended. Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

MECHANISMS OF IMMUNOTHERAPY

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, which is defined as a relative decrease in allergen-specific responsiveness, and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

The immunologic changes associated with immunotherapy are complex, and the exact mechanism or mechanisms responsible for its' clinical efficacy are continually being elucidated. Data support the concept that successful immunotherapy is associated with a change to a T_H1 $CD4^+$ cytokine profile.[29-34] Data indicate that increased production of IL-12, a strong inducer of T_H1 responses, contributes to this shift.[33] Clinically successful immunotherapy has been reported to be associated with immunologic tolerance, which is defined as a relative decrease in antigen-specific responsiveness, immune deviation, or anergy. For example, lymphoproliferative responses to allergen are reduced with immunotherapy.[32] Successful immunotherapy results in generation of a population of T regulatory cells, which are $CD4^+CD25^+$ T lymphocytes producing IL-10, TGF-β, or both.[35-39] Regulatory T-cell release has been described in allergen immunotherapy with Hymenoptera venom,[35] grass pollen extract,[37] and house dust mites.[38] IL-10 reduces B-cell antigen-specific IgE and increases IgG4 levels; reduces proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicits tolerance in T cells by means of selective inhibition of the CD28 costimulatory pathway.[36,37]

Allergen immunotherapy has been shown to block both the immediate and late-phase allergic response.[40] Allergen immunotherapy has been shown to decrease the recruitment of mast cells, basophils, and eosinophils in the skin, nose, eye, and bronchial mucosa after provocation or natural exposure to allergens.[41]

In patients receiving immunotherapy, initially there is an increase in specific IgE antibody levels, followed by a gradual decrease to a level that is still higher than that present before treatment. Clinical improvement in many patients develops before decreases in their IgE antibody levels occur or in other patients whose IgE antibody levels never decrease, thereby demonstrating that efficacy is not dependent on reductions in specific IgE levels.[42,43] Immunotherapy does diminish the seasonal increase in specific IgE levels.[44] Despite the persistence of significant levels of specific IgE antibody levels, immunotherapy usually causes a reduction in 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.[45-48]

An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, has also been associated with immunotherapy. The properties of allergen-specific IgA have yet to be determined, and there is a weak correlation between the increase in allergen-specific IgG levels and immunotherapy's clinical efficacy.[30,49,50]

Immunotherapy might alter the affinity and specificity of allergen-specific IgG.[51,52] During the initial phase of ultrarush VIT, a change in IgG specificity (ie, a change in the set of epitopes dominantly recognized by IgG on wasp venom antigens) occurred concomitantly with early clinical tolerance and was seen within 12 hours of ultrarush VIT ($P < .001$).[51] 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 individuals.[52] This change in IgG specificity preceded the increase in IgG titers and was sustained for up to 6 months.[52]

Allergen-specific IgG induced from immunotherapy can block IgE-dependent histamine release and subsequent IgE-mediated antigen presentation to T cells.[53] This effect might be dependent on IgE, allergen concentration, and CD23, the low-affinity receptor for IgE.

Whereas 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.[37,53]

The relationship between these immunologic changes and immunotherapy efficacy is not completely understood.

ALLERGEN EXTRACTS

Summary Statement 6: 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 has 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.[2,18,54-56] 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.

United States–licensed extracts can be obtained in aqueous, glycerinated, lyophilized, and acetone-precipitated and alum-precipitated formulations. Some commonly used allergens are standardized. These include extracts for cat hair, cat pelt, *Dermatophagoides pteronyssinus*, *Dermatophagoides 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.[57] 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.

Most standardized extracts are labeled in BAU. Short ragweed potency units were originally based on the content of the major allergen Amb a 1. Ragweed potency is reported in FDA units and BAU. One FDA unit of Amb a 1 equals 1 μg of Amb a 1, and 350 units of Amb a 1/mL is equivalent to 100,000 BAU/mL. Cat extracts were also originally standardized based on the content of major allergen (Fel d 1), with 100,000 arbitrary units (AU) per milliliter containing between 10 to 19.9 FDA units of Fel d 1 per milliliter (1 FDA unit of Fel d 1 equals 2 to 4 μg of Fel d 1).[55,58,59] Subsequently, $ID_{50}EAL$ testing suggested that 100,000 AU/mL was equal to 10,000 BAU/mL.[60] Approximately 22% of individuals with cat allergy have specific IgE antibodies to cat albumin.[61] Cat pelt extracts have a greater amount of albumin than cat hair extracts.[60]

Dust mites were originally standardized in AU by means of inhibition radioimmunoassay (RIA), and subsequent $ID_{50}EAL$ testing indicated that the AU was bioequivalent to the BAU, and the original AU nomenclature was kept. Dust mite extracts are still labeled in AU.

Summary Statement 7: Nonstandardized extracts can vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Nonstandardized extracts are labeled as wt/vol, which expresses weight in grams per volume in milliliters; that is, a potency of 1:100 indicates that 1 g 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 with a particular wt/vol or PNU potency can have widely varying biologic activities.[62-64] Therefore they should not be considered equipotent.

Summary Statement 8: 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**

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. The major clinically relevant aeroallergens of North America are listed in Table III. Furthermore, nonrelevant allergens in such mixtures could act as sensitizers rather than as tolerogens.[65,66] The physician must therefore select only those aeroallergens for testing and treatment that are clinically relevant in a particular geographic area.

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, dog), insect (cockroach), and Hymenoptera venom source materials.

Cross-reactivity of allergen extract

Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

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. A summary of cross-reactivity patterns of the clinically relevant North American aeroallergens can be found in Fig 2. 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,[67] inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[68-75] Grasses in other subfamilies (eg, Bermuda, Bahia, and Johnson) show greater diversity and should be evaluated separately.[76-78] Bermuda and Johnson grasses are increasingly important in the South,

TABLE III. The major clinically relevant aeroallergens of North America*

- Tree pollen
  - Chinese elm *(Ulmus parvifolia)*†‡; Siberian elm *(Ulmus pumila)*†‡; American elm *(Ulmus Americana)*†‡
  - Red oak *(Quercus rubra)*†; White oak *(Quercus alba)*†
  - Paper birch *(Betula papyrifera)*
  - Alder *(Alnus rubra)*
  - Box elder *(Acer negundo)*†; Red maple *(Acer rubra)*†
  - Eastern cottonwood *(Populus deltoides)*
  - Sycamore *(Platanus occidentalis)*
  - White ash *(Fraxinus americana)*†; Olive *(Olea europaea)*†‡
  - Black walnut *(Juglans nigra)*
  - Mulberry *(Morus rubra)*
  - Mountain cedar *(Juniperus ashei)*
  - Pecan *(Carya illinoensis)*
- Grass pollen
  - Rye *(Lolium perenne)*§‖
  - Timothy *(Phleum pratense)*§‖
  - Meadow fescue *(Festuca elatior)*§‖
  - Bermuda *(Cynodon dactylon)*‖
  - Johnson *(Holcus halepensis)*
  - Bahia *(Paspalum notatum)*
- Weed pollen
  - Short ragweed *(Ambrosia artemisiifolia)*‖
  - English (narrow leaf) plantain *(Plantago lanceolata)*
  - Mugwort *(Artemisia vulgaris)*
  - Russian thistle *(Salsola kali)*
  - Burning bush *(Kochia scoparia)*
  - Sheet (red) sorrel *(Rumex asetosella)*
  - Red root pigweed *(Amaranthus retroflexus)*
- Indoor aeroallergens
  - Cat epithelium *(Felis domesticus)*‖
  - Dog epithelium *(Canis familiaris)*
  - Arthropods (domestic mites: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*)‖
  - Insects (German cockroach: *Blattella germanica*)
- Fungi
  - *Alternaria alternata*¶
  - *Cladosporium* (*C cladosporioides*, *C herbarum*)¶
  - *Penicillium* (*P chrysogenum*, *P expansum*)¶
  - *Aspergillus fumigatus*¶
  - *Epicoccum nigrum*, *Drechslera* or *Bipolaris* type (eg, *Helminthosporium solani*)¶

*Compiled and selected in collaboration with the AAAAI Immunotherapy Committee Allergen Subcommittee for the identification of 35 key allergens of North America.
†Extensive cross-reaction of species within the genus.
‡Apart from regional prevalence, they are limited to local sites with substantial stands of these trees.
§Extensively cross-react with one another and bluegrass, orchard, red top, and sweet vernal.
‖Allergens for which standardized extracts are commercially available.
¶Species that are widely distributed and clinically important.

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.[79-82] 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.[83-85] Significant cross-reactivity between Betulaceae pollens and oak of the Fagaceae family has been demonstrated with percutaneous skin testing.[75] RAST inhibition studies have shown cross-inhibition between oaks and other *Fagales* species.[86] IgE immunoblot inhibition experiments have demonstrated that the *Fagales* species might be strongly inhibited by birch species.[87] The use of one of the locally prevalent members (eg, birch and alder) should be adequate.[88]

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.[89,90] Maple and box elder trees are found throughout the United States, except for the arid southwest. Although in the same genus as maple, *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,[91,92] and there are allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.[93]

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.[94] Similarly, Chenopod-Amaranth families have wide ranges in the western regions but are present throughout North America.[95] Current information on cross-reactivity of these families is limited.[96-98] 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.[99] The use of a single Amaranth extract should be sufficient to cover this family.[100,101] Similarly, *Atriplex* species (eg, saltbushes and scales) show near identity, and use of a single member is adequate. 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,

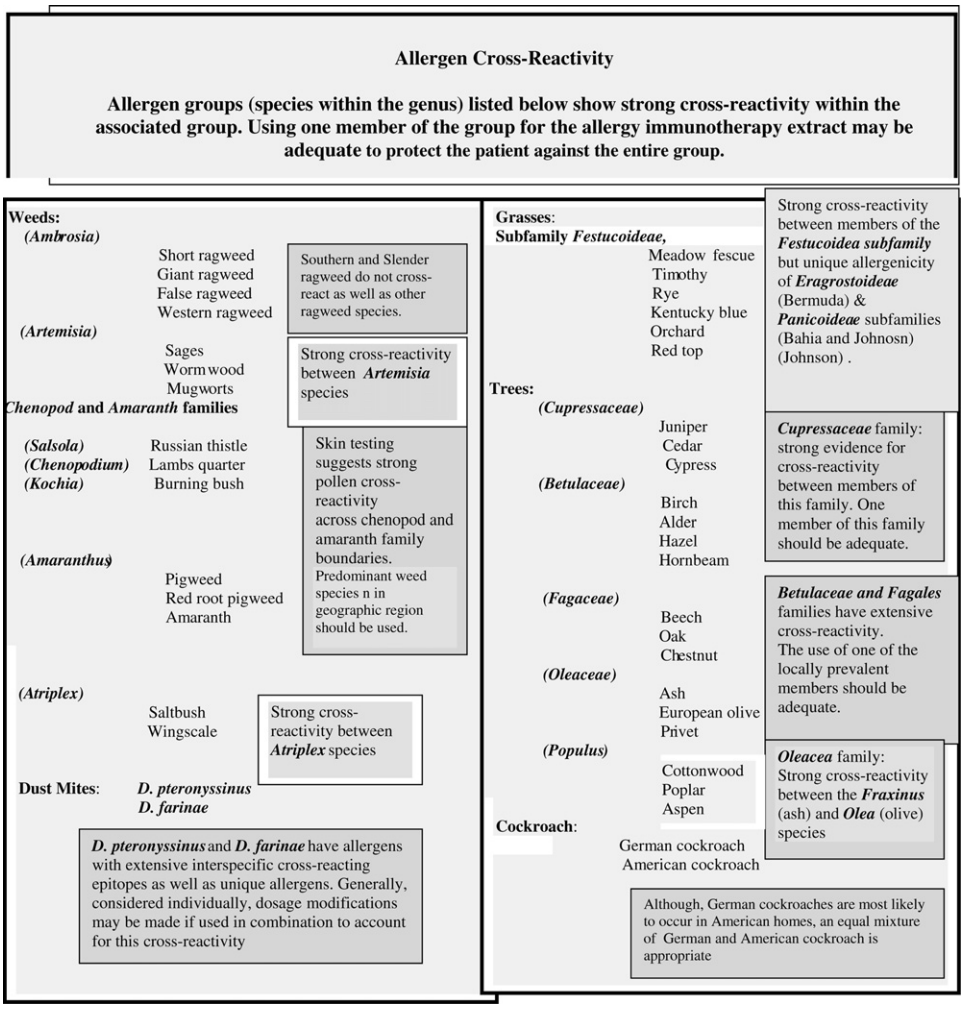


FIG 2. Patterns of allergen cross-reactivity.

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*).

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.[102,103] Stinging Hymenoptera insects occur throughout the United States; the fire ant is found only in Gulf Coast states, Texas, and some other southern and western states. Commercial venom extracts are available for some Hymenoptera species, except the fire ant, for which only whole-body extract is available.

EFFICACY OF IMMUNOTHERAPY

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity

Summary Statement 10: Immunotherapy is effective for 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.[104-111] Immunotherapy is effective for the treatment of allergic rhinitis[107] (including ocular symptoms[112,113]), allergic asthma,[104,109,111,114,115] and stinging insect hypersensitivity[108,116] and is effective in both adults and children.[117-124] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollens,[13,125-132] fungi,[133-138] animal allergens,[22,25,26,139-143] dust mite,[114,115,144-153] and cockroach.[154] There have been no controlled trials of fire ant whole-body extract, but it does appear to be effective in

TABLE IV. Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy

Outcome measure	House dust mite	Other allergens*†
Symptomatic improvement	2.7 (1.7-4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2-7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50)	5.5 (2.8-10.7)

Data are used with permission from Abramson et al.[104]
ND, Not done.
*Odds ratio (95% CI).
†Pollen, mold, or animal dander.

uncontrolled trials.[155-157] 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. A number of studies have also demonstrated a significant improvement in quality of life, as measured by using standardized questionnaires.[24,158-161] The magnitude of the effect depends on the outcome that is used (Table IV). For dust mite, the effect size ranges from a 2.7-fold improvement in symptoms to a 13.7-fold reduction in bronchial hyperresponsiveness. 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.[110] 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[107] and asthma[104,109,111] have been performed to deal with the issue of power. One review of 75 trials involving 3188 asthmatic patients found that, overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyperreactivity after immunotherapy, and it would have been necessary to treat 4 patients (95% CI, 3-5) with immunotherapy to avoid 1 deterioration in asthma symptoms and 5 (95% CI, 4-6) patients to avoid 1 requiring increased medication.[111] These meta-analyses strongly support the efficacy of allergen immunotherapy. Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued[13,162,163] and might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6,9,122,162-165] Allergen immunotherapy might also prevent the development of new allergen sensitivities in monosensitized patients.[120,166,167]

Food allergy, urticaria, and atopic dermatitis

Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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 use of allergen immunotherapy for individuals with the potential for IgE-mediated (anaphylaxis) reactions to foods should be regarded as investigational at this time.[168-171] There have been 2 investigational studies demonstrating efficacy in food hypersensitivity, the first using aqueous subcutaneous injections to peanut and the second using sublingual immunotherapy to hazelnut.[171-173]

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 a modified peanut extract is needed for clinical application of this method of treatment.[171] There is currently no FDA-approved formulation for sublingual immunotherapy, and this route of allergen immunotherapy is currently considered investigational at this time (see Summary Statement 73).

At the present time, there is not enough evidence to support food immunotherapy.

There is no evidence supporting the efficacy of immunotherapy for individuals with chronic urticaria, angioedema, or both.

There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[174-176] 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 ($P = .0379$) and topical corticosteroid use ($P = .0007$).[174]

The potential for benefit in symptoms related to oral allergy syndrome with the cross-reacting inhalant immunotherapy, which includes cross-reacting 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 subcutaneous immunotherapy directed against birch tree,[177] whereas another double-blind, double-dummy, placebo-controlled study comparing the effect of subcutaneous immunotherapy with sublingual immunotherapy 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, medication use, and decrease in IgE reactivity.[178] More investigation is required to substantiate the contention that benefits in oral symptoms will occur with immunotherapy.

Measures of efficacy

Summary Statement 12: 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. Objective measures, such as increase in allergen-specific IgG levels and decreased skin test reactivity, as measured by skin test titration, are changes generally associated with effective immunotherapy but, at present, are not practical for routine clinical use.[147] Nonquantitative skin testing or *in vitro* 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 are not very reliable given the strong placebo-like effect (Hawthorne effect) associated with any treatment. A more objective means for determining efficacy as validated in controlled clinical studies is the use of clinical symptom scores and the amount of medication required to control symptoms and maintain peak flow rates or pulmonary function tests within acceptable limits. Successful immunotherapy often results in a reduction in medication. Sequential measurement of disease-specific quality of life also might be helpful.

SAFETY OF IMMUNOTHERAPY

Reaction rates

Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Large local reactions associated with allergen immunotherapy are fairly common, with a frequency ranging from 26% to 86% of injections.[179] Two retrospective studies compared the effect of not adjusting immunotherapy dose based on large local reactions on the immunotherapy systemic reaction rate with dose-adjustment protocols.[179,180] There was a total of 12,464 injections administered with a dose-adjustment protocol in the 2 studies compared with 9542 injections administered with a no-dose-adjustment protocol. 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 for subsequent systemic reactions, 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 large local reactions, defined as 25 mm or larger, in patients who had experienced systemic reactions with age-, sex-, and allergen sensitivity–matched control subjects who had not had allergen immunotherapy systemic reactions found the rate of large local reactions was 4 times higher among the 258 patients who had subsequently experienced a systemic reaction compared with those who had never experienced a systemic reaction.[181] Patients who had experienced systemic reactions had 1573 large local reactions in 4460 visits (ie, 35.2% of visits) and 8081 injections (ie, 19.5% of injections) compared with the matched control group without systemic reactions who had 1388 large local reactions in 15,540 visits (8.9% per visit) and 26,259 injections (5.3% per injection; difference between groups, $P < .001$). Individual large local reactions were not predictive of future systemic reactions, but large local reactions preceded systemic reactions in approximately one third of the systemic reactions. These findings suggest that individuals with a greater frequency of large local reactions might be at greater risk for systemic reaction. Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy protocol modifications based on them are needed.

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

The prevalence of severe systemic reactions after allergen immunotherapy ranges from less than 1% of patients receiving conventional immunotherapy to greater than 36% of patients in some studies of patients receiving rush immunotherapy.[182,183]

In a recent survey of fatal and near-fatal reactions (NFRs) sent to physician members of the AAAAI, 273 of 646 respondents reported NFRs during the period of 1990-2001.[184]

The incidence of unconfirmed NFRs was 23 per year (5.4 events per million injections). Administration during the height of 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 angiotensin-converting enzyme 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 systemic reactions to subcutaneous immunotherapy over a 20-year period (1981-2000) during which 435,854 injections were administered to 4000 patients, 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.[185,186] In a prospective multicenter study there were 53 systemic reactions (0.3% of the doses) out of 17,526 administered doses in 18 (3.7%) of 423 patients.[187] 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 (21 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, there were 41 fatalities identified in the initial brief survey (20 directly reported and 17 with completed detailed questionnaire) from immunotherapy injections.[188] 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.[189,190] Therefore although severe systemic reactions to allergen immunotherapy are not common, serious systemic reactions (some fatal) can occur.

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

In the AAAAI survey of physician members on immunotherapy and skin testing, fatal reactions, and NFRs during the period of 1990-2001, 15 of the 17 fatalities had asthma, and in 9 patients asthma was considered the susceptibility factor that contributed to the fatal outcome.[188]

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.[184]

Administration during the peak pollen season (3 patients) and previous systemic reactions (4 patients) were cited as other contributing factors. Five fatalities occurred in outside medical facilities, and 2 fatalities occurred at home. No patients were receiving β-blockers; 1 patient was taking an angiotensin-converting enzyme inhibitor. In the most comprehensive evaluation of fatalities associated with allergen immunotherapy, from 1945-1987, there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[189] 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, with 73.3% of patients with an FEV_1 of less than 80% of predicted value experiencing 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 ($P < .0001$).[191] 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% of patients. These studies suggest that symptomatic asthma, severe asthma, or both might be a risk factor for immunotherapy.

In addition to symptomatic asthma and injections giving 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.[17] With the exception of dosing errors and 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 recent 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 or allergy symptom exacerbation, β-blocker use, change in health status (including pregnancy), or adverse reaction to previous allergen immunotherapy injection. The preinjection evaluation might also include a peak flow measurement to assess the airway function of asthmatic patients.

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 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

In a retrospective study the time to onset of a systemic reaction after an immunotherapy injection was less than 30 minutes in most cases.[189] A review of the literature indicates that 70% of systemic reactions occur within 30 minutes after an injection.[183] In the AAAAI 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.[184,188] 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.[190] 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 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.[192] In another prospective study 8% of systemic reactions occurred more than 2 hours after injection.[193]

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.[194]

Because most reactions that resulted from allergen immunotherapy occurred within 30 minutes after an injection, patients should remain in the physician's office for at least 30 minutes after receiving an injection, but longer waits are reasonable, as directed by the physician. In addition, patients who are at increased risk of a systemic reaction might need to carry injectable epinephrine. Such patients might also need to remain in the physician's office more than 30 minutes after an injection. 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.

β-Adrenergic blocking agents

Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

β-Blockade enhances pulmonary, cardiovascular, and dermatologic end-organ effects of mediators and increases mortality associated with experimental anaphylaxis induced by either immunologic or nonimmunologic mechanisms. Patients who are receiving β-adrenergic blocking medications might be at increased risk if they experience a systemic reaction to an allergen immunotherapy injection because the β-receptor blockade might attenuate the response to epinephrine.[195-202] Patients who are receiving β-blocking drugs were almost 9 times more likely to be hospitalized after an anaphylactoid reaction from radiocontrast media.[198] Although topical β-blockers have markedly less systemic β-antagonist effects than oral β-blockers, they still might exhibit some systemic β-antagonist effects. Whether topical β-blockers pose the same or a smaller risk than oral β-blockers in regard to the treatment of allergen immunotherapy–related systemic reactions is not known.

There have been very few studies that have examined the effect of β-blocker medications on allergen immunotherapy. A prospective 1-year study designed to determine whether patients taking β-blocker drugs were at increased risk of immunotherapy-induced systemic reactions found that there were 166 systemic reactions out of 56,105 injection visits in 3178 patients (68 were receiving a β-blocker).[203] The systemic reactions occurred in 144 (4.5%) patients, and only 1 of these patients was receiving a β-blocker medication. The authors calculated that by chance, 3.08 patients receiving the β-blocker medications drugs were expected to have had an systemic reaction and concluded that β-blocker medications did not increase the frequency of allergen immunotherapy systemic reactions ($P > .95$).

In another study of 1389 patients prescribed immunotherapy for Hymenoptera venom hypersensitivity who were followed for 34 months, there were 25 patients who received concomitant β-blocker medications.[204] Three (12%) of the 25 patients receiving β-blocker medications experienced systemic reactions during immunotherapy compared with 23 (16.7%) of 117 patients with cardiovascular disease not receiving β-blockers. Systemic reactions after a field sting or challenge occurred in 1 (14.3%) of 7 cardiovascular patients receiving β-blocker medications compared with 4 (13.8%) of 29 cardiovascular patients not receiving β-blocker medications. No severe reactions to immunotherapy or sting re-exposure were observed in patients receiving β-blockers medications.

Immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. In such cases, intravenous glucagon, which might reverse the refractory bronchospasm and hypotension by activating the adenyl cyclase directing and bypassing the β-adrenergic receptor, might be used if epinephrine has not been effective.[205,206] Prospective studies are necessary to clarify the magnitude of the risk of systemic reactions to allergens in patients who are receiving concomitant therapy with β-blockers, and a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy.

Contraindications

Summary Statement 18: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications

TABLE V. Actions to reduce the risk of anaphylaxis

- Assess the patient's general medical condition at the time of injection (eg, asthma exacerbation).
- Consider obtaining a PEFR before administration of the injection. If the PEFR is significantly less than the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.
- 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 with increased allergen sensitivity or those who have previously had a systemic reaction) might need to wait longer.
- Carefully evaluate any patient with a late reaction (eg, persistent large local reaction lasting >24 hours, systemic reaction occurring more than 30 minutes after the immunotherapy injection).
- 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.

PEFR, Peak expiratory flow rate measurement.

TABLE VI. Recommended equipment and medications to treat anaphylaxis

Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur. This should include at least the following equipment and medications:

- stethoscope and sphygmomanometer;
- tourniquet, syringes, hypodermic needles, and large-bore needles (14-gauge);
- aqueous epinephrine HCL 1:1000 wt/vol;
- equipment to administer oxygen by mask.
- intravenous fluid set-up;
- antihistamine for injection (second-line agents for anaphylaxis, but H_1 and H_2 antihistamines work better together than either one alone);
- corticosteroids for intravenous injection;
- vasopressor;
- equipment to maintain an airway appropriate for the supervising physician's expertise and skill.

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 venom hypersensitivity and cardiac disease being treated with β-blocker medications.

Reducing the risk of anaphylaxis to immunotherapy injections

Summary Statement 19: 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 extremely 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 or other health care professional appropriately trained in emergency treatment.

The 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. Epinephrine is the first-line treatment for anaphylaxis. 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.[12,207-213] It is important to administer epinephrine early in the management of anaphylaxis. 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 V and VI, respectively. Before allergen immunotherapy is chosen as a treatment, the physician should educate the patient about the benefits and risks of immunotherapy, as well as methods for minimizing risks. The patient also should be told that despite appropriate precautions, reactions might occur without warning signs or symptoms. Informed consent should include a discussion of the potential immunotherapy adverse reactions, and this discussion should be documented in the patient's medical record.

PATIENT SELECTION

Clinical indications

Summary Statement 20: Allergen immunotherapy should be considered for patients who have demonstrable

TABLE VII. Clinical indications for allergen immunotherapy

Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or both:
- symptoms of allergic rhinitis after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medications;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medication;
- coexisting allergic rhinitis and asthma;
- possible prevention of asthma in patients with allergic rhinitis

Symptoms of asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medication;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medications;
- coexisting allergic rhinitis and allergic asthma.

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);
- adults and children with a history of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.

evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic rhinitis.[107] Prospective, randomized, double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic asthma.[104,109,111]

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 proper identification and selection of component allergens on the basis of 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 (Table VII). The severity and duration of symptoms should also be considered in assessing the need for specific allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. In addition, specific allergen immunotherapy should be considered if the patient wishes to avoid long-term pharmacotherapy. Time lost from work, emergency department or physician's office visits, and responses to pharmacotherapy are important objective indicators of allergic disease severity.

Patients with allergic rhinitis who are unable to sleep because of symptoms or whose symptoms interfere with their work or school performance should be considered strong candidates for specific allergen immunotherapy. 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 considered. Unacceptable adverse effects of medications should also favor one's decision to initiate allergen immunotherapy. Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.[214]

Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued, and it might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6-9,122,162-165] These benefits of immunotherapy should be discussed with patients and might provide a clinical indication for immunotherapy for individual patients with allergic rhinitis.

Coexisting medical conditions should also be considered in the evaluation of a patient who might be a candidate for allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed with a combined aggressive regimen of allergen avoidance and pharmacotherapy and might also benefit from allergen immunotherapy.[215,216]

However, the patient's asthma must be stable before allergen immunotherapy is administered.[188,191]

Special precautions in patients with asthma

Summary Statement 21: 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 might be at increased risk for systemic reactions to immunotherapy injections.[182,188,191] Two surveys found that deaths from

immunotherapy were more common in symptomatic subjects with asthma.[188,189] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2,217]

Clinical indications for VIT

Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Systemic reactions to Hymenoptera stings, especially when associated with respiratory symptoms, cardiovascular symptoms, or both and positive skin test or *in vitro* test results for specific IgE antibodies, are a strong indication for allergen immunotherapy.[218] In the United States patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Several studies of patients with imported fire ant allergy have demonstrated the effectiveness of immunotherapy with whole-body extracts of fire ants.[155,156,219] 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. Patients younger than 16 years of age who present only with a cutaneous reaction to imported fire ant or Hymenoptera stings might not require immunotherapy.[218,220-222] In addition to allergen immunotherapy, patients with imported fire ant and Hymenoptera venom sensitivity should be instructed in how to best avoid insect stings, be prescribed epinephrine, and be taught how 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 the population that has not had a systemic reaction.[223] In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific IgE is recommended.[218] If the venom-specific IgE test result is also negative, it is recommended that the skin tests, venom-specific 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 IgE test result.[224] 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 re-stung. 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%).[225] 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 IgE test results who have had severe anaphylaxis to an insect sting.

Some patients who have negative venom skin test results and negative venom-specific IgE test results are reported to have had subsequent systemic reactions to stinging insects.[225-227] Controlled studies designed to evaluate the efficacy of immunotherapy in these patients have not been performed. There are very 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.[226] 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.

Summary Statement 23: 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.

ALLERGEN SELECTION AND HANDLING

Allergen selection

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

A careful history, noting environmental exposures and an understanding of the local and regional aerobiology of suspected allergens, such as pollen, fungi (mold), 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 skin or *in vitro* test results for specific IgE antibodies, provide good evidence that such exposures are relevant. Information concerning regional and local aerobiology is available on various Web sites or through the National Allergy Bureau at http://www.aaaai.org/nab. There are

no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma. 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 clinical history of an allergic disease.

There is no evidence to support the administration of immunotherapy based solely on results of specific *in vitro* 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.

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

The omission of clinically relevant allergens from an allergic patient's allergen immunotherapy extract contributes to decreased effectiveness of allergen immunotherapy. The 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 can make allergen immunotherapy less effective.

Knowledge of the total allergenic burden facing a patient and the realistic possibility of avoidance is important in determining whether allergen immunotherapy should be initiated. 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. Many individuals travel extensively for business or pleasure into different regions, and symptoms might worsen at these times. However, inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective. Determination of the significance of indoor allergens for a particular patient is harder because it is difficult to determine exposure in the home, school, and/or workplace. Historical factors, such as the presence of a furry animal in the home, a history of water damage and subsequent fungal exposure, or a history of insect infestation, might be helpful. However, such information is subjective and is often of uncertain reliability. In addition, some studies have demonstrated significant indoor levels of cat and dog allergen in households without pets[228] and significant levels of mouse allergen in suburban[229] and inner-city[230] homes 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 with increased asthma morbidity in inner-city children was found.[231] 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. Nevertheless, for most patients, determination of the clinical relevance of an allergen requires a strong correlation between the patient's history and evidence of allergen-specific IgE antibodies.

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted *in vitro* tests for specific IgE antibodies can also be used. **A**

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 the skin test results have demonstrated the efficacy of immunotherapy for relevant allergens.[25,26,112,130,134,135,140,141,149,154] 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 from skin testing in a highly sensitive individual.[232,233] In addition, skin tests might be difficult to perform in patients with dermatographism or atopic dermatitis. *In vitro* tests are particularly useful in such patients.

Studies indicate that skin testing is generally more sensitive than *in vitro* tests in detecting allergen-specific IgE.[234,235] Based on inhalation challenge test results, skin tests have shown specificity and sensitivity generally superior to those of *in vitro* tests. The comparability of skin tests and *in vitro* tests for specific IgE antibodies depends on the allergen being tested. For all of 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, prick testing is sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass[236] and cat,[237] are used. Intradermal/intracutaneous skin testing might be required for some allergen extracts. It is appropriate in some patients to use *in vitro* tests for specific IgE antibody as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. *In vitro* tests can also be used to define the allergens that should be used in allergen immunotherapy. If the allergy skin test result is negative and the *in vitro* test result is positive, a controlled challenge can be performed, and if the latter is positive, immunotherapy can be considered. 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 *in vitro* test results.

Specific allergens

Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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.[17,104,106,107,109] 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.[112,122] Because a particular pollen extract is a mixture of multiple glycoproteins, this suggests that mixing pollen allergens does not alter biologic activity.

Fungi (molds). Several studies with *Alternaria* and *Cladosporium* species suggest that allergen immunotherapy with fungi might be effective.[133-138] The allergen content of most mold extracts is highly variable.[238,239] However, there is evidence that proteolytic enzymes present in some mold extracts could digest other antigens, such as pollens, when combined in a mixture.[240] For this reason, it might be desirable to separate all pollen extracts from mold extracts when using mixtures.

Unfortunately, extracts for some potentially clinically important fungi are not available.[241] 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 distinguish 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.

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.

Because immunotherapy has been shown to be effective for cat[22,26,139-143,242] and dog,[25,141] the decision to include dog or cat allergen in an allergen immunotherapy extract should be considered in those circumstances in which there is exposure.

Dust mites and cockroach allergens. Crude house dust extract is generally an inappropriate substitute for house dust mite extract because the protein content measured is not restricted to dust mite allergens, nor does it necessarily guarantee inclusion of dust mite protein. Immunotherapy with standardized dust mite is generally more effective than that with crude house dust allergens. The house dust mites *D farinae* and *D 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, such as *Blomia tropicalis* and *Euroglyphus maynei*, partially cross-react with allergens from *Dermatophagoides* species. Only 50% of the projected amounts of each of the 2 house dust mites (*D pteronyssinus* and *D farinae*) need 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[144,147-149,151] 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. Dust mite hypersensitivity should particularly be considered in patients who have perennial symptoms exacerbated by a dusty environment at home, work, or both and periods of high humidity.

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. The major allergen of *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.[243] Immunotherapy with cockroach allergens is effective[154] and should 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.

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.[108,116,244] Efficacy has also been demonstrated with immunotherapy by using whole-body extracts of imported fire ants.[155,156]

Foods. Only a single clinical study accessing the efficacy and safety of subcutaneous immunotherapy with foods has been performed.[171,173] This study, which evaluated immunotherapy with peanut, found the incidence of systemic reactions, even during maintenance, was unacceptable. Thus there is no evidence to support the use of immunotherapy with food extracts. Currently, strict avoidance of the offending food is advisable, and subcutaneous immunotherapy for food allergy is not recommended.

Mixing of extracts

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Once the relevant allergens for each patient are identified, it is necessary to prepare a mixture that contains each of these allergens. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts. A number of 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 interactions between different types of allergens, when mixed, that could lead to degradation or unmasking of epitopes on exposure to proteolytic enzymes.

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Immunologic and 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.[71] 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 genera 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 the Allergen extract section, Fig 2, and the allergens and allergy diagnostic tests practice parameters).

Dose selection. Summary Statement 30: 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.[22-26,128,149,245] Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000 vol/vol).[28] A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy vaccine. Failure to do so might reduce the efficacy of immunotherapy. This occurs because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased (see the Immunotherapy schedules and doses section for further discussion and for recommended maintenance doses).

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as fungi (mold) and cockroach, from other extracts, such as pollens, is recommended. **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.[240,246,247] 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, and some weeds.[240,246,247] Cockroach had a similar deleterious effect on pollen extract potency.[246,248] Short ragweed appeared resistant to the effects of the proteolytic enzymes in one study,[240] 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.[247]

Dust mite extracts do not appear to have a deleterious effect on pollen extracts.[240,246,248] These studies suggest that pollen, dust mite, and cat extracts can be mixed together. 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. The evidence on mixing cockroach extract with other extracts is conflicting, and the clinical relevance of the changes is also unclear; therefore the clinician has the option of separating cockroach or not.

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 with lesser activities, such as pollen extracts.

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.

In this regard the number of separate injections that need to be given at each patient visit depends on whether all of the relevant extracts mixed into a single vial still deliver an optimal dose of each allergen. If mixing causes excessive dilution or if there are advantages to separating allergens into separate vials, then more than one vial might be necessary for successful immunotherapy.

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extracts are high-alert products that carry the risk for anaphylaxis. Policies, procedures, and processes intended for conventional drugs and medications might be highly 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 fatal anaphylactic reactions with allergenic products. 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. There are no reports of infection associated with allergen immunotherapy injections. Allergen vaccines are prepared by using sterile manufacturer's extracts and sterile diluents containing antibacterial constituents (usually phenol). A summary of the AAAAI/ACAAI/JCAAI proposed USP allergen immunotherapy extract preparation guidelines can be found in Table VIII.

TABLE VIII. AAAAI/ACAAI/JCAAI-proposed USP 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 below.*
   - 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.
2. **Physician responsibility**: A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in the preparation of immunotherapy using an aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files.
3. **Bacteriostasis**: Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if 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 the FDA-approved package insert 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 treatment with sanitizing agents containing alcohol and/or 70% isopropanol 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 the physical integrity of the vial.
10. **Labeling**: Immunotherapy vials are to be clearly labeled with the patient's name and 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.

*__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 media, such as from Valiteq (http://www.valiteq.com), 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.

Allergen immunotherapy extract handling

Storage. Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

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 a number of 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 extract, including reconstituted lyophilized extracts, should be stored at 4°C to minimize the rate of potency loss because storage at higher temperatures (eg, room temperature) can result in rapid deterioration.[249]

Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions (personal communication). These studies include actual shipments made by their carriers to places like

Phoenix in the summer and Alaska in the winter. 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.

Storing dilute extracts. Summary Statement 34a: More dilute concentrations of allergy immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than do more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: In determining the allergy vaccine expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of 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 allergen immunotherapy 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.[249,250]

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.[250] Phenol is a preservative added to extracts to prevent growth of microorganisms.

Phenol can denature proteins in allergen extracts.[251,252] Human serum albumin might protect against the deleterious effect of phenol on allergen extracts.[251] 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,[250,253] possibly through inhibition of the activity of proteolytic and glycosidic enzymes that are present in certain extracts. However, it is irritating when injected and should be diluted before beginning immunotherapy. Recommendations for extract stability are found in the manufacturers' product insert sheets. 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. The pain associated with glycerin increases in proportion to the glycerin concentration and injection volume, and the pain is proportional to the total injected dose of glycerin.[254] However, individual pain perception can vary substantially. Total glycerin doses of less than 0.05 mL rarely produce clinically important pain.

TABLE IX. Potency of selected manufacturer's extracts currently available

Extract	Potency
Cat hair and pelt	5000 and 10,000 BAU/mL
Dust mite	3000, 5000, 10,000, and 30,000 AU/mL
Bermuda grass	10,000 AU/mL
Short ragweed	1:10-1:20 wt/vol or 100,000 AU/mL
Other grasses*	10,000 and 100,000 BAU/mL
Other pollen	1:10 to 1:40 (wt/vol) or 10,000 PNU/mL
Molds	1:10 to 1:40 (wt/vol) or 20,000 to 100,000 PNU/mL

AU, Allergy unit; *BAU*, bioequivalent allergy unit; *PNU*, protein nitrogen unit.
*Perennial rye, Kentucky blue/June, timothy, sweet vernal, redtop, orchard, and meadow.

There have been few studies that have investigated the potency of dilutions of allergen extract mixture over time. Expiration dates for allergen extract dilutions are somewhat empiric and not strongly evidence based. A study undertaken by the AAAAI 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. Dust mite and cat at 1:10 and 1:100 vol/vol dilution were also stable in all conditions of storage over 12 months, as measured by an ELISA assay using 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.

IMMUNOTHERAPY SCHEDULES AND DOSES

Summary Statement 35: A customized individual 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 can be based on single or multiple allergens. **D**

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. Animal dander contains between 10 and 20 antigens,[255] house dust mites between 20 and 40 antigens,[256] and pollens between 30 and 50 antigens,[257,258] and fungal extract can contain as many as 80 antigens.[259]

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. This is designated as the patient's maintenance concentrate.

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. Standardized extracts are available with biologic potencies of 10,000 and 100,000 BAU for grasses; 5000 and 10,000 BAU for cat allergen; 5000, 10,000, or 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 wt/vol extracts (Table IX). 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.

Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

The highest concentration of an allergen extract mixture that is projected to be used as the therapeutically effective dose is called the maintenance concentrate. This should be prescribed individually for each patient by an allergist/immunologist. 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 individual manufacturer's extracts. Some patients might be unable to attain the projected therapeutically effective dose of the maintenance concentrate because of local reactions, systemic reactions, or both (eg, cat, 1000 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose]; see Table X for probable effective therapeutic dose range). Such patients might need weaker dilutions of their maintenance concentrate. Even so, 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 referred to as the maintenance dose. The consistent use of this nomenclature system is essential because errors in choosing the correct vial are a common cause of systemic reactions, especially when the patient transfers from one physician to another. Therefore it is important that standard terminology be adopted by all physicians who prescribe allergen immunotherapy.

Recommended doses

Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

The effective maintenance dose of immunotherapy for a particular patient must be individualized. To do this, the allergist/immunologist who prepares the allergen immunotherapy extract must balance the dose necessary to produce efficacy and the risk of reactions if such a dose is reached. The allergist/immunologist might need to prepare more than one maintenance concentrate to provide a therapeutic dose of each of the allergens for the polysensitized patient. Therapeutically effective doses for immunotherapy have been reported for some allergen extracts.[22,24,25,128,134,135,149,246,260,261] Effective doses have been determined for Hymenoptera venom, dust mite, cat allergen, dog, grass, and short ragweed (Table X).

Controlled studies demonstrate that the content of particular allergens in allergen immunotherapy extracts can be used to predict a therapeutic dose for those allergens, particularly when the extracts are standardized. For antigens 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. The therapeutically effective doses used in the most recent controlled clinical studies are the basis of the recommended dosage range of standardized extracts presented in Table X. 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 time that it is administered.[14]

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.[27] 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 risk of systemic reactions to immunotherapy injections with higher maintenance doses. The maintenance concentrate should be formulated to deliver a full therapeutic dose of each of its constituent components. However, some sensitive patients might not tolerate the targeted therapeutic dose, and their maintenance dose would be lower. Individuals 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 referred to as the maintenance dose.

Regardless of dose schedule, some patients are unable to progress to the predetermined maintenance dose because of large local or systemic reactions to the allergen

TABLE X. Probable effective dose range for allergen extracts US standardized units[a]

Antigen	Labeled potency or concentration[a,b]	Probable effective dose range
Dust mites: *D farinae* and *D pteronyssinus*[c]	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat[d]	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized[e]	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed[f]	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 μg of Amb a 1 1000-4000 AU Concentration of Amb a 1 is on the label of wt/vol extracts in FDA units[358]
Nonstandardized extract, dog[g]	1:10 to 1:100 wt/vol	15 μg of Can f 1
Nonstandardized extracts	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose

[a]Multiple studies have demonstrated that the efficacious dose for allergen immunotherapy is between 5 and 20 μg of the major allergen per injection. Only 2 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).

[b]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).

[c]There have been no dose-response studies with United States–licensed dust mite extracts, and dosing recommendations in AU value are extrapolated from published European studies that used aqueous[349] and alum-precipitated[149,151] extracts. 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.[149] The authors suggested the optimal maintenance dose was 7 μg of Der p 1. Corresponding doses were based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Extrapolating effective and safe doses in this manner might not be scientifically valid. *D farinae* and *D pteronyssinus* are similar in group 1 allergen content according to the FDA's current reference standards. 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*.

[d]The major cat allergen Fed d 1 is reported in FDA units, with 1 Fel d 1 unit equaling approximately 2 to 4 μg of Fel d 1.[55,58,59] The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 to 19.9 U/mL. One study demonstrated clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 dose in terms of decreased cat extract PD_{20}, titrated skin test results, and allergen-specific IgE and IgG levels.[350,351] In a recent study that investigated the efficacy in terms of immunologic changes of 3 doses of a United States–licensed cat extract (0.6, 3, and 15 μg) demonstrated that a significant effect on titrated skin prick test results, allergen-specific IgG4 levels, and $CD4^+$/IL-4 levels was only seen in the group treated with 15 μg of Fel d 1, although the 3-μg dose group did demonstrate a significant change in titrated skin test response and increase in cat-specific IgG4 levels.[22]

[e]There have been no dose-response studies with United States–licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,[130] alum-precipitated,[24,161] and calcium phosphate–precipitated grass pollen extracts.[352] One of these studies compared a dose of 2 μg with 20 μg of major timothy allergen (Phl p 5) and found clinical efficacy at both doses.[24] The efficacy was greater in the 20 μg of Phl p 5 dose, but the systemic reaction rate was also higher in the high-dose group. The package inserts for United States–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 BAU. Extrapolating effective and safe doses in this manner might not be scientifically valid. 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).

[f]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 suggested that 1 unit of Amb a 1 is equivalent to 1 μg of Amb a 1, and 350 Amb a 1 units/mL is equivalent to 100,000 BAU/mL.[60] The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2000 AU, with a range of 1000-4000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrated 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.[45] A ragweed dose-response study (0.6, 12.4, and 24.8 μg of Amb a 1) demonstrated efficacy, as measured by nasal challenge, at 12 and 24 μg of Amb a 1.[128] The efficacy of the 24-μg dose was not significantly better than the 12-μg dose, and the authors concluded that the optimal dose for ragweed extract was greater than 0.6 μg but not more than 12.4 μg of Amb a 1.

[g]Dog extracts are not standardized. However, one dose-response study with a United States–licensed acetone-precipitated dog extract investigated the efficacy of 3 doses (AP dog; Hollister-Stier, Spokane, Wash; 0.6, 3, and 15 μg) in terms of immunologic changes and found the dose of 15 μg of Can f 1 to be most efficacious.[25] 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 have assayed between 128 and 208 μg/mL (average Can f 1, 162 μg/mL [SD ± 26 μg/mL]; information provided by the extract manufacturer, Hollister-Stier).

immunotherapy extract. The evidence is not clear whether large local reactions are a potential risk for subsequent allergen immunotherapy systemic reactions.

Published studies do not indicate that an individual large local reaction is predictive of a subsequent systemic reaction.[179,180] However, one retrospective study found that individuals who have a history of repeated large local reactions (defined as >25 mm) might be at greater risk for a subsequent systemic reaction.[181]

The concept of highest tolerated dose does not apply for VIT, and all patients are expected to achieve the full recommended dose to achieve the necessary degree of protection. There are conflicting data over whether lower doses (50 μg) are less effective, but there are also data showing that 200 μg is more reliably effective.[245] In the case of VIT, patients are asked to tolerate more large local reactions to achieve the full dose, even though with inhalant immunotherapy the dose can be reduced for such large local reactions to minimize patient discomfort.

Effect of dilution on dose

Summary Statement 38: 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 vaccine, thereby limiting the ability to deliver a therapeutic effective dose for any given allergen.

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

Dilution from maintenance concentrate vaccine	Volume	Volume (mL)	Diluent volume (mL)	Final volume
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.

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 2000 BAU/mL, 2 mL of the manufacturer's extract (cat, 10,000 BAU/mL) can be added to 8 mL of diluent or 8 mL of other allergens, and the final concentration of cat will be 2000 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.

Dilutions of the maintenance concentrate

Summary Statement 39: 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 vol/vol 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, 1000 BAU or 100 BAU), but this system can be complicated if allergens with different potency units are used (eg, wt/vol, BAU, AU, or PNU) and make it difficult to easily interpret the vial label.

Instructions on how to prepare various allergen extracts 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.

Labeling dilutions

Summary Statement 40: 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, a number of 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 (vol/vol), a numbering system, a color-coding system, or an alphabetical system should be used. If this uniform labels 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.

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
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

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 3 and 4).

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 Appendix 2]).

Individualized treatment vials

Summary Statement 41: 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 (wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for 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). Labels on patient-specific vials can provide at least 2 patient identifiers (birth date and patient name), which would be consistent with the recommendations of the Joint Commission on Accreditation of Health Care Organizations National Patient Safety Goals: ''Goal 1: Improve the accuracy of patient identification by using at least two patient identifiers when providing care, treatment or services.''[5] 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 administration of the injection.[4,5]

In a survey of 1717 allergists endorsed by the AAAAI and JCAAI, 57% of the 476 respondents reported at least one wrong-patient injection, and 74% of the 473 respondents reported at least one wrong-dose injection.[4] 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 reasons why this might reduce incorrect injection errors. One reason was that patient-specific vials can be prepared in a quiet laboratory setting, which might provide substantially less distraction than the nurse in a room with a patient who is trying to concentrate only on drawing up the injection correctly. In addition, the specific components are mixed once with the preparation of individually prepared patient-labeled vials, whereas the mixing would be repeated on every injection visit if the allergen extract is withdrawn from different stock solutions, as it is in the off-the-board method. For safety reasons and to avoid cross-mixing of allergens removed from the manufacturer's extract, the mixing of antigens in the syringe (off the board) is not recommended.

Some allergists/immunologists prefer to administer immunotherapy doses drawn directly from a single stock dilution of individual allergens or common mixes (shared specific patient vials). In this way the immunotherapy dose is transferred to the patient without cross-contamination. If shared-patient (eg, mixed vespids and dust mite mix) vials are used, it is essential that policies and procedures are developed to verify that the correct dose from the correct vial is administered to the correct patient.

Starting doses

Summary Statement 42: The starting dose for build-up is usually a 1000- 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 slowly 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 1:1000 (vol/vol), although more diluted concentrations frequently are used for patients who are highly sensitive, as indicated by history or skin test reaction (see Appendix 3 for an example of a conventional immunotherapy schedule).

Frequency of build-up injections

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 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 2 times per week. 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 4 to 6 months, depending on the starting dilution and the occurrence of reactions. It is acceptable for patients to receive injections more frequently, provided there is adequate spacing between injections. The interval between injections is empiric but might be as short as 1 day without any increase in the occurrence of systemic reactions[262] if there is some urgency to achieve a maintenance dose (eg, allergy season is approaching) or for practical reasons (eg, patient's schedule). Alternatively, treatment schedules can be used that more rapidly achieve maintenance dosing. These cluster and rush dosing schedules are discussed in Summary Statements 47 through 49.

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 a number of 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).

Dose adjustments for systemic reactions

Summary Statement 44: 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 benefit/risk ratio justifies continuation of immunotherapy.

Reductions during periods of exacerbation of symptoms

Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Immunotherapy administered during periods of exacerbation of symptoms is considered a risk factor for immunotherapy.[17,184] Injections administered during periods when a patient is exposed to increased levels of allergen to which they are 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.[184] 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 sensitive, especially if their symptoms are poorly controlled.

Dose adjustments for late injections

Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

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 depends 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 Appendix 4 for an example of a dose-modification regimen for gaps in treatment).

Cluster schedules

Summary Statement 47: 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 (see Appendix 5).[22,26] 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. The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules.[145,263-266] The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.[267]

Rush schedules

Summary Statement 48: 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.[268] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.[191,269-272]

The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections over the course of 4 hours.[273] Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours.[274-276] 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 cluster[145,266] and rush[134,277] schedules.

Systemic reactions and rush schedules

Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

The advantages of rush immunotherapy come at a cost because there is an increased risk of local and systemic reactions. Systemic reaction rates have been reported to be

as high as 73% of patients, with the risk of such reactions reduced to 27% by premedication in one study.[272] Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing.[273]

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

Rush protocols for administration of Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions.[274-276,278,279]

Premedication and weekly immunotherapy

Summary Statement 50: Premedication can reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

There is concern that antihistamines taken before each injection with conventional immunotherapy might mask a minor reaction that would otherwise alert a physician to an impending systemic reaction. 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.[280] One study that compared terfenadine premedication with placebo premedication during rush VIT demonstrated greater clinical efficacy in the terfenadine-premedicated group in terms of subsequent responses to field stings or sting challenge.[281] There was also a significant difference in the systemic reaction rate between the 2 groups: 6 patients in the placebo-premedicated group had systemic reactions, whereas none of the patients in the terfenadine-premedicated group had systemic reactions ($P = .012$).

Unfortunately, patients might still have life-threatening anaphylaxis despite 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.

Premedication with cluster and rush immunotherapy

Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

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.[267] Premedication with a 3-day course of prednisone, an H_1 histamine receptor antagonist, and an H_2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.[272] In one study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on the safety and efficacy of rush immunotherapy, there was a 5-fold decrease in the risk of anaphylaxis in the group premedicated with omalizumab compared with the placebo premedication group.[282]

There are anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist, but there have been no published studies. Because the risk of a systemic reaction from rush VIT is relatively low, routine premedication before rush VIT is usually unnecessary.[274,276,278,279] In a study evaluating premedication with antihistamines and steroids for rush immunotherapy with imported fire ant venom, there was no statistically significant differences in the systemic reaction rates between the premedication and placebo premedication group (3.6% of the premedication group vs 6.7% of the placebo group, $P = .87$).[157]

Maintenance schedules

Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals 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 individuals might tolerate longer intervals between maintenance dose injections.

The interval between venom injections can be safely increased up to 8 weeks in some patients without loss of efficacy. 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.

Continuing care

Time course of improvement. Summary Statement 53: Clinical 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.[24,134,143,277] Improvement might not be observed for a number of reasons, including (1) failure to remove significant allergenic exposures (eg, a cat), (2) exposure to high levels of

allergen (eg, pollen or molds), (3) continued exposure to nonallergen triggers (eg, tobacco smoke), or (4) incomplete identification and treatment of clinically relevant allergens. 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 54: 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 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 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

The patient's response to immunotherapy should be evaluated on a regular basis. 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. 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.

There have been very 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 individuals.[283-285] However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported.[283,285] Nevertheless, systemic reactions to stings after discontinuing VIT were generally much milder than the pretreatment reactions and were rarely severe. Two studies did not find a difference in relapse rates between the patients treated for 3 years compared with those treated for 5 years,[283,286] but one of the studies noted that the small number of patients in the 3-year treatment group prevented them from making any conclusions about the risk of discontinuing treatment after 3 years.[283] However, one study found that patients who had experienced re-sting reactions after discontinuing VIT had received VIT for a significantly shorter duration (mean, 43.35 months) than those with continued protection (mean, 54.65 months; $P < .01$).[285] Another study reported that 5 years of VIT provided better immunologic and clinical outcomes than 2 to 4 years of treatment.[287]

Change in skin test reactivity did not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who experienced a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE.[286,288] Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment.[288] The relapse rate and the frequency of severe reactions were greater in patients who had a history of very severe reactions to stings before treatment, in patients who had systemic reactions during VIT (to a sting or a venom injection), in patients with honeybee allergy, and in those who had less than 5 years of treatment.

The duration of inhalant allergen immunotherapy efficacy has not been as extensively studied. Some studies have suggested 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 *(D pteronyssinus)* extract for 12 to 96 months.[14] 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.[13] There was a switch to placebo in half of 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. These studies demonstrate the uncertainty of the long-term benefit of inhalant immunotherapy after discontinuation.

Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained clinical remission after discontinuing inhalant immunotherapy, and 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 indication for continuation of immunotherapy can be found at http://www.aaaai.org or http://www.jcaai.org.

Documentation and record keeping. Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully 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 allergy immunotherapy and prescription forms can be found in the Appendix (Appendices 6-15), and these include examples of immunotherapy prescription and administration forms. These forms, along with examples of immunotherapy consent and instruction forms, can also be found at http://www.aaaai.org.

Injection techniques. Summary Statement 57: Allergen immunotherapy extract injections should be given using a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **C**

Immunotherapy should be given with a 26- to 27-gauge syringe with a half-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.[289-291]

If using shared specific patient vials (stock vials, such as mixed vespid or dust mite mix), a single dose should be drawn from each vial. Antigens from different vials should not be combined in a single syringe. Furthermore, extra care is needed to prevent using the wrong stock antigen.

Summary Statement 58: The injection should be given subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Each immunotherapy injection should be given in the posterior portion of the middle third of the upper 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.

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.

The syringe should be aspirated to check for blood return in the syringe before injecting. If blood is present, 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 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 syringe should be appropriately discarded. A fresh syringe and needle are necessary to determine whether a blood vessel has been entered.

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 could result in a local reaction.

LOCATION OF ALLERGEN IMMUNOTHERAPY ADMINISTRATION

Physician's office

Summary Statement 59: 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 to treat anaphylaxis should be in the immediate vicinity when immunotherapy injections are administered.

Summary Statement 60: 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.[292] 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.[184] 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 might be frequently necessary in the patient's immunotherapy schedule, as well as the patients total treatment program.

Other locations

Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **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.[292] The health care professional and staff 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, or allergy/asthma exacerbations at the time of allergen immunotherapy extract injection or poorly controlled asthma).

Appropriate adjustment of dose should be made as clinically indicated. The physician who prepared the patient's allergen immunotherapy extract should provide adequately labeled allergen immunotherapy extract vials, detailed directions regarding dosage schedule for build-up and maintenance, and instructions on adjustments that might be necessary under the following circumstances:

1. when providing patients with new vials;
2. during seasonal exposure to allergens that are in the patient's allergen vaccine, to which the patient is very sensitive, or both;
3. if the patient has missed injections; and
4. when reactions occur to the allergen immunotherapy extract.

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

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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 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 very 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 fully trained to administer the injection and to treat anaphylaxis if this should 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 supports (personnel, medications, supplies, and equipment) are more optimal for encouraging prompt recognition and treatment of anaphylaxis (Table V). 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.

Summary Statement 63: If a patient on 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for their immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extracts might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Patients often 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 brought from the previous physician (ie, an unchanged immunotherapy program) or one to be prepared by the current physician (ie, a new immunotherapy program).

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 full, clear, and detailed documentation of the patient's previous schedule and the contents of the allergen immunotherapy extract (see Appendices 7, 8, 11, 12, and 14 for examples of allergen immunotherapy prescription and administration forms and documentation guidelines for allergen immunotherapy forms). In addition, the patient's previous response to and compliance with this program 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 a schedule and the allergen immunotherapy extract, (2) the patient has shown significant improvement on this immunotherapy program, and (3) the contents of the allergen immunotherapy extract are appropriate for the area in which the patient is now living.

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, vaccine type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient's dose is not modified. This increased risk is due to the significant variability in content and potency of extracts and the variability in methods used by physicians to prepare the patient's maintenance concentrate and its dilutions. For example, the strength of a given concentration of nonstandardized extracts might vary significantly from vial to vial. The risk of systemic reactions in such a situation might be greater with nonstandardized extracts and allergen immunotherapy extracts that contain mixtures of allergens.

Therefore if the allergen immunotherapy extract is to be changed, the patient might need to be retested for specific IgE to the appropriate allergens 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 provided the interval of time since the last injection has not been too long. For lot changes from the same manufacturer, the physician can consider decreasing the dose by 50% to 90%. For changes in manufacturer and nonstandardized extracts, a greater decrease in dose might be necessary.

SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

Allergen immunotherapy in children

Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children

with allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Immunotherapy for children has been shown to be effective and often well tolerated,[137,242] although at least one study did not show efficacy.[293] 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.[294] In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (see the Patient selection section and Table VII). In recent studies children receiving allergen immunotherapy have demonstrated:

1. improvement in symptom control for asthma[117,119,121,122] and allergic rhinitis[118];
2. increased PC_{20} to histamine[121];
3. increased PC_{20} to cat and house dust mite allergens[121,149];
4. decreased risk of development of asthma[6,9,163-165];
5. decreased development of new sensitivities[120,166]; and
6. modification in release of mediators in children receiving immunotherapy that correlates with decreased clinical symptoms.[123]

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Although there is some disagreement about the role of allergen immunotherapy in children under the age of 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.[117,122] In children with allergic rhinitis, allergen immunotherapy might prevent the development of asthma.[6,9,163-165] However, allergen immunotherapy for inhalant allergens is usually not considered necessary in infants and toddlers because (1) there is 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 in pregnancy

Summary Statement 71: Allergen immunotherapy might be continued but is usually not initiated in the pregnant patient. **C**

The physician must be aware of the benefits and risks of immunotherapy in pregnant patients. The recommended precautions for prevention of adverse reactions are especially important in the pregnant patient. Allergen immunotherapy is effective in the pregnant patient. Thus allergen immunotherapy maintenance doses can be continued during pregnancy. Allergen immunotherapy is usually not initiated during pregnancy because of risks associated with systemic reactions and their treatment (ie, spontaneous abortion, premature labor, or fetal hypoxia). 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, and the patient is maintained on the dose that she is receiving at that time.

Immunotherapy in the elderly patient

Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy might be considered in the treatment of the elderly patient, but the benefit/risk assessment must be evaluated carefully in this population. Older 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. However, elderly patients may also benefit from allergen immunotherapy and age alone should not preclude the consideration of allergen immunotherapy.[295]

Immunotherapy in patients with immunodeficiency and autoimmune disorders

Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with immunodeficiency or autoimmune disorders. Therefore the decision to begin immunotherapy in patients with major humoral or cellular immune defects must be individualized. Concern about the increased risk of immunotherapy in such patients is largely hypothetical.

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

ALTERNATIVE ROUTES OF IMMUNOTHERAPY

Sublingual and oral immunotherapy

Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be

effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no FDA-approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **B**

Alternative routes of administration of allergen immunotherapy are ''a viable alternative to parenteral injection therapy'' in some cases.[106,296] Studies of oral immunotherapy have provided conflicting results for ragweed,[297] birch,[298] and cat[299] immunotherapy. The present dosage of oral immunotherapy extract is 20 to 200 times the parenteral injected dosage, which requires a cost assessment for this type of therapy. Furthermore, adverse effects have included gastrointestinal and oral reactions (50% in 1 study) that might preclude home therapy. Oral immunotherapy should be considered investigational at this time.

Optimal-dose (high-dose) sublingual swallow immunotherapy is effective in adults and children.[300-304] In a study of 855 patients with grass pollen allergy and allergic rhinitis randomized to placebo or one of 3 grass tablet doses, there was a significant reduction in symptom and medication scores in the highest-dose subgroup, who were treated for at least 8 weeks before the grass pollen season, compared with the placebo group (symptoms, 21%, $P = .0020$; medication use, 29%, $P = .0120$).[303]

Sublingual allergen studies have evaluated house dust, olive pollen, grass pollen, ragweed, birch, cat, latex, *Alternaria* species, and *Parietaria judaica*.[305-313] Sublingual immunotherapy has been shown to be effective in patients sensitized to 2 non–cross-reacting allergens, grass and birch.[314] It has been noted that the allergen is not degraded by saliva and that there is no direct sublingual absorption of allergen. Radiolabeled allergen has been detected after 48 hours in the sublingual region.[315,316] Alternative protocols, such as rush and ultra-rush (20 minutes) sublingual swallow[307,316,318] and no induction (build-up) phase,[301,303,317,319,320] have been studied. Several studies have suggested a relationship between dose and efficacy with sublingual immunotherapy,[303,310,321] but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. The majority of sublingual studies have demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both, but approximately 35% of the randomized, double-blind, placebo-controlled studies did not demonstrate efficacy in either parameter during the first year of treatment.[322] Further studies are needed to confirm the optimal dose for sublingual immunotherapy.

One of the potential advantages of sublingual immunotherapy is that it appears to be safe, even at very high doses (up to 500 times the usual monthly subcutaneous dose), and to be associated with a lower incidence of serious side effects.[310,320,323] This appears to apply to young children (<5 years), for whom there are prospective safety data[324,325] and a postmarketing survey.[326]



FIG 3. Sample of labels for allergen immunotherapy extract vials.

There have been no SLIT-related fatalities, but there have been 3 case reports of anaphylaxis caused by sublingual immunotherapy. One patient with latex hypersensitivity had anaphylactic shock 20 minutes after reaching the maximal dose on the fourth day of latex rush sublingual rush immunotherapy.[327]

The other 2 reported cases of SLIT anaphylaxis involved patients treated with multiple inhalant allergens. In one case a patient with allergic rhinitis and asthma who was prescribed a sublingual immunotherapy extract composed of multiple non–cross-reacting allergens (*Alternaria* species, dog, cat, ragweed mix, weed mix, and grass mix)[328] had generalized pruritis, followed by angioedema, shortness of breath, and dizziness, within a few minutes of administering 6 drops of the 1:100 vol/vol dilution on the third day of treatment. This episode was preceded by a milder systemic reaction the previous day (generalized pruritis). In the other case, a 13-year-old girl with allergic rhinitis and asthma had swelling of her lower lip 3 minutes after pollen drops, high fever, chest pain, nausea, and abdominal pain.[329] She was treated in the emergency department for anaphylaxis and hospitalized for observation. The reaction occurred 1 month after she had reached the maintenance dose during the peak of the spring season.

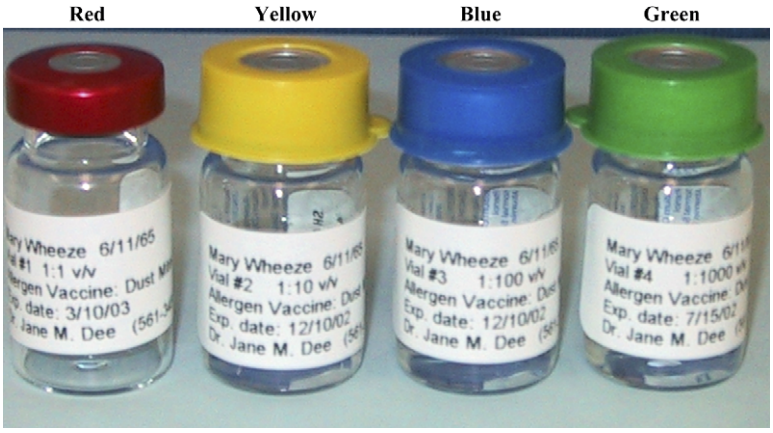


FIG 4. Sample set of color-coded vials of allergen vaccine.

There is currently no FDA-approved formulation for sublingual immunotherapy in the United States at this time, and this modality should be considered investigational. Current investigation of sublingual immunotherapy should not be confused with low-dose sublingual immunotherapy based on provocation neutralization testing or Rinkel-type skin testing.

Intranasal immunotherapy

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Based on controlled, well-designed studies, intranasal immunotherapy has been shown to improve the nasal symptoms of rhinitis.[330] Intranasal dry powder extract immunotherapy has been studied in grass,[330] birch,[331] *P judaica*,[332-334] and house dust mite[335] allergy. Clinical efficacy was noted in all of these studies. Nasal reactivity to allergen challenge was reduced, and only minor side effects were noted in 2 of the above studies. A 3-year study with *P judaica* reported to provide persistent benefits for up to 12 months after conclusion of allergen immunotherapy.[333] Local administration of nasal allergen in an aqueous solution for immunotherapy might be limited by the local side effects. Further studies in both pediatric and adult groups are needed. In human studies the antigen has been noted to appear in the serum within 15 to 30 minutes of administration, with a peak level occurring within 2 to 3 hours.[315] Some allergens have been reported to be retained in the nasal mucosa for up to 48 hours after administration. Intranasal immunotherapy is not currently available in the United States but has gained some acceptance in other parts of the world.

Immunotherapy techniques that are not recommended

Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

Low-dose regimens, including coseasonal low-dose immunotherapy for aeroallergens and the Rinkel low-dose titration techniques, are not effective.[27,28] Immunotherapy based on provocation–neutralization testing with food and aeroallergens and enzyme-potentiated desensitization is not effective.[336]

FUTURE TRENDS IN IMMUNOTHERAPY

Therapy with aeroallergen extracts will become more uniform (as is the current practice for insect venoms) as greater numbers of biologically standardized allergen extracts become available. The actual number of commercially available allergen extracts will be reduced based on consensus agreements about the regional prevalence of aeroallergens, their cross-allergenicity, and the relevance of their effect on human health in specific locales. Novel routes for more effective, convenient, and safer allergen immunotherapy are being investigated throughout the world.

For example, the sublingual route of administering allergen immunotherapy has been studied extensively in Europe. A meta-analysis confirmed its clinical effectiveness in allergic rhinitis,[302] and it has been reported to be effective in asthma as well.[337] Sublingual immunotherapy appears to have a very low risk of serious life-threatening systemic side effects, which might allow for home administration.[324,338] In some studies the clinical benefits of sublingual immunotherapy were not significant until the second year of treatment,[306,339] and comparisons suggest that the magnitude of the clinical benefit of sublingual immunotherapy might not be as great as that of subcutaneous immunotherapy.[311]

Trials with non–IgE-binding peptides containing T-cell stimulating peptides have been reported.[340] Site-directed mutagenesis has produced allergens with decreased IgE-binding capacity without decreased T-cell responses.[341,342]

Immunostimulatory sequences mimicking bacterial and viral DNA have been prepared that stimulate the innate immune system to direct T-cell responses toward

T_H1 rather than T_H2 phenotypes.[343] The results of clinical trials with a conjugate of the immunostimulatory sequence to the major allergen of ragweed, Amb a 1 (AIC), have been reported.[34,343] In a double-blind, placebo-controlled study of 25 adults who received 6 weekly injections of the AIC or placebo vaccine before ragweed season, the AIC group had better peak-season rhinitis scores on the visual analog scale ($P = .006$), peak-season daily nasal symptom diary scores ($P = .02$), and midseason overall quality-of-life scores ($P = .05$) than the placebo group during the first ragweed season, and this effect was observed in the subsequent ragweed season.[344]

Humanized anti-IgE mAb has been shown to have clinical effects in both allergic rhinitis and asthma.[345-348] Theoretically, this new therapeutic modality could be used as protective cover for clinical applications of rapid forms of immunotherapy. It is possible that preadministration of anti-IgE could provide a more effective protective effect than premedication with antihistamines and therefore permit a rush allergen immunotherapeutic regimen with reduced risk of serious systemic reactions.[282]

AUTHOR'S 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 2 systemic reaction grading systems (the European Academy of Allergy and Clinical Immunology's grading of severity for systemic side effects and the Portnoy method for numeric grading of reactions to allergen immunotherapy) can be found in the Appendix section. These forms can also be found along with examples of immunotherapy instruction and consent forms, preinjection health questionnaires, and indications for beginning and continuing immunotherapy forms at www.aaaai.org.

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APPENDIX 1. American College of Medical Quality's policy on the development and use of practice parameters for medical quality decision-making[1]

Practice parameters are strategies for patient management developed to assist health care professionals in clinical decision making. Practice parameters include standards, guidelines, and other patient management strategies. Standards are accepted principles for patient management. Guidelines are recommendations for patient management that identify a particular management strategy or a range of management strategies. Other strategies for patient management include practice policies and practice options. Practice parameters are to be used as screening tools to identify possible deviations from the applicable standards of care. Such parameters are not to be used as absolute standards or to profile or report on health care personnel. Parameters are designed to trigger a process in which possible deviations from the standard of care are identified as outlier practice patterns. Once a deviation from the parameter is identified, such a deviation should be referred to the appropriate qualified physician advisor or reviewer for a determination of medical necessity that conforms to the applicable standard of care. Parameters used in the day-to-day practice of clinical medicine should be clinically relevant. They should not be considered as substitutes for the standard of care but might contribute to its formulation.

Practice parameters must be developed, designed, and implemented only by board-certified, clinically practicing, specialty-matched physician advisors/reviewers with unrestricted medical licenses. Qualified nonphysicians might participate in the development of these parameters only in the areas in which their clinical expertise based on the standard of care is applicable. The health care personnel who develop these parameters should sign their names and date the final version as evidence of their participation and support. Practice parameters must be based on sound scientific research findings, professional literature, clinical experience and appropriate well-recognized methodologies and reflect professionally recognized national standards of care practiced in the clinical community of medicine. The development procedures followed, the participants involved, the evidence used, the assumptions and rationales accepted, and the analytic methods used should be meticulously documented, described, and made publicly available for national peer review. Parameters should be updated as needed.

Practice parameters are used as tools to enhance medical decision making but not as replacements for physicians' clinical judgment. They can be considered as means to enhance the performance of clinical and review personnel but not to replace them. It is below the standard of care of the medical review process to substitute qualified physician reviewer experts with unqualified reviewers who are using parameters.

APPENDIX 2. Examples of possible abbreviations for allergen immunotherapy extract 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

APPENDIX 3. 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

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

APPENDIX 4. Example of immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals (modification of the AAAAI skin testing and immunotherapy consent and instruction forms: immunotherapy administration instruction form, which can be found at http://www.aaaai.org)

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

- Up to 7 days, continue as scheduled (ie, if on weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection).
- Eight to 13 days after missed scheduled injection; repeat previous dose.
- Fourteen to 21 days after missed scheduled injection; reduce dose 25%.
- Twenty-one to 28 days after missed scheduled injection; reduce previous dose 50%.

Then increase dose each injection visit as directed on the immunotherapy schedule until therapeutic maintenance dose is reached.

This suggested approach to modification of doses of allergen immunotherapy because of gaps between treatment during the build-up phase is not based on retrospective or prospective published evidence, but it is presented as a sample for your consideration. The individual physician should use this or a similar protocol as a standard operating procedure for the specific clinical setting. A similar dose-reduction protocol should be developed for gaps in maintenance immunotherapy.

APPENDIX 5. Example of a cluster immunotherapy schedule[22,26]

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

APPENDIX 6. Recommended documentation for allergen immunotherapy prescription forms

The purpose of the allergen immunotherapy prescription form is to define the contents of the allergen immunotherapy extract in enough detail that it could be precisely duplicated. The following information should be on an immunotherapy prescription form:

Patient information:

- Patient name, patient number (if applicable), birth date, telephone number, and picture (if available) should be included.

Preparation information:

- Name of person and signature preparing the allergen immunotherapy extract should be included.
- Date of preparation should be recorded.
- Bottle name should be included (eg, trees and grass). If abbreviations are used, a 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 should be included.
- Volume of manufacturer's extract to add to achieve the projected effective concentration should be included. 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) should be included.
- Extract manufacturer should be included.
- Lot number should be included.
- Expiration date should be recorded and should not exceed the expiration date of any of the individual components.

APPENDIX 7. Allergen immunotherapy extract prescription 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:

_____
_____
_____
_____

_____ ____/____/____
Prescribing Physician Signature Date

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

APPENDIX 8. Maintenance concentrate prescription form

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: 6/10/06

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial **4** from Vial **1** on **8/30/06** Expiration date: **10/15/06**
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	Short ragweed	1:20 w/v G (150 Amb a1)	0.5ml	Greer	12345	1/01/08
2	Amaranthus Retroflexus	1:10 w/v G	0.5ml	H-S	6789	2/07/08
3	Ash	1:10 w/v G	0.5ml	Center	3333	3/17/08
4	Cat	10,000 BAU/ml G	2.00ml	ALO	9898	2/27/08
5	Timothy Grass	100,000 BAU/ml G	0.4ml	ALK	56789	7/09/08
6	Johnson Grass	1:10 w/v G	0.5ml	Greer	2434	7/20/08
7						
8						
9						
10						
Diluent	HSA		0.6ml	ALK	68597	12/08
Total Volume			5.00 ml			6/10/07

*** Components of mixes listed on a separate sheet**
**** Assumes 0.5 ml injection as target maintenance dose**

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

Specific Instructions:

_____

_____

Prescribing Physician Signature

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

APPENDIX 9. Labels for allergen immunotherapy extracts

Each vial of allergen immunotherapy extract should be labeled in a way that permits easy identification. Each label should include the following information (example in Figs 3 and 4):

- Appropriate patient identifiers might include the patient's name, patient's number, patient's picture, and birth date.
- The contents of the allergen immunotherapy extract in a general way should be included. The detail with which this can be identified depends on the size of the label and the number of allergens in the vial. Ideally, allergens should be identified as trees, grasses, weeds, mold, dust mite, cockroach, cat, and dog. Because of space limitations, it might be necessary to abbreviate the antigens (eg, T, G, W, M, DM, Cr, C, and D respectively [see Appendix 2]). A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate (vol/vol) should be recorded. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- The expiration date should be included.

APPENDIX 10. Allergen immunotherapy administration form recommended documentation

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

Patient information:

- Patient's name, date of birth, telephone number, and patient's picture (optional but helpful).

Allergen immunotherapy extract information:

- Allergen immunotherapy extract name and dilution from maintenance in vol/vol bottle letter (eg, A and B), bottle color, or number, if used.
- Expiration date of all dilutions.

Administration information in separate columns:

- Date of injection.
- Arm administered injection, which might facilitate determination of exact cause of local reaction.
- Projected build-up schedule.
- Delivered volume reported in milliliters.
- Description of any reactions. The details of any treatment given in response to a reaction would be documented elsewhere in the medical record and referenced on the administration form.
- *Patient's health before injection*. This can be performed through a verbal or written interview of the patient before administering the immunotherapy injection. The patient should be questioned about increased asthma or allergy symptoms, β-blocker use, change in health status (including pregnancy and recent infections), or an adverse reaction to a previous injection (including delayed large local reactions persisting through the next day). Patients with significant systemic illness generally should not receive an injection.
- *Antihistamine use*. Antihistamines are frequently a component of an allergy medication regimen, and it would be important to note whether a patient is taking an antihistamine on the day he or she receives his or her immunotherapy injection. For consistency in interpretation of reactions, it might be desirable for a patient to either take or avoid antihistamines on a regular basis on the days he or she receives immunotherapy. The physician should note on the form whether he or she recommends the patient consistently take an antihistamine on immunotherapy treatment days.
- *Peak flow reading*. Consider obtaining a peak expiratory flow rate measurement before administering an immunotherapy injection to asthmatic patients. Poorly controlled asthma is considered a risk factor for immunotherapy. Obtaining a peak expiratory flow rate measurement before the immunotherapy injection might help identify patients with symptomatic asthma. The patient's baseline peak expiratory flow rate should be provided on the form as a reference. Health care professionals administering immunotherapy injections should be provided with specific guidelines about the peak expiratory flow rate measurement for when an immunotherapy injection should be withheld and the patient referred for clinical evaluation.
- **Baseline blood pressure**. It might be useful to record the patient's blood pressure as a baseline for future reference.

APPENDIX 11. Allergen immunotherapy administration form

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 allergy or 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

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

Date to reorder: __/__/__

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 allergy or 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**	

APPENDIX 12. 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: _____
_____
Staff action taken (if any): _____

APPENDIX 13. 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.

APPENDIX 14. Allergen immunotherapy systemic reaction/anaphylaxis 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
__Epinephrine IM into 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	

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:
_____
_____
_____
_____

Clinical impression: True SR Questionable SR No SR

Systemic reaction severity classification: EAACI_____ **Portnoy** _____

Dosage adjustment? _____

Signatures_____ **RN** _____**MD/DO**

APPENDIX 15. Grading severity of allergen immunotherapy reactions: Two methods

1. **The European Academy of Allergy and Clinical Immunology grading of severity for systemic side effects***

Classification of systemic reactions

0 = No symptoms or nonspecific symptoms

I = Mild systemic reactions: symptoms—localized urticaria, rhinitis, or mild asthma (PF <20% decrease from baseline).

II = Moderate systemic reaction: symptoms—slow onset (>15 minutes) of generalized urticaria, moderate asthma, or both (PF < 40% decrease from baseline).

III = Severe (non–life-threatening) systemic reactions: symptoms—rapid onset (<15 minutes) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).

IV = Anaphylactic shock: symptoms—immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, and hypotension, for example.

2. **Portnoy method for numeric grading of reactions to allergen immunotherapy†**

Local

0+ = No significant reaction or small area of erythema less than the size of a half dollar without swelling or wheal formation

1+ = Erythema greater than the size of a half dollar, swelling or wheal formation, or both

Systemic

2+ = Systemic reactions: cutaneous only—might consist of a cutaneous eruption, such as urticaria

3+ = Systemic reaction: generalized pruritus, sneezing, or both—might consist of increased allergy symptoms, such as nasal congestion, sneezing, or pruritus, especially in the mouth or throat

4+ = Systemic reaction: pulmonary—consists of wheezing, shortness of breath, and tightness. Might be associated with decreased pulmonary function tests

5+ = Systemic reaction: anaphylaxis—a sensation of not feeling right is a frequent prelude; might consist of hypotension, laryngeal edema, severe wheezing, and cramping

6+ = Cardiopulmonary arrest

PF, Peak expiratory flow.

*Subcutaneous immunotherapy. Allergy 2006;61(suppl 82):5-13.

†Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80.

Allergen immunotherapy: A practice parameter second update

Supplement Editor: **Linda Cox, MD**
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These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology.

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the "Allergen immunotherapy: a practice parameter second 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 and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
5. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
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11. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999;83(suppl): S665–S700.
12. Diagnosis and management of urticaria: a practice parameter. Ann Allergy 2000;85(suppl):S521-S544.
13. Allergen immunotherapy: a practice parameter. Ann Allergy 2003;90(suppl):SI-S540.
14. Symptom severity assessment of allergic rhinitis: part I. Ann Allergy 2003;91:105-14.
15. Disease management of atopic dermatitis: an updated practice parameter. Ann Allergy 2004;93(suppl): S1-S21.
16. Stinging insect hypersensitivity: a practice parameter update. J Allergy Clin Immunol 2004;114:869-86.
17. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol 2005;115(suppl):S483-S523.

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22. Contact dermatitis: a practice parameter. Ann Allergy Asthma Immunol 2006;97(suppl 2):S1-S38.

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

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Allergen immunotherapy: A practice parameter second update

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PREFACE

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

The objective of ''Allergen immunotherapy: A practice parameter second update'' is to optimize the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. 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's ''Policy on development and use of practice parameters for medical quality decision-making'' (Appendix 1).[1]

This document builds on the previous Joint Task Force document, ''Allergen immunotherapy: a practice parameter'' published in the *Annals of Allergy, Asthma and Immunology* in 2003.[2] The updated practice parameters draft was prepared by Drs Linda Cox, James Li, Hal Nelson, and Richard Lockey. The Joint Task Force reworked the initial draft into a working draft of the document. The project was exclusively funded by the 3 allergy and immunology societies noted above.

In preparation for the 2003 ''Allergen immunotherapy: a practice parameter'' and the second update, a comprehensive search of the medical literature was conducted with various search engines, including PubMed; *immunotherapy*, *allergic rhinitis*, *asthma*, *stinging insect allergy*, and related search terms were used. 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 second update'' was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the ACAAI, AAAAI, and JCAAI. In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for review and comments from members of the sponsoring organizations. 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 allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. This document also contains recommendations for the safe practice of allergen immunotherapy, including specific recommendations on the prevention and management of 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 or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. Symptoms of allergic conjunctivitis (eg, itchy watery eyes) are often considered part of allergic rhinitis or are included in the diagnosis of rhinoconjunctivitis. Particularly good candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures, those in whom it is important to avoid the potential adverse effects of medications, and those who wish to reduce the long-term use of medications. Immunotherapy is recommended for patients with a history of systemic reaction to Hymenoptera stings and specific IgE antibodies to Hymenoptera venom.

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.[3]

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. 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 *maintenance concentrate* should be used to identify the allergen immunotherapy extract that contains a therapeutic effective dose for each of its individual constituents (see the Immunotherapy schedules and doses section).

The term *manufacturer's extract* refers to the allergy extract purchased from the manufacturer. The terms *stock*, *full-strength*, and *concentrate* are ambiguous and should not be used. 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).

Allergen immunotherapy is effective when appropriate doses of the allergens are administered. ''Allergen immunotherapy: A practice parameter'' recommends that vials of allergen immunotherapy extracts should be prepared individually for each patient to enhance the individualization of therapy, reduce the risk of allergen cross-contamination, and reduce the risk of error in administration.[4,5] This parameter recommends the use of standardized allergen immunotherapy prescription and administration forms to improve the safety, uniformity, and standardization of allergen immunotherapy practice.[4,5] The suggested forms are found in the Appendix (Appendices 7, 8, 11, 12, and 14) and in the members' section of the www.aaaai.org Web site. The routine use of these standardized forms should improve the quality of immunotherapy practice.

Members' feedback comments on the recommended allergen extract dilution dating in the 2003 ''Allergen immunotherapy: A practice parameter'' led to an allergen immunotherapy extract dilution stability study designed by the AAAAI Immunotherapy and Allergy Diagnostics Committee and funded by the AAAAI Board of Directors. The study was designed to investigate the effect of time, temperature, and dilution of standardized allergen extract potency, and the results of this study were considered in this update.

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 3 years after publication. Requests for information about or an interpretation of these practice parameters should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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. Allergen immunotherapy

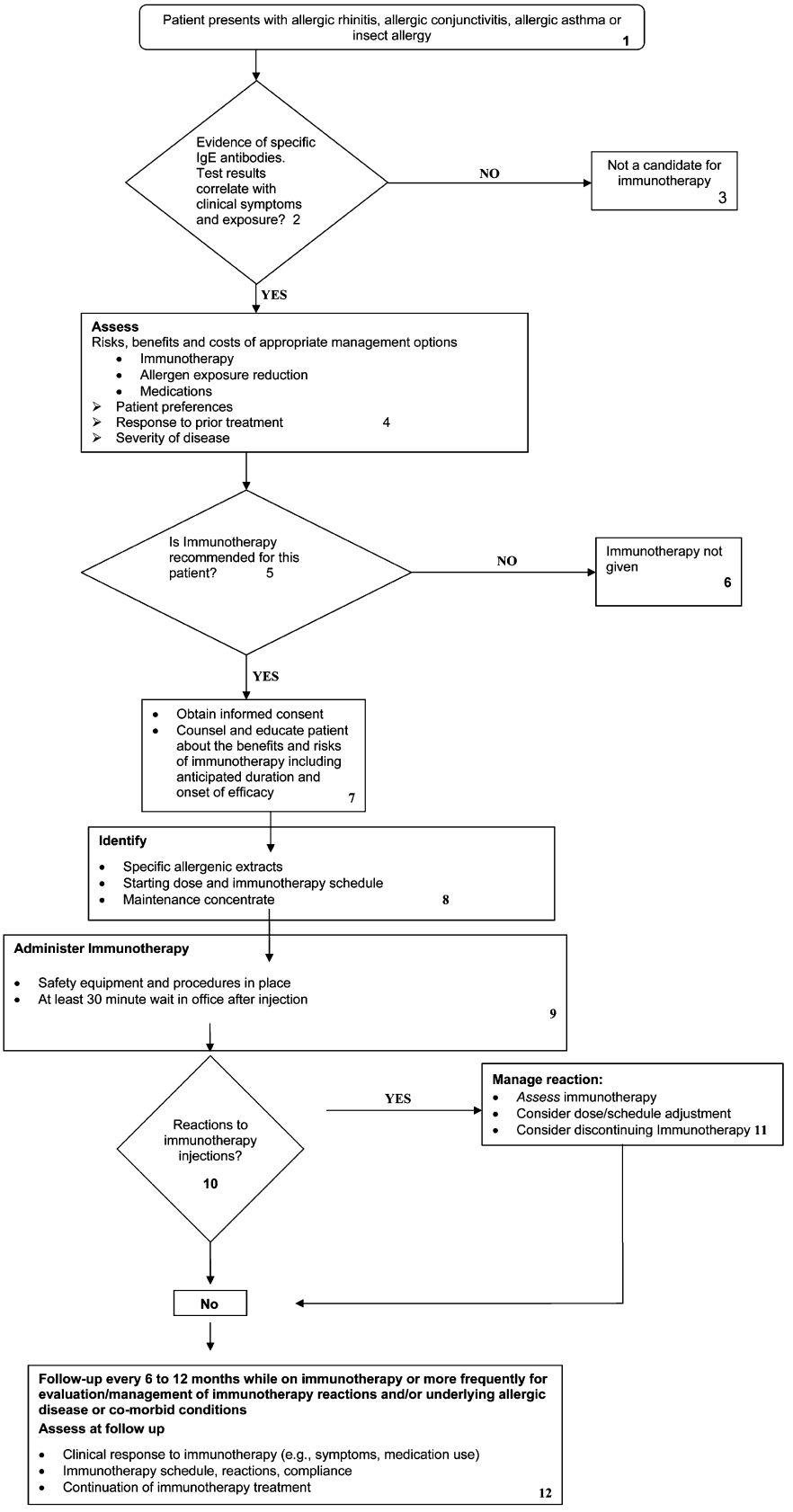


FIG 1. Algorithm for allergen immunotherapy.

might prevent the development of asthma in individuals with allergic rhinitis.[6-9] Evaluation of a patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic conjunctivitis, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for specific IgE antibody).[10]

Box 2

Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although *in vitro* testing for 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

Management of complex medical conditions, such as allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity, should include the careful evaluation of management 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 patient 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. On the basis of clinical considerations and patient 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 good candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy (VIT).

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 on the basis of 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 (see the Immunotherapy schedules and doses section). In general, the starting immunotherapy dose is 1000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 1000 to 4000 arbitrary units (AU; eg, for dust mite) or bioequivalent allergy units (BAU; eg, for grass) 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 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 referred to as *up-dosing*, *induction*, or the *dose-increase phase*) entails administration of gradually increasing doses during a period of approximately 14 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 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, in particular anaphylaxis. Patients should wait at the physician's office for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly, if they occur.

In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring 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. Some physicians recommend providing certain patients with epinephrine for self-administration in case of severe late reactions to immunotherapy injections.

Box 10

Injections of allergen immunotherapy extract can cause local or systemic reactions. Most severe reactions develop within 30 minutes after the immunotherapy injection, but reactions can occur after this time.

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 (anaphylaxis). Epinephrine is the treatment of choice in anaphylaxis, preferably when administered intramuscularly,[11] although subcutaneous administration is acceptable.[12]

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, see the practice parameters for anaphylaxis.[12]

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. After a severe systemic reaction, careful evaluation by the prescribing physician is recommended. For some patients, the immunotherapy maintenance dose might need to be reduced because of repeated systemic reactions to immunotherapy injections. The decision to continue immunotherapy should be re-evaluated after severe or repeated systemic reactions to allergen immunotherapy extracts.

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 doses, 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,[13] but others might experience a recurrence of their symptoms after discontinuation of allergen immunotherapy.[14] 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, and 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 on the basis of the patient's clinical response, disease severity, immunotherapy reaction history, and patient preference.

IMMUNOTHERAPY GLOSSARY

For more information on immunotherapy definitions, see the article by Kao.[15]

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 (pigments and salts; see the Allergen selection and handling section). Other terms used to describe the allergen immunotherapy extract include *allergen product*,[16] *allergy serum*, *allergen vaccine*,[17] 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.[18] Other terms that have been used for allergen immunotherapy include *hyposensitization*, *allergen-specific desensitization*, and the lay terms *allergy shots* or *allergy injections*.[15]

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

TABLE II. Allergen immunotherapy dose-calculation table

- Express weight per volume as a fraction: $\frac{1}{N}$ or 1:*N*.
- Calculate concentration of individual allergens in mixtures. If a mixture is made of equal amounts of N individual allergens to make a total concentration (C), the final concentration of an individual allergen (Ca) can be calculated by using the following equation:

$Ca = C \times \frac{1}{N} = \frac{C}{N}$ or *C*:*N*.

For example, if a mixture of equal amounts of 5 (N) allergens has a total concentration (C) of 100,000 BAU/mL, then the final concentration of each individual allergen (Ca) is: $Ca = \frac{C}{N} = \frac{100{,}000}{5} = 20{,}000\ BAU/mL$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{C}{N} = \frac{1/10}{5} = \frac{0.1}{5} = 0.02$ or $\frac{1}{50}$ or 1:50.

- Dilution of individual allergen: If an initial volume, Vi (in milliliters), of an individual antigen with concentration, Ci, is added to an allergen extract to make a final volume of Vf (in milliliters), the final allergen concentration (Ca) in the allergen extract mixture will be: $Ca = Ci \times \frac{Vi}{Vf}$.
- Final concentration of an allergen in a mixture of mixtures is determined by multiplying the initial concentration by the dilution factors from each mixing step.

For example, consider a mixture containing equal amounts of 5 (N) allergens with a total concentration (C) of 100,000 BAU/mL (first dilution). If an initial volume (Vi) of 0.5 mL of this mixture is further mixed with other components and diluent to make a final allergen extract mixture volume (Vf) of 5.0 mL (second dilution), the final concentration of an individual allergen (Ca) will be:

$$Ca = C \times \underbrace{\frac{1}{N}}_{\text{Mixture dilution}} \times \underbrace{\frac{Vi}{Vf}}_{\text{Allergen extract dilution}} = 100{,}000 \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{100{,}000}{50} = 2000\ BAU/mL$$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{1}{10} \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{1}{500}$ or 1:500.

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).

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 to 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-medicated 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 multiplied by volume of administered dose (see Table II for a dose-calculation table).

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, cat, 1000 BAU, [highest tolerated dose] vs 2000 BAU [projected effective dose]).

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 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 by a variety of immunologic transformations. Early definitions of the term immunotherapy included active and passive immunization for the purpose of improving 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 by means of induction of clonal deletion, anergy, immune tolerance, or immune deviation.

The *maintenance concentrate* is a preparation that contains individual 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 may not be the initially calculated projected effective dose.

The *maintenance goal* (or projected effective dose) is the allergen dose projected to provide therapeutic efficacy. The maintenance goal is based on published studies, but a projected effective dose has not been established for allergens. 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 the 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 large local reaction causing discomfort). The intervals between maintenance immunotherapy injections generally ranges 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 by means of immunoblotting or crossed allergoimmunoelectrophoresis.

For a definition of *projected effective dose*, see 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 test responses), and premedication with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similar high incidence of systemic reactions.

Off the board into one syringe is a phrase that describes a method of allergen immunotherapy preparation and administration that involves specifically mixing the patient's allergen immunotherapy injection in a single syringe, which is not recommended. This syringe might be inserted into more than one allergen extract vial, and this poses a risk of cross-contamination of the allergen extracts and might dull the needle with repeated penetration of the rubber stopper.

Shared specific patient vials is a method of allergen immunotherapy preparation and administration in which the allergy immunotherapy extract is withdrawn from a shared vial (eg, mixed vespids or dust mite mix). This is sometimes referred to as off the board, but it is distinct from the method of off the board into one syringe in that the syringe enters only one allergen extract vial.

INTRODUCTION

Immunity has been defined as protection against certain diseases. The initial immunotherapeutic interventions, which included the use of preventive vaccines and xenogenic 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 the field of allergen immunotherapy. From its humble empiric emergence in 1900, when ragweed injections were proposed as therapy for autumnal hay fever, allergen immunotherapy has progressed in both theory and practice from the passive immunologic approach to the active immunologic procedures pioneered by Noon[19] and Freeman.[20,21] 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 10 years. Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Some studies have suggested that allergen immunotherapy might prevent the development of asthma in individuals with allergic rhinitis.[6-9]

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,[22-26] and it should be differentiated from unproved methods, such as neutralization-provocation therapy and low-dose subcutaneous regimens based on the Rinkel technique, which have been found to ineffective in a double-blind placebo-controlled study.[27,28]

SUMMARY STATEMENTS

Mechanisms of immunotherapy

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, defined as a relative decrease in allergen-specific responsiveness and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

Allergen extracts

Summary Statement 6: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. **A**

Summary Statement 7: Nonstandardized extracts might vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Summary Statement 8: 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**

Cross-reactivity of allergen extract. Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

Efficacy of immunotherapy

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Summary Statement 10: Immunotherapy is effective for 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**

Food allergy, urticaria, and atopic dermatitis. Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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**

Measures of efficacy. Summary Statement 12: 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**

Safety of immunotherapy

Reaction rates. Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

Timing of anaphylactic reactions to immunotherapy injections. Summary Statement 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

β-*Adrenergic blocking agents.* Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

Contraindications. Summary Statement 18: 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**

Reducing the risk of anaphylaxis to immunotherapy injections. Summary Statement 19: 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**

Patient selection

Clinical indications. Summary Statement 20: 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 depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Special precautions in patients with asthma. Summary Statement 21: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. **C**

Clinical indications for VIT. Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Summary Statement 23: Patients selected for immunotherapy should be cooperative and compliant. **D**

Allergen selection and handling

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted in vitro tests for specific IgE antibodies can also be used. **A**

Specific allergens. Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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, supported by the presence of specific IgE antibodies. **A**

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Dose selection. Summary Statement 30: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. **A**

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens, is recommended. **B**

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extract handling

STORAGE

Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

STORING DILUTE EXTRACTS

Summary Statement 34a: More dilute concentrations of allergen immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: 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 a number of 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. **B**

Immunotherapy schedules and doses

Summary Statement 35: A customized individual 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 be based on single or multiple allergens. **D**

Maintenance concentrate. Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

Recommended doses. Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

Effect of dilution on dose. Summary Statement 38: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. **A**

Dilutions of the maintenance concentrate. Summary Statement 39: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. **D**

Labeling dilutions. Summary Statement 40: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. **D**

Individualized treatment vials. Summary Statement 41: 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. The mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. **C**

Starting doses. Summary Statement 42: The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. **D**

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

Dose adjustments for systemic reactions. Summary Statement 44: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. **D**

Reductions during periods of exacerbation of symptoms. Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Dose adjustments for late injections. Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

Cluster schedules. Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. **C**

Rush schedules. Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. **A**

Systemic reactions and rush schedules. Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

Premedication and weekly immunotherapy. Summary Statement 50: Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

Premedication with cluster and rush immunotherapy. Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

Maintenance schedules. Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. **A**

Continuing care

TIME COURSE OF IMPROVEMENT

Summary Statement 53: Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **A**

FOLLOW-UP VISITS

Summary Statement 54: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. **D**

DURATION OF TREATMENT

Summary Statement 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

DOCUMENTATION AND RECORD KEEPING

Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. **D**

INJECTION TECHNIQUES

Summary Statement 57: Allergen immunotherapy extract injections should be administered with a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **D**

Summary Statement 58: The injection should be administered subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Location of allergen immunotherapy administration

Physician's office. Summary Statement 59: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Summary Statement 60: 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**

Other locations. Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **D**

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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**

Summary Statement 63: 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for his or her immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extract might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Special considerations in immunotherapy

Allergen immunotherapy in children. Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Pregnancy. Summary Statement 71: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. **C**

Immunotherapy in the elderly patient. Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy in patients with immunodeficiency and autoimmune disorders. Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

Alternative routes of immunotherapy

Sublingual and oral immunotherapy. Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no US Food and Drug Administration (FDA)–approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **A**

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Immunotherapy techniques that are not recommended. Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

MECHANISMS OF IMMUNOTHERAPY

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, which is defined as a relative decrease in allergen-specific responsiveness, and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

The immunologic changes associated with immunotherapy are complex, and the exact mechanism or mechanisms responsible for its' clinical efficacy are continually being elucidated. Data support the concept that successful immunotherapy is associated with a change to a T_H1 $CD4^+$ cytokine profile.[29-34] Data indicate that increased production of IL-12, a strong inducer of T_H1 responses, contributes to this shift.[33] Clinically successful immunotherapy has been reported to be associated with immunologic tolerance, which is defined as a relative decrease in antigen-specific responsiveness, immune deviation, or anergy. For example, lymphoproliferative responses to allergen are reduced with immunotherapy.[32] Successful immunotherapy results in generation of a population of T regulatory cells, which are $CD4^+CD25^+$ T lymphocytes producing IL-10, TGF-β, or both.[35-39] Regulatory T-cell release has been described in allergen immunotherapy with Hymenoptera venom,[35] grass pollen extract,[37] and house dust mites.[38] IL-10 reduces B-cell antigen-specific IgE and increases IgG4 levels; reduces proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicits tolerance in T cells by means of selective inhibition of the CD28 costimulatory pathway.[36,37]

Allergen immunotherapy has been shown to block both the immediate and late-phase allergic response.[40] Allergen immunotherapy has been shown to decrease the recruitment of mast cells, basophils, and eosinophils in the skin, nose, eye, and bronchial mucosa after provocation or natural exposure to allergens.[41]

In patients receiving immunotherapy, initially there is an increase in specific IgE antibody levels, followed by a gradual decrease to a level that is still higher than that present before treatment. Clinical improvement in many patients develops before decreases in their IgE antibody levels occur or in other patients whose IgE antibody levels never decrease, thereby demonstrating that efficacy is not dependent on reductions in specific IgE levels.[42,43] Immunotherapy does diminish the seasonal increase in specific IgE levels.[44] Despite the persistence of significant levels of specific IgE antibody levels, immunotherapy usually causes a reduction in 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.[45-48]

An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, has also been associated with immunotherapy. The properties of allergen-specific IgA have yet to be determined, and there is a weak correlation between the increase in allergen-specific IgG levels and immunotherapy's clinical efficacy.[30,49,50]

Immunotherapy might alter the affinity and specificity of allergen-specific IgG.[51,52] During the initial phase of ultrarush VIT, a change in IgG specificity (ie, a change in the set of epitopes dominantly recognized by IgG on wasp venom antigens) occurred concomitantly with early clinical tolerance and was seen within 12 hours of ultrarush VIT ($P < .001$).[51] 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 individuals.[52] This change in IgG specificity preceded the increase in IgG titers and was sustained for up to 6 months.[52]

Allergen-specific IgG induced from immunotherapy can block IgE-dependent histamine release and subsequent IgE-mediated antigen presentation to T cells.[53] This effect might be dependent on IgE, allergen concentration, and CD23, the low-affinity receptor for IgE.

Whereas 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.[37,53]

The relationship between these immunologic changes and immunotherapy efficacy is not completely understood.

ALLERGEN EXTRACTS

Summary Statement 6: 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 has 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.[2,18,54-56] 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.

United States–licensed extracts can be obtained in aqueous, glycerinated, lyophilized, and acetone-precipitated and alum-precipitated formulations. Some commonly used allergens are standardized. These include extracts for cat hair, cat pelt, *Dermatophagoides pteronyssinus*, *Dermatophagoides 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.[57] 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.

Most standardized extracts are labeled in BAU. Short ragweed potency units were originally based on the content of the major allergen Amb a 1. Ragweed potency is reported in FDA units and BAU. One FDA unit of Amb a 1 equals 1 μg of Amb a 1, and 350 units of Amb a 1/mL is equivalent to 100,000 BAU/mL. Cat extracts were also originally standardized based on the content of major allergen (Fel d 1), with 100,000 arbitrary units (AU) per milliliter containing between 10 to 19.9 FDA units of Fel d 1 per milliliter (1 FDA unit of Fel d 1 equals 2 to 4 μg of Fel d 1).[55,58,59] Subsequently, $ID_{50}EAL$ testing suggested that 100,000 AU/mL was equal to 10,000 BAU/mL.[60] Approximately 22% of individuals with cat allergy have specific IgE antibodies to cat albumin.[61] Cat pelt extracts have a greater amount of albumin than cat hair extracts.[60]

Dust mites were originally standardized in AU by means of inhibition radioimmunoassay (RIA), and subsequent $ID_{50}EAL$ testing indicated that the AU was bioequivalent to the BAU, and the original AU nomenclature was kept. Dust mite extracts are still labeled in AU.

Summary Statement 7: Nonstandardized extracts can vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Nonstandardized extracts are labeled as wt/vol, which expresses weight in grams per volume in milliliters; that is, a potency of 1:100 indicates that 1 g 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 with a particular wt/vol or PNU potency can have widely varying biologic activities.[62-64] Therefore they should not be considered equipotent.

Summary Statement 8: 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**

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. The major clinically relevant aeroallergens of North America are listed in Table III. Furthermore, nonrelevant allergens in such mixtures could act as sensitizers rather than as tolerogens.[65,66] The physician must therefore select only those aeroallergens for testing and treatment that are clinically relevant in a particular geographic area.

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, dog), insect (cockroach), and Hymenoptera venom source materials.

Cross-reactivity of allergen extract

Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

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. A summary of cross-reactivity patterns of the clinically relevant North American aeroallergens can be found in Fig 2. 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,[67] inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[68-75] Grasses in other subfamilies (eg, Bermuda, Bahia, and Johnson) show greater diversity and should be evaluated separately.[76-78] Bermuda and Johnson grasses are increasingly important in the South,

TABLE III. The major clinically relevant aeroallergens of North America*

- Tree pollen
  - Chinese elm *(Ulmus parvifolia)*†‡; Siberian elm *(Ulmus pumila)*†‡; American elm *(Ulmus Americana)*†‡
  - Red oak *(Quercus rubra)*†; White oak *(Quercus alba)*†
  - Paper birch *(Betula papyrifera)*
  - Alder *(Alnus rubra)*
  - Box elder *(Acer negundo)*†; Red maple *(Acer rubra)*†
  - Eastern cottonwood *(Populus deltoides)*
  - Sycamore *(Platanus occidentalis)*
  - White ash *(Fraxinus americana)*†; Olive *(Olea europaea)*†‡
  - Black walnut *(Juglans nigra)*
  - Mulberry *(Morus rubra)*
  - Mountain cedar *(Juniperus ashei)*
  - Pecan *(Carya illinoensis)*
- Grass pollen
  - Rye *(Lolium perenne)*§‖
  - Timothy *(Phleum pratense)*§‖
  - Meadow fescue *(Festuca elatior)*§‖
  - Bermuda *(Cynodon dactylon)*‖
  - Johnson *(Holcus halepensis)*
  - Bahia *(Paspalum notatum)*
- Weed pollen
  - Short ragweed *(Ambrosia artemisiifolia)*‖
  - English (narrow leaf) plantain *(Plantago lanceolata)*
  - Mugwort *(Artemisia vulgaris)*
  - Russian thistle *(Salsola kali)*
  - Burning bush *(Kochia scoparia)*
  - Sheet (red) sorrel *(Rumex asetosella)*
  - Red root pigweed *(Amaranthus retroflexus)*
- Indoor aeroallergens
  - Cat epithelium *(Felis domesticus)*‖
  - Dog epithelium *(Canis familiaris)*
  - Arthropods (domestic mites: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*)‖
  - Insects (German cockroach: *Blattella germanica*)
- Fungi
  - *Alternaria alternata*¶
  - *Cladosporium* (*C cladosporioides*, *C herbarum*)¶
  - *Penicillium* (*P chrysogenum*, *P expansum*)¶
  - *Aspergillus fumigatus*¶
  - *Epicoccum nigrum*, *Drechslera* or *Bipolaris* type (eg, *Helminthosporium solani*)¶

*Compiled and selected in collaboration with the AAAAI Immunotherapy Committee Allergen Subcommittee for the identification of 35 key allergens of North America.
†Extensive cross-reaction of species within the genus.
‡Apart from regional prevalence, they are limited to local sites with substantial stands of these trees.
§Extensively cross-react with one another and bluegrass, orchard, red top, and sweet vernal.
‖Allergens for which standardized extracts are commercially available.
¶Species that are widely distributed and clinically important.

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.[79-82] 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.[83-85] Significant cross-reactivity between Betulaceae pollens and oak of the Fagaceae family has been demonstrated with percutaneous skin testing.[75] RAST inhibition studies have shown cross-inhibition between oaks and other *Fagales* species.[86] IgE immunoblot inhibition experiments have demonstrated that the *Fagales* species might be strongly inhibited by birch species.[87] The use of one of the locally prevalent members (eg, birch and alder) should be adequate.[88]

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.[89,90] Maple and box elder trees are found throughout the United States, except for the arid southwest. Although in the same genus as maple, *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,[91,92] and there are allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.[93]

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.[94] Similarly, Chenopod-Amaranth families have wide ranges in the western regions but are present throughout North America.[95] Current information on cross-reactivity of these families is limited.[96-98] 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.[99] The use of a single Amaranth extract should be sufficient to cover this family.[100,101] Similarly, *Atriplex* species (eg, saltbushes and scales) show near identity, and use of a single member is adequate. 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,

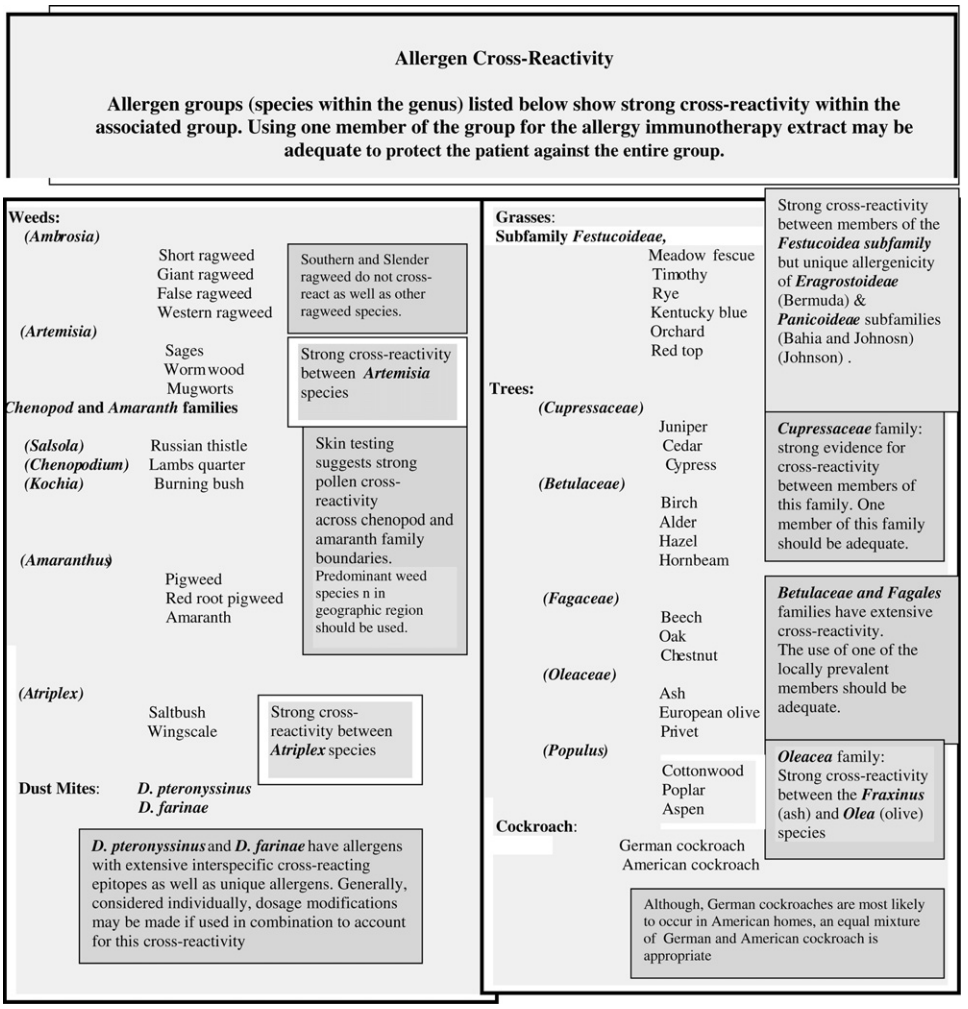


FIG 2. Patterns of allergen cross-reactivity.

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*).

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.[102,103] Stinging Hymenoptera insects occur throughout the United States; the fire ant is found only in Gulf Coast states, Texas, and some other southern and western states. Commercial venom extracts are available for some Hymenoptera species, except the fire ant, for which only whole-body extract is available.

EFFICACY OF IMMUNOTHERAPY

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity

Summary Statement 10: Immunotherapy is effective for 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.[104-111] Immunotherapy is effective for the treatment of allergic rhinitis[107] (including ocular symptoms[112,113]), allergic asthma,[104,109,111,114,115] and stinging insect hypersensitivity[108,116] and is effective in both adults and children.[117-124] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollens,[13,125-132] fungi,[133-138] animal allergens,[22,25,26,139-143] dust mite,[114,115,144-153] and cockroach.[154] There have been no controlled trials of fire ant whole-body extract, but it does appear to be effective in

TABLE IV. Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy

Outcome measure	House dust mite	Other allergens*†
Symptomatic improvement	2.7 (1.7-4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2-7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50)	5.5 (2.8-10.7)

Data are used with permission from Abramson et al.[104]
ND, Not done.
*Odds ratio (95% CI).
†Pollen, mold, or animal dander.

uncontrolled trials.[155-157] 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. A number of studies have also demonstrated a significant improvement in quality of life, as measured by using standardized questionnaires.[24,158-161] The magnitude of the effect depends on the outcome that is used (Table IV). For dust mite, the effect size ranges from a 2.7-fold improvement in symptoms to a 13.7-fold reduction in bronchial hyperresponsiveness. 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.[110] 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[107] and asthma[104,109,111] have been performed to deal with the issue of power. One review of 75 trials involving 3188 asthmatic patients found that, overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyperreactivity after immunotherapy, and it would have been necessary to treat 4 patients (95% CI, 3-5) with immunotherapy to avoid 1 deterioration in asthma symptoms and 5 (95% CI, 4-6) patients to avoid 1 requiring increased medication.[111] These meta-analyses strongly support the efficacy of allergen immunotherapy. Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued[13,162,163] and might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6,9,122,162-165] Allergen immunotherapy might also prevent the development of new allergen sensitivities in monosensitized patients.[120,166,167]

Food allergy, urticaria, and atopic dermatitis

Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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 use of allergen immunotherapy for individuals with the potential for IgE-mediated (anaphylaxis) reactions to foods should be regarded as investigational at this time.[168-171] There have been 2 investigational studies demonstrating efficacy in food hypersensitivity, the first using aqueous subcutaneous injections to peanut and the second using sublingual immunotherapy to hazelnut.[171-173]

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 a modified peanut extract is needed for clinical application of this method of treatment.[171] There is currently no FDA-approved formulation for sublingual immunotherapy, and this route of allergen immunotherapy is currently considered investigational at this time (see Summary Statement 73).

At the present time, there is not enough evidence to support food immunotherapy.

There is no evidence supporting the efficacy of immunotherapy for individuals with chronic urticaria, angioedema, or both.

There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[174-176] 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 ($P = .0379$) and topical corticosteroid use ($P = .0007$).[174]

The potential for benefit in symptoms related to oral allergy syndrome with the cross-reacting inhalant immunotherapy, which includes cross-reacting 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 subcutaneous immunotherapy directed against birch tree,[177] whereas another double-blind, double-dummy, placebo-controlled study comparing the effect of subcutaneous immunotherapy with sublingual immunotherapy 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, medication use, and decrease in IgE reactivity.[178] More investigation is required to substantiate the contention that benefits in oral symptoms will occur with immunotherapy.

Measures of efficacy

Summary Statement 12: 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. Objective measures, such as increase in allergen-specific IgG levels and decreased skin test reactivity, as measured by skin test titration, are changes generally associated with effective immunotherapy but, at present, are not practical for routine clinical use.[147] Nonquantitative skin testing or *in vitro* 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 are not very reliable given the strong placebo-like effect (Hawthorne effect) associated with any treatment. A more objective means for determining efficacy as validated in controlled clinical studies is the use of clinical symptom scores and the amount of medication required to control symptoms and maintain peak flow rates or pulmonary function tests within acceptable limits. Successful immunotherapy often results in a reduction in medication. Sequential measurement of disease-specific quality of life also might be helpful.

SAFETY OF IMMUNOTHERAPY

Reaction rates

Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Large local reactions associated with allergen immunotherapy are fairly common, with a frequency ranging from 26% to 86% of injections.[179] Two retrospective studies compared the effect of not adjusting immunotherapy dose based on large local reactions on the immunotherapy systemic reaction rate with dose-adjustment protocols.[179,180] There was a total of 12,464 injections administered with a dose-adjustment protocol in the 2 studies compared with 9542 injections administered with a no-dose-adjustment protocol. 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 for subsequent systemic reactions, 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 large local reactions, defined as 25 mm or larger, in patients who had experienced systemic reactions with age-, sex-, and allergen sensitivity–matched control subjects who had not had allergen immunotherapy systemic reactions found the rate of large local reactions was 4 times higher among the 258 patients who had subsequently experienced a systemic reaction compared with those who had never experienced a systemic reaction.[181] Patients who had experienced systemic reactions had 1573 large local reactions in 4460 visits (ie, 35.2% of visits) and 8081 injections (ie, 19.5% of injections) compared with the matched control group without systemic reactions who had 1388 large local reactions in 15,540 visits (8.9% per visit) and 26,259 injections (5.3% per injection; difference between groups, $P < .001$). Individual large local reactions were not predictive of future systemic reactions, but large local reactions preceded systemic reactions in approximately one third of the systemic reactions. These findings suggest that individuals with a greater frequency of large local reactions might be at greater risk for systemic reaction. Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy protocol modifications based on them are needed.

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

The prevalence of severe systemic reactions after allergen immunotherapy ranges from less than 1% of patients receiving conventional immunotherapy to greater than 36% of patients in some studies of patients receiving rush immunotherapy.[182,183]

In a recent survey of fatal and near-fatal reactions (NFRs) sent to physician members of the AAAAI, 273 of 646 respondents reported NFRs during the period of 1990-2001.[184]

The incidence of unconfirmed NFRs was 23 per year (5.4 events per million injections). Administration during the height of 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 angiotensin-converting enzyme 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 systemic reactions to subcutaneous immunotherapy over a 20-year period (1981-2000) during which 435,854 injections were administered to 4000 patients, 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.[185,186] In a prospective multicenter study there were 53 systemic reactions (0.3% of the doses) out of 17,526 administered doses in 18 (3.7%) of 423 patients.[187] 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 (21 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, there were 41 fatalities identified in the initial brief survey (20 directly reported and 17 with completed detailed questionnaire) from immunotherapy injections.[188] 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.[189,190] Therefore although severe systemic reactions to allergen immunotherapy are not common, serious systemic reactions (some fatal) can occur.

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

In the AAAAI survey of physician members on immunotherapy and skin testing, fatal reactions, and NFRs during the period of 1990-2001, 15 of the 17 fatalities had asthma, and in 9 patients asthma was considered the susceptibility factor that contributed to the fatal outcome.[188]

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.[184]

Administration during the peak pollen season (3 patients) and previous systemic reactions (4 patients) were cited as other contributing factors. Five fatalities occurred in outside medical facilities, and 2 fatalities occurred at home. No patients were receiving β-blockers; 1 patient was taking an angiotensin-converting enzyme inhibitor. In the most comprehensive evaluation of fatalities associated with allergen immunotherapy, from 1945-1987, there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[189] 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, with 73.3% of patients with an FEV_1 of less than 80% of predicted value experiencing 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 ($P < .0001$).[191] 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% of patients. These studies suggest that symptomatic asthma, severe asthma, or both might be a risk factor for immunotherapy.

In addition to symptomatic asthma and injections giving 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.[17] With the exception of dosing errors and 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 recent 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 or allergy symptom exacerbation, β-blocker use, change in health status (including pregnancy), or adverse reaction to previous allergen immunotherapy injection. The preinjection evaluation might also include a peak flow measurement to assess the airway function of asthmatic patients.

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 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

In a retrospective study the time to onset of a systemic reaction after an immunotherapy injection was less than 30 minutes in most cases.[189] A review of the literature indicates that 70% of systemic reactions occur within 30 minutes after an injection.[183] In the AAAAI 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.[184,188] 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.[190] 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 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.[192] In another prospective study 8% of systemic reactions occurred more than 2 hours after injection.[193]

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.[194]

Because most reactions that resulted from allergen immunotherapy occurred within 30 minutes after an injection, patients should remain in the physician's office for at least 30 minutes after receiving an injection, but longer waits are reasonable, as directed by the physician. In addition, patients who are at increased risk of a systemic reaction might need to carry injectable epinephrine. Such patients might also need to remain in the physician's office more than 30 minutes after an injection. 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.

β-Adrenergic blocking agents

Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

β-Blockade enhances pulmonary, cardiovascular, and dermatologic end-organ effects of mediators and increases mortality associated with experimental anaphylaxis induced by either immunologic or nonimmunologic mechanisms. Patients who are receiving β-adrenergic blocking medications might be at increased risk if they experience a systemic reaction to an allergen immunotherapy injection because the β-receptor blockade might attenuate the response to epinephrine.[195-202] Patients who are receiving β-blocking drugs were almost 9 times more likely to be hospitalized after an anaphylactoid reaction from radiocontrast media.[198] Although topical β-blockers have markedly less systemic β-antagonist effects than oral β-blockers, they still might exhibit some systemic β-antagonist effects. Whether topical β-blockers pose the same or a smaller risk than oral β-blockers in regard to the treatment of allergen immunotherapy–related systemic reactions is not known.

There have been very few studies that have examined the effect of β-blocker medications on allergen immunotherapy. A prospective 1-year study designed to determine whether patients taking β-blocker drugs were at increased risk of immunotherapy-induced systemic reactions found that there were 166 systemic reactions out of 56,105 injection visits in 3178 patients (68 were receiving a β-blocker).[203] The systemic reactions occurred in 144 (4.5%) patients, and only 1 of these patients was receiving a β-blocker medication. The authors calculated that by chance, 3.08 patients receiving the β-blocker medications drugs were expected to have had an systemic reaction and concluded that β-blocker medications did not increase the frequency of allergen immunotherapy systemic reactions ($P > .95$).

In another study of 1389 patients prescribed immunotherapy for Hymenoptera venom hypersensitivity who were followed for 34 months, there were 25 patients who received concomitant β-blocker medications.[204] Three (12%) of the 25 patients receiving β-blocker medications experienced systemic reactions during immunotherapy compared with 23 (16.7%) of 117 patients with cardiovascular disease not receiving β-blockers. Systemic reactions after a field sting or challenge occurred in 1 (14.3%) of 7 cardiovascular patients receiving β-blocker medications compared with 4 (13.8%) of 29 cardiovascular patients not receiving β-blocker medications. No severe reactions to immunotherapy or sting re-exposure were observed in patients receiving β-blockers medications.

Immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. In such cases, intravenous glucagon, which might reverse the refractory bronchospasm and hypotension by activating the adenyl cyclase directing and bypassing the β-adrenergic receptor, might be used if epinephrine has not been effective.[205,206] Prospective studies are necessary to clarify the magnitude of the risk of systemic reactions to allergens in patients who are receiving concomitant therapy with β-blockers, and a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy.

Contraindications

Summary Statement 18: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications

TABLE V. Actions to reduce the risk of anaphylaxis

- Assess the patient's general medical condition at the time of injection (eg, asthma exacerbation).
- Consider obtaining a PEFR before administration of the injection. If the PEFR is significantly less than the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.
- 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 with increased allergen sensitivity or those who have previously had a systemic reaction) might need to wait longer.
- Carefully evaluate any patient with a late reaction (eg, persistent large local reaction lasting >24 hours, systemic reaction occurring more than 30 minutes after the immunotherapy injection).
- 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.

PEFR, Peak expiratory flow rate measurement.

TABLE VI. Recommended equipment and medications to treat anaphylaxis

Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur. This should include at least the following equipment and medications:

- stethoscope and sphygmomanometer;
- tourniquet, syringes, hypodermic needles, and large-bore needles (14-gauge);
- aqueous epinephrine HCL 1:1000 wt/vol;
- equipment to administer oxygen by mask.
- intravenous fluid set-up;
- antihistamine for injection (second-line agents for anaphylaxis, but H_1 and H_2 antihistamines work better together than either one alone);
- corticosteroids for intravenous injection;
- vasopressor;
- equipment to maintain an airway appropriate for the supervising physician's expertise and skill.

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 venom hypersensitivity and cardiac disease being treated with β-blocker medications.

Reducing the risk of anaphylaxis to immunotherapy injections

Summary Statement 19: 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 extremely 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 or other health care professional appropriately trained in emergency treatment.

The 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. Epinephrine is the first-line treatment for anaphylaxis. 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.[12,207-213] It is important to administer epinephrine early in the management of anaphylaxis. 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 V and VI, respectively. Before allergen immunotherapy is chosen as a treatment, the physician should educate the patient about the benefits and risks of immunotherapy, as well as methods for minimizing risks. The patient also should be told that despite appropriate precautions, reactions might occur without warning signs or symptoms. Informed consent should include a discussion of the potential immunotherapy adverse reactions, and this discussion should be documented in the patient's medical record.

PATIENT SELECTION

Clinical indications

Summary Statement 20: Allergen immunotherapy should be considered for patients who have demonstrable

TABLE VII. Clinical indications for allergen immunotherapy

Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or both:
- symptoms of allergic rhinitis after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medications;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medication;
- coexisting allergic rhinitis and asthma;
- possible prevention of asthma in patients with allergic rhinitis

Symptoms of asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medication;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medications;
- coexisting allergic rhinitis and allergic asthma.

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);
- adults and children with a history of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.

evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic rhinitis.[107] Prospective, randomized, double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic asthma.[104,109,111]

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 proper identification and selection of component allergens on the basis of 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 (Table VII). The severity and duration of symptoms should also be considered in assessing the need for specific allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. In addition, specific allergen immunotherapy should be considered if the patient wishes to avoid long-term pharmacotherapy. Time lost from work, emergency department or physician's office visits, and responses to pharmacotherapy are important objective indicators of allergic disease severity.

Patients with allergic rhinitis who are unable to sleep because of symptoms or whose symptoms interfere with their work or school performance should be considered strong candidates for specific allergen immunotherapy. 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 considered. Unacceptable adverse effects of medications should also favor one's decision to initiate allergen immunotherapy. Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.[214]

Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued, and it might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6-9,122,162-165] These benefits of immunotherapy should be discussed with patients and might provide a clinical indication for immunotherapy for individual patients with allergic rhinitis.

Coexisting medical conditions should also be considered in the evaluation of a patient who might be a candidate for allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed with a combined aggressive regimen of allergen avoidance and pharmacotherapy and might also benefit from allergen immunotherapy.[215,216]

However, the patient's asthma must be stable before allergen immunotherapy is administered.[188,191]

Special precautions in patients with asthma

Summary Statement 21: 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 might be at increased risk for systemic reactions to immunotherapy injections.[182,188,191] Two surveys found that deaths from

immunotherapy were more common in symptomatic subjects with asthma.[188,189] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2,217]

Clinical indications for VIT

Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Systemic reactions to Hymenoptera stings, especially when associated with respiratory symptoms, cardiovascular symptoms, or both and positive skin test or *in vitro* test results for specific IgE antibodies, are a strong indication for allergen immunotherapy.[218] In the United States patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Several studies of patients with imported fire ant allergy have demonstrated the effectiveness of immunotherapy with whole-body extracts of fire ants.[155,156,219] 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. Patients younger than 16 years of age who present only with a cutaneous reaction to imported fire ant or Hymenoptera stings might not require immunotherapy.[218,220-222] In addition to allergen immunotherapy, patients with imported fire ant and Hymenoptera venom sensitivity should be instructed in how to best avoid insect stings, be prescribed epinephrine, and be taught how 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 the population that has not had a systemic reaction.[223] In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific IgE is recommended.[218] If the venom-specific IgE test result is also negative, it is recommended that the skin tests, venom-specific 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 IgE test result.[224] 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 re-stung. 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%).[225] 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 IgE test results who have had severe anaphylaxis to an insect sting.

Some patients who have negative venom skin test results and negative venom-specific IgE test results are reported to have had subsequent systemic reactions to stinging insects.[225-227] Controlled studies designed to evaluate the efficacy of immunotherapy in these patients have not been performed. There are very 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.[226] 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.

Summary Statement 23: 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.

ALLERGEN SELECTION AND HANDLING

Allergen selection

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

A careful history, noting environmental exposures and an understanding of the local and regional aerobiology of suspected allergens, such as pollen, fungi (mold), 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 skin or *in vitro* test results for specific IgE antibodies, provide good evidence that such exposures are relevant. Information concerning regional and local aerobiology is available on various Web sites or through the National Allergy Bureau at http://www.aaaai.org/nab. There are

no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma. 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 clinical history of an allergic disease.

There is no evidence to support the administration of immunotherapy based solely on results of specific *in vitro* 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.

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

The omission of clinically relevant allergens from an allergic patient's allergen immunotherapy extract contributes to decreased effectiveness of allergen immunotherapy. The 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 can make allergen immunotherapy less effective.

Knowledge of the total allergenic burden facing a patient and the realistic possibility of avoidance is important in determining whether allergen immunotherapy should be initiated. 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. Many individuals travel extensively for business or pleasure into different regions, and symptoms might worsen at these times. However, inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective. Determination of the significance of indoor allergens for a particular patient is harder because it is difficult to determine exposure in the home, school, and/or workplace. Historical factors, such as the presence of a furry animal in the home, a history of water damage and subsequent fungal exposure, or a history of insect infestation, might be helpful. However, such information is subjective and is often of uncertain reliability. In addition, some studies have demonstrated significant indoor levels of cat and dog allergen in households without pets[228] and significant levels of mouse allergen in suburban[229] and inner-city[230] homes 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 with increased asthma morbidity in inner-city children was found.[231] 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. Nevertheless, for most patients, determination of the clinical relevance of an allergen requires a strong correlation between the patient's history and evidence of allergen-specific IgE antibodies.

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted *in vitro* tests for specific IgE antibodies can also be used. **A**

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 the skin test results have demonstrated the efficacy of immunotherapy for relevant allergens.[25,26,112,130,134,135,140,141,149,154] 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 from skin testing in a highly sensitive individual.[232,233] In addition, skin tests might be difficult to perform in patients with dermatographism or atopic dermatitis. *In vitro* tests are particularly useful in such patients.

Studies indicate that skin testing is generally more sensitive than *in vitro* tests in detecting allergen-specific IgE.[234,235] Based on inhalation challenge test results, skin tests have shown specificity and sensitivity generally superior to those of *in vitro* tests. The comparability of skin tests and *in vitro* tests for specific IgE antibodies depends on the allergen being tested. For all of 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, prick testing is sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass[236] and cat,[237] are used. Intradermal/intracutaneous skin testing might be required for some allergen extracts. It is appropriate in some patients to use *in vitro* tests for specific IgE antibody as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. *In vitro* tests can also be used to define the allergens that should be used in allergen immunotherapy. If the allergy skin test result is negative and the *in vitro* test result is positive, a controlled challenge can be performed, and if the latter is positive, immunotherapy can be considered. 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 *in vitro* test results.

Specific allergens

Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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.[17,104,106,107,109] 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.[112,122] Because a particular pollen extract is a mixture of multiple glycoproteins, this suggests that mixing pollen allergens does not alter biologic activity.

Fungi (molds). Several studies with *Alternaria* and *Cladosporium* species suggest that allergen immunotherapy with fungi might be effective.[133-138] The allergen content of most mold extracts is highly variable.[238,239] However, there is evidence that proteolytic enzymes present in some mold extracts could digest other antigens, such as pollens, when combined in a mixture.[240] For this reason, it might be desirable to separate all pollen extracts from mold extracts when using mixtures.

Unfortunately, extracts for some potentially clinically important fungi are not available.[241] 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 distinguish 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.

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.

Because immunotherapy has been shown to be effective for cat[22,26,139-143,242] and dog,[25,141] the decision to include dog or cat allergen in an allergen immunotherapy extract should be considered in those circumstances in which there is exposure.

Dust mites and cockroach allergens. Crude house dust extract is generally an inappropriate substitute for house dust mite extract because the protein content measured is not restricted to dust mite allergens, nor does it necessarily guarantee inclusion of dust mite protein. Immunotherapy with standardized dust mite is generally more effective than that with crude house dust allergens. The house dust mites *D farinae* and *D 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, such as *Blomia tropicalis* and *Euroglyphus maynei*, partially cross-react with allergens from *Dermatophagoides* species. Only 50% of the projected amounts of each of the 2 house dust mites (*D pteronyssinus* and *D farinae*) need 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[144,147-149,151] 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. Dust mite hypersensitivity should particularly be considered in patients who have perennial symptoms exacerbated by a dusty environment at home, work, or both and periods of high humidity.

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. The major allergen of *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.[243] Immunotherapy with cockroach allergens is effective[154] and should 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.

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.[108,116,244] Efficacy has also been demonstrated with immunotherapy by using whole-body extracts of imported fire ants.[155,156]

Foods. Only a single clinical study accessing the efficacy and safety of subcutaneous immunotherapy with foods has been performed.[171,173] This study, which evaluated immunotherapy with peanut, found the incidence of systemic reactions, even during maintenance, was unacceptable. Thus there is no evidence to support the use of immunotherapy with food extracts. Currently, strict avoidance of the offending food is advisable, and subcutaneous immunotherapy for food allergy is not recommended.

Mixing of extracts

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Once the relevant allergens for each patient are identified, it is necessary to prepare a mixture that contains each of these allergens. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts. A number of 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 interactions between different types of allergens, when mixed, that could lead to degradation or unmasking of epitopes on exposure to proteolytic enzymes.

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Immunologic and 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.[71] 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 genera 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 the Allergen extract section, Fig 2, and the allergens and allergy diagnostic tests practice parameters).

Dose selection. Summary Statement 30: 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.[22-26,128,149,245] Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000 vol/vol).[28] A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy vaccine. Failure to do so might reduce the efficacy of immunotherapy. This occurs because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased (see the Immunotherapy schedules and doses section for further discussion and for recommended maintenance doses).

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as fungi (mold) and cockroach, from other extracts, such as pollens, is recommended. **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.[240,246,247] 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, and some weeds.[240,246,247] Cockroach had a similar deleterious effect on pollen extract potency.[246,248] Short ragweed appeared resistant to the effects of the proteolytic enzymes in one study,[240] 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.[247]

Dust mite extracts do not appear to have a deleterious effect on pollen extracts.[240,246,248] These studies suggest that pollen, dust mite, and cat extracts can be mixed together. 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. The evidence on mixing cockroach extract with other extracts is conflicting, and the clinical relevance of the changes is also unclear; therefore the clinician has the option of separating cockroach or not.

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 with lesser activities, such as pollen extracts.

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.

In this regard the number of separate injections that need to be given at each patient visit depends on whether all of the relevant extracts mixed into a single vial still deliver an optimal dose of each allergen. If mixing causes excessive dilution or if there are advantages to separating allergens into separate vials, then more than one vial might be necessary for successful immunotherapy.

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extracts are high-alert products that carry the risk for anaphylaxis. Policies, procedures, and processes intended for conventional drugs and medications might be highly 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 fatal anaphylactic reactions with allergenic products. 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. There are no reports of infection associated with allergen immunotherapy injections. Allergen vaccines are prepared by using sterile manufacturer's extracts and sterile diluents containing antibacterial constituents (usually phenol). A summary of the AAAAI/ACAAI/JCAAI proposed USP allergen immunotherapy extract preparation guidelines can be found in Table VIII.

TABLE VIII. AAAAI/ACAAI/JCAAI-proposed USP 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 below.*
   - 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.
2. **Physician responsibility**: A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in the preparation of immunotherapy using an aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files.
3. **Bacteriostasis**: Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if 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 the FDA-approved package insert 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 treatment with sanitizing agents containing alcohol and/or 70% isopropanol 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 the physical integrity of the vial.
10. **Labeling**: Immunotherapy vials are to be clearly labeled with the patient's name and 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.

*__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 media, such as from Valiteq (http://www.valiteq.com), 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.

Allergen immunotherapy extract handling

Storage. Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

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 a number of 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 extract, including reconstituted lyophilized extracts, should be stored at 4°C to minimize the rate of potency loss because storage at higher temperatures (eg, room temperature) can result in rapid deterioration.[249]

Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions (personal communication). These studies include actual shipments made by their carriers to places like

Phoenix in the summer and Alaska in the winter. 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.

Storing dilute extracts. Summary Statement 34a: More dilute concentrations of allergy immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than do more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: In determining the allergy vaccine expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of 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 allergen immunotherapy 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.[249,250]

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.[250] Phenol is a preservative added to extracts to prevent growth of microorganisms.

Phenol can denature proteins in allergen extracts.[251,252] Human serum albumin might protect against the deleterious effect of phenol on allergen extracts.[251] 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,[250,253] possibly through inhibition of the activity of proteolytic and glycosidic enzymes that are present in certain extracts. However, it is irritating when injected and should be diluted before beginning immunotherapy. Recommendations for extract stability are found in the manufacturers' product insert sheets. 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. The pain associated with glycerin increases in proportion to the glycerin concentration and injection volume, and the pain is proportional to the total injected dose of glycerin.[254] However, individual pain perception can vary substantially. Total glycerin doses of less than 0.05 mL rarely produce clinically important pain.

TABLE IX. Potency of selected manufacturer's extracts currently available

Extract	Potency
Cat hair and pelt	5000 and 10,000 BAU/mL
Dust mite	3000, 5000, 10,000, and 30,000 AU/mL
Bermuda grass	10,000 AU/mL
Short ragweed	1:10-1:20 wt/vol or 100,000 AU/mL
Other grasses*	10,000 and 100,000 BAU/mL
Other pollen	1:10 to 1:40 (wt/vol) or 10,000 PNU/mL
Molds	1:10 to 1:40 (wt/vol) or 20,000 to 100,000 PNU/mL

AU, Allergy unit; *BAU*, bioequivalent allergy unit; *PNU*, protein nitrogen unit.
*Perennial rye, Kentucky blue/June, timothy, sweet vernal, redtop, orchard, and meadow.

There have been few studies that have investigated the potency of dilutions of allergen extract mixture over time. Expiration dates for allergen extract dilutions are somewhat empiric and not strongly evidence based. A study undertaken by the AAAAI 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. Dust mite and cat at 1:10 and 1:100 vol/vol dilution were also stable in all conditions of storage over 12 months, as measured by an ELISA assay using 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.

IMMUNOTHERAPY SCHEDULES AND DOSES

Summary Statement 35: A customized individual 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 can be based on single or multiple allergens. **D**

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. Animal dander contains between 10 and 20 antigens,[255] house dust mites between 20 and 40 antigens,[256] and pollens between 30 and 50 antigens,[257,258] and fungal extract can contain as many as 80 antigens.[259]

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. This is designated as the patient's maintenance concentrate.

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. Standardized extracts are available with biologic potencies of 10,000 and 100,000 BAU for grasses; 5000 and 10,000 BAU for cat allergen; 5000, 10,000, or 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 wt/vol extracts (Table IX). 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.

Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

The highest concentration of an allergen extract mixture that is projected to be used as the therapeutically effective dose is called the maintenance concentrate. This should be prescribed individually for each patient by an allergist/immunologist. 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 individual manufacturer's extracts. Some patients might be unable to attain the projected therapeutically effective dose of the maintenance concentrate because of local reactions, systemic reactions, or both (eg, cat, 1000 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose]; see Table X for probable effective therapeutic dose range). Such patients might need weaker dilutions of their maintenance concentrate. Even so, 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 referred to as the maintenance dose. The consistent use of this nomenclature system is essential because errors in choosing the correct vial are a common cause of systemic reactions, especially when the patient transfers from one physician to another. Therefore it is important that standard terminology be adopted by all physicians who prescribe allergen immunotherapy.

Recommended doses

Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

The effective maintenance dose of immunotherapy for a particular patient must be individualized. To do this, the allergist/immunologist who prepares the allergen immunotherapy extract must balance the dose necessary to produce efficacy and the risk of reactions if such a dose is reached. The allergist/immunologist might need to prepare more than one maintenance concentrate to provide a therapeutic dose of each of the allergens for the polysensitized patient. Therapeutically effective doses for immunotherapy have been reported for some allergen extracts.[22,24,25,128,134,135,149,246,260,261] Effective doses have been determined for Hymenoptera venom, dust mite, cat allergen, dog, grass, and short ragweed (Table X).

Controlled studies demonstrate that the content of particular allergens in allergen immunotherapy extracts can be used to predict a therapeutic dose for those allergens, particularly when the extracts are standardized. For antigens 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. The therapeutically effective doses used in the most recent controlled clinical studies are the basis of the recommended dosage range of standardized extracts presented in Table X. 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 time that it is administered.[14]

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.[27] 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 risk of systemic reactions to immunotherapy injections with higher maintenance doses. The maintenance concentrate should be formulated to deliver a full therapeutic dose of each of its constituent components. However, some sensitive patients might not tolerate the targeted therapeutic dose, and their maintenance dose would be lower. Individuals 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 referred to as the maintenance dose.

Regardless of dose schedule, some patients are unable to progress to the predetermined maintenance dose because of large local or systemic reactions to the allergen

TABLE X. Probable effective dose range for allergen extracts US standardized units[a]

Antigen	Labeled potency or concentration[a,b]	Probable effective dose range
Dust mites: *D farinae* and *D pteronyssinus*[c]	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat[d]	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized[e]	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed[f]	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 μg of Amb a 1 1000-4000 AU Concentration of Amb a 1 is on the label of wt/vol extracts in FDA units[358]
Nonstandardized extract, dog[g]	1:10 to 1:100 wt/vol	15 μg of Can f 1
Nonstandardized extracts	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose

[a]Multiple studies have demonstrated that the efficacious dose for allergen immunotherapy is between 5 and 20 μg of the major allergen per injection. Only 2 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).

[b]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).

[c]There have been no dose-response studies with United States–licensed dust mite extracts, and dosing recommendations in AU value are extrapolated from published European studies that used aqueous[349] and alum-precipitated[149,151] extracts. 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.[149] The authors suggested the optimal maintenance dose was 7 μg of Der p 1. Corresponding doses were based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Extrapolating effective and safe doses in this manner might not be scientifically valid. *D farinae* and *D pteronyssinus* are similar in group 1 allergen content according to the FDA's current reference standards. 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*.

[d]The major cat allergen Fed d 1 is reported in FDA units, with 1 Fel d 1 unit equaling approximately 2 to 4 μg of Fel d 1.[55,58,59] The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 to 19.9 U/mL. One study demonstrated clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 dose in terms of decreased cat extract PD_{20}, titrated skin test results, and allergen-specific IgE and IgG levels.[350,351] In a recent study that investigated the efficacy in terms of immunologic changes of 3 doses of a United States–licensed cat extract (0.6, 3, and 15 μg) demonstrated that a significant effect on titrated skin prick test results, allergen-specific IgG4 levels, and $CD4^+$/IL-4 levels was only seen in the group treated with 15 μg of Fel d 1, although the 3-μg dose group did demonstrate a significant change in titrated skin test response and increase in cat-specific IgG4 levels.[22]

[e]There have been no dose-response studies with United States–licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,[130] alum-precipitated,[24,161] and calcium phosphate–precipitated grass pollen extracts.[352] One of these studies compared a dose of 2 μg with 20 μg of major timothy allergen (Phl p 5) and found clinical efficacy at both doses.[24] The efficacy was greater in the 20 μg of Phl p 5 dose, but the systemic reaction rate was also higher in the high-dose group. The package inserts for United States–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 BAU. Extrapolating effective and safe doses in this manner might not be scientifically valid. 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).

[f]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 suggested that 1 unit of Amb a 1 is equivalent to 1 μg of Amb a 1, and 350 Amb a 1 units/mL is equivalent to 100,000 BAU/mL.[60] The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2000 AU, with a range of 1000-4000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrated 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.[45] A ragweed dose-response study (0.6, 12.4, and 24.8 μg of Amb a 1) demonstrated efficacy, as measured by nasal challenge, at 12 and 24 μg of Amb a 1.[128] The efficacy of the 24-μg dose was not significantly better than the 12-μg dose, and the authors concluded that the optimal dose for ragweed extract was greater than 0.6 μg but not more than 12.4 μg of Amb a 1.

[g]Dog extracts are not standardized. However, one dose-response study with a United States–licensed acetone-precipitated dog extract investigated the efficacy of 3 doses (AP dog; Hollister-Stier, Spokane, Wash; 0.6, 3, and 15 μg) in terms of immunologic changes and found the dose of 15 μg of Can f 1 to be most efficacious.[25] 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 have assayed between 128 and 208 μg/mL (average Can f 1, 162 μg/mL [SD ± 26 μg/mL]; information provided by the extract manufacturer, Hollister-Stier).

immunotherapy extract. The evidence is not clear whether large local reactions are a potential risk for subsequent allergen immunotherapy systemic reactions.

Published studies do not indicate that an individual large local reaction is predictive of a subsequent systemic reaction.[179,180] However, one retrospective study found that individuals who have a history of repeated large local reactions (defined as >25 mm) might be at greater risk for a subsequent systemic reaction.[181]

The concept of highest tolerated dose does not apply for VIT, and all patients are expected to achieve the full recommended dose to achieve the necessary degree of protection. There are conflicting data over whether lower doses (50 μg) are less effective, but there are also data showing that 200 μg is more reliably effective.[245] In the case of VIT, patients are asked to tolerate more large local reactions to achieve the full dose, even though with inhalant immunotherapy the dose can be reduced for such large local reactions to minimize patient discomfort.

Effect of dilution on dose

Summary Statement 38: 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 vaccine, thereby limiting the ability to deliver a therapeutic effective dose for any given allergen.

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

Dilution from maintenance concentrate vaccine	Volume	Volume (mL)	Diluent volume (mL)	Final volume
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.

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 2000 BAU/mL, 2 mL of the manufacturer's extract (cat, 10,000 BAU/mL) can be added to 8 mL of diluent or 8 mL of other allergens, and the final concentration of cat will be 2000 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.

Dilutions of the maintenance concentrate

Summary Statement 39: 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 vol/vol 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, 1000 BAU or 100 BAU), but this system can be complicated if allergens with different potency units are used (eg, wt/vol, BAU, AU, or PNU) and make it difficult to easily interpret the vial label.

Instructions on how to prepare various allergen extracts 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.

Labeling dilutions

Summary Statement 40: 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, a number of 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 (vol/vol), a numbering system, a color-coding system, or an alphabetical system should be used. If this uniform labels 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.

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
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

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 3 and 4).

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 Appendix 2]).

Individualized treatment vials

Summary Statement 41: 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 (wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for 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). Labels on patient-specific vials can provide at least 2 patient identifiers (birth date and patient name), which would be consistent with the recommendations of the Joint Commission on Accreditation of Health Care Organizations National Patient Safety Goals: ''Goal 1: Improve the accuracy of patient identification by using at least two patient identifiers when providing care, treatment or services.''[5] 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 administration of the injection.[4,5]

In a survey of 1717 allergists endorsed by the AAAAI and JCAAI, 57% of the 476 respondents reported at least one wrong-patient injection, and 74% of the 473 respondents reported at least one wrong-dose injection.[4] 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 reasons why this might reduce incorrect injection errors. One reason was that patient-specific vials can be prepared in a quiet laboratory setting, which might provide substantially less distraction than the nurse in a room with a patient who is trying to concentrate only on drawing up the injection correctly. In addition, the specific components are mixed once with the preparation of individually prepared patient-labeled vials, whereas the mixing would be repeated on every injection visit if the allergen extract is withdrawn from different stock solutions, as it is in the off-the-board method. For safety reasons and to avoid cross-mixing of allergens removed from the manufacturer's extract, the mixing of antigens in the syringe (off the board) is not recommended.

Some allergists/immunologists prefer to administer immunotherapy doses drawn directly from a single stock dilution of individual allergens or common mixes (shared specific patient vials). In this way the immunotherapy dose is transferred to the patient without cross-contamination. If shared-patient (eg, mixed vespids and dust mite mix) vials are used, it is essential that policies and procedures are developed to verify that the correct dose from the correct vial is administered to the correct patient.

Starting doses

Summary Statement 42: The starting dose for build-up is usually a 1000- 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 slowly 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 1:1000 (vol/vol), although more diluted concentrations frequently are used for patients who are highly sensitive, as indicated by history or skin test reaction (see Appendix 3 for an example of a conventional immunotherapy schedule).

Frequency of build-up injections

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 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 2 times per week. 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 4 to 6 months, depending on the starting dilution and the occurrence of reactions. It is acceptable for patients to receive injections more frequently, provided there is adequate spacing between injections. The interval between injections is empiric but might be as short as 1 day without any increase in the occurrence of systemic reactions[262] if there is some urgency to achieve a maintenance dose (eg, allergy season is approaching) or for practical reasons (eg, patient's schedule). Alternatively, treatment schedules can be used that more rapidly achieve maintenance dosing. These cluster and rush dosing schedules are discussed in Summary Statements 47 through 49.

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 a number of 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).

Dose adjustments for systemic reactions

Summary Statement 44: 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 benefit/risk ratio justifies continuation of immunotherapy.

Reductions during periods of exacerbation of symptoms

Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Immunotherapy administered during periods of exacerbation of symptoms is considered a risk factor for immunotherapy.[17,184] Injections administered during periods when a patient is exposed to increased levels of allergen to which they are 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.[184] 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 sensitive, especially if their symptoms are poorly controlled.

Dose adjustments for late injections

Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

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 depends 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 Appendix 4 for an example of a dose-modification regimen for gaps in treatment).

Cluster schedules

Summary Statement 47: 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 (see Appendix 5).[22,26] 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. The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules.[145,263-266] The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.[267]

Rush schedules

Summary Statement 48: 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.[268] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.[191,269-272]

The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections over the course of 4 hours.[273] Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours.[274-276] 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 cluster[145,266] and rush[134,277] schedules.

Systemic reactions and rush schedules

Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

The advantages of rush immunotherapy come at a cost because there is an increased risk of local and systemic reactions. Systemic reaction rates have been reported to be

as high as 73% of patients, with the risk of such reactions reduced to 27% by premedication in one study.[272] Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing.[273]

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

Rush protocols for administration of Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions.[274-276,278,279]

Premedication and weekly immunotherapy

Summary Statement 50: Premedication can reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

There is concern that antihistamines taken before each injection with conventional immunotherapy might mask a minor reaction that would otherwise alert a physician to an impending systemic reaction. 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.[280] One study that compared terfenadine premedication with placebo premedication during rush VIT demonstrated greater clinical efficacy in the terfenadine-premedicated group in terms of subsequent responses to field stings or sting challenge.[281] There was also a significant difference in the systemic reaction rate between the 2 groups: 6 patients in the placebo-premedicated group had systemic reactions, whereas none of the patients in the terfenadine-premedicated group had systemic reactions ($P = .012$).

Unfortunately, patients might still have life-threatening anaphylaxis despite 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.

Premedication with cluster and rush immunotherapy

Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

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.[267] Premedication with a 3-day course of prednisone, an H_1 histamine receptor antagonist, and an H_2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.[272] In one study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on the safety and efficacy of rush immunotherapy, there was a 5-fold decrease in the risk of anaphylaxis in the group premedicated with omalizumab compared with the placebo premedication group.[282]

There are anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist, but there have been no published studies. Because the risk of a systemic reaction from rush VIT is relatively low, routine premedication before rush VIT is usually unnecessary.[274,276,278,279] In a study evaluating premedication with antihistamines and steroids for rush immunotherapy with imported fire ant venom, there was no statistically significant differences in the systemic reaction rates between the premedication and placebo premedication group (3.6% of the premedication group vs 6.7% of the placebo group, $P = .87$).[157]

Maintenance schedules

Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals 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 individuals might tolerate longer intervals between maintenance dose injections.

The interval between venom injections can be safely increased up to 8 weeks in some patients without loss of efficacy. 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.

Continuing care

Time course of improvement. Summary Statement 53: Clinical 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.[24,134,143,277] Improvement might not be observed for a number of reasons, including (1) failure to remove significant allergenic exposures (eg, a cat), (2) exposure to high levels of

allergen (eg, pollen or molds), (3) continued exposure to nonallergen triggers (eg, tobacco smoke), or (4) incomplete identification and treatment of clinically relevant allergens. 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 54: 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 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 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

The patient's response to immunotherapy should be evaluated on a regular basis. 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. 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.

There have been very 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 individuals.[283-285] However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported.[283,285] Nevertheless, systemic reactions to stings after discontinuing VIT were generally much milder than the pretreatment reactions and were rarely severe. Two studies did not find a difference in relapse rates between the patients treated for 3 years compared with those treated for 5 years,[283,286] but one of the studies noted that the small number of patients in the 3-year treatment group prevented them from making any conclusions about the risk of discontinuing treatment after 3 years.[283] However, one study found that patients who had experienced re-sting reactions after discontinuing VIT had received VIT for a significantly shorter duration (mean, 43.35 months) than those with continued protection (mean, 54.65 months; $P < .01$).[285] Another study reported that 5 years of VIT provided better immunologic and clinical outcomes than 2 to 4 years of treatment.[287]

Change in skin test reactivity did not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who experienced a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE.[286,288] Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment.[288] The relapse rate and the frequency of severe reactions were greater in patients who had a history of very severe reactions to stings before treatment, in patients who had systemic reactions during VIT (to a sting or a venom injection), in patients with honeybee allergy, and in those who had less than 5 years of treatment.

The duration of inhalant allergen immunotherapy efficacy has not been as extensively studied. Some studies have suggested 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 *(D pteronyssinus)* extract for 12 to 96 months.[14] 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.[13] There was a switch to placebo in half of 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. These studies demonstrate the uncertainty of the long-term benefit of inhalant immunotherapy after discontinuation.

Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained clinical remission after discontinuing inhalant immunotherapy, and 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 indication for continuation of immunotherapy can be found at http://www.aaaai.org or http://www.jcaai.org.

Documentation and record keeping. Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully 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 allergy immunotherapy and prescription forms can be found in the Appendix (Appendices 6-15), and these include examples of immunotherapy prescription and administration forms. These forms, along with examples of immunotherapy consent and instruction forms, can also be found at http://www.aaaai.org.

Injection techniques. Summary Statement 57: Allergen immunotherapy extract injections should be given using a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **C**

Immunotherapy should be given with a 26- to 27-gauge syringe with a half-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.[289-291]

If using shared specific patient vials (stock vials, such as mixed vespid or dust mite mix), a single dose should be drawn from each vial. Antigens from different vials should not be combined in a single syringe. Furthermore, extra care is needed to prevent using the wrong stock antigen.

Summary Statement 58: The injection should be given subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Each immunotherapy injection should be given in the posterior portion of the middle third of the upper 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.

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.

The syringe should be aspirated to check for blood return in the syringe before injecting. If blood is present, 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 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 syringe should be appropriately discarded. A fresh syringe and needle are necessary to determine whether a blood vessel has been entered.

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 could result in a local reaction.

LOCATION OF ALLERGEN IMMUNOTHERAPY ADMINISTRATION

Physician's office

Summary Statement 59: 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 to treat anaphylaxis should be in the immediate vicinity when immunotherapy injections are administered.

Summary Statement 60: 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.[292] 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.[184] 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 might be frequently necessary in the patient's immunotherapy schedule, as well as the patients total treatment program.

Other locations

Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **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.[292] The health care professional and staff 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, or allergy/asthma exacerbations at the time of allergen immunotherapy extract injection or poorly controlled asthma).

Appropriate adjustment of dose should be made as clinically indicated. The physician who prepared the patient's allergen immunotherapy extract should provide adequately labeled allergen immunotherapy extract vials, detailed directions regarding dosage schedule for build-up and maintenance, and instructions on adjustments that might be necessary under the following circumstances:

1. when providing patients with new vials;
2. during seasonal exposure to allergens that are in the patient's allergen vaccine, to which the patient is very sensitive, or both;
3. if the patient has missed injections; and
4. when reactions occur to the allergen immunotherapy extract.

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

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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 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 very 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 fully trained to administer the injection and to treat anaphylaxis if this should 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 supports (personnel, medications, supplies, and equipment) are more optimal for encouraging prompt recognition and treatment of anaphylaxis (Table V). 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.

Summary Statement 63: If a patient on 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for their immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extracts might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Patients often 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 brought from the previous physician (ie, an unchanged immunotherapy program) or one to be prepared by the current physician (ie, a new immunotherapy program).

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 full, clear, and detailed documentation of the patient's previous schedule and the contents of the allergen immunotherapy extract (see Appendices 7, 8, 11, 12, and 14 for examples of allergen immunotherapy prescription and administration forms and documentation guidelines for allergen immunotherapy forms). In addition, the patient's previous response to and compliance with this program 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 a schedule and the allergen immunotherapy extract, (2) the patient has shown significant improvement on this immunotherapy program, and (3) the contents of the allergen immunotherapy extract are appropriate for the area in which the patient is now living.

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, vaccine type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient's dose is not modified. This increased risk is due to the significant variability in content and potency of extracts and the variability in methods used by physicians to prepare the patient's maintenance concentrate and its dilutions. For example, the strength of a given concentration of nonstandardized extracts might vary significantly from vial to vial. The risk of systemic reactions in such a situation might be greater with nonstandardized extracts and allergen immunotherapy extracts that contain mixtures of allergens.

Therefore if the allergen immunotherapy extract is to be changed, the patient might need to be retested for specific IgE to the appropriate allergens 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 provided the interval of time since the last injection has not been too long. For lot changes from the same manufacturer, the physician can consider decreasing the dose by 50% to 90%. For changes in manufacturer and nonstandardized extracts, a greater decrease in dose might be necessary.

SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

Allergen immunotherapy in children

Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children

with allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Immunotherapy for children has been shown to be effective and often well tolerated,[137,242] although at least one study did not show efficacy.[293] 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.[294] In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (see the Patient selection section and Table VII). In recent studies children receiving allergen immunotherapy have demonstrated:

1. improvement in symptom control for asthma[117,119,121,122] and allergic rhinitis[118];
2. increased PC_{20} to histamine[121];
3. increased PC_{20} to cat and house dust mite allergens[121,149];
4. decreased risk of development of asthma[6,9,163-165];
5. decreased development of new sensitivities[120,166]; and
6. modification in release of mediators in children receiving immunotherapy that correlates with decreased clinical symptoms.[123]

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Although there is some disagreement about the role of allergen immunotherapy in children under the age of 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.[117,122] In children with allergic rhinitis, allergen immunotherapy might prevent the development of asthma.[6,9,163-165] However, allergen immunotherapy for inhalant allergens is usually not considered necessary in infants and toddlers because (1) there is 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 in pregnancy

Summary Statement 71: Allergen immunotherapy might be continued but is usually not initiated in the pregnant patient. **C**

The physician must be aware of the benefits and risks of immunotherapy in pregnant patients. The recommended precautions for prevention of adverse reactions are especially important in the pregnant patient. Allergen immunotherapy is effective in the pregnant patient. Thus allergen immunotherapy maintenance doses can be continued during pregnancy. Allergen immunotherapy is usually not initiated during pregnancy because of risks associated with systemic reactions and their treatment (ie, spontaneous abortion, premature labor, or fetal hypoxia). 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, and the patient is maintained on the dose that she is receiving at that time.

Immunotherapy in the elderly patient

Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy might be considered in the treatment of the elderly patient, but the benefit/risk assessment must be evaluated carefully in this population. Older 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. However, elderly patients may also benefit from allergen immunotherapy and age alone should not preclude the consideration of allergen immunotherapy.[295]

Immunotherapy in patients with immunodeficiency and autoimmune disorders

Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with immunodeficiency or autoimmune disorders. Therefore the decision to begin immunotherapy in patients with major humoral or cellular immune defects must be individualized. Concern about the increased risk of immunotherapy in such patients is largely hypothetical.

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

ALTERNATIVE ROUTES OF IMMUNOTHERAPY

Sublingual and oral immunotherapy

Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be

effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no FDA-approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **B**

Alternative routes of administration of allergen immunotherapy are ''a viable alternative to parenteral injection therapy'' in some cases.[106,296] Studies of oral immunotherapy have provided conflicting results for ragweed,[297] birch,[298] and cat[299] immunotherapy. The present dosage of oral immunotherapy extract is 20 to 200 times the parenteral injected dosage, which requires a cost assessment for this type of therapy. Furthermore, adverse effects have included gastrointestinal and oral reactions (50% in 1 study) that might preclude home therapy. Oral immunotherapy should be considered investigational at this time.

Optimal-dose (high-dose) sublingual swallow immunotherapy is effective in adults and children.[300-304] In a study of 855 patients with grass pollen allergy and allergic rhinitis randomized to placebo or one of 3 grass tablet doses, there was a significant reduction in symptom and medication scores in the highest-dose subgroup, who were treated for at least 8 weeks before the grass pollen season, compared with the placebo group (symptoms, 21%, $P = .0020$; medication use, 29%, $P = .0120$).[303]

Sublingual allergen studies have evaluated house dust, olive pollen, grass pollen, ragweed, birch, cat, latex, *Alternaria* species, and *Parietaria judaica*.[305-313] Sublingual immunotherapy has been shown to be effective in patients sensitized to 2 non–cross-reacting allergens, grass and birch.[314] It has been noted that the allergen is not degraded by saliva and that there is no direct sublingual absorption of allergen. Radiolabeled allergen has been detected after 48 hours in the sublingual region.[315,316] Alternative protocols, such as rush and ultra-rush (20 minutes) sublingual swallow[307,316,318] and no induction (build-up) phase,[301,303,317,319,320] have been studied. Several studies have suggested a relationship between dose and efficacy with sublingual immunotherapy,[303,310,321] but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. The majority of sublingual studies have demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both, but approximately 35% of the randomized, double-blind, placebo-controlled studies did not demonstrate efficacy in either parameter during the first year of treatment.[322] Further studies are needed to confirm the optimal dose for sublingual immunotherapy.

One of the potential advantages of sublingual immunotherapy is that it appears to be safe, even at very high doses (up to 500 times the usual monthly subcutaneous dose), and to be associated with a lower incidence of serious side effects.[310,320,323] This appears to apply to young children (<5 years), for whom there are prospective safety data[324,325] and a postmarketing survey.[326]



FIG 3. Sample of labels for allergen immunotherapy extract vials.

There have been no SLIT-related fatalities, but there have been 3 case reports of anaphylaxis caused by sublingual immunotherapy. One patient with latex hypersensitivity had anaphylactic shock 20 minutes after reaching the maximal dose on the fourth day of latex rush sublingual rush immunotherapy.[327]

The other 2 reported cases of SLIT anaphylaxis involved patients treated with multiple inhalant allergens. In one case a patient with allergic rhinitis and asthma who was prescribed a sublingual immunotherapy extract composed of multiple non–cross-reacting allergens (*Alternaria* species, dog, cat, ragweed mix, weed mix, and grass mix)[328] had generalized pruritis, followed by angioedema, shortness of breath, and dizziness, within a few minutes of administering 6 drops of the 1:100 vol/vol dilution on the third day of treatment. This episode was preceded by a milder systemic reaction the previous day (generalized pruritis). In the other case, a 13-year-old girl with allergic rhinitis and asthma had swelling of her lower lip 3 minutes after pollen drops, high fever, chest pain, nausea, and abdominal pain.[329] She was treated in the emergency department for anaphylaxis and hospitalized for observation. The reaction occurred 1 month after she had reached the maintenance dose during the peak of the spring season.

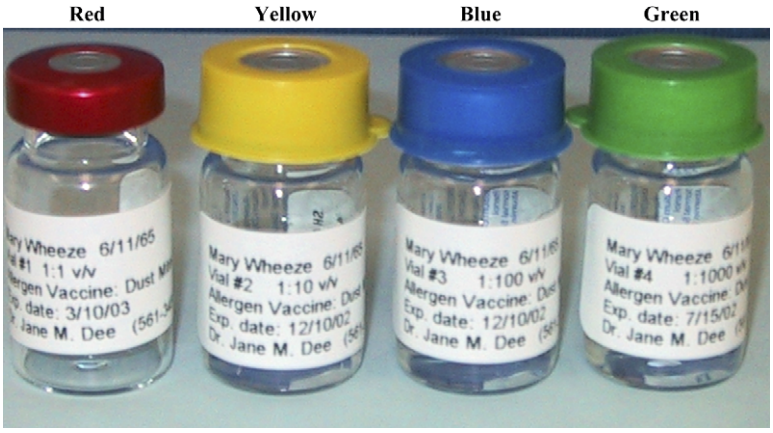


FIG 4. Sample set of color-coded vials of allergen vaccine.

There is currently no FDA-approved formulation for sublingual immunotherapy in the United States at this time, and this modality should be considered investigational. Current investigation of sublingual immunotherapy should not be confused with low-dose sublingual immunotherapy based on provocation neutralization testing or Rinkel-type skin testing.

Intranasal immunotherapy

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Based on controlled, well-designed studies, intranasal immunotherapy has been shown to improve the nasal symptoms of rhinitis.[330] Intranasal dry powder extract immunotherapy has been studied in grass,[330] birch,[331] *P judaica*,[332-334] and house dust mite[335] allergy. Clinical efficacy was noted in all of these studies. Nasal reactivity to allergen challenge was reduced, and only minor side effects were noted in 2 of the above studies. A 3-year study with *P judaica* reported to provide persistent benefits for up to 12 months after conclusion of allergen immunotherapy.[333] Local administration of nasal allergen in an aqueous solution for immunotherapy might be limited by the local side effects. Further studies in both pediatric and adult groups are needed. In human studies the antigen has been noted to appear in the serum within 15 to 30 minutes of administration, with a peak level occurring within 2 to 3 hours.[315] Some allergens have been reported to be retained in the nasal mucosa for up to 48 hours after administration. Intranasal immunotherapy is not currently available in the United States but has gained some acceptance in other parts of the world.

Immunotherapy techniques that are not recommended

Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

Low-dose regimens, including coseasonal low-dose immunotherapy for aeroallergens and the Rinkel low-dose titration techniques, are not effective.[27,28] Immunotherapy based on provocation–neutralization testing with food and aeroallergens and enzyme-potentiated desensitization is not effective.[336]

FUTURE TRENDS IN IMMUNOTHERAPY

Therapy with aeroallergen extracts will become more uniform (as is the current practice for insect venoms) as greater numbers of biologically standardized allergen extracts become available. The actual number of commercially available allergen extracts will be reduced based on consensus agreements about the regional prevalence of aeroallergens, their cross-allergenicity, and the relevance of their effect on human health in specific locales. Novel routes for more effective, convenient, and safer allergen immunotherapy are being investigated throughout the world.

For example, the sublingual route of administering allergen immunotherapy has been studied extensively in Europe. A meta-analysis confirmed its clinical effectiveness in allergic rhinitis,[302] and it has been reported to be effective in asthma as well.[337] Sublingual immunotherapy appears to have a very low risk of serious life-threatening systemic side effects, which might allow for home administration.[324,338] In some studies the clinical benefits of sublingual immunotherapy were not significant until the second year of treatment,[306,339] and comparisons suggest that the magnitude of the clinical benefit of sublingual immunotherapy might not be as great as that of subcutaneous immunotherapy.[311]

Trials with non–IgE-binding peptides containing T-cell stimulating peptides have been reported.[340] Site-directed mutagenesis has produced allergens with decreased IgE-binding capacity without decreased T-cell responses.[341,342]

Immunostimulatory sequences mimicking bacterial and viral DNA have been prepared that stimulate the innate immune system to direct T-cell responses toward

T_H1 rather than T_H2 phenotypes.[343] The results of clinical trials with a conjugate of the immunostimulatory sequence to the major allergen of ragweed, Amb a 1 (AIC), have been reported.[34,343] In a double-blind, placebo-controlled study of 25 adults who received 6 weekly injections of the AIC or placebo vaccine before ragweed season, the AIC group had better peak-season rhinitis scores on the visual analog scale ($P = .006$), peak-season daily nasal symptom diary scores ($P = .02$), and midseason overall quality-of-life scores ($P = .05$) than the placebo group during the first ragweed season, and this effect was observed in the subsequent ragweed season.[344]

Humanized anti-IgE mAb has been shown to have clinical effects in both allergic rhinitis and asthma.[345-348] Theoretically, this new therapeutic modality could be used as protective cover for clinical applications of rapid forms of immunotherapy. It is possible that preadministration of anti-IgE could provide a more effective protective effect than premedication with antihistamines and therefore permit a rush allergen immunotherapeutic regimen with reduced risk of serious systemic reactions.[282]

AUTHOR'S 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 2 systemic reaction grading systems (the European Academy of Allergy and Clinical Immunology's grading of severity for systemic side effects and the Portnoy method for numeric grading of reactions to allergen immunotherapy) can be found in the Appendix section. These forms can also be found along with examples of immunotherapy instruction and consent forms, preinjection health questionnaires, and indications for beginning and continuing immunotherapy forms at www.aaaai.org.

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APPENDIX 1. American College of Medical Quality's policy on the development and use of practice parameters for medical quality decision-making[1]

Practice parameters are strategies for patient management developed to assist health care professionals in clinical decision making. Practice parameters include standards, guidelines, and other patient management strategies. Standards are accepted principles for patient management. Guidelines are recommendations for patient management that identify a particular management strategy or a range of management strategies. Other strategies for patient management include practice policies and practice options. Practice parameters are to be used as screening tools to identify possible deviations from the applicable standards of care. Such parameters are not to be used as absolute standards or to profile or report on health care personnel. Parameters are designed to trigger a process in which possible deviations from the standard of care are identified as outlier practice patterns. Once a deviation from the parameter is identified, such a deviation should be referred to the appropriate qualified physician advisor or reviewer for a determination of medical necessity that conforms to the applicable standard of care. Parameters used in the day-to-day practice of clinical medicine should be clinically relevant. They should not be considered as substitutes for the standard of care but might contribute to its formulation.

Practice parameters must be developed, designed, and implemented only by board-certified, clinically practicing, specialty-matched physician advisors/reviewers with unrestricted medical licenses. Qualified nonphysicians might participate in the development of these parameters only in the areas in which their clinical expertise based on the standard of care is applicable. The health care personnel who develop these parameters should sign their names and date the final version as evidence of their participation and support. Practice parameters must be based on sound scientific research findings, professional literature, clinical experience and appropriate well-recognized methodologies and reflect professionally recognized national standards of care practiced in the clinical community of medicine. The development procedures followed, the participants involved, the evidence used, the assumptions and rationales accepted, and the analytic methods used should be meticulously documented, described, and made publicly available for national peer review. Parameters should be updated as needed.

Practice parameters are used as tools to enhance medical decision making but not as replacements for physicians' clinical judgment. They can be considered as means to enhance the performance of clinical and review personnel but not to replace them. It is below the standard of care of the medical review process to substitute qualified physician reviewer experts with unqualified reviewers who are using parameters.

APPENDIX 2. Examples of possible abbreviations for allergen immunotherapy extract 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

APPENDIX 3. 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

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

APPENDIX 4. Example of immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals (modification of the AAAAI skin testing and immunotherapy consent and instruction forms: immunotherapy administration instruction form, which can be found at http://www.aaaai.org)

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

- Up to 7 days, continue as scheduled (ie, if on weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection).
- Eight to 13 days after missed scheduled injection; repeat previous dose.
- Fourteen to 21 days after missed scheduled injection; reduce dose 25%.
- Twenty-one to 28 days after missed scheduled injection; reduce previous dose 50%.

Then increase dose each injection visit as directed on the immunotherapy schedule until therapeutic maintenance dose is reached.

This suggested approach to modification of doses of allergen immunotherapy because of gaps between treatment during the build-up phase is not based on retrospective or prospective published evidence, but it is presented as a sample for your consideration. The individual physician should use this or a similar protocol as a standard operating procedure for the specific clinical setting. A similar dose-reduction protocol should be developed for gaps in maintenance immunotherapy.

APPENDIX 5. Example of a cluster immunotherapy schedule[22,26]

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

APPENDIX 6. Recommended documentation for allergen immunotherapy prescription forms

The purpose of the allergen immunotherapy prescription form is to define the contents of the allergen immunotherapy extract in enough detail that it could be precisely duplicated. The following information should be on an immunotherapy prescription form:

Patient information:

- Patient name, patient number (if applicable), birth date, telephone number, and picture (if available) should be included.

Preparation information:

- Name of person and signature preparing the allergen immunotherapy extract should be included.
- Date of preparation should be recorded.
- Bottle name should be included (eg, trees and grass). If abbreviations are used, a 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 should be included.
- Volume of manufacturer's extract to add to achieve the projected effective concentration should be included. 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) should be included.
- Extract manufacturer should be included.
- Lot number should be included.
- Expiration date should be recorded and should not exceed the expiration date of any of the individual components.

APPENDIX 7. Allergen immunotherapy extract prescription 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:

_____
_____
_____
_____

_____ ____/____/____
Prescribing Physician Signature Date

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

APPENDIX 8. Maintenance concentrate prescription form

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: 6/10/06

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial **4** from Vial **1** on **8/30/06** Expiration date: **10/15/06**
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	Short ragweed	1:20 w/v G (150 Amb a1)	0.5ml	Greer	12345	1/01/08
2	Amaranthus Retroflexus	1:10 w/v G	0.5ml	H-S	6789	2/07/08
3	Ash	1:10 w/v G	0.5ml	Center	3333	3/17/08
4	Cat	10,000 BAU/ml G	2.00ml	ALO	9898	2/27/08
5	Timothy Grass	100,000 BAU/ml G	0.4ml	ALK	56789	7/09/08
6	Johnson Grass	1:10 w/v G	0.5ml	Greer	2434	7/20/08
7						
8						
9						
10						
Diluent	HSA		0.6ml	ALK	68597	12/08
Total Volume			5.00 ml			6/10/07

*** Components of mixes listed on a separate sheet**
**** Assumes 0.5 ml injection as target maintenance dose**

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

Specific Instructions:

_____

_____

Prescribing Physician Signature

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

APPENDIX 9. Labels for allergen immunotherapy extracts

Each vial of allergen immunotherapy extract should be labeled in a way that permits easy identification. Each label should include the following information (example in Figs 3 and 4):

- Appropriate patient identifiers might include the patient's name, patient's number, patient's picture, and birth date.
- The contents of the allergen immunotherapy extract in a general way should be included. The detail with which this can be identified depends on the size of the label and the number of allergens in the vial. Ideally, allergens should be identified as trees, grasses, weeds, mold, dust mite, cockroach, cat, and dog. Because of space limitations, it might be necessary to abbreviate the antigens (eg, T, G, W, M, DM, Cr, C, and D respectively [see Appendix 2]). A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate (vol/vol) should be recorded. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- The expiration date should be included.

APPENDIX 10. Allergen immunotherapy administration form recommended documentation

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

Patient information:

- Patient's name, date of birth, telephone number, and patient's picture (optional but helpful).

Allergen immunotherapy extract information:

- Allergen immunotherapy extract name and dilution from maintenance in vol/vol bottle letter (eg, A and B), bottle color, or number, if used.
- Expiration date of all dilutions.

Administration information in separate columns:

- Date of injection.
- Arm administered injection, which might facilitate determination of exact cause of local reaction.
- Projected build-up schedule.
- Delivered volume reported in milliliters.
- Description of any reactions. The details of any treatment given in response to a reaction would be documented elsewhere in the medical record and referenced on the administration form.
- *Patient's health before injection*. This can be performed through a verbal or written interview of the patient before administering the immunotherapy injection. The patient should be questioned about increased asthma or allergy symptoms, β-blocker use, change in health status (including pregnancy and recent infections), or an adverse reaction to a previous injection (including delayed large local reactions persisting through the next day). Patients with significant systemic illness generally should not receive an injection.
- *Antihistamine use*. Antihistamines are frequently a component of an allergy medication regimen, and it would be important to note whether a patient is taking an antihistamine on the day he or she receives his or her immunotherapy injection. For consistency in interpretation of reactions, it might be desirable for a patient to either take or avoid antihistamines on a regular basis on the days he or she receives immunotherapy. The physician should note on the form whether he or she recommends the patient consistently take an antihistamine on immunotherapy treatment days.
- *Peak flow reading*. Consider obtaining a peak expiratory flow rate measurement before administering an immunotherapy injection to asthmatic patients. Poorly controlled asthma is considered a risk factor for immunotherapy. Obtaining a peak expiratory flow rate measurement before the immunotherapy injection might help identify patients with symptomatic asthma. The patient's baseline peak expiratory flow rate should be provided on the form as a reference. Health care professionals administering immunotherapy injections should be provided with specific guidelines about the peak expiratory flow rate measurement for when an immunotherapy injection should be withheld and the patient referred for clinical evaluation.
- **Baseline blood pressure**. It might be useful to record the patient's blood pressure as a baseline for future reference.

APPENDIX 11. Allergen immunotherapy administration form

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 allergy or 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

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

Date to reorder: __/__/__

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 allergy or 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**	

APPENDIX 12. 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: _____
_____
Staff action taken (if any): _____

APPENDIX 13. 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.

APPENDIX 14. Allergen immunotherapy systemic reaction/anaphylaxis 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
__Epinephrine IM into 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	

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:
_____
_____
_____
_____

Clinical impression: True SR Questionable SR No SR

Systemic reaction severity classification: EAACI_____ **Portnoy** _____

Dosage adjustment? _____

Signatures_____ **RN** _____**MD/DO**

APPENDIX 15. Grading severity of allergen immunotherapy reactions: Two methods

1. **The European Academy of Allergy and Clinical Immunology grading of severity for systemic side effects***

Classification of systemic reactions

0 = No symptoms or nonspecific symptoms

I = Mild systemic reactions: symptoms—localized urticaria, rhinitis, or mild asthma (PF <20% decrease from baseline).

II = Moderate systemic reaction: symptoms—slow onset (>15 minutes) of generalized urticaria, moderate asthma, or both (PF < 40% decrease from baseline).

III = Severe (non–life-threatening) systemic reactions: symptoms—rapid onset (<15 minutes) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).

IV = Anaphylactic shock: symptoms—immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, and hypotension, for example.

2. **Portnoy method for numeric grading of reactions to allergen immunotherapy†**

Local

0+ = No significant reaction or small area of erythema less than the size of a half dollar without swelling or wheal formation

1+ = Erythema greater than the size of a half dollar, swelling or wheal formation, or both

Systemic

2+ = Systemic reactions: cutaneous only—might consist of a cutaneous eruption, such as urticaria

3+ = Systemic reaction: generalized pruritus, sneezing, or both—might consist of increased allergy symptoms, such as nasal congestion, sneezing, or pruritus, especially in the mouth or throat

4+ = Systemic reaction: pulmonary—consists of wheezing, shortness of breath, and tightness. Might be associated with decreased pulmonary function tests

5+ = Systemic reaction: anaphylaxis—a sensation of not feeling right is a frequent prelude; might consist of hypotension, laryngeal edema, severe wheezing, and cramping

6+ = Cardiopulmonary arrest

PF, Peak expiratory flow.

*Subcutaneous immunotherapy. Allergy 2006;61(suppl 82):5-13.

†Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80.

Allergen immunotherapy: A practice parameter second update

Supplement Editor: **Linda Cox, MD**
Co-editors: **James T. Li, MD, Harold Nelson, MD, and Richard Lockey, MD**

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

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the "Allergen immunotherapy: a practice parameter second 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 and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
5. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
6. The diagnosis and management of anaphylaxis. J Allergy Clin Immunol 1998;101(suppl):S465-S528.
7. Algorithm for the diagnosis and management of asthma: a practice parameter update. Ann Allergy 1998;81:415-20.
8. Diagnosis and management of rhinitis: parameter documents of the Joint Task Force on Practice parameters in Allergy, Asthma and Immunology. Ann Allergy 1998;81(suppl):S463-S518.
9. Parameters for the diagnosis and management of sinusitis. J Allergy Clin Immunol 1998;102(suppl): S107-S144.
10. Stinging insect hypersensitivity: a practice parameter. J Allergy Clin Immunol 1999;103:963-80.
11. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999;83(suppl): S665–S700.
12. Diagnosis and management of urticaria: a practice parameter. Ann Allergy 2000;85(suppl):S521-S544.
13. Allergen immunotherapy: a practice parameter. Ann Allergy 2003;90(suppl):SI-S540.
14. Symptom severity assessment of allergic rhinitis: part I. Ann Allergy 2003;91:105-14.
15. Disease management of atopic dermatitis: an updated practice parameter. Ann Allergy 2004;93(suppl): S1-S21.
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These parameters are also available on the internet at http://www.jcaai.org.

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PREFACE

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

The objective of ''Allergen immunotherapy: A practice parameter second update'' is to optimize the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. 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's ''Policy on development and use of practice parameters for medical quality decision-making'' (Appendix 1).[1]

This document builds on the previous Joint Task Force document, ''Allergen immunotherapy: a practice parameter'' published in the *Annals of Allergy, Asthma and Immunology* in 2003.[2] The updated practice parameters draft was prepared by Drs Linda Cox, James Li, Hal Nelson, and Richard Lockey. The Joint Task Force reworked the initial draft into a working draft of the document. The project was exclusively funded by the 3 allergy and immunology societies noted above.

In preparation for the 2003 ''Allergen immunotherapy: a practice parameter'' and the second update, a comprehensive search of the medical literature was conducted with various search engines, including PubMed; *immunotherapy*, *allergic rhinitis*, *asthma*, *stinging insect allergy*, and related search terms were used. 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 second update'' was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the ACAAI, AAAAI, and JCAAI. In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for review and comments from members of the sponsoring organizations. 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 allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. This document also contains recommendations for the safe practice of allergen immunotherapy, including specific recommendations on the prevention and management of 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 or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. Symptoms of allergic conjunctivitis (eg, itchy watery eyes) are often considered part of allergic rhinitis or are included in the diagnosis of rhinoconjunctivitis. Particularly good candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures, those in whom it is important to avoid the potential adverse effects of medications, and those who wish to reduce the long-term use of medications. Immunotherapy is recommended for patients with a history of systemic reaction to Hymenoptera stings and specific IgE antibodies to Hymenoptera venom.

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.[3]

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. 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 *maintenance concentrate* should be used to identify the allergen immunotherapy extract that contains a therapeutic effective dose for each of its individual constituents (see the Immunotherapy schedules and doses section).

The term *manufacturer's extract* refers to the allergy extract purchased from the manufacturer. The terms *stock*, *full-strength*, and *concentrate* are ambiguous and should not be used. 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).

Allergen immunotherapy is effective when appropriate doses of the allergens are administered. ''Allergen immunotherapy: A practice parameter'' recommends that vials of allergen immunotherapy extracts should be prepared individually for each patient to enhance the individualization of therapy, reduce the risk of allergen cross-contamination, and reduce the risk of error in administration.[4,5] This parameter recommends the use of standardized allergen immunotherapy prescription and administration forms to improve the safety, uniformity, and standardization of allergen immunotherapy practice.[4,5] The suggested forms are found in the Appendix (Appendices 7, 8, 11, 12, and 14) and in the members' section of the www.aaaai.org Web site. The routine use of these standardized forms should improve the quality of immunotherapy practice.

Members' feedback comments on the recommended allergen extract dilution dating in the 2003 ''Allergen immunotherapy: A practice parameter'' led to an allergen immunotherapy extract dilution stability study designed by the AAAAI Immunotherapy and Allergy Diagnostics Committee and funded by the AAAAI Board of Directors. The study was designed to investigate the effect of time, temperature, and dilution of standardized allergen extract potency, and the results of this study were considered in this update.

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 3 years after publication. Requests for information about or an interpretation of these practice parameters should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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. Allergen immunotherapy

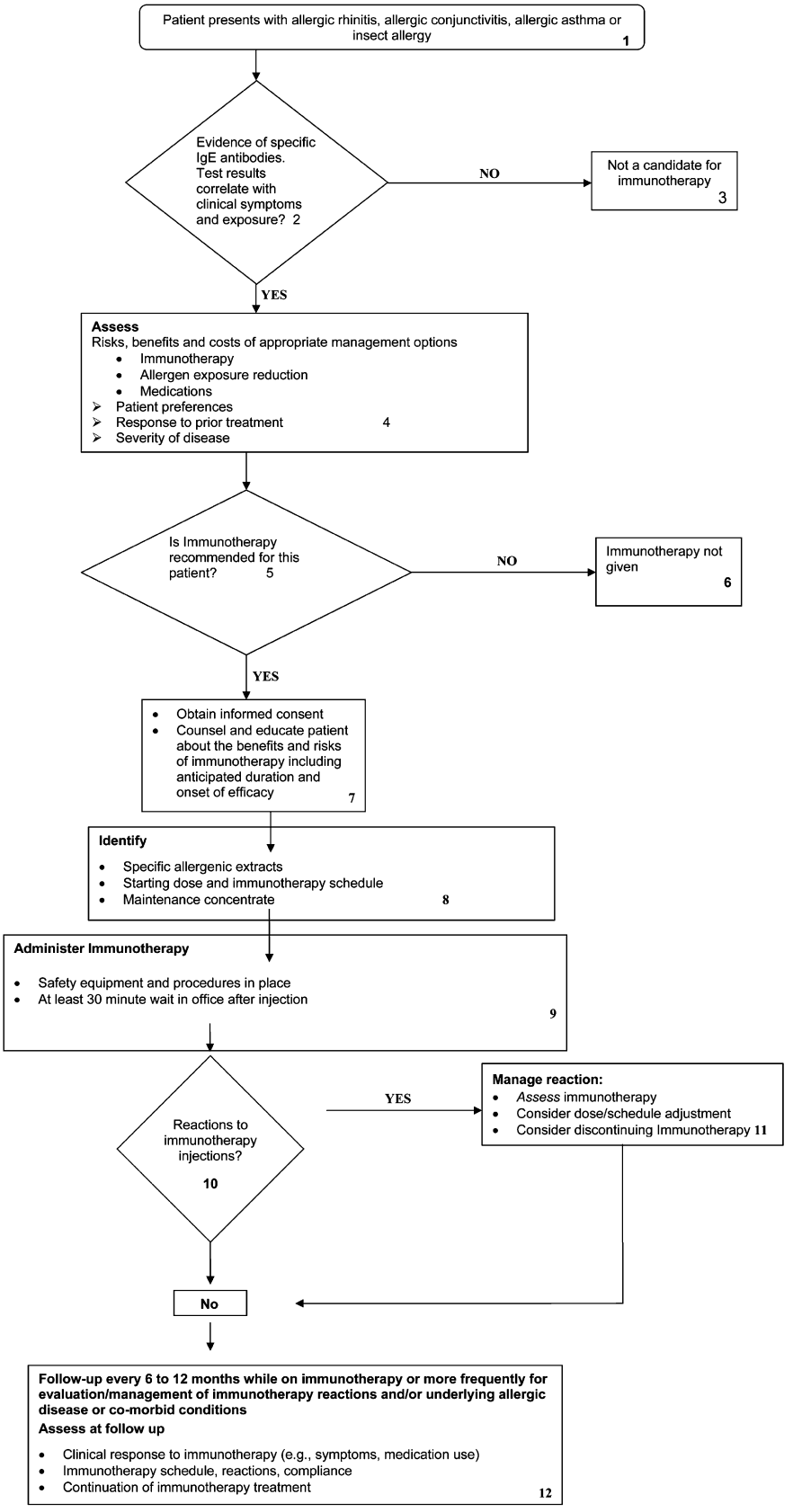


FIG 1. Algorithm for allergen immunotherapy.

might prevent the development of asthma in individuals with allergic rhinitis.[6-9] Evaluation of a patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic conjunctivitis, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for specific IgE antibody).[10]

Box 2

Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although *in vitro* testing for 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

Management of complex medical conditions, such as allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity, should include the careful evaluation of management 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 patient 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. On the basis of clinical considerations and patient 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 good candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy (VIT).

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 on the basis of 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 (see the Immunotherapy schedules and doses section). In general, the starting immunotherapy dose is 1000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 1000 to 4000 arbitrary units (AU; eg, for dust mite) or bioequivalent allergy units (BAU; eg, for grass) 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 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 referred to as *up-dosing*, *induction*, or the *dose-increase phase*) entails administration of gradually increasing doses during a period of approximately 14 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 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, in particular anaphylaxis. Patients should wait at the physician's office for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly, if they occur.

In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring 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. Some physicians recommend providing certain patients with epinephrine for self-administration in case of severe late reactions to immunotherapy injections.

Box 10

Injections of allergen immunotherapy extract can cause local or systemic reactions. Most severe reactions develop within 30 minutes after the immunotherapy injection, but reactions can occur after this time.

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 (anaphylaxis). Epinephrine is the treatment of choice in anaphylaxis, preferably when administered intramuscularly,[11] although subcutaneous administration is acceptable.[12]

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, see the practice parameters for anaphylaxis.[12]

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. After a severe systemic reaction, careful evaluation by the prescribing physician is recommended. For some patients, the immunotherapy maintenance dose might need to be reduced because of repeated systemic reactions to immunotherapy injections. The decision to continue immunotherapy should be re-evaluated after severe or repeated systemic reactions to allergen immunotherapy extracts.

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 doses, 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,[13] but others might experience a recurrence of their symptoms after discontinuation of allergen immunotherapy.[14] 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, and 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 on the basis of the patient's clinical response, disease severity, immunotherapy reaction history, and patient preference.

IMMUNOTHERAPY GLOSSARY

For more information on immunotherapy definitions, see the article by Kao.[15]

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 (pigments and salts; see the Allergen selection and handling section). Other terms used to describe the allergen immunotherapy extract include *allergen product*,[16] *allergy serum*, *allergen vaccine*,[17] 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.[18] Other terms that have been used for allergen immunotherapy include *hyposensitization*, *allergen-specific desensitization*, and the lay terms *allergy shots* or *allergy injections*.[15]

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

TABLE II. Allergen immunotherapy dose-calculation table

- Express weight per volume as a fraction: $\frac{1}{N}$ or 1:*N*.
- Calculate concentration of individual allergens in mixtures. If a mixture is made of equal amounts of N individual allergens to make a total concentration (C), the final concentration of an individual allergen (Ca) can be calculated by using the following equation:

$Ca = C \times \frac{1}{N} = \frac{C}{N}$ or *C*:*N*.

For example, if a mixture of equal amounts of 5 (N) allergens has a total concentration (C) of 100,000 BAU/mL, then the final concentration of each individual allergen (Ca) is: $Ca = \frac{C}{N} = \frac{100{,}000}{5} = 20{,}000\ BAU/mL$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{C}{N} = \frac{1/10}{5} = \frac{0.1}{5} = 0.02$ or $\frac{1}{50}$ or 1:50.

- Dilution of individual allergen: If an initial volume, Vi (in milliliters), of an individual antigen with concentration, Ci, is added to an allergen extract to make a final volume of Vf (in milliliters), the final allergen concentration (Ca) in the allergen extract mixture will be: $Ca = Ci \times \frac{Vi}{Vf}$.
- Final concentration of an allergen in a mixture of mixtures is determined by multiplying the initial concentration by the dilution factors from each mixing step.

For example, consider a mixture containing equal amounts of 5 (N) allergens with a total concentration (C) of 100,000 BAU/mL (first dilution). If an initial volume (Vi) of 0.5 mL of this mixture is further mixed with other components and diluent to make a final allergen extract mixture volume (Vf) of 5.0 mL (second dilution), the final concentration of an individual allergen (Ca) will be:

$$Ca = C \times \underbrace{\frac{1}{N}}_{\text{Mixture dilution}} \times \underbrace{\frac{Vi}{Vf}}_{\text{Allergen extract dilution}} = 100{,}000 \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{100{,}000}{50} = 2000\ BAU/mL$$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{1}{10} \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{1}{500}$ or 1:500.

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).

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 to 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-medicated 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 multiplied by volume of administered dose (see Table II for a dose-calculation table).

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, cat, 1000 BAU, [highest tolerated dose] vs 2000 BAU [projected effective dose]).

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 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 by a variety of immunologic transformations. Early definitions of the term immunotherapy included active and passive immunization for the purpose of improving 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 by means of induction of clonal deletion, anergy, immune tolerance, or immune deviation.

The *maintenance concentrate* is a preparation that contains individual 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 may not be the initially calculated projected effective dose.

The *maintenance goal* (or projected effective dose) is the allergen dose projected to provide therapeutic efficacy. The maintenance goal is based on published studies, but a projected effective dose has not been established for allergens. 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 the 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 large local reaction causing discomfort). The intervals between maintenance immunotherapy injections generally ranges 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 by means of immunoblotting or crossed allergoimmunoelectrophoresis.

For a definition of *projected effective dose*, see 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 test responses), and premedication with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similar high incidence of systemic reactions.

Off the board into one syringe is a phrase that describes a method of allergen immunotherapy preparation and administration that involves specifically mixing the patient's allergen immunotherapy injection in a single syringe, which is not recommended. This syringe might be inserted into more than one allergen extract vial, and this poses a risk of cross-contamination of the allergen extracts and might dull the needle with repeated penetration of the rubber stopper.

Shared specific patient vials is a method of allergen immunotherapy preparation and administration in which the allergy immunotherapy extract is withdrawn from a shared vial (eg, mixed vespids or dust mite mix). This is sometimes referred to as off the board, but it is distinct from the method of off the board into one syringe in that the syringe enters only one allergen extract vial.

INTRODUCTION

Immunity has been defined as protection against certain diseases. The initial immunotherapeutic interventions, which included the use of preventive vaccines and xenogenic 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 the field of allergen immunotherapy. From its humble empiric emergence in 1900, when ragweed injections were proposed as therapy for autumnal hay fever, allergen immunotherapy has progressed in both theory and practice from the passive immunologic approach to the active immunologic procedures pioneered by Noon[19] and Freeman.[20,21] 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 10 years. Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Some studies have suggested that allergen immunotherapy might prevent the development of asthma in individuals with allergic rhinitis.[6-9]

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,[22-26] and it should be differentiated from unproved methods, such as neutralization-provocation therapy and low-dose subcutaneous regimens based on the Rinkel technique, which have been found to ineffective in a double-blind placebo-controlled study.[27,28]

SUMMARY STATEMENTS

Mechanisms of immunotherapy

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, defined as a relative decrease in allergen-specific responsiveness and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

Allergen extracts

Summary Statement 6: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. **A**

Summary Statement 7: Nonstandardized extracts might vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Summary Statement 8: 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**

Cross-reactivity of allergen extract. Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

Efficacy of immunotherapy

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Summary Statement 10: Immunotherapy is effective for 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**

Food allergy, urticaria, and atopic dermatitis. Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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**

Measures of efficacy. Summary Statement 12: 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**

Safety of immunotherapy

Reaction rates. Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

Timing of anaphylactic reactions to immunotherapy injections. Summary Statement 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

β-*Adrenergic blocking agents.* Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

Contraindications. Summary Statement 18: 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**

Reducing the risk of anaphylaxis to immunotherapy injections. Summary Statement 19: 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**

Patient selection

Clinical indications. Summary Statement 20: 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 depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Special precautions in patients with asthma. Summary Statement 21: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. **C**

Clinical indications for VIT. Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Summary Statement 23: Patients selected for immunotherapy should be cooperative and compliant. **D**

Allergen selection and handling

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted in vitro tests for specific IgE antibodies can also be used. **A**

Specific allergens. Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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, supported by the presence of specific IgE antibodies. **A**

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Dose selection. Summary Statement 30: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. **A**

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens, is recommended. **B**

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extract handling

STORAGE

Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

STORING DILUTE EXTRACTS

Summary Statement 34a: More dilute concentrations of allergen immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: 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 a number of 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. **B**

Immunotherapy schedules and doses

Summary Statement 35: A customized individual 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 be based on single or multiple allergens. **D**

Maintenance concentrate. Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

Recommended doses. Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

Effect of dilution on dose. Summary Statement 38: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. **A**

Dilutions of the maintenance concentrate. Summary Statement 39: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. **D**

Labeling dilutions. Summary Statement 40: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. **D**

Individualized treatment vials. Summary Statement 41: 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. The mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. **C**

Starting doses. Summary Statement 42: The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. **D**

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

Dose adjustments for systemic reactions. Summary Statement 44: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. **D**

Reductions during periods of exacerbation of symptoms. Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Dose adjustments for late injections. Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

Cluster schedules. Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. **C**

Rush schedules. Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. **A**

Systemic reactions and rush schedules. Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

Premedication and weekly immunotherapy. Summary Statement 50: Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

Premedication with cluster and rush immunotherapy. Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

Maintenance schedules. Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. **A**

Continuing care

TIME COURSE OF IMPROVEMENT

Summary Statement 53: Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **A**

FOLLOW-UP VISITS

Summary Statement 54: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. **D**

DURATION OF TREATMENT

Summary Statement 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

DOCUMENTATION AND RECORD KEEPING

Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. **D**

INJECTION TECHNIQUES

Summary Statement 57: Allergen immunotherapy extract injections should be administered with a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **D**

Summary Statement 58: The injection should be administered subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Location of allergen immunotherapy administration

Physician's office. Summary Statement 59: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Summary Statement 60: 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**

Other locations. Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **D**

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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**

Summary Statement 63: 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for his or her immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extract might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Special considerations in immunotherapy

Allergen immunotherapy in children. Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Pregnancy. Summary Statement 71: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. **C**

Immunotherapy in the elderly patient. Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy in patients with immunodeficiency and autoimmune disorders. Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

Alternative routes of immunotherapy

Sublingual and oral immunotherapy. Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no US Food and Drug Administration (FDA)–approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **A**

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Immunotherapy techniques that are not recommended. Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

MECHANISMS OF IMMUNOTHERAPY

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, which is defined as a relative decrease in allergen-specific responsiveness, and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

The immunologic changes associated with immunotherapy are complex, and the exact mechanism or mechanisms responsible for its' clinical efficacy are continually being elucidated. Data support the concept that successful immunotherapy is associated with a change to a T_H1 $CD4^+$ cytokine profile.[29-34] Data indicate that increased production of IL-12, a strong inducer of T_H1 responses, contributes to this shift.[33] Clinically successful immunotherapy has been reported to be associated with immunologic tolerance, which is defined as a relative decrease in antigen-specific responsiveness, immune deviation, or anergy. For example, lymphoproliferative responses to allergen are reduced with immunotherapy.[32] Successful immunotherapy results in generation of a population of T regulatory cells, which are $CD4^+CD25^+$ T lymphocytes producing IL-10, TGF-β, or both.[35-39] Regulatory T-cell release has been described in allergen immunotherapy with Hymenoptera venom,[35] grass pollen extract,[37] and house dust mites.[38] IL-10 reduces B-cell antigen-specific IgE and increases IgG4 levels; reduces proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicits tolerance in T cells by means of selective inhibition of the CD28 costimulatory pathway.[36,37]

Allergen immunotherapy has been shown to block both the immediate and late-phase allergic response.[40] Allergen immunotherapy has been shown to decrease the recruitment of mast cells, basophils, and eosinophils in the skin, nose, eye, and bronchial mucosa after provocation or natural exposure to allergens.[41]

In patients receiving immunotherapy, initially there is an increase in specific IgE antibody levels, followed by a gradual decrease to a level that is still higher than that present before treatment. Clinical improvement in many patients develops before decreases in their IgE antibody levels occur or in other patients whose IgE antibody levels never decrease, thereby demonstrating that efficacy is not dependent on reductions in specific IgE levels.[42,43] Immunotherapy does diminish the seasonal increase in specific IgE levels.[44] Despite the persistence of significant levels of specific IgE antibody levels, immunotherapy usually causes a reduction in 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.[45-48]

An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, has also been associated with immunotherapy. The properties of allergen-specific IgA have yet to be determined, and there is a weak correlation between the increase in allergen-specific IgG levels and immunotherapy's clinical efficacy.[30,49,50]

Immunotherapy might alter the affinity and specificity of allergen-specific IgG.[51,52] During the initial phase of ultrarush VIT, a change in IgG specificity (ie, a change in the set of epitopes dominantly recognized by IgG on wasp venom antigens) occurred concomitantly with early clinical tolerance and was seen within 12 hours of ultrarush VIT ($P < .001$).[51] 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 individuals.[52] This change in IgG specificity preceded the increase in IgG titers and was sustained for up to 6 months.[52]

Allergen-specific IgG induced from immunotherapy can block IgE-dependent histamine release and subsequent IgE-mediated antigen presentation to T cells.[53] This effect might be dependent on IgE, allergen concentration, and CD23, the low-affinity receptor for IgE.

Whereas 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.[37,53]

The relationship between these immunologic changes and immunotherapy efficacy is not completely understood.

ALLERGEN EXTRACTS

Summary Statement 6: 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 has 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.[2,18,54-56] 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.

United States–licensed extracts can be obtained in aqueous, glycerinated, lyophilized, and acetone-precipitated and alum-precipitated formulations. Some commonly used allergens are standardized. These include extracts for cat hair, cat pelt, *Dermatophagoides pteronyssinus*, *Dermatophagoides 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.[57] 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.

Most standardized extracts are labeled in BAU. Short ragweed potency units were originally based on the content of the major allergen Amb a 1. Ragweed potency is reported in FDA units and BAU. One FDA unit of Amb a 1 equals 1 μg of Amb a 1, and 350 units of Amb a 1/mL is equivalent to 100,000 BAU/mL. Cat extracts were also originally standardized based on the content of major allergen (Fel d 1), with 100,000 arbitrary units (AU) per milliliter containing between 10 to 19.9 FDA units of Fel d 1 per milliliter (1 FDA unit of Fel d 1 equals 2 to 4 μg of Fel d 1).[55,58,59] Subsequently, $ID_{50}EAL$ testing suggested that 100,000 AU/mL was equal to 10,000 BAU/mL.[60] Approximately 22% of individuals with cat allergy have specific IgE antibodies to cat albumin.[61] Cat pelt extracts have a greater amount of albumin than cat hair extracts.[60]

Dust mites were originally standardized in AU by means of inhibition radioimmunoassay (RIA), and subsequent $ID_{50}EAL$ testing indicated that the AU was bioequivalent to the BAU, and the original AU nomenclature was kept. Dust mite extracts are still labeled in AU.

Summary Statement 7: Nonstandardized extracts can vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Nonstandardized extracts are labeled as wt/vol, which expresses weight in grams per volume in milliliters; that is, a potency of 1:100 indicates that 1 g 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 with a particular wt/vol or PNU potency can have widely varying biologic activities.[62-64] Therefore they should not be considered equipotent.

Summary Statement 8: 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**

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. The major clinically relevant aeroallergens of North America are listed in Table III. Furthermore, nonrelevant allergens in such mixtures could act as sensitizers rather than as tolerogens.[65,66] The physician must therefore select only those aeroallergens for testing and treatment that are clinically relevant in a particular geographic area.

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, dog), insect (cockroach), and Hymenoptera venom source materials.

Cross-reactivity of allergen extract

Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

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. A summary of cross-reactivity patterns of the clinically relevant North American aeroallergens can be found in Fig 2. 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,[67] inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[68-75] Grasses in other subfamilies (eg, Bermuda, Bahia, and Johnson) show greater diversity and should be evaluated separately.[76-78] Bermuda and Johnson grasses are increasingly important in the South,

TABLE III. The major clinically relevant aeroallergens of North America*

- Tree pollen
  - Chinese elm *(Ulmus parvifolia)*†‡; Siberian elm *(Ulmus pumila)*†‡; American elm *(Ulmus Americana)*†‡
  - Red oak *(Quercus rubra)*†; White oak *(Quercus alba)*†
  - Paper birch *(Betula papyrifera)*
  - Alder *(Alnus rubra)*
  - Box elder *(Acer negundo)*†; Red maple *(Acer rubra)*†
  - Eastern cottonwood *(Populus deltoides)*
  - Sycamore *(Platanus occidentalis)*
  - White ash *(Fraxinus americana)*†; Olive *(Olea europaea)*†‡
  - Black walnut *(Juglans nigra)*
  - Mulberry *(Morus rubra)*
  - Mountain cedar *(Juniperus ashei)*
  - Pecan *(Carya illinoensis)*
- Grass pollen
  - Rye *(Lolium perenne)*§‖
  - Timothy *(Phleum pratense)*§‖
  - Meadow fescue *(Festuca elatior)*§‖
  - Bermuda *(Cynodon dactylon)*‖
  - Johnson *(Holcus halepensis)*
  - Bahia *(Paspalum notatum)*
- Weed pollen
  - Short ragweed *(Ambrosia artemisiifolia)*‖
  - English (narrow leaf) plantain *(Plantago lanceolata)*
  - Mugwort *(Artemisia vulgaris)*
  - Russian thistle *(Salsola kali)*
  - Burning bush *(Kochia scoparia)*
  - Sheet (red) sorrel *(Rumex asetosella)*
  - Red root pigweed *(Amaranthus retroflexus)*
- Indoor aeroallergens
  - Cat epithelium *(Felis domesticus)*‖
  - Dog epithelium *(Canis familiaris)*
  - Arthropods (domestic mites: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*)‖
  - Insects (German cockroach: *Blattella germanica*)
- Fungi
  - *Alternaria alternata*¶
  - *Cladosporium* (*C cladosporioides*, *C herbarum*)¶
  - *Penicillium* (*P chrysogenum*, *P expansum*)¶
  - *Aspergillus fumigatus*¶
  - *Epicoccum nigrum*, *Drechslera* or *Bipolaris* type (eg, *Helminthosporium solani*)¶

*Compiled and selected in collaboration with the AAAAI Immunotherapy Committee Allergen Subcommittee for the identification of 35 key allergens of North America.
†Extensive cross-reaction of species within the genus.
‡Apart from regional prevalence, they are limited to local sites with substantial stands of these trees.
§Extensively cross-react with one another and bluegrass, orchard, red top, and sweet vernal.
‖Allergens for which standardized extracts are commercially available.
¶Species that are widely distributed and clinically important.

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.[79-82] 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.[83-85] Significant cross-reactivity between Betulaceae pollens and oak of the Fagaceae family has been demonstrated with percutaneous skin testing.[75] RAST inhibition studies have shown cross-inhibition between oaks and other *Fagales* species.[86] IgE immunoblot inhibition experiments have demonstrated that the *Fagales* species might be strongly inhibited by birch species.[87] The use of one of the locally prevalent members (eg, birch and alder) should be adequate.[88]

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.[89,90] Maple and box elder trees are found throughout the United States, except for the arid southwest. Although in the same genus as maple, *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,[91,92] and there are allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.[93]

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.[94] Similarly, Chenopod-Amaranth families have wide ranges in the western regions but are present throughout North America.[95] Current information on cross-reactivity of these families is limited.[96-98] 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.[99] The use of a single Amaranth extract should be sufficient to cover this family.[100,101] Similarly, *Atriplex* species (eg, saltbushes and scales) show near identity, and use of a single member is adequate. 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,

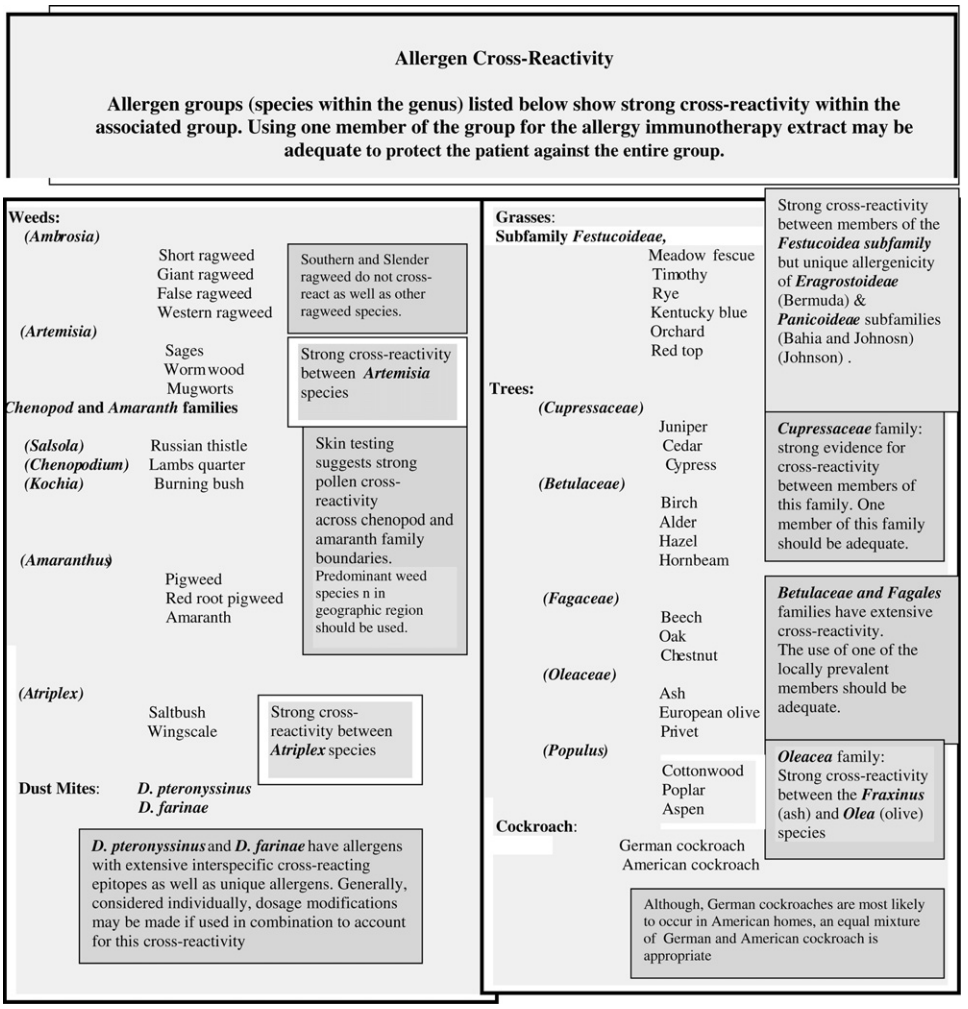


FIG 2. Patterns of allergen cross-reactivity.

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*).

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.[102,103] Stinging Hymenoptera insects occur throughout the United States; the fire ant is found only in Gulf Coast states, Texas, and some other southern and western states. Commercial venom extracts are available for some Hymenoptera species, except the fire ant, for which only whole-body extract is available.

EFFICACY OF IMMUNOTHERAPY

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity

Summary Statement 10: Immunotherapy is effective for 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.[104-111] Immunotherapy is effective for the treatment of allergic rhinitis[107] (including ocular symptoms[112,113]), allergic asthma,[104,109,111,114,115] and stinging insect hypersensitivity[108,116] and is effective in both adults and children.[117-124] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollens,[13,125-132] fungi,[133-138] animal allergens,[22,25,26,139-143] dust mite,[114,115,144-153] and cockroach.[154] There have been no controlled trials of fire ant whole-body extract, but it does appear to be effective in

TABLE IV. Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy

Outcome measure	House dust mite	Other allergens*†
Symptomatic improvement	2.7 (1.7-4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2-7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50)	5.5 (2.8-10.7)

Data are used with permission from Abramson et al.[104]
ND, Not done.
*Odds ratio (95% CI).
†Pollen, mold, or animal dander.

uncontrolled trials.[155-157] 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. A number of studies have also demonstrated a significant improvement in quality of life, as measured by using standardized questionnaires.[24,158-161] The magnitude of the effect depends on the outcome that is used (Table IV). For dust mite, the effect size ranges from a 2.7-fold improvement in symptoms to a 13.7-fold reduction in bronchial hyperresponsiveness. 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.[110] 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[107] and asthma[104,109,111] have been performed to deal with the issue of power. One review of 75 trials involving 3188 asthmatic patients found that, overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyperreactivity after immunotherapy, and it would have been necessary to treat 4 patients (95% CI, 3-5) with immunotherapy to avoid 1 deterioration in asthma symptoms and 5 (95% CI, 4-6) patients to avoid 1 requiring increased medication.[111] These meta-analyses strongly support the efficacy of allergen immunotherapy. Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued[13,162,163] and might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6,9,122,162-165] Allergen immunotherapy might also prevent the development of new allergen sensitivities in monosensitized patients.[120,166,167]

Food allergy, urticaria, and atopic dermatitis

Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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 use of allergen immunotherapy for individuals with the potential for IgE-mediated (anaphylaxis) reactions to foods should be regarded as investigational at this time.[168-171] There have been 2 investigational studies demonstrating efficacy in food hypersensitivity, the first using aqueous subcutaneous injections to peanut and the second using sublingual immunotherapy to hazelnut.[171-173]

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 a modified peanut extract is needed for clinical application of this method of treatment.[171] There is currently no FDA-approved formulation for sublingual immunotherapy, and this route of allergen immunotherapy is currently considered investigational at this time (see Summary Statement 73).

At the present time, there is not enough evidence to support food immunotherapy.

There is no evidence supporting the efficacy of immunotherapy for individuals with chronic urticaria, angioedema, or both.

There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[174-176] 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 ($P = .0379$) and topical corticosteroid use ($P = .0007$).[174]

The potential for benefit in symptoms related to oral allergy syndrome with the cross-reacting inhalant immunotherapy, which includes cross-reacting 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 subcutaneous immunotherapy directed against birch tree,[177] whereas another double-blind, double-dummy, placebo-controlled study comparing the effect of subcutaneous immunotherapy with sublingual immunotherapy 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, medication use, and decrease in IgE reactivity.[178] More investigation is required to substantiate the contention that benefits in oral symptoms will occur with immunotherapy.

Measures of efficacy

Summary Statement 12: 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. Objective measures, such as increase in allergen-specific IgG levels and decreased skin test reactivity, as measured by skin test titration, are changes generally associated with effective immunotherapy but, at present, are not practical for routine clinical use.[147] Nonquantitative skin testing or *in vitro* 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 are not very reliable given the strong placebo-like effect (Hawthorne effect) associated with any treatment. A more objective means for determining efficacy as validated in controlled clinical studies is the use of clinical symptom scores and the amount of medication required to control symptoms and maintain peak flow rates or pulmonary function tests within acceptable limits. Successful immunotherapy often results in a reduction in medication. Sequential measurement of disease-specific quality of life also might be helpful.

SAFETY OF IMMUNOTHERAPY

Reaction rates

Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Large local reactions associated with allergen immunotherapy are fairly common, with a frequency ranging from 26% to 86% of injections.[179] Two retrospective studies compared the effect of not adjusting immunotherapy dose based on large local reactions on the immunotherapy systemic reaction rate with dose-adjustment protocols.[179,180] There was a total of 12,464 injections administered with a dose-adjustment protocol in the 2 studies compared with 9542 injections administered with a no-dose-adjustment protocol. 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 for subsequent systemic reactions, 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 large local reactions, defined as 25 mm or larger, in patients who had experienced systemic reactions with age-, sex-, and allergen sensitivity–matched control subjects who had not had allergen immunotherapy systemic reactions found the rate of large local reactions was 4 times higher among the 258 patients who had subsequently experienced a systemic reaction compared with those who had never experienced a systemic reaction.[181] Patients who had experienced systemic reactions had 1573 large local reactions in 4460 visits (ie, 35.2% of visits) and 8081 injections (ie, 19.5% of injections) compared with the matched control group without systemic reactions who had 1388 large local reactions in 15,540 visits (8.9% per visit) and 26,259 injections (5.3% per injection; difference between groups, $P < .001$). Individual large local reactions were not predictive of future systemic reactions, but large local reactions preceded systemic reactions in approximately one third of the systemic reactions. These findings suggest that individuals with a greater frequency of large local reactions might be at greater risk for systemic reaction. Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy protocol modifications based on them are needed.

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

The prevalence of severe systemic reactions after allergen immunotherapy ranges from less than 1% of patients receiving conventional immunotherapy to greater than 36% of patients in some studies of patients receiving rush immunotherapy.[182,183]

In a recent survey of fatal and near-fatal reactions (NFRs) sent to physician members of the AAAAI, 273 of 646 respondents reported NFRs during the period of 1990-2001.[184]

The incidence of unconfirmed NFRs was 23 per year (5.4 events per million injections). Administration during the height of 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 angiotensin-converting enzyme 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 systemic reactions to subcutaneous immunotherapy over a 20-year period (1981-2000) during which 435,854 injections were administered to 4000 patients, 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.[185,186] In a prospective multicenter study there were 53 systemic reactions (0.3% of the doses) out of 17,526 administered doses in 18 (3.7%) of 423 patients.[187] 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 (21 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, there were 41 fatalities identified in the initial brief survey (20 directly reported and 17 with completed detailed questionnaire) from immunotherapy injections.[188] 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.[189,190] Therefore although severe systemic reactions to allergen immunotherapy are not common, serious systemic reactions (some fatal) can occur.

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

In the AAAAI survey of physician members on immunotherapy and skin testing, fatal reactions, and NFRs during the period of 1990-2001, 15 of the 17 fatalities had asthma, and in 9 patients asthma was considered the susceptibility factor that contributed to the fatal outcome.[188]

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.[184]

Administration during the peak pollen season (3 patients) and previous systemic reactions (4 patients) were cited as other contributing factors. Five fatalities occurred in outside medical facilities, and 2 fatalities occurred at home. No patients were receiving β-blockers; 1 patient was taking an angiotensin-converting enzyme inhibitor. In the most comprehensive evaluation of fatalities associated with allergen immunotherapy, from 1945-1987, there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[189] 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, with 73.3% of patients with an FEV_1 of less than 80% of predicted value experiencing 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 ($P < .0001$).[191] 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% of patients. These studies suggest that symptomatic asthma, severe asthma, or both might be a risk factor for immunotherapy.

In addition to symptomatic asthma and injections giving 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.[17] With the exception of dosing errors and 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 recent 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 or allergy symptom exacerbation, β-blocker use, change in health status (including pregnancy), or adverse reaction to previous allergen immunotherapy injection. The preinjection evaluation might also include a peak flow measurement to assess the airway function of asthmatic patients.

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 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

In a retrospective study the time to onset of a systemic reaction after an immunotherapy injection was less than 30 minutes in most cases.[189] A review of the literature indicates that 70% of systemic reactions occur within 30 minutes after an injection.[183] In the AAAAI 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.[184,188] 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.[190] 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 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.[192] In another prospective study 8% of systemic reactions occurred more than 2 hours after injection.[193]

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.[194]

Because most reactions that resulted from allergen immunotherapy occurred within 30 minutes after an injection, patients should remain in the physician's office for at least 30 minutes after receiving an injection, but longer waits are reasonable, as directed by the physician. In addition, patients who are at increased risk of a systemic reaction might need to carry injectable epinephrine. Such patients might also need to remain in the physician's office more than 30 minutes after an injection. 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.

β-Adrenergic blocking agents

Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

β-Blockade enhances pulmonary, cardiovascular, and dermatologic end-organ effects of mediators and increases mortality associated with experimental anaphylaxis induced by either immunologic or nonimmunologic mechanisms. Patients who are receiving β-adrenergic blocking medications might be at increased risk if they experience a systemic reaction to an allergen immunotherapy injection because the β-receptor blockade might attenuate the response to epinephrine.[195-202] Patients who are receiving β-blocking drugs were almost 9 times more likely to be hospitalized after an anaphylactoid reaction from radiocontrast media.[198] Although topical β-blockers have markedly less systemic β-antagonist effects than oral β-blockers, they still might exhibit some systemic β-antagonist effects. Whether topical β-blockers pose the same or a smaller risk than oral β-blockers in regard to the treatment of allergen immunotherapy–related systemic reactions is not known.

There have been very few studies that have examined the effect of β-blocker medications on allergen immunotherapy. A prospective 1-year study designed to determine whether patients taking β-blocker drugs were at increased risk of immunotherapy-induced systemic reactions found that there were 166 systemic reactions out of 56,105 injection visits in 3178 patients (68 were receiving a β-blocker).[203] The systemic reactions occurred in 144 (4.5%) patients, and only 1 of these patients was receiving a β-blocker medication. The authors calculated that by chance, 3.08 patients receiving the β-blocker medications drugs were expected to have had an systemic reaction and concluded that β-blocker medications did not increase the frequency of allergen immunotherapy systemic reactions ($P > .95$).

In another study of 1389 patients prescribed immunotherapy for Hymenoptera venom hypersensitivity who were followed for 34 months, there were 25 patients who received concomitant β-blocker medications.[204] Three (12%) of the 25 patients receiving β-blocker medications experienced systemic reactions during immunotherapy compared with 23 (16.7%) of 117 patients with cardiovascular disease not receiving β-blockers. Systemic reactions after a field sting or challenge occurred in 1 (14.3%) of 7 cardiovascular patients receiving β-blocker medications compared with 4 (13.8%) of 29 cardiovascular patients not receiving β-blocker medications. No severe reactions to immunotherapy or sting re-exposure were observed in patients receiving β-blockers medications.

Immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. In such cases, intravenous glucagon, which might reverse the refractory bronchospasm and hypotension by activating the adenyl cyclase directing and bypassing the β-adrenergic receptor, might be used if epinephrine has not been effective.[205,206] Prospective studies are necessary to clarify the magnitude of the risk of systemic reactions to allergens in patients who are receiving concomitant therapy with β-blockers, and a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy.

Contraindications

Summary Statement 18: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications

TABLE V. Actions to reduce the risk of anaphylaxis

- Assess the patient's general medical condition at the time of injection (eg, asthma exacerbation).
- Consider obtaining a PEFR before administration of the injection. If the PEFR is significantly less than the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.
- 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 with increased allergen sensitivity or those who have previously had a systemic reaction) might need to wait longer.
- Carefully evaluate any patient with a late reaction (eg, persistent large local reaction lasting >24 hours, systemic reaction occurring more than 30 minutes after the immunotherapy injection).
- 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.

PEFR, Peak expiratory flow rate measurement.

TABLE VI. Recommended equipment and medications to treat anaphylaxis

Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur. This should include at least the following equipment and medications:

- stethoscope and sphygmomanometer;
- tourniquet, syringes, hypodermic needles, and large-bore needles (14-gauge);
- aqueous epinephrine HCL 1:1000 wt/vol;
- equipment to administer oxygen by mask.
- intravenous fluid set-up;
- antihistamine for injection (second-line agents for anaphylaxis, but H_1 and H_2 antihistamines work better together than either one alone);
- corticosteroids for intravenous injection;
- vasopressor;
- equipment to maintain an airway appropriate for the supervising physician's expertise and skill.

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 venom hypersensitivity and cardiac disease being treated with β-blocker medications.

Reducing the risk of anaphylaxis to immunotherapy injections

Summary Statement 19: 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 extremely 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 or other health care professional appropriately trained in emergency treatment.

The 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. Epinephrine is the first-line treatment for anaphylaxis. 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.[12,207-213] It is important to administer epinephrine early in the management of anaphylaxis. 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 V and VI, respectively. Before allergen immunotherapy is chosen as a treatment, the physician should educate the patient about the benefits and risks of immunotherapy, as well as methods for minimizing risks. The patient also should be told that despite appropriate precautions, reactions might occur without warning signs or symptoms. Informed consent should include a discussion of the potential immunotherapy adverse reactions, and this discussion should be documented in the patient's medical record.

PATIENT SELECTION

Clinical indications

Summary Statement 20: Allergen immunotherapy should be considered for patients who have demonstrable

TABLE VII. Clinical indications for allergen immunotherapy

Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or both:
- symptoms of allergic rhinitis after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medications;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medication;
- coexisting allergic rhinitis and asthma;
- possible prevention of asthma in patients with allergic rhinitis

Symptoms of asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medication;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medications;
- coexisting allergic rhinitis and allergic asthma.

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);
- adults and children with a history of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.

evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic rhinitis.[107] Prospective, randomized, double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic asthma.[104,109,111]

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 proper identification and selection of component allergens on the basis of 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 (Table VII). The severity and duration of symptoms should also be considered in assessing the need for specific allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. In addition, specific allergen immunotherapy should be considered if the patient wishes to avoid long-term pharmacotherapy. Time lost from work, emergency department or physician's office visits, and responses to pharmacotherapy are important objective indicators of allergic disease severity.

Patients with allergic rhinitis who are unable to sleep because of symptoms or whose symptoms interfere with their work or school performance should be considered strong candidates for specific allergen immunotherapy. 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 considered. Unacceptable adverse effects of medications should also favor one's decision to initiate allergen immunotherapy. Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.[214]

Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued, and it might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6-9,122,162-165] These benefits of immunotherapy should be discussed with patients and might provide a clinical indication for immunotherapy for individual patients with allergic rhinitis.

Coexisting medical conditions should also be considered in the evaluation of a patient who might be a candidate for allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed with a combined aggressive regimen of allergen avoidance and pharmacotherapy and might also benefit from allergen immunotherapy.[215,216]

However, the patient's asthma must be stable before allergen immunotherapy is administered.[188,191]

Special precautions in patients with asthma

Summary Statement 21: 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 might be at increased risk for systemic reactions to immunotherapy injections.[182,188,191] Two surveys found that deaths from

immunotherapy were more common in symptomatic subjects with asthma.[188,189] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2,217]

Clinical indications for VIT

Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Systemic reactions to Hymenoptera stings, especially when associated with respiratory symptoms, cardiovascular symptoms, or both and positive skin test or *in vitro* test results for specific IgE antibodies, are a strong indication for allergen immunotherapy.[218] In the United States patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Several studies of patients with imported fire ant allergy have demonstrated the effectiveness of immunotherapy with whole-body extracts of fire ants.[155,156,219] 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. Patients younger than 16 years of age who present only with a cutaneous reaction to imported fire ant or Hymenoptera stings might not require immunotherapy.[218,220-222] In addition to allergen immunotherapy, patients with imported fire ant and Hymenoptera venom sensitivity should be instructed in how to best avoid insect stings, be prescribed epinephrine, and be taught how 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 the population that has not had a systemic reaction.[223] In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific IgE is recommended.[218] If the venom-specific IgE test result is also negative, it is recommended that the skin tests, venom-specific 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 IgE test result.[224] 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 re-stung. 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%).[225] 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 IgE test results who have had severe anaphylaxis to an insect sting.

Some patients who have negative venom skin test results and negative venom-specific IgE test results are reported to have had subsequent systemic reactions to stinging insects.[225-227] Controlled studies designed to evaluate the efficacy of immunotherapy in these patients have not been performed. There are very 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.[226] 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.

Summary Statement 23: 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.

ALLERGEN SELECTION AND HANDLING

Allergen selection

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

A careful history, noting environmental exposures and an understanding of the local and regional aerobiology of suspected allergens, such as pollen, fungi (mold), 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 skin or *in vitro* test results for specific IgE antibodies, provide good evidence that such exposures are relevant. Information concerning regional and local aerobiology is available on various Web sites or through the National Allergy Bureau at http://www.aaaai.org/nab. There are

no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma. 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 clinical history of an allergic disease.

There is no evidence to support the administration of immunotherapy based solely on results of specific *in vitro* 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.

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

The omission of clinically relevant allergens from an allergic patient's allergen immunotherapy extract contributes to decreased effectiveness of allergen immunotherapy. The 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 can make allergen immunotherapy less effective.

Knowledge of the total allergenic burden facing a patient and the realistic possibility of avoidance is important in determining whether allergen immunotherapy should be initiated. 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. Many individuals travel extensively for business or pleasure into different regions, and symptoms might worsen at these times. However, inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective. Determination of the significance of indoor allergens for a particular patient is harder because it is difficult to determine exposure in the home, school, and/or workplace. Historical factors, such as the presence of a furry animal in the home, a history of water damage and subsequent fungal exposure, or a history of insect infestation, might be helpful. However, such information is subjective and is often of uncertain reliability. In addition, some studies have demonstrated significant indoor levels of cat and dog allergen in households without pets[228] and significant levels of mouse allergen in suburban[229] and inner-city[230] homes 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 with increased asthma morbidity in inner-city children was found.[231] 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. Nevertheless, for most patients, determination of the clinical relevance of an allergen requires a strong correlation between the patient's history and evidence of allergen-specific IgE antibodies.

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted *in vitro* tests for specific IgE antibodies can also be used. **A**

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 the skin test results have demonstrated the efficacy of immunotherapy for relevant allergens.[25,26,112,130,134,135,140,141,149,154] 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 from skin testing in a highly sensitive individual.[232,233] In addition, skin tests might be difficult to perform in patients with dermatographism or atopic dermatitis. *In vitro* tests are particularly useful in such patients.

Studies indicate that skin testing is generally more sensitive than *in vitro* tests in detecting allergen-specific IgE.[234,235] Based on inhalation challenge test results, skin tests have shown specificity and sensitivity generally superior to those of *in vitro* tests. The comparability of skin tests and *in vitro* tests for specific IgE antibodies depends on the allergen being tested. For all of 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, prick testing is sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass[236] and cat,[237] are used. Intradermal/intracutaneous skin testing might be required for some allergen extracts. It is appropriate in some patients to use *in vitro* tests for specific IgE antibody as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. *In vitro* tests can also be used to define the allergens that should be used in allergen immunotherapy. If the allergy skin test result is negative and the *in vitro* test result is positive, a controlled challenge can be performed, and if the latter is positive, immunotherapy can be considered. 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 *in vitro* test results.

Specific allergens

Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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.[17,104,106,107,109] 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.[112,122] Because a particular pollen extract is a mixture of multiple glycoproteins, this suggests that mixing pollen allergens does not alter biologic activity.

Fungi (molds). Several studies with *Alternaria* and *Cladosporium* species suggest that allergen immunotherapy with fungi might be effective.[133-138] The allergen content of most mold extracts is highly variable.[238,239] However, there is evidence that proteolytic enzymes present in some mold extracts could digest other antigens, such as pollens, when combined in a mixture.[240] For this reason, it might be desirable to separate all pollen extracts from mold extracts when using mixtures.

Unfortunately, extracts for some potentially clinically important fungi are not available.[241] 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 distinguish 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.

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.

Because immunotherapy has been shown to be effective for cat[22,26,139-143,242] and dog,[25,141] the decision to include dog or cat allergen in an allergen immunotherapy extract should be considered in those circumstances in which there is exposure.

Dust mites and cockroach allergens. Crude house dust extract is generally an inappropriate substitute for house dust mite extract because the protein content measured is not restricted to dust mite allergens, nor does it necessarily guarantee inclusion of dust mite protein. Immunotherapy with standardized dust mite is generally more effective than that with crude house dust allergens. The house dust mites *D farinae* and *D 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, such as *Blomia tropicalis* and *Euroglyphus maynei*, partially cross-react with allergens from *Dermatophagoides* species. Only 50% of the projected amounts of each of the 2 house dust mites (*D pteronyssinus* and *D farinae*) need 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[144,147-149,151] 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. Dust mite hypersensitivity should particularly be considered in patients who have perennial symptoms exacerbated by a dusty environment at home, work, or both and periods of high humidity.

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. The major allergen of *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.[243] Immunotherapy with cockroach allergens is effective[154] and should 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.

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.[108,116,244] Efficacy has also been demonstrated with immunotherapy by using whole-body extracts of imported fire ants.[155,156]

Foods. Only a single clinical study accessing the efficacy and safety of subcutaneous immunotherapy with foods has been performed.[171,173] This study, which evaluated immunotherapy with peanut, found the incidence of systemic reactions, even during maintenance, was unacceptable. Thus there is no evidence to support the use of immunotherapy with food extracts. Currently, strict avoidance of the offending food is advisable, and subcutaneous immunotherapy for food allergy is not recommended.

Mixing of extracts

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Once the relevant allergens for each patient are identified, it is necessary to prepare a mixture that contains each of these allergens. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts. A number of 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 interactions between different types of allergens, when mixed, that could lead to degradation or unmasking of epitopes on exposure to proteolytic enzymes.

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Immunologic and 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.[71] 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 genera 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 the Allergen extract section, Fig 2, and the allergens and allergy diagnostic tests practice parameters).

Dose selection. Summary Statement 30: 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.[22-26,128,149,245] Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000 vol/vol).[28] A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy vaccine. Failure to do so might reduce the efficacy of immunotherapy. This occurs because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased (see the Immunotherapy schedules and doses section for further discussion and for recommended maintenance doses).

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as fungi (mold) and cockroach, from other extracts, such as pollens, is recommended. **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.[240,246,247] 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, and some weeds.[240,246,247] Cockroach had a similar deleterious effect on pollen extract potency.[246,248] Short ragweed appeared resistant to the effects of the proteolytic enzymes in one study,[240] 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.[247]

Dust mite extracts do not appear to have a deleterious effect on pollen extracts.[240,246,248] These studies suggest that pollen, dust mite, and cat extracts can be mixed together. 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. The evidence on mixing cockroach extract with other extracts is conflicting, and the clinical relevance of the changes is also unclear; therefore the clinician has the option of separating cockroach or not.

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 with lesser activities, such as pollen extracts.

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.

In this regard the number of separate injections that need to be given at each patient visit depends on whether all of the relevant extracts mixed into a single vial still deliver an optimal dose of each allergen. If mixing causes excessive dilution or if there are advantages to separating allergens into separate vials, then more than one vial might be necessary for successful immunotherapy.

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extracts are high-alert products that carry the risk for anaphylaxis. Policies, procedures, and processes intended for conventional drugs and medications might be highly 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 fatal anaphylactic reactions with allergenic products. 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. There are no reports of infection associated with allergen immunotherapy injections. Allergen vaccines are prepared by using sterile manufacturer's extracts and sterile diluents containing antibacterial constituents (usually phenol). A summary of the AAAAI/ACAAI/JCAAI proposed USP allergen immunotherapy extract preparation guidelines can be found in Table VIII.

TABLE VIII. AAAAI/ACAAI/JCAAI-proposed USP 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 below.*
   - 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.
2. **Physician responsibility**: A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in the preparation of immunotherapy using an aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files.
3. **Bacteriostasis**: Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if 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 the FDA-approved package insert 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 treatment with sanitizing agents containing alcohol and/or 70% isopropanol 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 the physical integrity of the vial.
10. **Labeling**: Immunotherapy vials are to be clearly labeled with the patient's name and 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.

*__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 media, such as from Valiteq (http://www.valiteq.com), 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.

Allergen immunotherapy extract handling

Storage. Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

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 a number of 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 extract, including reconstituted lyophilized extracts, should be stored at 4°C to minimize the rate of potency loss because storage at higher temperatures (eg, room temperature) can result in rapid deterioration.[249]

Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions (personal communication). These studies include actual shipments made by their carriers to places like

Phoenix in the summer and Alaska in the winter. 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.

Storing dilute extracts. Summary Statement 34a: More dilute concentrations of allergy immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than do more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: In determining the allergy vaccine expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of 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 allergen immunotherapy 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.[249,250]

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.[250] Phenol is a preservative added to extracts to prevent growth of microorganisms.

Phenol can denature proteins in allergen extracts.[251,252] Human serum albumin might protect against the deleterious effect of phenol on allergen extracts.[251] 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,[250,253] possibly through inhibition of the activity of proteolytic and glycosidic enzymes that are present in certain extracts. However, it is irritating when injected and should be diluted before beginning immunotherapy. Recommendations for extract stability are found in the manufacturers' product insert sheets. 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. The pain associated with glycerin increases in proportion to the glycerin concentration and injection volume, and the pain is proportional to the total injected dose of glycerin.[254] However, individual pain perception can vary substantially. Total glycerin doses of less than 0.05 mL rarely produce clinically important pain.

TABLE IX. Potency of selected manufacturer's extracts currently available

Extract	Potency
Cat hair and pelt	5000 and 10,000 BAU/mL
Dust mite	3000, 5000, 10,000, and 30,000 AU/mL
Bermuda grass	10,000 AU/mL
Short ragweed	1:10-1:20 wt/vol or 100,000 AU/mL
Other grasses*	10,000 and 100,000 BAU/mL
Other pollen	1:10 to 1:40 (wt/vol) or 10,000 PNU/mL
Molds	1:10 to 1:40 (wt/vol) or 20,000 to 100,000 PNU/mL

AU, Allergy unit; *BAU*, bioequivalent allergy unit; *PNU*, protein nitrogen unit.
*Perennial rye, Kentucky blue/June, timothy, sweet vernal, redtop, orchard, and meadow.

There have been few studies that have investigated the potency of dilutions of allergen extract mixture over time. Expiration dates for allergen extract dilutions are somewhat empiric and not strongly evidence based. A study undertaken by the AAAAI 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. Dust mite and cat at 1:10 and 1:100 vol/vol dilution were also stable in all conditions of storage over 12 months, as measured by an ELISA assay using 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.

IMMUNOTHERAPY SCHEDULES AND DOSES

Summary Statement 35: A customized individual 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 can be based on single or multiple allergens. **D**

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. Animal dander contains between 10 and 20 antigens,[255] house dust mites between 20 and 40 antigens,[256] and pollens between 30 and 50 antigens,[257,258] and fungal extract can contain as many as 80 antigens.[259]

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. This is designated as the patient's maintenance concentrate.

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. Standardized extracts are available with biologic potencies of 10,000 and 100,000 BAU for grasses; 5000 and 10,000 BAU for cat allergen; 5000, 10,000, or 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 wt/vol extracts (Table IX). 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.

Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

The highest concentration of an allergen extract mixture that is projected to be used as the therapeutically effective dose is called the maintenance concentrate. This should be prescribed individually for each patient by an allergist/immunologist. 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 individual manufacturer's extracts. Some patients might be unable to attain the projected therapeutically effective dose of the maintenance concentrate because of local reactions, systemic reactions, or both (eg, cat, 1000 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose]; see Table X for probable effective therapeutic dose range). Such patients might need weaker dilutions of their maintenance concentrate. Even so, 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 referred to as the maintenance dose. The consistent use of this nomenclature system is essential because errors in choosing the correct vial are a common cause of systemic reactions, especially when the patient transfers from one physician to another. Therefore it is important that standard terminology be adopted by all physicians who prescribe allergen immunotherapy.

Recommended doses

Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

The effective maintenance dose of immunotherapy for a particular patient must be individualized. To do this, the allergist/immunologist who prepares the allergen immunotherapy extract must balance the dose necessary to produce efficacy and the risk of reactions if such a dose is reached. The allergist/immunologist might need to prepare more than one maintenance concentrate to provide a therapeutic dose of each of the allergens for the polysensitized patient. Therapeutically effective doses for immunotherapy have been reported for some allergen extracts.[22,24,25,128,134,135,149,246,260,261] Effective doses have been determined for Hymenoptera venom, dust mite, cat allergen, dog, grass, and short ragweed (Table X).

Controlled studies demonstrate that the content of particular allergens in allergen immunotherapy extracts can be used to predict a therapeutic dose for those allergens, particularly when the extracts are standardized. For antigens 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. The therapeutically effective doses used in the most recent controlled clinical studies are the basis of the recommended dosage range of standardized extracts presented in Table X. 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 time that it is administered.[14]

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.[27] 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 risk of systemic reactions to immunotherapy injections with higher maintenance doses. The maintenance concentrate should be formulated to deliver a full therapeutic dose of each of its constituent components. However, some sensitive patients might not tolerate the targeted therapeutic dose, and their maintenance dose would be lower. Individuals 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 referred to as the maintenance dose.

Regardless of dose schedule, some patients are unable to progress to the predetermined maintenance dose because of large local or systemic reactions to the allergen

TABLE X. Probable effective dose range for allergen extracts US standardized units[a]

Antigen	Labeled potency or concentration[a,b]	Probable effective dose range
Dust mites: *D farinae* and *D pteronyssinus*[c]	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat[d]	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized[e]	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed[f]	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 μg of Amb a 1 1000-4000 AU Concentration of Amb a 1 is on the label of wt/vol extracts in FDA units[358]
Nonstandardized extract, dog[g]	1:10 to 1:100 wt/vol	15 μg of Can f 1
Nonstandardized extracts	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose

[a]Multiple studies have demonstrated that the efficacious dose for allergen immunotherapy is between 5 and 20 μg of the major allergen per injection. Only 2 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).

[b]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).

[c]There have been no dose-response studies with United States–licensed dust mite extracts, and dosing recommendations in AU value are extrapolated from published European studies that used aqueous[349] and alum-precipitated[149,151] extracts. 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.[149] The authors suggested the optimal maintenance dose was 7 μg of Der p 1. Corresponding doses were based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Extrapolating effective and safe doses in this manner might not be scientifically valid. *D farinae* and *D pteronyssinus* are similar in group 1 allergen content according to the FDA's current reference standards. 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*.

[d]The major cat allergen Fed d 1 is reported in FDA units, with 1 Fel d 1 unit equaling approximately 2 to 4 μg of Fel d 1.[55,58,59] The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 to 19.9 U/mL. One study demonstrated clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 dose in terms of decreased cat extract PD_{20}, titrated skin test results, and allergen-specific IgE and IgG levels.[350,351] In a recent study that investigated the efficacy in terms of immunologic changes of 3 doses of a United States–licensed cat extract (0.6, 3, and 15 μg) demonstrated that a significant effect on titrated skin prick test results, allergen-specific IgG4 levels, and $CD4^+$/IL-4 levels was only seen in the group treated with 15 μg of Fel d 1, although the 3-μg dose group did demonstrate a significant change in titrated skin test response and increase in cat-specific IgG4 levels.[22]

[e]There have been no dose-response studies with United States–licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,[130] alum-precipitated,[24,161] and calcium phosphate–precipitated grass pollen extracts.[352] One of these studies compared a dose of 2 μg with 20 μg of major timothy allergen (Phl p 5) and found clinical efficacy at both doses.[24] The efficacy was greater in the 20 μg of Phl p 5 dose, but the systemic reaction rate was also higher in the high-dose group. The package inserts for United States–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 BAU. Extrapolating effective and safe doses in this manner might not be scientifically valid. 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).

[f]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 suggested that 1 unit of Amb a 1 is equivalent to 1 μg of Amb a 1, and 350 Amb a 1 units/mL is equivalent to 100,000 BAU/mL.[60] The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2000 AU, with a range of 1000-4000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrated 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.[45] A ragweed dose-response study (0.6, 12.4, and 24.8 μg of Amb a 1) demonstrated efficacy, as measured by nasal challenge, at 12 and 24 μg of Amb a 1.[128] The efficacy of the 24-μg dose was not significantly better than the 12-μg dose, and the authors concluded that the optimal dose for ragweed extract was greater than 0.6 μg but not more than 12.4 μg of Amb a 1.

[g]Dog extracts are not standardized. However, one dose-response study with a United States–licensed acetone-precipitated dog extract investigated the efficacy of 3 doses (AP dog; Hollister-Stier, Spokane, Wash; 0.6, 3, and 15 μg) in terms of immunologic changes and found the dose of 15 μg of Can f 1 to be most efficacious.[25] 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 have assayed between 128 and 208 μg/mL (average Can f 1, 162 μg/mL [SD ± 26 μg/mL]; information provided by the extract manufacturer, Hollister-Stier).

immunotherapy extract. The evidence is not clear whether large local reactions are a potential risk for subsequent allergen immunotherapy systemic reactions.

Published studies do not indicate that an individual large local reaction is predictive of a subsequent systemic reaction.[179,180] However, one retrospective study found that individuals who have a history of repeated large local reactions (defined as >25 mm) might be at greater risk for a subsequent systemic reaction.[181]

The concept of highest tolerated dose does not apply for VIT, and all patients are expected to achieve the full recommended dose to achieve the necessary degree of protection. There are conflicting data over whether lower doses (50 μg) are less effective, but there are also data showing that 200 μg is more reliably effective.[245] In the case of VIT, patients are asked to tolerate more large local reactions to achieve the full dose, even though with inhalant immunotherapy the dose can be reduced for such large local reactions to minimize patient discomfort.

Effect of dilution on dose

Summary Statement 38: 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 vaccine, thereby limiting the ability to deliver a therapeutic effective dose for any given allergen.

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

Dilution from maintenance concentrate vaccine	Volume	Volume (mL)	Diluent volume (mL)	Final volume
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.

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 2000 BAU/mL, 2 mL of the manufacturer's extract (cat, 10,000 BAU/mL) can be added to 8 mL of diluent or 8 mL of other allergens, and the final concentration of cat will be 2000 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.

Dilutions of the maintenance concentrate

Summary Statement 39: 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 vol/vol 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, 1000 BAU or 100 BAU), but this system can be complicated if allergens with different potency units are used (eg, wt/vol, BAU, AU, or PNU) and make it difficult to easily interpret the vial label.

Instructions on how to prepare various allergen extracts 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.

Labeling dilutions

Summary Statement 40: 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, a number of 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 (vol/vol), a numbering system, a color-coding system, or an alphabetical system should be used. If this uniform labels 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.

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
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

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 3 and 4).

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 Appendix 2]).

Individualized treatment vials

Summary Statement 41: 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 (wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for 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). Labels on patient-specific vials can provide at least 2 patient identifiers (birth date and patient name), which would be consistent with the recommendations of the Joint Commission on Accreditation of Health Care Organizations National Patient Safety Goals: ''Goal 1: Improve the accuracy of patient identification by using at least two patient identifiers when providing care, treatment or services.''[5] 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 administration of the injection.[4,5]

In a survey of 1717 allergists endorsed by the AAAAI and JCAAI, 57% of the 476 respondents reported at least one wrong-patient injection, and 74% of the 473 respondents reported at least one wrong-dose injection.[4] 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 reasons why this might reduce incorrect injection errors. One reason was that patient-specific vials can be prepared in a quiet laboratory setting, which might provide substantially less distraction than the nurse in a room with a patient who is trying to concentrate only on drawing up the injection correctly. In addition, the specific components are mixed once with the preparation of individually prepared patient-labeled vials, whereas the mixing would be repeated on every injection visit if the allergen extract is withdrawn from different stock solutions, as it is in the off-the-board method. For safety reasons and to avoid cross-mixing of allergens removed from the manufacturer's extract, the mixing of antigens in the syringe (off the board) is not recommended.

Some allergists/immunologists prefer to administer immunotherapy doses drawn directly from a single stock dilution of individual allergens or common mixes (shared specific patient vials). In this way the immunotherapy dose is transferred to the patient without cross-contamination. If shared-patient (eg, mixed vespids and dust mite mix) vials are used, it is essential that policies and procedures are developed to verify that the correct dose from the correct vial is administered to the correct patient.

Starting doses

Summary Statement 42: The starting dose for build-up is usually a 1000- 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 slowly 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 1:1000 (vol/vol), although more diluted concentrations frequently are used for patients who are highly sensitive, as indicated by history or skin test reaction (see Appendix 3 for an example of a conventional immunotherapy schedule).

Frequency of build-up injections

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 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 2 times per week. 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 4 to 6 months, depending on the starting dilution and the occurrence of reactions. It is acceptable for patients to receive injections more frequently, provided there is adequate spacing between injections. The interval between injections is empiric but might be as short as 1 day without any increase in the occurrence of systemic reactions[262] if there is some urgency to achieve a maintenance dose (eg, allergy season is approaching) or for practical reasons (eg, patient's schedule). Alternatively, treatment schedules can be used that more rapidly achieve maintenance dosing. These cluster and rush dosing schedules are discussed in Summary Statements 47 through 49.

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 a number of 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).

Dose adjustments for systemic reactions

Summary Statement 44: 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 benefit/risk ratio justifies continuation of immunotherapy.

Reductions during periods of exacerbation of symptoms

Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Immunotherapy administered during periods of exacerbation of symptoms is considered a risk factor for immunotherapy.[17,184] Injections administered during periods when a patient is exposed to increased levels of allergen to which they are 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.[184] 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 sensitive, especially if their symptoms are poorly controlled.

Dose adjustments for late injections

Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

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 depends 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 Appendix 4 for an example of a dose-modification regimen for gaps in treatment).

Cluster schedules

Summary Statement 47: 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 (see Appendix 5).[22,26] 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. The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules.[145,263-266] The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.[267]

Rush schedules

Summary Statement 48: 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.[268] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.[191,269-272]

The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections over the course of 4 hours.[273] Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours.[274-276] 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 cluster[145,266] and rush[134,277] schedules.

Systemic reactions and rush schedules

Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

The advantages of rush immunotherapy come at a cost because there is an increased risk of local and systemic reactions. Systemic reaction rates have been reported to be

as high as 73% of patients, with the risk of such reactions reduced to 27% by premedication in one study.[272] Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing.[273]

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

Rush protocols for administration of Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions.[274-276,278,279]

Premedication and weekly immunotherapy

Summary Statement 50: Premedication can reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

There is concern that antihistamines taken before each injection with conventional immunotherapy might mask a minor reaction that would otherwise alert a physician to an impending systemic reaction. 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.[280] One study that compared terfenadine premedication with placebo premedication during rush VIT demonstrated greater clinical efficacy in the terfenadine-premedicated group in terms of subsequent responses to field stings or sting challenge.[281] There was also a significant difference in the systemic reaction rate between the 2 groups: 6 patients in the placebo-premedicated group had systemic reactions, whereas none of the patients in the terfenadine-premedicated group had systemic reactions ($P = .012$).

Unfortunately, patients might still have life-threatening anaphylaxis despite 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.

Premedication with cluster and rush immunotherapy

Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

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.[267] Premedication with a 3-day course of prednisone, an H_1 histamine receptor antagonist, and an H_2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.[272] In one study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on the safety and efficacy of rush immunotherapy, there was a 5-fold decrease in the risk of anaphylaxis in the group premedicated with omalizumab compared with the placebo premedication group.[282]

There are anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist, but there have been no published studies. Because the risk of a systemic reaction from rush VIT is relatively low, routine premedication before rush VIT is usually unnecessary.[274,276,278,279] In a study evaluating premedication with antihistamines and steroids for rush immunotherapy with imported fire ant venom, there was no statistically significant differences in the systemic reaction rates between the premedication and placebo premedication group (3.6% of the premedication group vs 6.7% of the placebo group, $P = .87$).[157]

Maintenance schedules

Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals 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 individuals might tolerate longer intervals between maintenance dose injections.

The interval between venom injections can be safely increased up to 8 weeks in some patients without loss of efficacy. 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.

Continuing care

Time course of improvement. Summary Statement 53: Clinical 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.[24,134,143,277] Improvement might not be observed for a number of reasons, including (1) failure to remove significant allergenic exposures (eg, a cat), (2) exposure to high levels of

allergen (eg, pollen or molds), (3) continued exposure to nonallergen triggers (eg, tobacco smoke), or (4) incomplete identification and treatment of clinically relevant allergens. 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 54: 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 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 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

The patient's response to immunotherapy should be evaluated on a regular basis. 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. 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.

There have been very 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 individuals.[283-285] However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported.[283,285] Nevertheless, systemic reactions to stings after discontinuing VIT were generally much milder than the pretreatment reactions and were rarely severe. Two studies did not find a difference in relapse rates between the patients treated for 3 years compared with those treated for 5 years,[283,286] but one of the studies noted that the small number of patients in the 3-year treatment group prevented them from making any conclusions about the risk of discontinuing treatment after 3 years.[283] However, one study found that patients who had experienced re-sting reactions after discontinuing VIT had received VIT for a significantly shorter duration (mean, 43.35 months) than those with continued protection (mean, 54.65 months; $P < .01$).[285] Another study reported that 5 years of VIT provided better immunologic and clinical outcomes than 2 to 4 years of treatment.[287]

Change in skin test reactivity did not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who experienced a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE.[286,288] Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment.[288] The relapse rate and the frequency of severe reactions were greater in patients who had a history of very severe reactions to stings before treatment, in patients who had systemic reactions during VIT (to a sting or a venom injection), in patients with honeybee allergy, and in those who had less than 5 years of treatment.

The duration of inhalant allergen immunotherapy efficacy has not been as extensively studied. Some studies have suggested 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 *(D pteronyssinus)* extract for 12 to 96 months.[14] 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.[13] There was a switch to placebo in half of 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. These studies demonstrate the uncertainty of the long-term benefit of inhalant immunotherapy after discontinuation.

Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained clinical remission after discontinuing inhalant immunotherapy, and 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 indication for continuation of immunotherapy can be found at http://www.aaaai.org or http://www.jcaai.org.

Documentation and record keeping. Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully 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 allergy immunotherapy and prescription forms can be found in the Appendix (Appendices 6-15), and these include examples of immunotherapy prescription and administration forms. These forms, along with examples of immunotherapy consent and instruction forms, can also be found at http://www.aaaai.org.

Injection techniques. Summary Statement 57: Allergen immunotherapy extract injections should be given using a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **C**

Immunotherapy should be given with a 26- to 27-gauge syringe with a half-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.[289-291]

If using shared specific patient vials (stock vials, such as mixed vespid or dust mite mix), a single dose should be drawn from each vial. Antigens from different vials should not be combined in a single syringe. Furthermore, extra care is needed to prevent using the wrong stock antigen.

Summary Statement 58: The injection should be given subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Each immunotherapy injection should be given in the posterior portion of the middle third of the upper 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.

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.

The syringe should be aspirated to check for blood return in the syringe before injecting. If blood is present, 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 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 syringe should be appropriately discarded. A fresh syringe and needle are necessary to determine whether a blood vessel has been entered.

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 could result in a local reaction.

LOCATION OF ALLERGEN IMMUNOTHERAPY ADMINISTRATION

Physician's office

Summary Statement 59: 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 to treat anaphylaxis should be in the immediate vicinity when immunotherapy injections are administered.

Summary Statement 60: 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.[292] 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.[184] 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 might be frequently necessary in the patient's immunotherapy schedule, as well as the patients total treatment program.

Other locations

Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **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.[292] The health care professional and staff 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, or allergy/asthma exacerbations at the time of allergen immunotherapy extract injection or poorly controlled asthma).

Appropriate adjustment of dose should be made as clinically indicated. The physician who prepared the patient's allergen immunotherapy extract should provide adequately labeled allergen immunotherapy extract vials, detailed directions regarding dosage schedule for build-up and maintenance, and instructions on adjustments that might be necessary under the following circumstances:

1. when providing patients with new vials;
2. during seasonal exposure to allergens that are in the patient's allergen vaccine, to which the patient is very sensitive, or both;
3. if the patient has missed injections; and
4. when reactions occur to the allergen immunotherapy extract.

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

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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 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 very 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 fully trained to administer the injection and to treat anaphylaxis if this should 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 supports (personnel, medications, supplies, and equipment) are more optimal for encouraging prompt recognition and treatment of anaphylaxis (Table V). 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.

Summary Statement 63: If a patient on 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for their immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extracts might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Patients often 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 brought from the previous physician (ie, an unchanged immunotherapy program) or one to be prepared by the current physician (ie, a new immunotherapy program).

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 full, clear, and detailed documentation of the patient's previous schedule and the contents of the allergen immunotherapy extract (see Appendices 7, 8, 11, 12, and 14 for examples of allergen immunotherapy prescription and administration forms and documentation guidelines for allergen immunotherapy forms). In addition, the patient's previous response to and compliance with this program 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 a schedule and the allergen immunotherapy extract, (2) the patient has shown significant improvement on this immunotherapy program, and (3) the contents of the allergen immunotherapy extract are appropriate for the area in which the patient is now living.

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, vaccine type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient's dose is not modified. This increased risk is due to the significant variability in content and potency of extracts and the variability in methods used by physicians to prepare the patient's maintenance concentrate and its dilutions. For example, the strength of a given concentration of nonstandardized extracts might vary significantly from vial to vial. The risk of systemic reactions in such a situation might be greater with nonstandardized extracts and allergen immunotherapy extracts that contain mixtures of allergens.

Therefore if the allergen immunotherapy extract is to be changed, the patient might need to be retested for specific IgE to the appropriate allergens 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 provided the interval of time since the last injection has not been too long. For lot changes from the same manufacturer, the physician can consider decreasing the dose by 50% to 90%. For changes in manufacturer and nonstandardized extracts, a greater decrease in dose might be necessary.

SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

Allergen immunotherapy in children

Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children

with allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Immunotherapy for children has been shown to be effective and often well tolerated,[137,242] although at least one study did not show efficacy.[293] 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.[294] In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (see the Patient selection section and Table VII). In recent studies children receiving allergen immunotherapy have demonstrated:

1. improvement in symptom control for asthma[117,119,121,122] and allergic rhinitis[118];
2. increased PC_{20} to histamine[121];
3. increased PC_{20} to cat and house dust mite allergens[121,149];
4. decreased risk of development of asthma[6,9,163-165];
5. decreased development of new sensitivities[120,166]; and
6. modification in release of mediators in children receiving immunotherapy that correlates with decreased clinical symptoms.[123]

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Although there is some disagreement about the role of allergen immunotherapy in children under the age of 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.[117,122] In children with allergic rhinitis, allergen immunotherapy might prevent the development of asthma.[6,9,163-165] However, allergen immunotherapy for inhalant allergens is usually not considered necessary in infants and toddlers because (1) there is 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 in pregnancy

Summary Statement 71: Allergen immunotherapy might be continued but is usually not initiated in the pregnant patient. **C**

The physician must be aware of the benefits and risks of immunotherapy in pregnant patients. The recommended precautions for prevention of adverse reactions are especially important in the pregnant patient. Allergen immunotherapy is effective in the pregnant patient. Thus allergen immunotherapy maintenance doses can be continued during pregnancy. Allergen immunotherapy is usually not initiated during pregnancy because of risks associated with systemic reactions and their treatment (ie, spontaneous abortion, premature labor, or fetal hypoxia). 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, and the patient is maintained on the dose that she is receiving at that time.

Immunotherapy in the elderly patient

Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy might be considered in the treatment of the elderly patient, but the benefit/risk assessment must be evaluated carefully in this population. Older 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. However, elderly patients may also benefit from allergen immunotherapy and age alone should not preclude the consideration of allergen immunotherapy.[295]

Immunotherapy in patients with immunodeficiency and autoimmune disorders

Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with immunodeficiency or autoimmune disorders. Therefore the decision to begin immunotherapy in patients with major humoral or cellular immune defects must be individualized. Concern about the increased risk of immunotherapy in such patients is largely hypothetical.

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

ALTERNATIVE ROUTES OF IMMUNOTHERAPY

Sublingual and oral immunotherapy

Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be

effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no FDA-approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **B**

Alternative routes of administration of allergen immunotherapy are ''a viable alternative to parenteral injection therapy'' in some cases.[106,296] Studies of oral immunotherapy have provided conflicting results for ragweed,[297] birch,[298] and cat[299] immunotherapy. The present dosage of oral immunotherapy extract is 20 to 200 times the parenteral injected dosage, which requires a cost assessment for this type of therapy. Furthermore, adverse effects have included gastrointestinal and oral reactions (50% in 1 study) that might preclude home therapy. Oral immunotherapy should be considered investigational at this time.

Optimal-dose (high-dose) sublingual swallow immunotherapy is effective in adults and children.[300-304] In a study of 855 patients with grass pollen allergy and allergic rhinitis randomized to placebo or one of 3 grass tablet doses, there was a significant reduction in symptom and medication scores in the highest-dose subgroup, who were treated for at least 8 weeks before the grass pollen season, compared with the placebo group (symptoms, 21%, $P = .0020$; medication use, 29%, $P = .0120$).[303]

Sublingual allergen studies have evaluated house dust, olive pollen, grass pollen, ragweed, birch, cat, latex, *Alternaria* species, and *Parietaria judaica*.[305-313] Sublingual immunotherapy has been shown to be effective in patients sensitized to 2 non–cross-reacting allergens, grass and birch.[314] It has been noted that the allergen is not degraded by saliva and that there is no direct sublingual absorption of allergen. Radiolabeled allergen has been detected after 48 hours in the sublingual region.[315,316] Alternative protocols, such as rush and ultra-rush (20 minutes) sublingual swallow[307,316,318] and no induction (build-up) phase,[301,303,317,319,320] have been studied. Several studies have suggested a relationship between dose and efficacy with sublingual immunotherapy,[303,310,321] but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. The majority of sublingual studies have demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both, but approximately 35% of the randomized, double-blind, placebo-controlled studies did not demonstrate efficacy in either parameter during the first year of treatment.[322] Further studies are needed to confirm the optimal dose for sublingual immunotherapy.

One of the potential advantages of sublingual immunotherapy is that it appears to be safe, even at very high doses (up to 500 times the usual monthly subcutaneous dose), and to be associated with a lower incidence of serious side effects.[310,320,323] This appears to apply to young children (<5 years), for whom there are prospective safety data[324,325] and a postmarketing survey.[326]



FIG 3. Sample of labels for allergen immunotherapy extract vials.

There have been no SLIT-related fatalities, but there have been 3 case reports of anaphylaxis caused by sublingual immunotherapy. One patient with latex hypersensitivity had anaphylactic shock 20 minutes after reaching the maximal dose on the fourth day of latex rush sublingual rush immunotherapy.[327]

The other 2 reported cases of SLIT anaphylaxis involved patients treated with multiple inhalant allergens. In one case a patient with allergic rhinitis and asthma who was prescribed a sublingual immunotherapy extract composed of multiple non–cross-reacting allergens (*Alternaria* species, dog, cat, ragweed mix, weed mix, and grass mix)[328] had generalized pruritis, followed by angioedema, shortness of breath, and dizziness, within a few minutes of administering 6 drops of the 1:100 vol/vol dilution on the third day of treatment. This episode was preceded by a milder systemic reaction the previous day (generalized pruritis). In the other case, a 13-year-old girl with allergic rhinitis and asthma had swelling of her lower lip 3 minutes after pollen drops, high fever, chest pain, nausea, and abdominal pain.[329] She was treated in the emergency department for anaphylaxis and hospitalized for observation. The reaction occurred 1 month after she had reached the maintenance dose during the peak of the spring season.

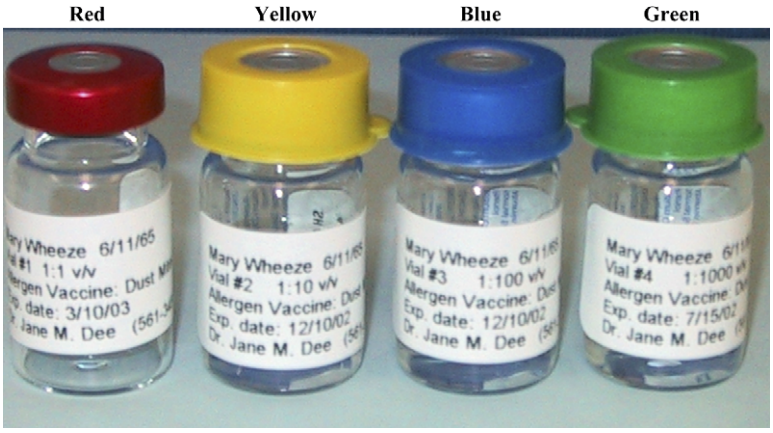


FIG 4. Sample set of color-coded vials of allergen vaccine.

There is currently no FDA-approved formulation for sublingual immunotherapy in the United States at this time, and this modality should be considered investigational. Current investigation of sublingual immunotherapy should not be confused with low-dose sublingual immunotherapy based on provocation neutralization testing or Rinkel-type skin testing.

Intranasal immunotherapy

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Based on controlled, well-designed studies, intranasal immunotherapy has been shown to improve the nasal symptoms of rhinitis.[330] Intranasal dry powder extract immunotherapy has been studied in grass,[330] birch,[331] *P judaica*,[332-334] and house dust mite[335] allergy. Clinical efficacy was noted in all of these studies. Nasal reactivity to allergen challenge was reduced, and only minor side effects were noted in 2 of the above studies. A 3-year study with *P judaica* reported to provide persistent benefits for up to 12 months after conclusion of allergen immunotherapy.[333] Local administration of nasal allergen in an aqueous solution for immunotherapy might be limited by the local side effects. Further studies in both pediatric and adult groups are needed. In human studies the antigen has been noted to appear in the serum within 15 to 30 minutes of administration, with a peak level occurring within 2 to 3 hours.[315] Some allergens have been reported to be retained in the nasal mucosa for up to 48 hours after administration. Intranasal immunotherapy is not currently available in the United States but has gained some acceptance in other parts of the world.

Immunotherapy techniques that are not recommended

Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

Low-dose regimens, including coseasonal low-dose immunotherapy for aeroallergens and the Rinkel low-dose titration techniques, are not effective.[27,28] Immunotherapy based on provocation–neutralization testing with food and aeroallergens and enzyme-potentiated desensitization is not effective.[336]

FUTURE TRENDS IN IMMUNOTHERAPY

Therapy with aeroallergen extracts will become more uniform (as is the current practice for insect venoms) as greater numbers of biologically standardized allergen extracts become available. The actual number of commercially available allergen extracts will be reduced based on consensus agreements about the regional prevalence of aeroallergens, their cross-allergenicity, and the relevance of their effect on human health in specific locales. Novel routes for more effective, convenient, and safer allergen immunotherapy are being investigated throughout the world.

For example, the sublingual route of administering allergen immunotherapy has been studied extensively in Europe. A meta-analysis confirmed its clinical effectiveness in allergic rhinitis,[302] and it has been reported to be effective in asthma as well.[337] Sublingual immunotherapy appears to have a very low risk of serious life-threatening systemic side effects, which might allow for home administration.[324,338] In some studies the clinical benefits of sublingual immunotherapy were not significant until the second year of treatment,[306,339] and comparisons suggest that the magnitude of the clinical benefit of sublingual immunotherapy might not be as great as that of subcutaneous immunotherapy.[311]

Trials with non–IgE-binding peptides containing T-cell stimulating peptides have been reported.[340] Site-directed mutagenesis has produced allergens with decreased IgE-binding capacity without decreased T-cell responses.[341,342]

Immunostimulatory sequences mimicking bacterial and viral DNA have been prepared that stimulate the innate immune system to direct T-cell responses toward

T_H1 rather than T_H2 phenotypes.[343] The results of clinical trials with a conjugate of the immunostimulatory sequence to the major allergen of ragweed, Amb a 1 (AIC), have been reported.[34,343] In a double-blind, placebo-controlled study of 25 adults who received 6 weekly injections of the AIC or placebo vaccine before ragweed season, the AIC group had better peak-season rhinitis scores on the visual analog scale ($P = .006$), peak-season daily nasal symptom diary scores ($P = .02$), and midseason overall quality-of-life scores ($P = .05$) than the placebo group during the first ragweed season, and this effect was observed in the subsequent ragweed season.[344]

Humanized anti-IgE mAb has been shown to have clinical effects in both allergic rhinitis and asthma.[345-348] Theoretically, this new therapeutic modality could be used as protective cover for clinical applications of rapid forms of immunotherapy. It is possible that preadministration of anti-IgE could provide a more effective protective effect than premedication with antihistamines and therefore permit a rush allergen immunotherapeutic regimen with reduced risk of serious systemic reactions.[282]

AUTHOR'S 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 2 systemic reaction grading systems (the European Academy of Allergy and Clinical Immunology's grading of severity for systemic side effects and the Portnoy method for numeric grading of reactions to allergen immunotherapy) can be found in the Appendix section. These forms can also be found along with examples of immunotherapy instruction and consent forms, preinjection health questionnaires, and indications for beginning and continuing immunotherapy forms at www.aaaai.org.

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APPENDIX 1. American College of Medical Quality's policy on the development and use of practice parameters for medical quality decision-making[1]

Practice parameters are strategies for patient management developed to assist health care professionals in clinical decision making. Practice parameters include standards, guidelines, and other patient management strategies. Standards are accepted principles for patient management. Guidelines are recommendations for patient management that identify a particular management strategy or a range of management strategies. Other strategies for patient management include practice policies and practice options. Practice parameters are to be used as screening tools to identify possible deviations from the applicable standards of care. Such parameters are not to be used as absolute standards or to profile or report on health care personnel. Parameters are designed to trigger a process in which possible deviations from the standard of care are identified as outlier practice patterns. Once a deviation from the parameter is identified, such a deviation should be referred to the appropriate qualified physician advisor or reviewer for a determination of medical necessity that conforms to the applicable standard of care. Parameters used in the day-to-day practice of clinical medicine should be clinically relevant. They should not be considered as substitutes for the standard of care but might contribute to its formulation.

Practice parameters must be developed, designed, and implemented only by board-certified, clinically practicing, specialty-matched physician advisors/reviewers with unrestricted medical licenses. Qualified nonphysicians might participate in the development of these parameters only in the areas in which their clinical expertise based on the standard of care is applicable. The health care personnel who develop these parameters should sign their names and date the final version as evidence of their participation and support. Practice parameters must be based on sound scientific research findings, professional literature, clinical experience and appropriate well-recognized methodologies and reflect professionally recognized national standards of care practiced in the clinical community of medicine. The development procedures followed, the participants involved, the evidence used, the assumptions and rationales accepted, and the analytic methods used should be meticulously documented, described, and made publicly available for national peer review. Parameters should be updated as needed.

Practice parameters are used as tools to enhance medical decision making but not as replacements for physicians' clinical judgment. They can be considered as means to enhance the performance of clinical and review personnel but not to replace them. It is below the standard of care of the medical review process to substitute qualified physician reviewer experts with unqualified reviewers who are using parameters.

APPENDIX 2. Examples of possible abbreviations for allergen immunotherapy extract 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

APPENDIX 3. 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

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

APPENDIX 4. Example of immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals (modification of the AAAAI skin testing and immunotherapy consent and instruction forms: immunotherapy administration instruction form, which can be found at http://www.aaaai.org)

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

- Up to 7 days, continue as scheduled (ie, if on weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection).
- Eight to 13 days after missed scheduled injection; repeat previous dose.
- Fourteen to 21 days after missed scheduled injection; reduce dose 25%.
- Twenty-one to 28 days after missed scheduled injection; reduce previous dose 50%.

Then increase dose each injection visit as directed on the immunotherapy schedule until therapeutic maintenance dose is reached.

This suggested approach to modification of doses of allergen immunotherapy because of gaps between treatment during the build-up phase is not based on retrospective or prospective published evidence, but it is presented as a sample for your consideration. The individual physician should use this or a similar protocol as a standard operating procedure for the specific clinical setting. A similar dose-reduction protocol should be developed for gaps in maintenance immunotherapy.

APPENDIX 5. Example of a cluster immunotherapy schedule[22,26]

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

APPENDIX 6. Recommended documentation for allergen immunotherapy prescription forms

The purpose of the allergen immunotherapy prescription form is to define the contents of the allergen immunotherapy extract in enough detail that it could be precisely duplicated. The following information should be on an immunotherapy prescription form:

Patient information:

- Patient name, patient number (if applicable), birth date, telephone number, and picture (if available) should be included.

Preparation information:

- Name of person and signature preparing the allergen immunotherapy extract should be included.
- Date of preparation should be recorded.
- Bottle name should be included (eg, trees and grass). If abbreviations are used, a 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 should be included.
- Volume of manufacturer's extract to add to achieve the projected effective concentration should be included. 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) should be included.
- Extract manufacturer should be included.
- Lot number should be included.
- Expiration date should be recorded and should not exceed the expiration date of any of the individual components.

APPENDIX 7. Allergen immunotherapy extract prescription 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:

_____
_____
_____
_____

_____ ____/____/____
Prescribing Physician Signature Date

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

APPENDIX 8. Maintenance concentrate prescription form

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: 6/10/06

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial **4** from Vial **1** on **8/30/06** Expiration date: **10/15/06**
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	Short ragweed	1:20 w/v G (150 Amb a1)	0.5ml	Greer	12345	1/01/08
2	Amaranthus Retroflexus	1:10 w/v G	0.5ml	H-S	6789	2/07/08
3	Ash	1:10 w/v G	0.5ml	Center	3333	3/17/08
4	Cat	10,000 BAU/ml G	2.00ml	ALO	9898	2/27/08
5	Timothy Grass	100,000 BAU/ml G	0.4ml	ALK	56789	7/09/08
6	Johnson Grass	1:10 w/v G	0.5ml	Greer	2434	7/20/08
7						
8						
9						
10						
Diluent	HSA		0.6ml	ALK	68597	12/08
Total Volume			5.00 ml			6/10/07

*** Components of mixes listed on a separate sheet**
**** Assumes 0.5 ml injection as target maintenance dose**

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

Specific Instructions:

_____

_____

Prescribing Physician Signature

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

APPENDIX 9. Labels for allergen immunotherapy extracts

Each vial of allergen immunotherapy extract should be labeled in a way that permits easy identification. Each label should include the following information (example in Figs 3 and 4):

- Appropriate patient identifiers might include the patient's name, patient's number, patient's picture, and birth date.
- The contents of the allergen immunotherapy extract in a general way should be included. The detail with which this can be identified depends on the size of the label and the number of allergens in the vial. Ideally, allergens should be identified as trees, grasses, weeds, mold, dust mite, cockroach, cat, and dog. Because of space limitations, it might be necessary to abbreviate the antigens (eg, T, G, W, M, DM, Cr, C, and D respectively [see Appendix 2]). A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate (vol/vol) should be recorded. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- The expiration date should be included.

APPENDIX 10. Allergen immunotherapy administration form recommended documentation

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

Patient information:

- Patient's name, date of birth, telephone number, and patient's picture (optional but helpful).

Allergen immunotherapy extract information:

- Allergen immunotherapy extract name and dilution from maintenance in vol/vol bottle letter (eg, A and B), bottle color, or number, if used.
- Expiration date of all dilutions.

Administration information in separate columns:

- Date of injection.
- Arm administered injection, which might facilitate determination of exact cause of local reaction.
- Projected build-up schedule.
- Delivered volume reported in milliliters.
- Description of any reactions. The details of any treatment given in response to a reaction would be documented elsewhere in the medical record and referenced on the administration form.
- *Patient's health before injection*. This can be performed through a verbal or written interview of the patient before administering the immunotherapy injection. The patient should be questioned about increased asthma or allergy symptoms, β-blocker use, change in health status (including pregnancy and recent infections), or an adverse reaction to a previous injection (including delayed large local reactions persisting through the next day). Patients with significant systemic illness generally should not receive an injection.
- *Antihistamine use*. Antihistamines are frequently a component of an allergy medication regimen, and it would be important to note whether a patient is taking an antihistamine on the day he or she receives his or her immunotherapy injection. For consistency in interpretation of reactions, it might be desirable for a patient to either take or avoid antihistamines on a regular basis on the days he or she receives immunotherapy. The physician should note on the form whether he or she recommends the patient consistently take an antihistamine on immunotherapy treatment days.
- *Peak flow reading*. Consider obtaining a peak expiratory flow rate measurement before administering an immunotherapy injection to asthmatic patients. Poorly controlled asthma is considered a risk factor for immunotherapy. Obtaining a peak expiratory flow rate measurement before the immunotherapy injection might help identify patients with symptomatic asthma. The patient's baseline peak expiratory flow rate should be provided on the form as a reference. Health care professionals administering immunotherapy injections should be provided with specific guidelines about the peak expiratory flow rate measurement for when an immunotherapy injection should be withheld and the patient referred for clinical evaluation.
- **Baseline blood pressure**. It might be useful to record the patient's blood pressure as a baseline for future reference.

APPENDIX 11. Allergen immunotherapy administration form

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 allergy or 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

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

Date to reorder: __/__/__

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 allergy or 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**	

APPENDIX 12. 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: _____
_____
Staff action taken (if any): _____

APPENDIX 13. 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.

APPENDIX 14. Allergen immunotherapy systemic reaction/anaphylaxis 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
__Epinephrine IM into 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	

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:
_____
_____
_____
_____

Clinical impression: True SR Questionable SR No SR

Systemic reaction severity classification: EAACI_____ **Portnoy** _____

Dosage adjustment? _____

Signatures_____ **RN** _____**MD/DO**

APPENDIX 15. Grading severity of allergen immunotherapy reactions: Two methods

1. **The European Academy of Allergy and Clinical Immunology grading of severity for systemic side effects***

Classification of systemic reactions

0 = No symptoms or nonspecific symptoms

I = Mild systemic reactions: symptoms—localized urticaria, rhinitis, or mild asthma (PF <20% decrease from baseline).

II = Moderate systemic reaction: symptoms—slow onset (>15 minutes) of generalized urticaria, moderate asthma, or both (PF < 40% decrease from baseline).

III = Severe (non–life-threatening) systemic reactions: symptoms—rapid onset (<15 minutes) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).

IV = Anaphylactic shock: symptoms—immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, and hypotension, for example.

2. **Portnoy method for numeric grading of reactions to allergen immunotherapy†**

Local

0+ = No significant reaction or small area of erythema less than the size of a half dollar without swelling or wheal formation

1+ = Erythema greater than the size of a half dollar, swelling or wheal formation, or both

Systemic

2+ = Systemic reactions: cutaneous only—might consist of a cutaneous eruption, such as urticaria

3+ = Systemic reaction: generalized pruritus, sneezing, or both—might consist of increased allergy symptoms, such as nasal congestion, sneezing, or pruritus, especially in the mouth or throat

4+ = Systemic reaction: pulmonary—consists of wheezing, shortness of breath, and tightness. Might be associated with decreased pulmonary function tests

5+ = Systemic reaction: anaphylaxis—a sensation of not feeling right is a frequent prelude; might consist of hypotension, laryngeal edema, severe wheezing, and cramping

6+ = Cardiopulmonary arrest

PF, Peak expiratory flow.

*Subcutaneous immunotherapy. Allergy 2006;61(suppl 82):5-13.

†Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80.

Allergen immunotherapy: A practice parameter second update

Supplement Editor: **Linda Cox, MD**
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These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology.

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the "Allergen immunotherapy: a practice parameter second 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 and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
5. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
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These parameters are also available on the internet at http://www.jcaai.org.

CONTRIBUTORS

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Allergen immunotherapy: A practice parameter second update

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PREFACE

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

The objective of ''Allergen immunotherapy: A practice parameter second update'' is to optimize the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. 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's ''Policy on development and use of practice parameters for medical quality decision-making'' (Appendix 1).[1]

This document builds on the previous Joint Task Force document, ''Allergen immunotherapy: a practice parameter'' published in the *Annals of Allergy, Asthma and Immunology* in 2003.[2] The updated practice parameters draft was prepared by Drs Linda Cox, James Li, Hal Nelson, and Richard Lockey. The Joint Task Force reworked the initial draft into a working draft of the document. The project was exclusively funded by the 3 allergy and immunology societies noted above.

In preparation for the 2003 ''Allergen immunotherapy: a practice parameter'' and the second update, a comprehensive search of the medical literature was conducted with various search engines, including PubMed; *immunotherapy*, *allergic rhinitis*, *asthma*, *stinging insect allergy*, and related search terms were used. 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 second update'' was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the ACAAI, AAAAI, and JCAAI. In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for review and comments from members of the sponsoring organizations. 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 allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. This document also contains recommendations for the safe practice of allergen immunotherapy, including specific recommendations on the prevention and management of 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 or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. Symptoms of allergic conjunctivitis (eg, itchy watery eyes) are often considered part of allergic rhinitis or are included in the diagnosis of rhinoconjunctivitis. Particularly good candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures, those in whom it is important to avoid the potential adverse effects of medications, and those who wish to reduce the long-term use of medications. Immunotherapy is recommended for patients with a history of systemic reaction to Hymenoptera stings and specific IgE antibodies to Hymenoptera venom.

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.[3]

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. 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 *maintenance concentrate* should be used to identify the allergen immunotherapy extract that contains a therapeutic effective dose for each of its individual constituents (see the Immunotherapy schedules and doses section).

The term *manufacturer's extract* refers to the allergy extract purchased from the manufacturer. The terms *stock*, *full-strength*, and *concentrate* are ambiguous and should not be used. 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).

Allergen immunotherapy is effective when appropriate doses of the allergens are administered. ''Allergen immunotherapy: A practice parameter'' recommends that vials of allergen immunotherapy extracts should be prepared individually for each patient to enhance the individualization of therapy, reduce the risk of allergen cross-contamination, and reduce the risk of error in administration.[4,5] This parameter recommends the use of standardized allergen immunotherapy prescription and administration forms to improve the safety, uniformity, and standardization of allergen immunotherapy practice.[4,5] The suggested forms are found in the Appendix (Appendices 7, 8, 11, 12, and 14) and in the members' section of the www.aaaai.org Web site. The routine use of these standardized forms should improve the quality of immunotherapy practice.

Members' feedback comments on the recommended allergen extract dilution dating in the 2003 ''Allergen immunotherapy: A practice parameter'' led to an allergen immunotherapy extract dilution stability study designed by the AAAAI Immunotherapy and Allergy Diagnostics Committee and funded by the AAAAI Board of Directors. The study was designed to investigate the effect of time, temperature, and dilution of standardized allergen extract potency, and the results of this study were considered in this update.

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 3 years after publication. Requests for information about or an interpretation of these practice parameters should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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. Allergen immunotherapy

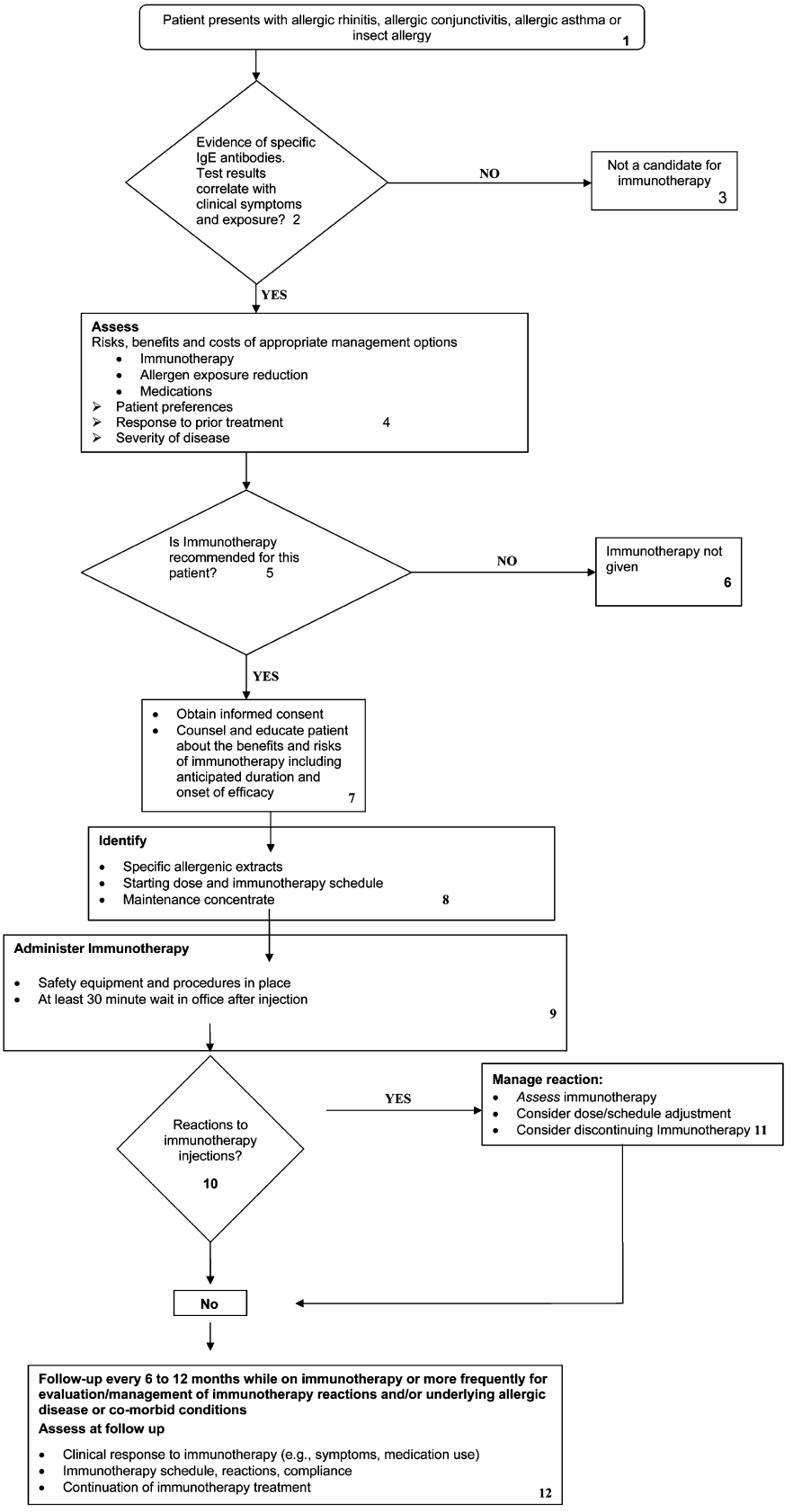


FIG 1. Algorithm for allergen immunotherapy.

might prevent the development of asthma in individuals with allergic rhinitis.[6-9] Evaluation of a patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic conjunctivitis, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for specific IgE antibody).[10]

Box 2

Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although *in vitro* testing for 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

Management of complex medical conditions, such as allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity, should include the careful evaluation of management 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 patient 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. On the basis of clinical considerations and patient 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 good candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy (VIT).

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 on the basis of 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 (see the Immunotherapy schedules and doses section). In general, the starting immunotherapy dose is 1000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 1000 to 4000 arbitrary units (AU; eg, for dust mite) or bioequivalent allergy units (BAU; eg, for grass) 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 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 referred to as *up-dosing*, *induction*, or the *dose-increase phase*) entails administration of gradually increasing doses during a period of approximately 14 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 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, in particular anaphylaxis. Patients should wait at the physician's office for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly, if they occur.

In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring 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. Some physicians recommend providing certain patients with epinephrine for self-administration in case of severe late reactions to immunotherapy injections.

Box 10

Injections of allergen immunotherapy extract can cause local or systemic reactions. Most severe reactions develop within 30 minutes after the immunotherapy injection, but reactions can occur after this time.

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 (anaphylaxis). Epinephrine is the treatment of choice in anaphylaxis, preferably when administered intramuscularly,[11] although subcutaneous administration is acceptable.[12]

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, see the practice parameters for anaphylaxis.[12]

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. After a severe systemic reaction, careful evaluation by the prescribing physician is recommended. For some patients, the immunotherapy maintenance dose might need to be reduced because of repeated systemic reactions to immunotherapy injections. The decision to continue immunotherapy should be re-evaluated after severe or repeated systemic reactions to allergen immunotherapy extracts.

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 doses, 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,[13] but others might experience a recurrence of their symptoms after discontinuation of allergen immunotherapy.[14] 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, and 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 on the basis of the patient's clinical response, disease severity, immunotherapy reaction history, and patient preference.

IMMUNOTHERAPY GLOSSARY

For more information on immunotherapy definitions, see the article by Kao.[15]

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 (pigments and salts; see the Allergen selection and handling section). Other terms used to describe the allergen immunotherapy extract include *allergen product*,[16] *allergy serum*, *allergen vaccine*,[17] 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.[18] Other terms that have been used for allergen immunotherapy include *hyposensitization*, *allergen-specific desensitization*, and the lay terms *allergy shots* or *allergy injections*.[15]

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

TABLE II. Allergen immunotherapy dose-calculation table

- Express weight per volume as a fraction: $\frac{1}{N}$ or 1:*N*.
- Calculate concentration of individual allergens in mixtures. If a mixture is made of equal amounts of N individual allergens to make a total concentration (C), the final concentration of an individual allergen (Ca) can be calculated by using the following equation:

$Ca = C \times \frac{1}{N} = \frac{C}{N}$ or *C*:*N*.

For example, if a mixture of equal amounts of 5 (N) allergens has a total concentration (C) of 100,000 BAU/mL, then the final concentration of each individual allergen (Ca) is: $Ca = \frac{C}{N} = \frac{100{,}000}{5} = 20{,}000\ BAU/mL$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{C}{N} = \frac{1/10}{5} = \frac{0.1}{5} = 0.02$ or $\frac{1}{50}$ or 1:50.

- Dilution of individual allergen: If an initial volume, Vi (in milliliters), of an individual antigen with concentration, Ci, is added to an allergen extract to make a final volume of Vf (in milliliters), the final allergen concentration (Ca) in the allergen extract mixture will be: $Ca = Ci \times \frac{Vi}{Vf}$.
- Final concentration of an allergen in a mixture of mixtures is determined by multiplying the initial concentration by the dilution factors from each mixing step.

For example, consider a mixture containing equal amounts of 5 (N) allergens with a total concentration (C) of 100,000 BAU/mL (first dilution). If an initial volume (Vi) of 0.5 mL of this mixture is further mixed with other components and diluent to make a final allergen extract mixture volume (Vf) of 5.0 mL (second dilution), the final concentration of an individual allergen (Ca) will be:

$$Ca = C \times \underbrace{\frac{1}{N}}_{\text{Mixture dilution}} \times \underbrace{\frac{Vi}{Vf}}_{\text{Allergen extract dilution}} = 100{,}000 \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{100{,}000}{50} = 2000\ BAU/mL$$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{1}{10} \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{1}{500}$ or 1:500.

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).

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 to 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-medicated 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 multiplied by volume of administered dose (see Table II for a dose-calculation table).

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, cat, 1000 BAU, [highest tolerated dose] vs 2000 BAU [projected effective dose]).

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 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 by a variety of immunologic transformations. Early definitions of the term immunotherapy included active and passive immunization for the purpose of improving 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 by means of induction of clonal deletion, anergy, immune tolerance, or immune deviation.

The *maintenance concentrate* is a preparation that contains individual 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 may not be the initially calculated projected effective dose.

The *maintenance goal* (or projected effective dose) is the allergen dose projected to provide therapeutic efficacy. The maintenance goal is based on published studies, but a projected effective dose has not been established for allergens. 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 the 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 large local reaction causing discomfort). The intervals between maintenance immunotherapy injections generally ranges 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 by means of immunoblotting or crossed allergoimmunoelectrophoresis.

For a definition of *projected effective dose*, see 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 test responses), and premedication with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similar high incidence of systemic reactions.

Off the board into one syringe is a phrase that describes a method of allergen immunotherapy preparation and administration that involves specifically mixing the patient's allergen immunotherapy injection in a single syringe, which is not recommended. This syringe might be inserted into more than one allergen extract vial, and this poses a risk of cross-contamination of the allergen extracts and might dull the needle with repeated penetration of the rubber stopper.

Shared specific patient vials is a method of allergen immunotherapy preparation and administration in which the allergy immunotherapy extract is withdrawn from a shared vial (eg, mixed vespids or dust mite mix). This is sometimes referred to as off the board, but it is distinct from the method of off the board into one syringe in that the syringe enters only one allergen extract vial.

INTRODUCTION

Immunity has been defined as protection against certain diseases. The initial immunotherapeutic interventions, which included the use of preventive vaccines and xenogenic 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 the field of allergen immunotherapy. From its humble empiric emergence in 1900, when ragweed injections were proposed as therapy for autumnal hay fever, allergen immunotherapy has progressed in both theory and practice from the passive immunologic approach to the active immunologic procedures pioneered by Noon[19] and Freeman.[20,21] 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 10 years. Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Some studies have suggested that allergen immunotherapy might prevent the development of asthma in individuals with allergic rhinitis.[6-9]

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,[22-26] and it should be differentiated from unproved methods, such as neutralization-provocation therapy and low-dose subcutaneous regimens based on the Rinkel technique, which have been found to ineffective in a double-blind placebo-controlled study.[27,28]

SUMMARY STATEMENTS

Mechanisms of immunotherapy

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, defined as a relative decrease in allergen-specific responsiveness and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

Allergen extracts

Summary Statement 6: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. **A**

Summary Statement 7: Nonstandardized extracts might vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Summary Statement 8: 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**

Cross-reactivity of allergen extract. Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

Efficacy of immunotherapy

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Summary Statement 10: Immunotherapy is effective for 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**

Food allergy, urticaria, and atopic dermatitis. Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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**

Measures of efficacy. Summary Statement 12: 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**

Safety of immunotherapy

Reaction rates. Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

Timing of anaphylactic reactions to immunotherapy injections. Summary Statement 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

β-*Adrenergic blocking agents.* Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

Contraindications. Summary Statement 18: 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**

Reducing the risk of anaphylaxis to immunotherapy injections. Summary Statement 19: 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**

Patient selection

Clinical indications. Summary Statement 20: 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 depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Special precautions in patients with asthma. Summary Statement 21: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. **C**

Clinical indications for VIT. Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Summary Statement 23: Patients selected for immunotherapy should be cooperative and compliant. **D**

Allergen selection and handling

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted in vitro tests for specific IgE antibodies can also be used. **A**

Specific allergens. Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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, supported by the presence of specific IgE antibodies. **A**

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Dose selection. Summary Statement 30: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. **A**

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens, is recommended. **B**

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extract handling

STORAGE

Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

STORING DILUTE EXTRACTS

Summary Statement 34a: More dilute concentrations of allergen immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: 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 a number of 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. **B**

Immunotherapy schedules and doses

Summary Statement 35: A customized individual 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 be based on single or multiple allergens. **D**

Maintenance concentrate. Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

Recommended doses. Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

Effect of dilution on dose. Summary Statement 38: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. **A**

Dilutions of the maintenance concentrate. Summary Statement 39: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. **D**

Labeling dilutions. Summary Statement 40: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. **D**

Individualized treatment vials. Summary Statement 41: 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. The mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. **C**

Starting doses. Summary Statement 42: The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. **D**

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

Dose adjustments for systemic reactions. Summary Statement 44: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. **D**

Reductions during periods of exacerbation of symptoms. Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Dose adjustments for late injections. Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

Cluster schedules. Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. **C**

Rush schedules. Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. **A**

Systemic reactions and rush schedules. Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

Premedication and weekly immunotherapy. Summary Statement 50: Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

Premedication with cluster and rush immunotherapy. Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

Maintenance schedules. Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. **A**

Continuing care

TIME COURSE OF IMPROVEMENT

Summary Statement 53: Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **A**

FOLLOW-UP VISITS

Summary Statement 54: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. **D**

DURATION OF TREATMENT

Summary Statement 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

DOCUMENTATION AND RECORD KEEPING

Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. **D**

INJECTION TECHNIQUES

Summary Statement 57: Allergen immunotherapy extract injections should be administered with a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **D**

Summary Statement 58: The injection should be administered subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Location of allergen immunotherapy administration

Physician's office. Summary Statement 59: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Summary Statement 60: 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**

Other locations. Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **D**

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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**

Summary Statement 63: 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for his or her immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extract might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Special considerations in immunotherapy

Allergen immunotherapy in children. Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Pregnancy. Summary Statement 71: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. **C**

Immunotherapy in the elderly patient. Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy in patients with immunodeficiency and autoimmune disorders. Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

Alternative routes of immunotherapy

Sublingual and oral immunotherapy. Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no US Food and Drug Administration (FDA)–approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **A**

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Immunotherapy techniques that are not recommended. Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

MECHANISMS OF IMMUNOTHERAPY

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, which is defined as a relative decrease in allergen-specific responsiveness, and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

The immunologic changes associated with immunotherapy are complex, and the exact mechanism or mechanisms responsible for its' clinical efficacy are continually being elucidated. Data support the concept that successful immunotherapy is associated with a change to a T_H1 $CD4^+$ cytokine profile.[29-34] Data indicate that increased production of IL-12, a strong inducer of T_H1 responses, contributes to this shift.[33] Clinically successful immunotherapy has been reported to be associated with immunologic tolerance, which is defined as a relative decrease in antigen-specific responsiveness, immune deviation, or anergy. For example, lymphoproliferative responses to allergen are reduced with immunotherapy.[32] Successful immunotherapy results in generation of a population of T regulatory cells, which are $CD4^+CD25^+$ T lymphocytes producing IL-10, TGF-β, or both.[35-39] Regulatory T-cell release has been described in allergen immunotherapy with Hymenoptera venom,[35] grass pollen extract,[37] and house dust mites.[38] IL-10 reduces B-cell antigen-specific IgE and increases IgG4 levels; reduces proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicits tolerance in T cells by means of selective inhibition of the CD28 costimulatory pathway.[36,37]

Allergen immunotherapy has been shown to block both the immediate and late-phase allergic response.[40] Allergen immunotherapy has been shown to decrease the recruitment of mast cells, basophils, and eosinophils in the skin, nose, eye, and bronchial mucosa after provocation or natural exposure to allergens.[41]

In patients receiving immunotherapy, initially there is an increase in specific IgE antibody levels, followed by a gradual decrease to a level that is still higher than that present before treatment. Clinical improvement in many patients develops before decreases in their IgE antibody levels occur or in other patients whose IgE antibody levels never decrease, thereby demonstrating that efficacy is not dependent on reductions in specific IgE levels.[42,43] Immunotherapy does diminish the seasonal increase in specific IgE levels.[44] Despite the persistence of significant levels of specific IgE antibody levels, immunotherapy usually causes a reduction in 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.[45-48]

An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, has also been associated with immunotherapy. The properties of allergen-specific IgA have yet to be determined, and there is a weak correlation between the increase in allergen-specific IgG levels and immunotherapy's clinical efficacy.[30,49,50]

Immunotherapy might alter the affinity and specificity of allergen-specific IgG.[51,52] During the initial phase of ultrarush VIT, a change in IgG specificity (ie, a change in the set of epitopes dominantly recognized by IgG on wasp venom antigens) occurred concomitantly with early clinical tolerance and was seen within 12 hours of ultrarush VIT ($P < .001$).[51] 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 individuals.[52] This change in IgG specificity preceded the increase in IgG titers and was sustained for up to 6 months.[52]

Allergen-specific IgG induced from immunotherapy can block IgE-dependent histamine release and subsequent IgE-mediated antigen presentation to T cells.[53] This effect might be dependent on IgE, allergen concentration, and CD23, the low-affinity receptor for IgE.

Whereas 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.[37,53]

The relationship between these immunologic changes and immunotherapy efficacy is not completely understood.

ALLERGEN EXTRACTS

Summary Statement 6: 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 has 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.[2,18,54-56] 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.

United States–licensed extracts can be obtained in aqueous, glycerinated, lyophilized, and acetone-precipitated and alum-precipitated formulations. Some commonly used allergens are standardized. These include extracts for cat hair, cat pelt, *Dermatophagoides pteronyssinus*, *Dermatophagoides 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.[57] 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.

Most standardized extracts are labeled in BAU. Short ragweed potency units were originally based on the content of the major allergen Amb a 1. Ragweed potency is reported in FDA units and BAU. One FDA unit of Amb a 1 equals 1 μg of Amb a 1, and 350 units of Amb a 1/mL is equivalent to 100,000 BAU/mL. Cat extracts were also originally standardized based on the content of major allergen (Fel d 1), with 100,000 arbitrary units (AU) per milliliter containing between 10 to 19.9 FDA units of Fel d 1 per milliliter (1 FDA unit of Fel d 1 equals 2 to 4 μg of Fel d 1).[55,58,59] Subsequently, $ID_{50}EAL$ testing suggested that 100,000 AU/mL was equal to 10,000 BAU/mL.[60] Approximately 22% of individuals with cat allergy have specific IgE antibodies to cat albumin.[61] Cat pelt extracts have a greater amount of albumin than cat hair extracts.[60]

Dust mites were originally standardized in AU by means of inhibition radioimmunoassay (RIA), and subsequent $ID_{50}EAL$ testing indicated that the AU was bioequivalent to the BAU, and the original AU nomenclature was kept. Dust mite extracts are still labeled in AU.

Summary Statement 7: Nonstandardized extracts can vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Nonstandardized extracts are labeled as wt/vol, which expresses weight in grams per volume in milliliters; that is, a potency of 1:100 indicates that 1 g 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 with a particular wt/vol or PNU potency can have widely varying biologic activities.[62-64] Therefore they should not be considered equipotent.

Summary Statement 8: 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**

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. The major clinically relevant aeroallergens of North America are listed in Table III. Furthermore, nonrelevant allergens in such mixtures could act as sensitizers rather than as tolerogens.[65,66] The physician must therefore select only those aeroallergens for testing and treatment that are clinically relevant in a particular geographic area.

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, dog), insect (cockroach), and Hymenoptera venom source materials.

Cross-reactivity of allergen extract

Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

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. A summary of cross-reactivity patterns of the clinically relevant North American aeroallergens can be found in Fig 2. 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,[67] inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[68-75] Grasses in other subfamilies (eg, Bermuda, Bahia, and Johnson) show greater diversity and should be evaluated separately.[76-78] Bermuda and Johnson grasses are increasingly important in the South,

TABLE III. The major clinically relevant aeroallergens of North America*

- Tree pollen
  - Chinese elm *(Ulmus parvifolia)*†‡; Siberian elm *(Ulmus pumila)*†‡; American elm *(Ulmus Americana)*†‡
  - Red oak *(Quercus rubra)*†; White oak *(Quercus alba)*†
  - Paper birch *(Betula papyrifera)*
  - Alder *(Alnus rubra)*
  - Box elder *(Acer negundo)*†; Red maple *(Acer rubra)*†
  - Eastern cottonwood *(Populus deltoides)*
  - Sycamore *(Platanus occidentalis)*
  - White ash *(Fraxinus americana)*†; Olive *(Olea europaea)*†‡
  - Black walnut *(Juglans nigra)*
  - Mulberry *(Morus rubra)*
  - Mountain cedar *(Juniperus ashei)*
  - Pecan *(Carya illinoensis)*
- Grass pollen
  - Rye *(Lolium perenne)*§‖
  - Timothy *(Phleum pratense)*§‖
  - Meadow fescue *(Festuca elatior)*§‖
  - Bermuda *(Cynodon dactylon)*‖
  - Johnson *(Holcus halepensis)*
  - Bahia *(Paspalum notatum)*
- Weed pollen
  - Short ragweed *(Ambrosia artemisiifolia)*‖
  - English (narrow leaf) plantain *(Plantago lanceolata)*
  - Mugwort *(Artemisia vulgaris)*
  - Russian thistle *(Salsola kali)*
  - Burning bush *(Kochia scoparia)*
  - Sheet (red) sorrel *(Rumex asetosella)*
  - Red root pigweed *(Amaranthus retroflexus)*
- Indoor aeroallergens
  - Cat epithelium *(Felis domesticus)*‖
  - Dog epithelium *(Canis familiaris)*
  - Arthropods (domestic mites: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*)‖
  - Insects (German cockroach: *Blattella germanica*)
- Fungi
  - *Alternaria alternata*¶
  - *Cladosporium* (*C cladosporioides*, *C herbarum*)¶
  - *Penicillium* (*P chrysogenum*, *P expansum*)¶
  - *Aspergillus fumigatus*¶
  - *Epicoccum nigrum*, *Drechslera* or *Bipolaris* type (eg, *Helminthosporium solani*)¶

*Compiled and selected in collaboration with the AAAAI Immunotherapy Committee Allergen Subcommittee for the identification of 35 key allergens of North America.
†Extensive cross-reaction of species within the genus.
‡Apart from regional prevalence, they are limited to local sites with substantial stands of these trees.
§Extensively cross-react with one another and bluegrass, orchard, red top, and sweet vernal.
‖Allergens for which standardized extracts are commercially available.
¶Species that are widely distributed and clinically important.

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.[79-82] 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.[83-85] Significant cross-reactivity between Betulaceae pollens and oak of the Fagaceae family has been demonstrated with percutaneous skin testing.[75] RAST inhibition studies have shown cross-inhibition between oaks and other *Fagales* species.[86] IgE immunoblot inhibition experiments have demonstrated that the *Fagales* species might be strongly inhibited by birch species.[87] The use of one of the locally prevalent members (eg, birch and alder) should be adequate.[88]

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.[89,90] Maple and box elder trees are found throughout the United States, except for the arid southwest. Although in the same genus as maple, *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,[91,92] and there are allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.[93]

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.[94] Similarly, Chenopod-Amaranth families have wide ranges in the western regions but are present throughout North America.[95] Current information on cross-reactivity of these families is limited.[96-98] 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.[99] The use of a single Amaranth extract should be sufficient to cover this family.[100,101] Similarly, *Atriplex* species (eg, saltbushes and scales) show near identity, and use of a single member is adequate. 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,

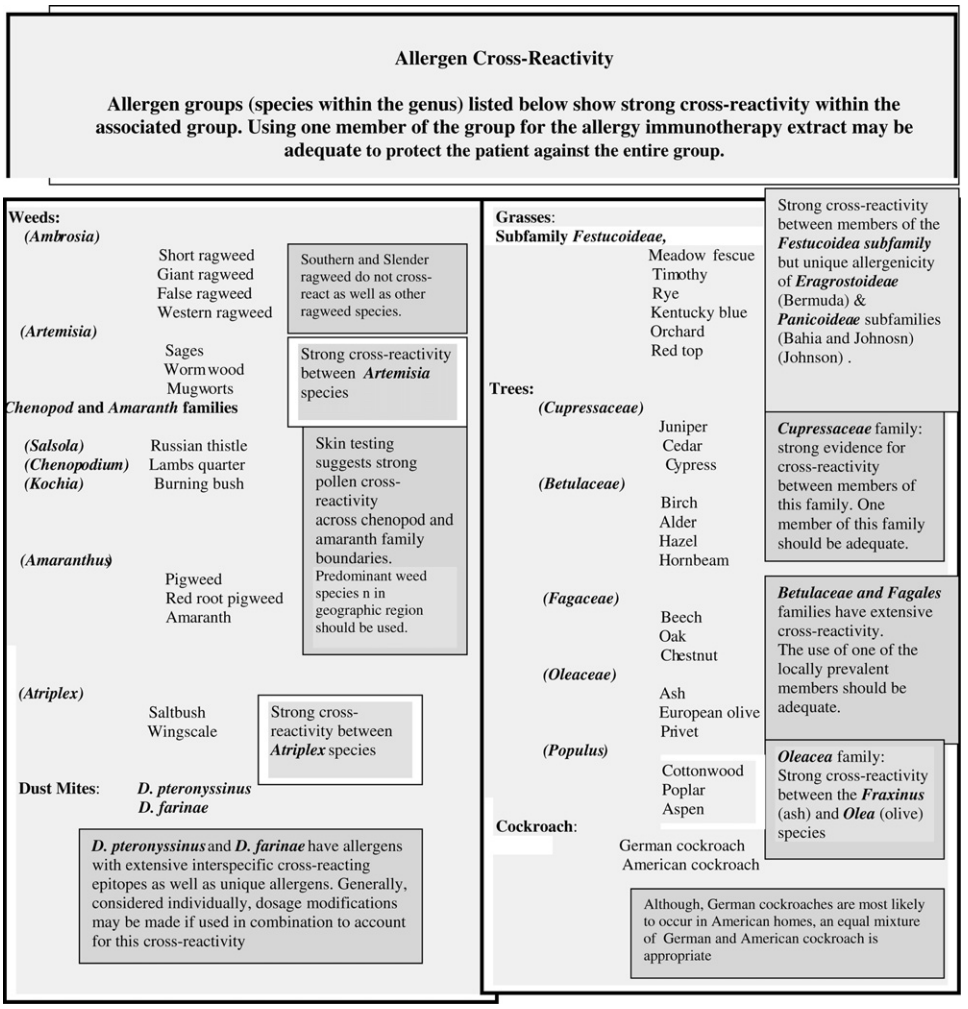


FIG 2. Patterns of allergen cross-reactivity.

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*).

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.[102,103] Stinging Hymenoptera insects occur throughout the United States; the fire ant is found only in Gulf Coast states, Texas, and some other southern and western states. Commercial venom extracts are available for some Hymenoptera species, except the fire ant, for which only whole-body extract is available.

EFFICACY OF IMMUNOTHERAPY

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity

Summary Statement 10: Immunotherapy is effective for 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.[104-111] Immunotherapy is effective for the treatment of allergic rhinitis[107] (including ocular symptoms[112,113]), allergic asthma,[104,109,111,114,115] and stinging insect hypersensitivity[108,116] and is effective in both adults and children.[117-124] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollens,[13,125-132] fungi,[133-138] animal allergens,[22,25,26,139-143] dust mite,[114,115,144-153] and cockroach.[154] There have been no controlled trials of fire ant whole-body extract, but it does appear to be effective in

TABLE IV. Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy

Outcome measure	House dust mite	Other allergens*†
Symptomatic improvement	2.7 (1.7-4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2-7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50)	5.5 (2.8-10.7)

Data are used with permission from Abramson et al.[104]
ND, Not done.
*Odds ratio (95% CI).
†Pollen, mold, or animal dander.

uncontrolled trials.[155-157] 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. A number of studies have also demonstrated a significant improvement in quality of life, as measured by using standardized questionnaires.[24,158-161] The magnitude of the effect depends on the outcome that is used (Table IV). For dust mite, the effect size ranges from a 2.7-fold improvement in symptoms to a 13.7-fold reduction in bronchial hyperresponsiveness. 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.[110] 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[107] and asthma[104,109,111] have been performed to deal with the issue of power. One review of 75 trials involving 3188 asthmatic patients found that, overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyperreactivity after immunotherapy, and it would have been necessary to treat 4 patients (95% CI, 3-5) with immunotherapy to avoid 1 deterioration in asthma symptoms and 5 (95% CI, 4-6) patients to avoid 1 requiring increased medication.[111] These meta-analyses strongly support the efficacy of allergen immunotherapy. Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued[13,162,163] and might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6,9,122,162-165] Allergen immunotherapy might also prevent the development of new allergen sensitivities in monosensitized patients.[120,166,167]

Food allergy, urticaria, and atopic dermatitis

Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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 use of allergen immunotherapy for individuals with the potential for IgE-mediated (anaphylaxis) reactions to foods should be regarded as investigational at this time.[168-171] There have been 2 investigational studies demonstrating efficacy in food hypersensitivity, the first using aqueous subcutaneous injections to peanut and the second using sublingual immunotherapy to hazelnut.[171-173]

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 a modified peanut extract is needed for clinical application of this method of treatment.[171] There is currently no FDA-approved formulation for sublingual immunotherapy, and this route of allergen immunotherapy is currently considered investigational at this time (see Summary Statement 73).

At the present time, there is not enough evidence to support food immunotherapy.

There is no evidence supporting the efficacy of immunotherapy for individuals with chronic urticaria, angioedema, or both.

There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[174-176] 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 ($P = .0379$) and topical corticosteroid use ($P = .0007$).[174]

The potential for benefit in symptoms related to oral allergy syndrome with the cross-reacting inhalant immunotherapy, which includes cross-reacting 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 subcutaneous immunotherapy directed against birch tree,[177] whereas another double-blind, double-dummy, placebo-controlled study comparing the effect of subcutaneous immunotherapy with sublingual immunotherapy 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, medication use, and decrease in IgE reactivity.[178] More investigation is required to substantiate the contention that benefits in oral symptoms will occur with immunotherapy.

Measures of efficacy

Summary Statement 12: 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. Objective measures, such as increase in allergen-specific IgG levels and decreased skin test reactivity, as measured by skin test titration, are changes generally associated with effective immunotherapy but, at present, are not practical for routine clinical use.[147] Nonquantitative skin testing or *in vitro* 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 are not very reliable given the strong placebo-like effect (Hawthorne effect) associated with any treatment. A more objective means for determining efficacy as validated in controlled clinical studies is the use of clinical symptom scores and the amount of medication required to control symptoms and maintain peak flow rates or pulmonary function tests within acceptable limits. Successful immunotherapy often results in a reduction in medication. Sequential measurement of disease-specific quality of life also might be helpful.

SAFETY OF IMMUNOTHERAPY

Reaction rates

Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Large local reactions associated with allergen immunotherapy are fairly common, with a frequency ranging from 26% to 86% of injections.[179] Two retrospective studies compared the effect of not adjusting immunotherapy dose based on large local reactions on the immunotherapy systemic reaction rate with dose-adjustment protocols.[179,180] There was a total of 12,464 injections administered with a dose-adjustment protocol in the 2 studies compared with 9542 injections administered with a no-dose-adjustment protocol. 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 for subsequent systemic reactions, 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 large local reactions, defined as 25 mm or larger, in patients who had experienced systemic reactions with age-, sex-, and allergen sensitivity–matched control subjects who had not had allergen immunotherapy systemic reactions found the rate of large local reactions was 4 times higher among the 258 patients who had subsequently experienced a systemic reaction compared with those who had never experienced a systemic reaction.[181] Patients who had experienced systemic reactions had 1573 large local reactions in 4460 visits (ie, 35.2% of visits) and 8081 injections (ie, 19.5% of injections) compared with the matched control group without systemic reactions who had 1388 large local reactions in 15,540 visits (8.9% per visit) and 26,259 injections (5.3% per injection; difference between groups, $P < .001$). Individual large local reactions were not predictive of future systemic reactions, but large local reactions preceded systemic reactions in approximately one third of the systemic reactions. These findings suggest that individuals with a greater frequency of large local reactions might be at greater risk for systemic reaction. Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy protocol modifications based on them are needed.

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

The prevalence of severe systemic reactions after allergen immunotherapy ranges from less than 1% of patients receiving conventional immunotherapy to greater than 36% of patients in some studies of patients receiving rush immunotherapy.[182,183]

In a recent survey of fatal and near-fatal reactions (NFRs) sent to physician members of the AAAAI, 273 of 646 respondents reported NFRs during the period of 1990-2001.[184]

The incidence of unconfirmed NFRs was 23 per year (5.4 events per million injections). Administration during the height of 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 angiotensin-converting enzyme 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 systemic reactions to subcutaneous immunotherapy over a 20-year period (1981-2000) during which 435,854 injections were administered to 4000 patients, 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.[185,186] In a prospective multicenter study there were 53 systemic reactions (0.3% of the doses) out of 17,526 administered doses in 18 (3.7%) of 423 patients.[187] 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 (21 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, there were 41 fatalities identified in the initial brief survey (20 directly reported and 17 with completed detailed questionnaire) from immunotherapy injections.[188] 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.[189,190] Therefore although severe systemic reactions to allergen immunotherapy are not common, serious systemic reactions (some fatal) can occur.

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

In the AAAAI survey of physician members on immunotherapy and skin testing, fatal reactions, and NFRs during the period of 1990-2001, 15 of the 17 fatalities had asthma, and in 9 patients asthma was considered the susceptibility factor that contributed to the fatal outcome.[188]

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.[184]

Administration during the peak pollen season (3 patients) and previous systemic reactions (4 patients) were cited as other contributing factors. Five fatalities occurred in outside medical facilities, and 2 fatalities occurred at home. No patients were receiving β-blockers; 1 patient was taking an angiotensin-converting enzyme inhibitor. In the most comprehensive evaluation of fatalities associated with allergen immunotherapy, from 1945-1987, there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[189] 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, with 73.3% of patients with an FEV_1 of less than 80% of predicted value experiencing 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 ($P < .0001$).[191] 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% of patients. These studies suggest that symptomatic asthma, severe asthma, or both might be a risk factor for immunotherapy.

In addition to symptomatic asthma and injections giving 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.[17] With the exception of dosing errors and 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 recent 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 or allergy symptom exacerbation, β-blocker use, change in health status (including pregnancy), or adverse reaction to previous allergen immunotherapy injection. The preinjection evaluation might also include a peak flow measurement to assess the airway function of asthmatic patients.

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 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

In a retrospective study the time to onset of a systemic reaction after an immunotherapy injection was less than 30 minutes in most cases.[189] A review of the literature indicates that 70% of systemic reactions occur within 30 minutes after an injection.[183] In the AAAAI 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.[184,188] 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.[190] 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 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.[192] In another prospective study 8% of systemic reactions occurred more than 2 hours after injection.[193]

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.[194]

Because most reactions that resulted from allergen immunotherapy occurred within 30 minutes after an injection, patients should remain in the physician's office for at least 30 minutes after receiving an injection, but longer waits are reasonable, as directed by the physician. In addition, patients who are at increased risk of a systemic reaction might need to carry injectable epinephrine. Such patients might also need to remain in the physician's office more than 30 minutes after an injection. 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.

β-Adrenergic blocking agents

Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

β-Blockade enhances pulmonary, cardiovascular, and dermatologic end-organ effects of mediators and increases mortality associated with experimental anaphylaxis induced by either immunologic or nonimmunologic mechanisms. Patients who are receiving β-adrenergic blocking medications might be at increased risk if they experience a systemic reaction to an allergen immunotherapy injection because the β-receptor blockade might attenuate the response to epinephrine.[195-202] Patients who are receiving β-blocking drugs were almost 9 times more likely to be hospitalized after an anaphylactoid reaction from radiocontrast media.[198] Although topical β-blockers have markedly less systemic β-antagonist effects than oral β-blockers, they still might exhibit some systemic β-antagonist effects. Whether topical β-blockers pose the same or a smaller risk than oral β-blockers in regard to the treatment of allergen immunotherapy–related systemic reactions is not known.

There have been very few studies that have examined the effect of β-blocker medications on allergen immunotherapy. A prospective 1-year study designed to determine whether patients taking β-blocker drugs were at increased risk of immunotherapy-induced systemic reactions found that there were 166 systemic reactions out of 56,105 injection visits in 3178 patients (68 were receiving a β-blocker).[203] The systemic reactions occurred in 144 (4.5%) patients, and only 1 of these patients was receiving a β-blocker medication. The authors calculated that by chance, 3.08 patients receiving the β-blocker medications drugs were expected to have had an systemic reaction and concluded that β-blocker medications did not increase the frequency of allergen immunotherapy systemic reactions ($P > .95$).

In another study of 1389 patients prescribed immunotherapy for Hymenoptera venom hypersensitivity who were followed for 34 months, there were 25 patients who received concomitant β-blocker medications.[204] Three (12%) of the 25 patients receiving β-blocker medications experienced systemic reactions during immunotherapy compared with 23 (16.7%) of 117 patients with cardiovascular disease not receiving β-blockers. Systemic reactions after a field sting or challenge occurred in 1 (14.3%) of 7 cardiovascular patients receiving β-blocker medications compared with 4 (13.8%) of 29 cardiovascular patients not receiving β-blocker medications. No severe reactions to immunotherapy or sting re-exposure were observed in patients receiving β-blockers medications.

Immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. In such cases, intravenous glucagon, which might reverse the refractory bronchospasm and hypotension by activating the adenyl cyclase directing and bypassing the β-adrenergic receptor, might be used if epinephrine has not been effective.[205,206] Prospective studies are necessary to clarify the magnitude of the risk of systemic reactions to allergens in patients who are receiving concomitant therapy with β-blockers, and a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy.

Contraindications

Summary Statement 18: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications

TABLE V. Actions to reduce the risk of anaphylaxis

- Assess the patient's general medical condition at the time of injection (eg, asthma exacerbation).
- Consider obtaining a PEFR before administration of the injection. If the PEFR is significantly less than the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.
- 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 with increased allergen sensitivity or those who have previously had a systemic reaction) might need to wait longer.
- Carefully evaluate any patient with a late reaction (eg, persistent large local reaction lasting >24 hours, systemic reaction occurring more than 30 minutes after the immunotherapy injection).
- 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.

PEFR, Peak expiratory flow rate measurement.

TABLE VI. Recommended equipment and medications to treat anaphylaxis

Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur. This should include at least the following equipment and medications:

- stethoscope and sphygmomanometer;
- tourniquet, syringes, hypodermic needles, and large-bore needles (14-gauge);
- aqueous epinephrine HCL 1:1000 wt/vol;
- equipment to administer oxygen by mask.
- intravenous fluid set-up;
- antihistamine for injection (second-line agents for anaphylaxis, but H_1 and H_2 antihistamines work better together than either one alone);
- corticosteroids for intravenous injection;
- vasopressor;
- equipment to maintain an airway appropriate for the supervising physician's expertise and skill.

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 venom hypersensitivity and cardiac disease being treated with β-blocker medications.

Reducing the risk of anaphylaxis to immunotherapy injections

Summary Statement 19: 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 extremely 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 or other health care professional appropriately trained in emergency treatment.

The 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. Epinephrine is the first-line treatment for anaphylaxis. 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.[12,207-213] It is important to administer epinephrine early in the management of anaphylaxis. 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 V and VI, respectively. Before allergen immunotherapy is chosen as a treatment, the physician should educate the patient about the benefits and risks of immunotherapy, as well as methods for minimizing risks. The patient also should be told that despite appropriate precautions, reactions might occur without warning signs or symptoms. Informed consent should include a discussion of the potential immunotherapy adverse reactions, and this discussion should be documented in the patient's medical record.

PATIENT SELECTION

Clinical indications

Summary Statement 20: Allergen immunotherapy should be considered for patients who have demonstrable

TABLE VII. Clinical indications for allergen immunotherapy

Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or both:
- symptoms of allergic rhinitis after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medications;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medication;
- coexisting allergic rhinitis and asthma;
- possible prevention of asthma in patients with allergic rhinitis

Symptoms of asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medication;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medications;
- coexisting allergic rhinitis and allergic asthma.

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);
- adults and children with a history of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.

evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic rhinitis.[107] Prospective, randomized, double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic asthma.[104,109,111]

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 proper identification and selection of component allergens on the basis of 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 (Table VII). The severity and duration of symptoms should also be considered in assessing the need for specific allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. In addition, specific allergen immunotherapy should be considered if the patient wishes to avoid long-term pharmacotherapy. Time lost from work, emergency department or physician's office visits, and responses to pharmacotherapy are important objective indicators of allergic disease severity.

Patients with allergic rhinitis who are unable to sleep because of symptoms or whose symptoms interfere with their work or school performance should be considered strong candidates for specific allergen immunotherapy. 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 considered. Unacceptable adverse effects of medications should also favor one's decision to initiate allergen immunotherapy. Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.[214]

Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued, and it might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6-9,122,162-165] These benefits of immunotherapy should be discussed with patients and might provide a clinical indication for immunotherapy for individual patients with allergic rhinitis.

Coexisting medical conditions should also be considered in the evaluation of a patient who might be a candidate for allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed with a combined aggressive regimen of allergen avoidance and pharmacotherapy and might also benefit from allergen immunotherapy.[215,216]

However, the patient's asthma must be stable before allergen immunotherapy is administered.[188,191]

Special precautions in patients with asthma

Summary Statement 21: 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 might be at increased risk for systemic reactions to immunotherapy injections.[182,188,191] Two surveys found that deaths from

immunotherapy were more common in symptomatic subjects with asthma.[188,189] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2,217]

Clinical indications for VIT

Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Systemic reactions to Hymenoptera stings, especially when associated with respiratory symptoms, cardiovascular symptoms, or both and positive skin test or *in vitro* test results for specific IgE antibodies, are a strong indication for allergen immunotherapy.[218] In the United States patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Several studies of patients with imported fire ant allergy have demonstrated the effectiveness of immunotherapy with whole-body extracts of fire ants.[155,156,219] 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. Patients younger than 16 years of age who present only with a cutaneous reaction to imported fire ant or Hymenoptera stings might not require immunotherapy.[218,220-222] In addition to allergen immunotherapy, patients with imported fire ant and Hymenoptera venom sensitivity should be instructed in how to best avoid insect stings, be prescribed epinephrine, and be taught how 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 the population that has not had a systemic reaction.[223] In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific IgE is recommended.[218] If the venom-specific IgE test result is also negative, it is recommended that the skin tests, venom-specific 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 IgE test result.[224] 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 re-stung. 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%).[225] 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 IgE test results who have had severe anaphylaxis to an insect sting.

Some patients who have negative venom skin test results and negative venom-specific IgE test results are reported to have had subsequent systemic reactions to stinging insects.[225-227] Controlled studies designed to evaluate the efficacy of immunotherapy in these patients have not been performed. There are very 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.[226] 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.

Summary Statement 23: 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.

ALLERGEN SELECTION AND HANDLING

Allergen selection

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

A careful history, noting environmental exposures and an understanding of the local and regional aerobiology of suspected allergens, such as pollen, fungi (mold), 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 skin or *in vitro* test results for specific IgE antibodies, provide good evidence that such exposures are relevant. Information concerning regional and local aerobiology is available on various Web sites or through the National Allergy Bureau at http://www.aaaai.org/nab. There are

no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma. 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 clinical history of an allergic disease.

There is no evidence to support the administration of immunotherapy based solely on results of specific *in vitro* 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.

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

The omission of clinically relevant allergens from an allergic patient's allergen immunotherapy extract contributes to decreased effectiveness of allergen immunotherapy. The 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 can make allergen immunotherapy less effective.

Knowledge of the total allergenic burden facing a patient and the realistic possibility of avoidance is important in determining whether allergen immunotherapy should be initiated. 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. Many individuals travel extensively for business or pleasure into different regions, and symptoms might worsen at these times. However, inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective. Determination of the significance of indoor allergens for a particular patient is harder because it is difficult to determine exposure in the home, school, and/or workplace. Historical factors, such as the presence of a furry animal in the home, a history of water damage and subsequent fungal exposure, or a history of insect infestation, might be helpful. However, such information is subjective and is often of uncertain reliability. In addition, some studies have demonstrated significant indoor levels of cat and dog allergen in households without pets[228] and significant levels of mouse allergen in suburban[229] and inner-city[230] homes 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 with increased asthma morbidity in inner-city children was found.[231] 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. Nevertheless, for most patients, determination of the clinical relevance of an allergen requires a strong correlation between the patient's history and evidence of allergen-specific IgE antibodies.

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted *in vitro* tests for specific IgE antibodies can also be used. **A**

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 the skin test results have demonstrated the efficacy of immunotherapy for relevant allergens.[25,26,112,130,134,135,140,141,149,154] 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 from skin testing in a highly sensitive individual.[232,233] In addition, skin tests might be difficult to perform in patients with dermatographism or atopic dermatitis. *In vitro* tests are particularly useful in such patients.

Studies indicate that skin testing is generally more sensitive than *in vitro* tests in detecting allergen-specific IgE.[234,235] Based on inhalation challenge test results, skin tests have shown specificity and sensitivity generally superior to those of *in vitro* tests. The comparability of skin tests and *in vitro* tests for specific IgE antibodies depends on the allergen being tested. For all of 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, prick testing is sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass[236] and cat,[237] are used. Intradermal/intracutaneous skin testing might be required for some allergen extracts. It is appropriate in some patients to use *in vitro* tests for specific IgE antibody as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. *In vitro* tests can also be used to define the allergens that should be used in allergen immunotherapy. If the allergy skin test result is negative and the *in vitro* test result is positive, a controlled challenge can be performed, and if the latter is positive, immunotherapy can be considered. 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 *in vitro* test results.

Specific allergens

Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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.[17,104,106,107,109] 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.[112,122] Because a particular pollen extract is a mixture of multiple glycoproteins, this suggests that mixing pollen allergens does not alter biologic activity.

Fungi (molds). Several studies with *Alternaria* and *Cladosporium* species suggest that allergen immunotherapy with fungi might be effective.[133-138] The allergen content of most mold extracts is highly variable.[238,239] However, there is evidence that proteolytic enzymes present in some mold extracts could digest other antigens, such as pollens, when combined in a mixture.[240] For this reason, it might be desirable to separate all pollen extracts from mold extracts when using mixtures.

Unfortunately, extracts for some potentially clinically important fungi are not available.[241] 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 distinguish 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.

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.

Because immunotherapy has been shown to be effective for cat[22,26,139-143,242] and dog,[25,141] the decision to include dog or cat allergen in an allergen immunotherapy extract should be considered in those circumstances in which there is exposure.

Dust mites and cockroach allergens. Crude house dust extract is generally an inappropriate substitute for house dust mite extract because the protein content measured is not restricted to dust mite allergens, nor does it necessarily guarantee inclusion of dust mite protein. Immunotherapy with standardized dust mite is generally more effective than that with crude house dust allergens. The house dust mites *D farinae* and *D 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, such as *Blomia tropicalis* and *Euroglyphus maynei*, partially cross-react with allergens from *Dermatophagoides* species. Only 50% of the projected amounts of each of the 2 house dust mites (*D pteronyssinus* and *D farinae*) need 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[144,147-149,151] 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. Dust mite hypersensitivity should particularly be considered in patients who have perennial symptoms exacerbated by a dusty environment at home, work, or both and periods of high humidity.

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. The major allergen of *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.[243] Immunotherapy with cockroach allergens is effective[154] and should 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.

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.[108,116,244] Efficacy has also been demonstrated with immunotherapy by using whole-body extracts of imported fire ants.[155,156]

Foods. Only a single clinical study accessing the efficacy and safety of subcutaneous immunotherapy with foods has been performed.[171,173] This study, which evaluated immunotherapy with peanut, found the incidence of systemic reactions, even during maintenance, was unacceptable. Thus there is no evidence to support the use of immunotherapy with food extracts. Currently, strict avoidance of the offending food is advisable, and subcutaneous immunotherapy for food allergy is not recommended.

Mixing of extracts

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Once the relevant allergens for each patient are identified, it is necessary to prepare a mixture that contains each of these allergens. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts. A number of 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 interactions between different types of allergens, when mixed, that could lead to degradation or unmasking of epitopes on exposure to proteolytic enzymes.

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Immunologic and 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.[71] 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 genera 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 the Allergen extract section, Fig 2, and the allergens and allergy diagnostic tests practice parameters).

Dose selection. Summary Statement 30: 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.[22-26,128,149,245] Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000 vol/vol).[28] A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy vaccine. Failure to do so might reduce the efficacy of immunotherapy. This occurs because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased (see the Immunotherapy schedules and doses section for further discussion and for recommended maintenance doses).

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as fungi (mold) and cockroach, from other extracts, such as pollens, is recommended. **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.[240,246,247] 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, and some weeds.[240,246,247] Cockroach had a similar deleterious effect on pollen extract potency.[246,248] Short ragweed appeared resistant to the effects of the proteolytic enzymes in one study,[240] 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.[247]

Dust mite extracts do not appear to have a deleterious effect on pollen extracts.[240,246,248] These studies suggest that pollen, dust mite, and cat extracts can be mixed together. 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. The evidence on mixing cockroach extract with other extracts is conflicting, and the clinical relevance of the changes is also unclear; therefore the clinician has the option of separating cockroach or not.

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 with lesser activities, such as pollen extracts.

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.

In this regard the number of separate injections that need to be given at each patient visit depends on whether all of the relevant extracts mixed into a single vial still deliver an optimal dose of each allergen. If mixing causes excessive dilution or if there are advantages to separating allergens into separate vials, then more than one vial might be necessary for successful immunotherapy.

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extracts are high-alert products that carry the risk for anaphylaxis. Policies, procedures, and processes intended for conventional drugs and medications might be highly 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 fatal anaphylactic reactions with allergenic products. 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. There are no reports of infection associated with allergen immunotherapy injections. Allergen vaccines are prepared by using sterile manufacturer's extracts and sterile diluents containing antibacterial constituents (usually phenol). A summary of the AAAAI/ACAAI/JCAAI proposed USP allergen immunotherapy extract preparation guidelines can be found in Table VIII.

TABLE VIII. AAAAI/ACAAI/JCAAI-proposed USP 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 below.*
   - 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.
2. **Physician responsibility**: A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in the preparation of immunotherapy using an aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files.
3. **Bacteriostasis**: Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if 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 the FDA-approved package insert 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 treatment with sanitizing agents containing alcohol and/or 70% isopropanol 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 the physical integrity of the vial.
10. **Labeling**: Immunotherapy vials are to be clearly labeled with the patient's name and 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.

*__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 media, such as from Valiteq (http://www.valiteq.com), 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.

Allergen immunotherapy extract handling

Storage. Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

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 a number of 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 extract, including reconstituted lyophilized extracts, should be stored at 4°C to minimize the rate of potency loss because storage at higher temperatures (eg, room temperature) can result in rapid deterioration.[249]

Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions (personal communication). These studies include actual shipments made by their carriers to places like

Phoenix in the summer and Alaska in the winter. 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.

Storing dilute extracts. Summary Statement 34a: More dilute concentrations of allergy immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than do more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: In determining the allergy vaccine expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of 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 allergen immunotherapy 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.[249,250]

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.[250] Phenol is a preservative added to extracts to prevent growth of microorganisms.

Phenol can denature proteins in allergen extracts.[251,252] Human serum albumin might protect against the deleterious effect of phenol on allergen extracts.[251] 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,[250,253] possibly through inhibition of the activity of proteolytic and glycosidic enzymes that are present in certain extracts. However, it is irritating when injected and should be diluted before beginning immunotherapy. Recommendations for extract stability are found in the manufacturers' product insert sheets. 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. The pain associated with glycerin increases in proportion to the glycerin concentration and injection volume, and the pain is proportional to the total injected dose of glycerin.[254] However, individual pain perception can vary substantially. Total glycerin doses of less than 0.05 mL rarely produce clinically important pain.

TABLE IX. Potency of selected manufacturer's extracts currently available

Extract	Potency
Cat hair and pelt	5000 and 10,000 BAU/mL
Dust mite	3000, 5000, 10,000, and 30,000 AU/mL
Bermuda grass	10,000 AU/mL
Short ragweed	1:10-1:20 wt/vol or 100,000 AU/mL
Other grasses*	10,000 and 100,000 BAU/mL
Other pollen	1:10 to 1:40 (wt/vol) or 10,000 PNU/mL
Molds	1:10 to 1:40 (wt/vol) or 20,000 to 100,000 PNU/mL

AU, Allergy unit; *BAU*, bioequivalent allergy unit; *PNU*, protein nitrogen unit.
*Perennial rye, Kentucky blue/June, timothy, sweet vernal, redtop, orchard, and meadow.

There have been few studies that have investigated the potency of dilutions of allergen extract mixture over time. Expiration dates for allergen extract dilutions are somewhat empiric and not strongly evidence based. A study undertaken by the AAAAI 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. Dust mite and cat at 1:10 and 1:100 vol/vol dilution were also stable in all conditions of storage over 12 months, as measured by an ELISA assay using 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.

IMMUNOTHERAPY SCHEDULES AND DOSES

Summary Statement 35: A customized individual 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 can be based on single or multiple allergens. **D**

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. Animal dander contains between 10 and 20 antigens,[255] house dust mites between 20 and 40 antigens,[256] and pollens between 30 and 50 antigens,[257,258] and fungal extract can contain as many as 80 antigens.[259]

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. This is designated as the patient's maintenance concentrate.

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. Standardized extracts are available with biologic potencies of 10,000 and 100,000 BAU for grasses; 5000 and 10,000 BAU for cat allergen; 5000, 10,000, or 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 wt/vol extracts (Table IX). 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.

Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

The highest concentration of an allergen extract mixture that is projected to be used as the therapeutically effective dose is called the maintenance concentrate. This should be prescribed individually for each patient by an allergist/immunologist. 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 individual manufacturer's extracts. Some patients might be unable to attain the projected therapeutically effective dose of the maintenance concentrate because of local reactions, systemic reactions, or both (eg, cat, 1000 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose]; see Table X for probable effective therapeutic dose range). Such patients might need weaker dilutions of their maintenance concentrate. Even so, 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 referred to as the maintenance dose. The consistent use of this nomenclature system is essential because errors in choosing the correct vial are a common cause of systemic reactions, especially when the patient transfers from one physician to another. Therefore it is important that standard terminology be adopted by all physicians who prescribe allergen immunotherapy.

Recommended doses

Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

The effective maintenance dose of immunotherapy for a particular patient must be individualized. To do this, the allergist/immunologist who prepares the allergen immunotherapy extract must balance the dose necessary to produce efficacy and the risk of reactions if such a dose is reached. The allergist/immunologist might need to prepare more than one maintenance concentrate to provide a therapeutic dose of each of the allergens for the polysensitized patient. Therapeutically effective doses for immunotherapy have been reported for some allergen extracts.[22,24,25,128,134,135,149,246,260,261] Effective doses have been determined for Hymenoptera venom, dust mite, cat allergen, dog, grass, and short ragweed (Table X).

Controlled studies demonstrate that the content of particular allergens in allergen immunotherapy extracts can be used to predict a therapeutic dose for those allergens, particularly when the extracts are standardized. For antigens 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. The therapeutically effective doses used in the most recent controlled clinical studies are the basis of the recommended dosage range of standardized extracts presented in Table X. 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 time that it is administered.[14]

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.[27] 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 risk of systemic reactions to immunotherapy injections with higher maintenance doses. The maintenance concentrate should be formulated to deliver a full therapeutic dose of each of its constituent components. However, some sensitive patients might not tolerate the targeted therapeutic dose, and their maintenance dose would be lower. Individuals 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 referred to as the maintenance dose.

Regardless of dose schedule, some patients are unable to progress to the predetermined maintenance dose because of large local or systemic reactions to the allergen

TABLE X. Probable effective dose range for allergen extracts US standardized units[a]

Antigen	Labeled potency or concentration[a,b]	Probable effective dose range
Dust mites: *D farinae* and *D pteronyssinus*[c]	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat[d]	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized[e]	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed[f]	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 μg of Amb a 1 1000-4000 AU Concentration of Amb a 1 is on the label of wt/vol extracts in FDA units[358]
Nonstandardized extract, dog[g]	1:10 to 1:100 wt/vol	15 μg of Can f 1
Nonstandardized extracts	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose

[a]Multiple studies have demonstrated that the efficacious dose for allergen immunotherapy is between 5 and 20 μg of the major allergen per injection. Only 2 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).

[b]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).

[c]There have been no dose-response studies with United States–licensed dust mite extracts, and dosing recommendations in AU value are extrapolated from published European studies that used aqueous[349] and alum-precipitated[149,151] extracts. 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.[149] The authors suggested the optimal maintenance dose was 7 μg of Der p 1. Corresponding doses were based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Extrapolating effective and safe doses in this manner might not be scientifically valid. *D farinae* and *D pteronyssinus* are similar in group 1 allergen content according to the FDA's current reference standards. 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*.

[d]The major cat allergen Fed d 1 is reported in FDA units, with 1 Fel d 1 unit equaling approximately 2 to 4 μg of Fel d 1.[55,58,59] The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 to 19.9 U/mL. One study demonstrated clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 dose in terms of decreased cat extract PD_{20}, titrated skin test results, and allergen-specific IgE and IgG levels.[350,351] In a recent study that investigated the efficacy in terms of immunologic changes of 3 doses of a United States–licensed cat extract (0.6, 3, and 15 μg) demonstrated that a significant effect on titrated skin prick test results, allergen-specific IgG4 levels, and $CD4^+$/IL-4 levels was only seen in the group treated with 15 μg of Fel d 1, although the 3-μg dose group did demonstrate a significant change in titrated skin test response and increase in cat-specific IgG4 levels.[22]

[e]There have been no dose-response studies with United States–licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,[130] alum-precipitated,[24,161] and calcium phosphate–precipitated grass pollen extracts.[352] One of these studies compared a dose of 2 μg with 20 μg of major timothy allergen (Phl p 5) and found clinical efficacy at both doses.[24] The efficacy was greater in the 20 μg of Phl p 5 dose, but the systemic reaction rate was also higher in the high-dose group. The package inserts for United States–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 BAU. Extrapolating effective and safe doses in this manner might not be scientifically valid. 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).

[f]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 suggested that 1 unit of Amb a 1 is equivalent to 1 μg of Amb a 1, and 350 Amb a 1 units/mL is equivalent to 100,000 BAU/mL.[60] The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2000 AU, with a range of 1000-4000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrated 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.[45] A ragweed dose-response study (0.6, 12.4, and 24.8 μg of Amb a 1) demonstrated efficacy, as measured by nasal challenge, at 12 and 24 μg of Amb a 1.[128] The efficacy of the 24-μg dose was not significantly better than the 12-μg dose, and the authors concluded that the optimal dose for ragweed extract was greater than 0.6 μg but not more than 12.4 μg of Amb a 1.

[g]Dog extracts are not standardized. However, one dose-response study with a United States–licensed acetone-precipitated dog extract investigated the efficacy of 3 doses (AP dog; Hollister-Stier, Spokane, Wash; 0.6, 3, and 15 μg) in terms of immunologic changes and found the dose of 15 μg of Can f 1 to be most efficacious.[25] 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 have assayed between 128 and 208 μg/mL (average Can f 1, 162 μg/mL [SD ± 26 μg/mL]; information provided by the extract manufacturer, Hollister-Stier).

immunotherapy extract. The evidence is not clear whether large local reactions are a potential risk for subsequent allergen immunotherapy systemic reactions.

Published studies do not indicate that an individual large local reaction is predictive of a subsequent systemic reaction.[179,180] However, one retrospective study found that individuals who have a history of repeated large local reactions (defined as >25 mm) might be at greater risk for a subsequent systemic reaction.[181]

The concept of highest tolerated dose does not apply for VIT, and all patients are expected to achieve the full recommended dose to achieve the necessary degree of protection. There are conflicting data over whether lower doses (50 μg) are less effective, but there are also data showing that 200 μg is more reliably effective.[245] In the case of VIT, patients are asked to tolerate more large local reactions to achieve the full dose, even though with inhalant immunotherapy the dose can be reduced for such large local reactions to minimize patient discomfort.

Effect of dilution on dose

Summary Statement 38: 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 vaccine, thereby limiting the ability to deliver a therapeutic effective dose for any given allergen.

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

Dilution from maintenance concentrate vaccine	Volume	Volume (mL)	Diluent volume (mL)	Final volume
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.

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 2000 BAU/mL, 2 mL of the manufacturer's extract (cat, 10,000 BAU/mL) can be added to 8 mL of diluent or 8 mL of other allergens, and the final concentration of cat will be 2000 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.

Dilutions of the maintenance concentrate

Summary Statement 39: 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 vol/vol 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, 1000 BAU or 100 BAU), but this system can be complicated if allergens with different potency units are used (eg, wt/vol, BAU, AU, or PNU) and make it difficult to easily interpret the vial label.

Instructions on how to prepare various allergen extracts 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.

Labeling dilutions

Summary Statement 40: 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, a number of 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 (vol/vol), a numbering system, a color-coding system, or an alphabetical system should be used. If this uniform labels 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.

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
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

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 3 and 4).

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 Appendix 2]).

Individualized treatment vials

Summary Statement 41: 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 (wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for 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). Labels on patient-specific vials can provide at least 2 patient identifiers (birth date and patient name), which would be consistent with the recommendations of the Joint Commission on Accreditation of Health Care Organizations National Patient Safety Goals: ''Goal 1: Improve the accuracy of patient identification by using at least two patient identifiers when providing care, treatment or services.''[5] 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 administration of the injection.[4,5]

In a survey of 1717 allergists endorsed by the AAAAI and JCAAI, 57% of the 476 respondents reported at least one wrong-patient injection, and 74% of the 473 respondents reported at least one wrong-dose injection.[4] 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 reasons why this might reduce incorrect injection errors. One reason was that patient-specific vials can be prepared in a quiet laboratory setting, which might provide substantially less distraction than the nurse in a room with a patient who is trying to concentrate only on drawing up the injection correctly. In addition, the specific components are mixed once with the preparation of individually prepared patient-labeled vials, whereas the mixing would be repeated on every injection visit if the allergen extract is withdrawn from different stock solutions, as it is in the off-the-board method. For safety reasons and to avoid cross-mixing of allergens removed from the manufacturer's extract, the mixing of antigens in the syringe (off the board) is not recommended.

Some allergists/immunologists prefer to administer immunotherapy doses drawn directly from a single stock dilution of individual allergens or common mixes (shared specific patient vials). In this way the immunotherapy dose is transferred to the patient without cross-contamination. If shared-patient (eg, mixed vespids and dust mite mix) vials are used, it is essential that policies and procedures are developed to verify that the correct dose from the correct vial is administered to the correct patient.

Starting doses

Summary Statement 42: The starting dose for build-up is usually a 1000- 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 slowly 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 1:1000 (vol/vol), although more diluted concentrations frequently are used for patients who are highly sensitive, as indicated by history or skin test reaction (see Appendix 3 for an example of a conventional immunotherapy schedule).

Frequency of build-up injections

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 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 2 times per week. 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 4 to 6 months, depending on the starting dilution and the occurrence of reactions. It is acceptable for patients to receive injections more frequently, provided there is adequate spacing between injections. The interval between injections is empiric but might be as short as 1 day without any increase in the occurrence of systemic reactions[262] if there is some urgency to achieve a maintenance dose (eg, allergy season is approaching) or for practical reasons (eg, patient's schedule). Alternatively, treatment schedules can be used that more rapidly achieve maintenance dosing. These cluster and rush dosing schedules are discussed in Summary Statements 47 through 49.

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 a number of 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).

Dose adjustments for systemic reactions

Summary Statement 44: 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 benefit/risk ratio justifies continuation of immunotherapy.

Reductions during periods of exacerbation of symptoms

Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Immunotherapy administered during periods of exacerbation of symptoms is considered a risk factor for immunotherapy.[17,184] Injections administered during periods when a patient is exposed to increased levels of allergen to which they are 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.[184] 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 sensitive, especially if their symptoms are poorly controlled.

Dose adjustments for late injections

Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

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 depends 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 Appendix 4 for an example of a dose-modification regimen for gaps in treatment).

Cluster schedules

Summary Statement 47: 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 (see Appendix 5).[22,26] 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. The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules.[145,263-266] The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.[267]

Rush schedules

Summary Statement 48: 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.[268] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.[191,269-272]

The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections over the course of 4 hours.[273] Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours.[274-276] 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 cluster[145,266] and rush[134,277] schedules.

Systemic reactions and rush schedules

Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

The advantages of rush immunotherapy come at a cost because there is an increased risk of local and systemic reactions. Systemic reaction rates have been reported to be

as high as 73% of patients, with the risk of such reactions reduced to 27% by premedication in one study.[272] Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing.[273]

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

Rush protocols for administration of Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions.[274-276,278,279]

Premedication and weekly immunotherapy

Summary Statement 50: Premedication can reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

There is concern that antihistamines taken before each injection with conventional immunotherapy might mask a minor reaction that would otherwise alert a physician to an impending systemic reaction. 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.[280] One study that compared terfenadine premedication with placebo premedication during rush VIT demonstrated greater clinical efficacy in the terfenadine-premedicated group in terms of subsequent responses to field stings or sting challenge.[281] There was also a significant difference in the systemic reaction rate between the 2 groups: 6 patients in the placebo-premedicated group had systemic reactions, whereas none of the patients in the terfenadine-premedicated group had systemic reactions ($P = .012$).

Unfortunately, patients might still have life-threatening anaphylaxis despite 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.

Premedication with cluster and rush immunotherapy

Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

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.[267] Premedication with a 3-day course of prednisone, an H_1 histamine receptor antagonist, and an H_2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.[272] In one study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on the safety and efficacy of rush immunotherapy, there was a 5-fold decrease in the risk of anaphylaxis in the group premedicated with omalizumab compared with the placebo premedication group.[282]

There are anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist, but there have been no published studies. Because the risk of a systemic reaction from rush VIT is relatively low, routine premedication before rush VIT is usually unnecessary.[274,276,278,279] In a study evaluating premedication with antihistamines and steroids for rush immunotherapy with imported fire ant venom, there was no statistically significant differences in the systemic reaction rates between the premedication and placebo premedication group (3.6% of the premedication group vs 6.7% of the placebo group, $P = .87$).[157]

Maintenance schedules

Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals 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 individuals might tolerate longer intervals between maintenance dose injections.

The interval between venom injections can be safely increased up to 8 weeks in some patients without loss of efficacy. 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.

Continuing care

Time course of improvement. Summary Statement 53: Clinical 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.[24,134,143,277] Improvement might not be observed for a number of reasons, including (1) failure to remove significant allergenic exposures (eg, a cat), (2) exposure to high levels of

allergen (eg, pollen or molds), (3) continued exposure to nonallergen triggers (eg, tobacco smoke), or (4) incomplete identification and treatment of clinically relevant allergens. 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 54: 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 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 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

The patient's response to immunotherapy should be evaluated on a regular basis. 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. 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.

There have been very 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 individuals.[283-285] However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported.[283,285] Nevertheless, systemic reactions to stings after discontinuing VIT were generally much milder than the pretreatment reactions and were rarely severe. Two studies did not find a difference in relapse rates between the patients treated for 3 years compared with those treated for 5 years,[283,286] but one of the studies noted that the small number of patients in the 3-year treatment group prevented them from making any conclusions about the risk of discontinuing treatment after 3 years.[283] However, one study found that patients who had experienced re-sting reactions after discontinuing VIT had received VIT for a significantly shorter duration (mean, 43.35 months) than those with continued protection (mean, 54.65 months; $P < .01$).[285] Another study reported that 5 years of VIT provided better immunologic and clinical outcomes than 2 to 4 years of treatment.[287]

Change in skin test reactivity did not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who experienced a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE.[286,288] Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment.[288] The relapse rate and the frequency of severe reactions were greater in patients who had a history of very severe reactions to stings before treatment, in patients who had systemic reactions during VIT (to a sting or a venom injection), in patients with honeybee allergy, and in those who had less than 5 years of treatment.

The duration of inhalant allergen immunotherapy efficacy has not been as extensively studied. Some studies have suggested 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 *(D pteronyssinus)* extract for 12 to 96 months.[14] 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.[13] There was a switch to placebo in half of 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. These studies demonstrate the uncertainty of the long-term benefit of inhalant immunotherapy after discontinuation.

Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained clinical remission after discontinuing inhalant immunotherapy, and 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 indication for continuation of immunotherapy can be found at http://www.aaaai.org or http://www.jcaai.org.

Documentation and record keeping. Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully 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 allergy immunotherapy and prescription forms can be found in the Appendix (Appendices 6-15), and these include examples of immunotherapy prescription and administration forms. These forms, along with examples of immunotherapy consent and instruction forms, can also be found at http://www.aaaai.org.

Injection techniques. Summary Statement 57: Allergen immunotherapy extract injections should be given using a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **C**

Immunotherapy should be given with a 26- to 27-gauge syringe with a half-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.[289-291]

If using shared specific patient vials (stock vials, such as mixed vespid or dust mite mix), a single dose should be drawn from each vial. Antigens from different vials should not be combined in a single syringe. Furthermore, extra care is needed to prevent using the wrong stock antigen.

Summary Statement 58: The injection should be given subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Each immunotherapy injection should be given in the posterior portion of the middle third of the upper 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.

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.

The syringe should be aspirated to check for blood return in the syringe before injecting. If blood is present, 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 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 syringe should be appropriately discarded. A fresh syringe and needle are necessary to determine whether a blood vessel has been entered.

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 could result in a local reaction.

LOCATION OF ALLERGEN IMMUNOTHERAPY ADMINISTRATION

Physician's office

Summary Statement 59: 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 to treat anaphylaxis should be in the immediate vicinity when immunotherapy injections are administered.

Summary Statement 60: 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.[292] 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.[184] 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 might be frequently necessary in the patient's immunotherapy schedule, as well as the patients total treatment program.

Other locations

Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **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.[292] The health care professional and staff 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, or allergy/asthma exacerbations at the time of allergen immunotherapy extract injection or poorly controlled asthma).

Appropriate adjustment of dose should be made as clinically indicated. The physician who prepared the patient's allergen immunotherapy extract should provide adequately labeled allergen immunotherapy extract vials, detailed directions regarding dosage schedule for build-up and maintenance, and instructions on adjustments that might be necessary under the following circumstances:

1. when providing patients with new vials;
2. during seasonal exposure to allergens that are in the patient's allergen vaccine, to which the patient is very sensitive, or both;
3. if the patient has missed injections; and
4. when reactions occur to the allergen immunotherapy extract.

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

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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 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 very 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 fully trained to administer the injection and to treat anaphylaxis if this should 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 supports (personnel, medications, supplies, and equipment) are more optimal for encouraging prompt recognition and treatment of anaphylaxis (Table V). 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.

Summary Statement 63: If a patient on 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for their immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extracts might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Patients often 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 brought from the previous physician (ie, an unchanged immunotherapy program) or one to be prepared by the current physician (ie, a new immunotherapy program).

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 full, clear, and detailed documentation of the patient's previous schedule and the contents of the allergen immunotherapy extract (see Appendices 7, 8, 11, 12, and 14 for examples of allergen immunotherapy prescription and administration forms and documentation guidelines for allergen immunotherapy forms). In addition, the patient's previous response to and compliance with this program 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 a schedule and the allergen immunotherapy extract, (2) the patient has shown significant improvement on this immunotherapy program, and (3) the contents of the allergen immunotherapy extract are appropriate for the area in which the patient is now living.

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, vaccine type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient's dose is not modified. This increased risk is due to the significant variability in content and potency of extracts and the variability in methods used by physicians to prepare the patient's maintenance concentrate and its dilutions. For example, the strength of a given concentration of nonstandardized extracts might vary significantly from vial to vial. The risk of systemic reactions in such a situation might be greater with nonstandardized extracts and allergen immunotherapy extracts that contain mixtures of allergens.

Therefore if the allergen immunotherapy extract is to be changed, the patient might need to be retested for specific IgE to the appropriate allergens 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 provided the interval of time since the last injection has not been too long. For lot changes from the same manufacturer, the physician can consider decreasing the dose by 50% to 90%. For changes in manufacturer and nonstandardized extracts, a greater decrease in dose might be necessary.

SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

Allergen immunotherapy in children

Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children

with allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Immunotherapy for children has been shown to be effective and often well tolerated,[137,242] although at least one study did not show efficacy.[293] 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.[294] In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (see the Patient selection section and Table VII). In recent studies children receiving allergen immunotherapy have demonstrated:

1. improvement in symptom control for asthma[117,119,121,122] and allergic rhinitis[118];
2. increased PC_{20} to histamine[121];
3. increased PC_{20} to cat and house dust mite allergens[121,149];
4. decreased risk of development of asthma[6,9,163-165];
5. decreased development of new sensitivities[120,166]; and
6. modification in release of mediators in children receiving immunotherapy that correlates with decreased clinical symptoms.[123]

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Although there is some disagreement about the role of allergen immunotherapy in children under the age of 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.[117,122] In children with allergic rhinitis, allergen immunotherapy might prevent the development of asthma.[6,9,163-165] However, allergen immunotherapy for inhalant allergens is usually not considered necessary in infants and toddlers because (1) there is 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 in pregnancy

Summary Statement 71: Allergen immunotherapy might be continued but is usually not initiated in the pregnant patient. **C**

The physician must be aware of the benefits and risks of immunotherapy in pregnant patients. The recommended precautions for prevention of adverse reactions are especially important in the pregnant patient. Allergen immunotherapy is effective in the pregnant patient. Thus allergen immunotherapy maintenance doses can be continued during pregnancy. Allergen immunotherapy is usually not initiated during pregnancy because of risks associated with systemic reactions and their treatment (ie, spontaneous abortion, premature labor, or fetal hypoxia). 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, and the patient is maintained on the dose that she is receiving at that time.

Immunotherapy in the elderly patient

Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy might be considered in the treatment of the elderly patient, but the benefit/risk assessment must be evaluated carefully in this population. Older 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. However, elderly patients may also benefit from allergen immunotherapy and age alone should not preclude the consideration of allergen immunotherapy.[295]

Immunotherapy in patients with immunodeficiency and autoimmune disorders

Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with immunodeficiency or autoimmune disorders. Therefore the decision to begin immunotherapy in patients with major humoral or cellular immune defects must be individualized. Concern about the increased risk of immunotherapy in such patients is largely hypothetical.

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

ALTERNATIVE ROUTES OF IMMUNOTHERAPY

Sublingual and oral immunotherapy

Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be

effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no FDA-approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **B**

Alternative routes of administration of allergen immunotherapy are ''a viable alternative to parenteral injection therapy'' in some cases.[106,296] Studies of oral immunotherapy have provided conflicting results for ragweed,[297] birch,[298] and cat[299] immunotherapy. The present dosage of oral immunotherapy extract is 20 to 200 times the parenteral injected dosage, which requires a cost assessment for this type of therapy. Furthermore, adverse effects have included gastrointestinal and oral reactions (50% in 1 study) that might preclude home therapy. Oral immunotherapy should be considered investigational at this time.

Optimal-dose (high-dose) sublingual swallow immunotherapy is effective in adults and children.[300-304] In a study of 855 patients with grass pollen allergy and allergic rhinitis randomized to placebo or one of 3 grass tablet doses, there was a significant reduction in symptom and medication scores in the highest-dose subgroup, who were treated for at least 8 weeks before the grass pollen season, compared with the placebo group (symptoms, 21%, $P = .0020$; medication use, 29%, $P = .0120$).[303]

Sublingual allergen studies have evaluated house dust, olive pollen, grass pollen, ragweed, birch, cat, latex, *Alternaria* species, and *Parietaria judaica*.[305-313] Sublingual immunotherapy has been shown to be effective in patients sensitized to 2 non–cross-reacting allergens, grass and birch.[314] It has been noted that the allergen is not degraded by saliva and that there is no direct sublingual absorption of allergen. Radiolabeled allergen has been detected after 48 hours in the sublingual region.[315,316] Alternative protocols, such as rush and ultra-rush (20 minutes) sublingual swallow[307,316,318] and no induction (build-up) phase,[301,303,317,319,320] have been studied. Several studies have suggested a relationship between dose and efficacy with sublingual immunotherapy,[303,310,321] but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. The majority of sublingual studies have demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both, but approximately 35% of the randomized, double-blind, placebo-controlled studies did not demonstrate efficacy in either parameter during the first year of treatment.[322] Further studies are needed to confirm the optimal dose for sublingual immunotherapy.

One of the potential advantages of sublingual immunotherapy is that it appears to be safe, even at very high doses (up to 500 times the usual monthly subcutaneous dose), and to be associated with a lower incidence of serious side effects.[310,320,323] This appears to apply to young children (<5 years), for whom there are prospective safety data[324,325] and a postmarketing survey.[326]



FIG 3. Sample of labels for allergen immunotherapy extract vials.

There have been no SLIT-related fatalities, but there have been 3 case reports of anaphylaxis caused by sublingual immunotherapy. One patient with latex hypersensitivity had anaphylactic shock 20 minutes after reaching the maximal dose on the fourth day of latex rush sublingual rush immunotherapy.[327]

The other 2 reported cases of SLIT anaphylaxis involved patients treated with multiple inhalant allergens. In one case a patient with allergic rhinitis and asthma who was prescribed a sublingual immunotherapy extract composed of multiple non–cross-reacting allergens (*Alternaria* species, dog, cat, ragweed mix, weed mix, and grass mix)[328] had generalized pruritis, followed by angioedema, shortness of breath, and dizziness, within a few minutes of administering 6 drops of the 1:100 vol/vol dilution on the third day of treatment. This episode was preceded by a milder systemic reaction the previous day (generalized pruritis). In the other case, a 13-year-old girl with allergic rhinitis and asthma had swelling of her lower lip 3 minutes after pollen drops, high fever, chest pain, nausea, and abdominal pain.[329] She was treated in the emergency department for anaphylaxis and hospitalized for observation. The reaction occurred 1 month after she had reached the maintenance dose during the peak of the spring season.

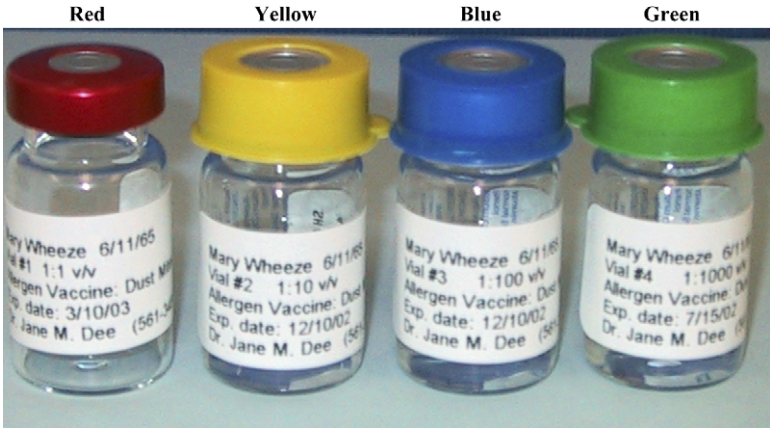


FIG 4. Sample set of color-coded vials of allergen vaccine.

There is currently no FDA-approved formulation for sublingual immunotherapy in the United States at this time, and this modality should be considered investigational. Current investigation of sublingual immunotherapy should not be confused with low-dose sublingual immunotherapy based on provocation neutralization testing or Rinkel-type skin testing.

Intranasal immunotherapy

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Based on controlled, well-designed studies, intranasal immunotherapy has been shown to improve the nasal symptoms of rhinitis.[330] Intranasal dry powder extract immunotherapy has been studied in grass,[330] birch,[331] *P judaica*,[332-334] and house dust mite[335] allergy. Clinical efficacy was noted in all of these studies. Nasal reactivity to allergen challenge was reduced, and only minor side effects were noted in 2 of the above studies. A 3-year study with *P judaica* reported to provide persistent benefits for up to 12 months after conclusion of allergen immunotherapy.[333] Local administration of nasal allergen in an aqueous solution for immunotherapy might be limited by the local side effects. Further studies in both pediatric and adult groups are needed. In human studies the antigen has been noted to appear in the serum within 15 to 30 minutes of administration, with a peak level occurring within 2 to 3 hours.[315] Some allergens have been reported to be retained in the nasal mucosa for up to 48 hours after administration. Intranasal immunotherapy is not currently available in the United States but has gained some acceptance in other parts of the world.

Immunotherapy techniques that are not recommended

Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

Low-dose regimens, including coseasonal low-dose immunotherapy for aeroallergens and the Rinkel low-dose titration techniques, are not effective.[27,28] Immunotherapy based on provocation–neutralization testing with food and aeroallergens and enzyme-potentiated desensitization is not effective.[336]

FUTURE TRENDS IN IMMUNOTHERAPY

Therapy with aeroallergen extracts will become more uniform (as is the current practice for insect venoms) as greater numbers of biologically standardized allergen extracts become available. The actual number of commercially available allergen extracts will be reduced based on consensus agreements about the regional prevalence of aeroallergens, their cross-allergenicity, and the relevance of their effect on human health in specific locales. Novel routes for more effective, convenient, and safer allergen immunotherapy are being investigated throughout the world.

For example, the sublingual route of administering allergen immunotherapy has been studied extensively in Europe. A meta-analysis confirmed its clinical effectiveness in allergic rhinitis,[302] and it has been reported to be effective in asthma as well.[337] Sublingual immunotherapy appears to have a very low risk of serious life-threatening systemic side effects, which might allow for home administration.[324,338] In some studies the clinical benefits of sublingual immunotherapy were not significant until the second year of treatment,[306,339] and comparisons suggest that the magnitude of the clinical benefit of sublingual immunotherapy might not be as great as that of subcutaneous immunotherapy.[311]

Trials with non–IgE-binding peptides containing T-cell stimulating peptides have been reported.[340] Site-directed mutagenesis has produced allergens with decreased IgE-binding capacity without decreased T-cell responses.[341,342]

Immunostimulatory sequences mimicking bacterial and viral DNA have been prepared that stimulate the innate immune system to direct T-cell responses toward

T_H1 rather than T_H2 phenotypes.[343] The results of clinical trials with a conjugate of the immunostimulatory sequence to the major allergen of ragweed, Amb a 1 (AIC), have been reported.[34,343] In a double-blind, placebo-controlled study of 25 adults who received 6 weekly injections of the AIC or placebo vaccine before ragweed season, the AIC group had better peak-season rhinitis scores on the visual analog scale ($P = .006$), peak-season daily nasal symptom diary scores ($P = .02$), and midseason overall quality-of-life scores ($P = .05$) than the placebo group during the first ragweed season, and this effect was observed in the subsequent ragweed season.[344]

Humanized anti-IgE mAb has been shown to have clinical effects in both allergic rhinitis and asthma.[345-348] Theoretically, this new therapeutic modality could be used as protective cover for clinical applications of rapid forms of immunotherapy. It is possible that preadministration of anti-IgE could provide a more effective protective effect than premedication with antihistamines and therefore permit a rush allergen immunotherapeutic regimen with reduced risk of serious systemic reactions.[282]

AUTHOR'S 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 2 systemic reaction grading systems (the European Academy of Allergy and Clinical Immunology's grading of severity for systemic side effects and the Portnoy method for numeric grading of reactions to allergen immunotherapy) can be found in the Appendix section. These forms can also be found along with examples of immunotherapy instruction and consent forms, preinjection health questionnaires, and indications for beginning and continuing immunotherapy forms at www.aaaai.org.

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APPENDIX 1. American College of Medical Quality's policy on the development and use of practice parameters for medical quality decision-making[1]

Practice parameters are strategies for patient management developed to assist health care professionals in clinical decision making. Practice parameters include standards, guidelines, and other patient management strategies. Standards are accepted principles for patient management. Guidelines are recommendations for patient management that identify a particular management strategy or a range of management strategies. Other strategies for patient management include practice policies and practice options. Practice parameters are to be used as screening tools to identify possible deviations from the applicable standards of care. Such parameters are not to be used as absolute standards or to profile or report on health care personnel. Parameters are designed to trigger a process in which possible deviations from the standard of care are identified as outlier practice patterns. Once a deviation from the parameter is identified, such a deviation should be referred to the appropriate qualified physician advisor or reviewer for a determination of medical necessity that conforms to the applicable standard of care. Parameters used in the day-to-day practice of clinical medicine should be clinically relevant. They should not be considered as substitutes for the standard of care but might contribute to its formulation.

Practice parameters must be developed, designed, and implemented only by board-certified, clinically practicing, specialty-matched physician advisors/reviewers with unrestricted medical licenses. Qualified nonphysicians might participate in the development of these parameters only in the areas in which their clinical expertise based on the standard of care is applicable. The health care personnel who develop these parameters should sign their names and date the final version as evidence of their participation and support. Practice parameters must be based on sound scientific research findings, professional literature, clinical experience and appropriate well-recognized methodologies and reflect professionally recognized national standards of care practiced in the clinical community of medicine. The development procedures followed, the participants involved, the evidence used, the assumptions and rationales accepted, and the analytic methods used should be meticulously documented, described, and made publicly available for national peer review. Parameters should be updated as needed.

Practice parameters are used as tools to enhance medical decision making but not as replacements for physicians' clinical judgment. They can be considered as means to enhance the performance of clinical and review personnel but not to replace them. It is below the standard of care of the medical review process to substitute qualified physician reviewer experts with unqualified reviewers who are using parameters.

APPENDIX 2. Examples of possible abbreviations for allergen immunotherapy extract 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

APPENDIX 3. 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

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

APPENDIX 4. Example of immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals (modification of the AAAAI skin testing and immunotherapy consent and instruction forms: immunotherapy administration instruction form, which can be found at http://www.aaaai.org)

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

- Up to 7 days, continue as scheduled (ie, if on weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection).
- Eight to 13 days after missed scheduled injection; repeat previous dose.
- Fourteen to 21 days after missed scheduled injection; reduce dose 25%.
- Twenty-one to 28 days after missed scheduled injection; reduce previous dose 50%.

Then increase dose each injection visit as directed on the immunotherapy schedule until therapeutic maintenance dose is reached.

This suggested approach to modification of doses of allergen immunotherapy because of gaps between treatment during the build-up phase is not based on retrospective or prospective published evidence, but it is presented as a sample for your consideration. The individual physician should use this or a similar protocol as a standard operating procedure for the specific clinical setting. A similar dose-reduction protocol should be developed for gaps in maintenance immunotherapy.

APPENDIX 5. Example of a cluster immunotherapy schedule[22,26]

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

APPENDIX 6. Recommended documentation for allergen immunotherapy prescription forms

The purpose of the allergen immunotherapy prescription form is to define the contents of the allergen immunotherapy extract in enough detail that it could be precisely duplicated. The following information should be on an immunotherapy prescription form:

Patient information:

- Patient name, patient number (if applicable), birth date, telephone number, and picture (if available) should be included.

Preparation information:

- Name of person and signature preparing the allergen immunotherapy extract should be included.
- Date of preparation should be recorded.
- Bottle name should be included (eg, trees and grass). If abbreviations are used, a 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 should be included.
- Volume of manufacturer's extract to add to achieve the projected effective concentration should be included. 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) should be included.
- Extract manufacturer should be included.
- Lot number should be included.
- Expiration date should be recorded and should not exceed the expiration date of any of the individual components.

APPENDIX 7. Allergen immunotherapy extract prescription 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:

_____
_____
_____
_____

_____ ____/____/____
Prescribing Physician Signature Date

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

APPENDIX 8. Maintenance concentrate prescription form

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: 6/10/06

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial **4** from Vial **1** on **8/30/06** Expiration date: **10/15/06**
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	Short ragweed	1:20 w/v G (150 Amb a1)	0.5ml	Greer	12345	1/01/08
2	Amaranthus Retroflexus	1:10 w/v G	0.5ml	H-S	6789	2/07/08
3	Ash	1:10 w/v G	0.5ml	Center	3333	3/17/08
4	Cat	10,000 BAU/ml G	2.00ml	ALO	9898	2/27/08
5	Timothy Grass	100,000 BAU/ml G	0.4ml	ALK	56789	7/09/08
6	Johnson Grass	1:10 w/v G	0.5ml	Greer	2434	7/20/08
7						
8						
9						
10						
Diluent	HSA		0.6ml	ALK	68597	12/08
Total Volume			5.00 ml			6/10/07

*** Components of mixes listed on a separate sheet**
**** Assumes 0.5 ml injection as target maintenance dose**

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

Specific Instructions:

_____

_____

Prescribing Physician Signature

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

APPENDIX 9. Labels for allergen immunotherapy extracts

Each vial of allergen immunotherapy extract should be labeled in a way that permits easy identification. Each label should include the following information (example in Figs 3 and 4):

- Appropriate patient identifiers might include the patient's name, patient's number, patient's picture, and birth date.
- The contents of the allergen immunotherapy extract in a general way should be included. The detail with which this can be identified depends on the size of the label and the number of allergens in the vial. Ideally, allergens should be identified as trees, grasses, weeds, mold, dust mite, cockroach, cat, and dog. Because of space limitations, it might be necessary to abbreviate the antigens (eg, T, G, W, M, DM, Cr, C, and D respectively [see Appendix 2]). A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate (vol/vol) should be recorded. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- The expiration date should be included.

APPENDIX 10. Allergen immunotherapy administration form recommended documentation

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

Patient information:

- Patient's name, date of birth, telephone number, and patient's picture (optional but helpful).

Allergen immunotherapy extract information:

- Allergen immunotherapy extract name and dilution from maintenance in vol/vol bottle letter (eg, A and B), bottle color, or number, if used.
- Expiration date of all dilutions.

Administration information in separate columns:

- Date of injection.
- Arm administered injection, which might facilitate determination of exact cause of local reaction.
- Projected build-up schedule.
- Delivered volume reported in milliliters.
- Description of any reactions. The details of any treatment given in response to a reaction would be documented elsewhere in the medical record and referenced on the administration form.
- *Patient's health before injection*. This can be performed through a verbal or written interview of the patient before administering the immunotherapy injection. The patient should be questioned about increased asthma or allergy symptoms, β-blocker use, change in health status (including pregnancy and recent infections), or an adverse reaction to a previous injection (including delayed large local reactions persisting through the next day). Patients with significant systemic illness generally should not receive an injection.
- *Antihistamine use*. Antihistamines are frequently a component of an allergy medication regimen, and it would be important to note whether a patient is taking an antihistamine on the day he or she receives his or her immunotherapy injection. For consistency in interpretation of reactions, it might be desirable for a patient to either take or avoid antihistamines on a regular basis on the days he or she receives immunotherapy. The physician should note on the form whether he or she recommends the patient consistently take an antihistamine on immunotherapy treatment days.
- *Peak flow reading*. Consider obtaining a peak expiratory flow rate measurement before administering an immunotherapy injection to asthmatic patients. Poorly controlled asthma is considered a risk factor for immunotherapy. Obtaining a peak expiratory flow rate measurement before the immunotherapy injection might help identify patients with symptomatic asthma. The patient's baseline peak expiratory flow rate should be provided on the form as a reference. Health care professionals administering immunotherapy injections should be provided with specific guidelines about the peak expiratory flow rate measurement for when an immunotherapy injection should be withheld and the patient referred for clinical evaluation.
- **Baseline blood pressure**. It might be useful to record the patient's blood pressure as a baseline for future reference.

APPENDIX 11. Allergen immunotherapy administration form

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 allergy or 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

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

Date to reorder: __/__/__

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 allergy or 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**	

APPENDIX 12. 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: _____
_____
Staff action taken (if any): _____

APPENDIX 13. 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.

APPENDIX 14. Allergen immunotherapy systemic reaction/anaphylaxis 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
__Epinephrine IM into 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	

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:
_____
_____
_____
_____

Clinical impression: True SR Questionable SR No SR

Systemic reaction severity classification: EAACI_____ **Portnoy** _____

Dosage adjustment? _____

Signatures_____ **RN** _____**MD/DO**

APPENDIX 15. Grading severity of allergen immunotherapy reactions: Two methods

1. **The European Academy of Allergy and Clinical Immunology grading of severity for systemic side effects***

Classification of systemic reactions

0 = No symptoms or nonspecific symptoms

I = Mild systemic reactions: symptoms—localized urticaria, rhinitis, or mild asthma (PF <20% decrease from baseline).

II = Moderate systemic reaction: symptoms—slow onset (>15 minutes) of generalized urticaria, moderate asthma, or both (PF < 40% decrease from baseline).

III = Severe (non–life-threatening) systemic reactions: symptoms—rapid onset (<15 minutes) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).

IV = Anaphylactic shock: symptoms—immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, and hypotension, for example.

2. **Portnoy method for numeric grading of reactions to allergen immunotherapy†**

Local

0+ = No significant reaction or small area of erythema less than the size of a half dollar without swelling or wheal formation

1+ = Erythema greater than the size of a half dollar, swelling or wheal formation, or both

Systemic

2+ = Systemic reactions: cutaneous only—might consist of a cutaneous eruption, such as urticaria

3+ = Systemic reaction: generalized pruritus, sneezing, or both—might consist of increased allergy symptoms, such as nasal congestion, sneezing, or pruritus, especially in the mouth or throat

4+ = Systemic reaction: pulmonary—consists of wheezing, shortness of breath, and tightness. Might be associated with decreased pulmonary function tests

5+ = Systemic reaction: anaphylaxis—a sensation of not feeling right is a frequent prelude; might consist of hypotension, laryngeal edema, severe wheezing, and cramping

6+ = Cardiopulmonary arrest

PF, Peak expiratory flow.

*Subcutaneous immunotherapy. Allergy 2006;61(suppl 82):5-13.

†Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80.

Allergen immunotherapy: A practice parameter second update

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

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the "Allergen immunotherapy: a practice parameter second 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 and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
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11. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999;83(suppl): S665–S700.
12. Diagnosis and management of urticaria: a practice parameter. Ann Allergy 2000;85(suppl):S521-S544.
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14. Symptom severity assessment of allergic rhinitis: part I. Ann Allergy 2003;91:105-14.
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16. Stinging insect hypersensitivity: a practice parameter update. J Allergy Clin Immunol 2004;114:869-86.
17. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol 2005;115(suppl):S483-S523.

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22. Contact dermatitis: a practice parameter. Ann Allergy Asthma Immunol 2006;97(suppl 2):S1-S38.

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

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Allergen immunotherapy: A practice parameter second update

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PREFACE

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

The objective of ''Allergen immunotherapy: A practice parameter second update'' is to optimize the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. 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's ''Policy on development and use of practice parameters for medical quality decision-making'' (Appendix 1).[1]

This document builds on the previous Joint Task Force document, ''Allergen immunotherapy: a practice parameter'' published in the *Annals of Allergy, Asthma and Immunology* in 2003.[2] The updated practice parameters draft was prepared by Drs Linda Cox, James Li, Hal Nelson, and Richard Lockey. The Joint Task Force reworked the initial draft into a working draft of the document. The project was exclusively funded by the 3 allergy and immunology societies noted above.

In preparation for the 2003 ''Allergen immunotherapy: a practice parameter'' and the second update, a comprehensive search of the medical literature was conducted with various search engines, including PubMed; *immunotherapy*, *allergic rhinitis*, *asthma*, *stinging insect allergy*, and related search terms were used. 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 second update'' was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the ACAAI, AAAAI, and JCAAI. In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for review and comments from members of the sponsoring organizations. 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 allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. This document also contains recommendations for the safe practice of allergen immunotherapy, including specific recommendations on the prevention and management of 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 or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. Symptoms of allergic conjunctivitis (eg, itchy watery eyes) are often considered part of allergic rhinitis or are included in the diagnosis of rhinoconjunctivitis. Particularly good candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures, those in whom it is important to avoid the potential adverse effects of medications, and those who wish to reduce the long-term use of medications. Immunotherapy is recommended for patients with a history of systemic reaction to Hymenoptera stings and specific IgE antibodies to Hymenoptera venom.

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.[3]

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. 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 *maintenance concentrate* should be used to identify the allergen immunotherapy extract that contains a therapeutic effective dose for each of its individual constituents (see the Immunotherapy schedules and doses section).

The term *manufacturer's extract* refers to the allergy extract purchased from the manufacturer. The terms *stock*, *full-strength*, and *concentrate* are ambiguous and should not be used. 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).

Allergen immunotherapy is effective when appropriate doses of the allergens are administered. ''Allergen immunotherapy: A practice parameter'' recommends that vials of allergen immunotherapy extracts should be prepared individually for each patient to enhance the individualization of therapy, reduce the risk of allergen cross-contamination, and reduce the risk of error in administration.[4,5] This parameter recommends the use of standardized allergen immunotherapy prescription and administration forms to improve the safety, uniformity, and standardization of allergen immunotherapy practice.[4,5] The suggested forms are found in the Appendix (Appendices 7, 8, 11, 12, and 14) and in the members' section of the www.aaaai.org Web site. The routine use of these standardized forms should improve the quality of immunotherapy practice.

Members' feedback comments on the recommended allergen extract dilution dating in the 2003 ''Allergen immunotherapy: A practice parameter'' led to an allergen immunotherapy extract dilution stability study designed by the AAAAI Immunotherapy and Allergy Diagnostics Committee and funded by the AAAAI Board of Directors. The study was designed to investigate the effect of time, temperature, and dilution of standardized allergen extract potency, and the results of this study were considered in this update.

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 3 years after publication. Requests for information about or an interpretation of these practice parameters should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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. Allergen immunotherapy

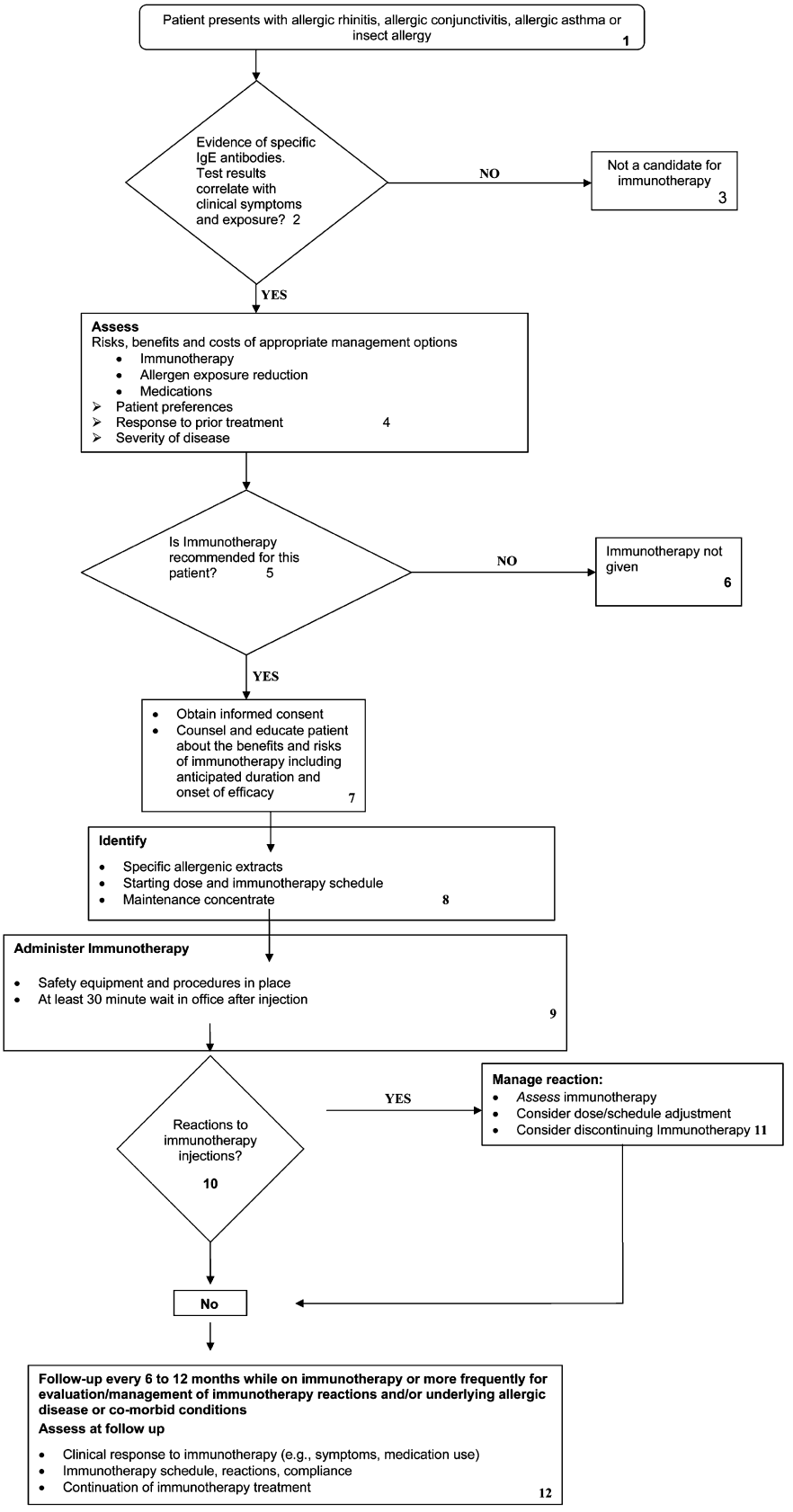


FIG 1. Algorithm for allergen immunotherapy.

might prevent the development of asthma in individuals with allergic rhinitis.[6-9] Evaluation of a patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic conjunctivitis, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for specific IgE antibody).[10]

Box 2

Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although *in vitro* testing for 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

Management of complex medical conditions, such as allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity, should include the careful evaluation of management 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 patient 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. On the basis of clinical considerations and patient 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 good candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy (VIT).

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 on the basis of 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 (see the Immunotherapy schedules and doses section). In general, the starting immunotherapy dose is 1000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 1000 to 4000 arbitrary units (AU; eg, for dust mite) or bioequivalent allergy units (BAU; eg, for grass) 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 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 referred to as *up-dosing*, *induction*, or the *dose-increase phase*) entails administration of gradually increasing doses during a period of approximately 14 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 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, in particular anaphylaxis. Patients should wait at the physician's office for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly, if they occur.

In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring 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. Some physicians recommend providing certain patients with epinephrine for self-administration in case of severe late reactions to immunotherapy injections.

Box 10

Injections of allergen immunotherapy extract can cause local or systemic reactions. Most severe reactions develop within 30 minutes after the immunotherapy injection, but reactions can occur after this time.

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 (anaphylaxis). Epinephrine is the treatment of choice in anaphylaxis, preferably when administered intramuscularly,[11] although subcutaneous administration is acceptable.[12]

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, see the practice parameters for anaphylaxis.[12]

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. After a severe systemic reaction, careful evaluation by the prescribing physician is recommended. For some patients, the immunotherapy maintenance dose might need to be reduced because of repeated systemic reactions to immunotherapy injections. The decision to continue immunotherapy should be re-evaluated after severe or repeated systemic reactions to allergen immunotherapy extracts.

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 doses, 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,[13] but others might experience a recurrence of their symptoms after discontinuation of allergen immunotherapy.[14] 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, and 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 on the basis of the patient's clinical response, disease severity, immunotherapy reaction history, and patient preference.

IMMUNOTHERAPY GLOSSARY

For more information on immunotherapy definitions, see the article by Kao.[15]

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 (pigments and salts; see the Allergen selection and handling section). Other terms used to describe the allergen immunotherapy extract include *allergen product*,[16] *allergy serum*, *allergen vaccine*,[17] 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.[18] Other terms that have been used for allergen immunotherapy include *hyposensitization*, *allergen-specific desensitization*, and the lay terms *allergy shots* or *allergy injections*.[15]

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

TABLE II. Allergen immunotherapy dose-calculation table

- Express weight per volume as a fraction: $\frac{1}{N}$ or 1:*N*.
- Calculate concentration of individual allergens in mixtures. If a mixture is made of equal amounts of N individual allergens to make a total concentration (C), the final concentration of an individual allergen (Ca) can be calculated by using the following equation:

$Ca = C \times \frac{1}{N} = \frac{C}{N}$ or *C*:*N*.

For example, if a mixture of equal amounts of 5 (N) allergens has a total concentration (C) of 100,000 BAU/mL, then the final concentration of each individual allergen (Ca) is: $Ca = \frac{C}{N} = \frac{100{,}000}{5} = 20{,}000\ BAU/mL$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{C}{N} = \frac{1/10}{5} = \frac{0.1}{5} = 0.02$ or $\frac{1}{50}$ or 1:50.

- Dilution of individual allergen: If an initial volume, Vi (in milliliters), of an individual antigen with concentration, Ci, is added to an allergen extract to make a final volume of Vf (in milliliters), the final allergen concentration (Ca) in the allergen extract mixture will be: $Ca = Ci \times \frac{Vi}{Vf}$.
- Final concentration of an allergen in a mixture of mixtures is determined by multiplying the initial concentration by the dilution factors from each mixing step.

For example, consider a mixture containing equal amounts of 5 (N) allergens with a total concentration (C) of 100,000 BAU/mL (first dilution). If an initial volume (Vi) of 0.5 mL of this mixture is further mixed with other components and diluent to make a final allergen extract mixture volume (Vf) of 5.0 mL (second dilution), the final concentration of an individual allergen (Ca) will be:

$$Ca = C \times \underbrace{\frac{1}{N}}_{\text{Mixture dilution}} \times \underbrace{\frac{Vi}{Vf}}_{\text{Allergen extract dilution}} = 100{,}000 \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{100{,}000}{50} = 2000\ BAU/mL$$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{1}{10} \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{1}{500}$ or 1:500.

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).

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 to 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-medicated 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 multiplied by volume of administered dose (see Table II for a dose-calculation table).

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, cat, 1000 BAU, [highest tolerated dose] vs 2000 BAU [projected effective dose]).

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 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 by a variety of immunologic transformations. Early definitions of the term immunotherapy included active and passive immunization for the purpose of improving 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 by means of induction of clonal deletion, anergy, immune tolerance, or immune deviation.

The *maintenance concentrate* is a preparation that contains individual 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 may not be the initially calculated projected effective dose.

The *maintenance goal* (or projected effective dose) is the allergen dose projected to provide therapeutic efficacy. The maintenance goal is based on published studies, but a projected effective dose has not been established for allergens. 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 the 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 large local reaction causing discomfort). The intervals between maintenance immunotherapy injections generally ranges 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 by means of immunoblotting or crossed allergoimmunoelectrophoresis.

For a definition of *projected effective dose*, see 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 test responses), and premedication with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similar high incidence of systemic reactions.

Off the board into one syringe is a phrase that describes a method of allergen immunotherapy preparation and administration that involves specifically mixing the patient's allergen immunotherapy injection in a single syringe, which is not recommended. This syringe might be inserted into more than one allergen extract vial, and this poses a risk of cross-contamination of the allergen extracts and might dull the needle with repeated penetration of the rubber stopper.

Shared specific patient vials is a method of allergen immunotherapy preparation and administration in which the allergy immunotherapy extract is withdrawn from a shared vial (eg, mixed vespids or dust mite mix). This is sometimes referred to as off the board, but it is distinct from the method of off the board into one syringe in that the syringe enters only one allergen extract vial.

INTRODUCTION

Immunity has been defined as protection against certain diseases. The initial immunotherapeutic interventions, which included the use of preventive vaccines and xenogenic 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 the field of allergen immunotherapy. From its humble empiric emergence in 1900, when ragweed injections were proposed as therapy for autumnal hay fever, allergen immunotherapy has progressed in both theory and practice from the passive immunologic approach to the active immunologic procedures pioneered by Noon[19] and Freeman.[20,21] 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 10 years. Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Some studies have suggested that allergen immunotherapy might prevent the development of asthma in individuals with allergic rhinitis.[6-9]

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,[22-26] and it should be differentiated from unproved methods, such as neutralization-provocation therapy and low-dose subcutaneous regimens based on the Rinkel technique, which have been found to ineffective in a double-blind placebo-controlled study.[27,28]

SUMMARY STATEMENTS

Mechanisms of immunotherapy

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, defined as a relative decrease in allergen-specific responsiveness and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

Allergen extracts

Summary Statement 6: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. **A**

Summary Statement 7: Nonstandardized extracts might vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Summary Statement 8: 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**

Cross-reactivity of allergen extract. Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

Efficacy of immunotherapy

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Summary Statement 10: Immunotherapy is effective for 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**

Food allergy, urticaria, and atopic dermatitis. Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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**

Measures of efficacy. Summary Statement 12: 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**

Safety of immunotherapy

Reaction rates. Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

Timing of anaphylactic reactions to immunotherapy injections. Summary Statement 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

β-*Adrenergic blocking agents.* Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

Contraindications. Summary Statement 18: 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**

Reducing the risk of anaphylaxis to immunotherapy injections. Summary Statement 19: 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**

Patient selection

Clinical indications. Summary Statement 20: 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 depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Special precautions in patients with asthma. Summary Statement 21: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. **C**

Clinical indications for VIT. Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Summary Statement 23: Patients selected for immunotherapy should be cooperative and compliant. **D**

Allergen selection and handling

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted in vitro tests for specific IgE antibodies can also be used. **A**

Specific allergens. Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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, supported by the presence of specific IgE antibodies. **A**

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Dose selection. Summary Statement 30: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. **A**

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens, is recommended. **B**

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extract handling

STORAGE

Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

STORING DILUTE EXTRACTS

Summary Statement 34a: More dilute concentrations of allergen immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: 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 a number of 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. **B**

Immunotherapy schedules and doses

Summary Statement 35: A customized individual 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 be based on single or multiple allergens. **D**

Maintenance concentrate. Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

Recommended doses. Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

Effect of dilution on dose. Summary Statement 38: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. **A**

Dilutions of the maintenance concentrate. Summary Statement 39: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. **D**

Labeling dilutions. Summary Statement 40: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. **D**

Individualized treatment vials. Summary Statement 41: 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. The mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. **C**

Starting doses. Summary Statement 42: The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. **D**

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

Dose adjustments for systemic reactions. Summary Statement 44: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. **D**

Reductions during periods of exacerbation of symptoms. Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Dose adjustments for late injections. Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

Cluster schedules. Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. **C**

Rush schedules. Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. **A**

Systemic reactions and rush schedules. Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

Premedication and weekly immunotherapy. Summary Statement 50: Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

Premedication with cluster and rush immunotherapy. Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

Maintenance schedules. Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. **A**

Continuing care

TIME COURSE OF IMPROVEMENT

Summary Statement 53: Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **A**

FOLLOW-UP VISITS

Summary Statement 54: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. **D**

DURATION OF TREATMENT

Summary Statement 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

DOCUMENTATION AND RECORD KEEPING

Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. **D**

INJECTION TECHNIQUES

Summary Statement 57: Allergen immunotherapy extract injections should be administered with a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **D**

Summary Statement 58: The injection should be administered subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Location of allergen immunotherapy administration

Physician's office. Summary Statement 59: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Summary Statement 60: 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**

Other locations. Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **D**

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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**

Summary Statement 63: 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for his or her immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extract might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Special considerations in immunotherapy

Allergen immunotherapy in children. Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Pregnancy. Summary Statement 71: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. **C**

Immunotherapy in the elderly patient. Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy in patients with immunodeficiency and autoimmune disorders. Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

Alternative routes of immunotherapy

Sublingual and oral immunotherapy. Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no US Food and Drug Administration (FDA)–approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **A**

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Immunotherapy techniques that are not recommended. Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

MECHANISMS OF IMMUNOTHERAPY

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, which is defined as a relative decrease in allergen-specific responsiveness, and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

The immunologic changes associated with immunotherapy are complex, and the exact mechanism or mechanisms responsible for its' clinical efficacy are continually being elucidated. Data support the concept that successful immunotherapy is associated with a change to a T_H1 $CD4^+$ cytokine profile.[29-34] Data indicate that increased production of IL-12, a strong inducer of T_H1 responses, contributes to this shift.[33] Clinically successful immunotherapy has been reported to be associated with immunologic tolerance, which is defined as a relative decrease in antigen-specific responsiveness, immune deviation, or anergy. For example, lymphoproliferative responses to allergen are reduced with immunotherapy.[32] Successful immunotherapy results in generation of a population of T regulatory cells, which are $CD4^+CD25^+$ T lymphocytes producing IL-10, TGF-β, or both.[35-39] Regulatory T-cell release has been described in allergen immunotherapy with Hymenoptera venom,[35] grass pollen extract,[37] and house dust mites.[38] IL-10 reduces B-cell antigen-specific IgE and increases IgG4 levels; reduces proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicits tolerance in T cells by means of selective inhibition of the CD28 costimulatory pathway.[36,37]

Allergen immunotherapy has been shown to block both the immediate and late-phase allergic response.[40] Allergen immunotherapy has been shown to decrease the recruitment of mast cells, basophils, and eosinophils in the skin, nose, eye, and bronchial mucosa after provocation or natural exposure to allergens.[41]

In patients receiving immunotherapy, initially there is an increase in specific IgE antibody levels, followed by a gradual decrease to a level that is still higher than that present before treatment. Clinical improvement in many patients develops before decreases in their IgE antibody levels occur or in other patients whose IgE antibody levels never decrease, thereby demonstrating that efficacy is not dependent on reductions in specific IgE levels.[42,43] Immunotherapy does diminish the seasonal increase in specific IgE levels.[44] Despite the persistence of significant levels of specific IgE antibody levels, immunotherapy usually causes a reduction in 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.[45-48]

An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, has also been associated with immunotherapy. The properties of allergen-specific IgA have yet to be determined, and there is a weak correlation between the increase in allergen-specific IgG levels and immunotherapy's clinical efficacy.[30,49,50]

Immunotherapy might alter the affinity and specificity of allergen-specific IgG.[51,52] During the initial phase of ultrarush VIT, a change in IgG specificity (ie, a change in the set of epitopes dominantly recognized by IgG on wasp venom antigens) occurred concomitantly with early clinical tolerance and was seen within 12 hours of ultrarush VIT ($P < .001$).[51] 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 individuals.[52] This change in IgG specificity preceded the increase in IgG titers and was sustained for up to 6 months.[52]

Allergen-specific IgG induced from immunotherapy can block IgE-dependent histamine release and subsequent IgE-mediated antigen presentation to T cells.[53] This effect might be dependent on IgE, allergen concentration, and CD23, the low-affinity receptor for IgE.

Whereas 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.[37,53]

The relationship between these immunologic changes and immunotherapy efficacy is not completely understood.

ALLERGEN EXTRACTS

Summary Statement 6: 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 has 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.[2,18,54-56] 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.

United States–licensed extracts can be obtained in aqueous, glycerinated, lyophilized, and acetone-precipitated and alum-precipitated formulations. Some commonly used allergens are standardized. These include extracts for cat hair, cat pelt, *Dermatophagoides pteronyssinus*, *Dermatophagoides 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.[57] 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.

Most standardized extracts are labeled in BAU. Short ragweed potency units were originally based on the content of the major allergen Amb a 1. Ragweed potency is reported in FDA units and BAU. One FDA unit of Amb a 1 equals 1 μg of Amb a 1, and 350 units of Amb a 1/mL is equivalent to 100,000 BAU/mL. Cat extracts were also originally standardized based on the content of major allergen (Fel d 1), with 100,000 arbitrary units (AU) per milliliter containing between 10 to 19.9 FDA units of Fel d 1 per milliliter (1 FDA unit of Fel d 1 equals 2 to 4 μg of Fel d 1).[55,58,59] Subsequently, $ID_{50}EAL$ testing suggested that 100,000 AU/mL was equal to 10,000 BAU/mL.[60] Approximately 22% of individuals with cat allergy have specific IgE antibodies to cat albumin.[61] Cat pelt extracts have a greater amount of albumin than cat hair extracts.[60]

Dust mites were originally standardized in AU by means of inhibition radioimmunoassay (RIA), and subsequent $ID_{50}EAL$ testing indicated that the AU was bioequivalent to the BAU, and the original AU nomenclature was kept. Dust mite extracts are still labeled in AU.

Summary Statement 7: Nonstandardized extracts can vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Nonstandardized extracts are labeled as wt/vol, which expresses weight in grams per volume in milliliters; that is, a potency of 1:100 indicates that 1 g 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 with a particular wt/vol or PNU potency can have widely varying biologic activities.[62-64] Therefore they should not be considered equipotent.

Summary Statement 8: 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**

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. The major clinically relevant aeroallergens of North America are listed in Table III. Furthermore, nonrelevant allergens in such mixtures could act as sensitizers rather than as tolerogens.[65,66] The physician must therefore select only those aeroallergens for testing and treatment that are clinically relevant in a particular geographic area.

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, dog), insect (cockroach), and Hymenoptera venom source materials.

Cross-reactivity of allergen extract

Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

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. A summary of cross-reactivity patterns of the clinically relevant North American aeroallergens can be found in Fig 2. 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,[67] inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[68-75] Grasses in other subfamilies (eg, Bermuda, Bahia, and Johnson) show greater diversity and should be evaluated separately.[76-78] Bermuda and Johnson grasses are increasingly important in the South,

TABLE III. The major clinically relevant aeroallergens of North America*

- Tree pollen
  - Chinese elm *(Ulmus parvifolia)*†‡; Siberian elm *(Ulmus pumila)*†‡; American elm *(Ulmus Americana)*†‡
  - Red oak *(Quercus rubra)*†; White oak *(Quercus alba)*†
  - Paper birch *(Betula papyrifera)*
  - Alder *(Alnus rubra)*
  - Box elder *(Acer negundo)*†; Red maple *(Acer rubra)*†
  - Eastern cottonwood *(Populus deltoides)*
  - Sycamore *(Platanus occidentalis)*
  - White ash *(Fraxinus americana)*†; Olive *(Olea europaea)*†‡
  - Black walnut *(Juglans nigra)*
  - Mulberry *(Morus rubra)*
  - Mountain cedar *(Juniperus ashei)*
  - Pecan *(Carya illinoensis)*
- Grass pollen
  - Rye *(Lolium perenne)*§‖
  - Timothy *(Phleum pratense)*§‖
  - Meadow fescue *(Festuca elatior)*§‖
  - Bermuda *(Cynodon dactylon)*‖
  - Johnson *(Holcus halepensis)*
  - Bahia *(Paspalum notatum)*
- Weed pollen
  - Short ragweed *(Ambrosia artemisiifolia)*‖
  - English (narrow leaf) plantain *(Plantago lanceolata)*
  - Mugwort *(Artemisia vulgaris)*
  - Russian thistle *(Salsola kali)*
  - Burning bush *(Kochia scoparia)*
  - Sheet (red) sorrel *(Rumex asetosella)*
  - Red root pigweed *(Amaranthus retroflexus)*
- Indoor aeroallergens
  - Cat epithelium *(Felis domesticus)*‖
  - Dog epithelium *(Canis familiaris)*
  - Arthropods (domestic mites: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*)‖
  - Insects (German cockroach: *Blattella germanica*)
- Fungi
  - *Alternaria alternata*¶
  - *Cladosporium* (*C cladosporioides*, *C herbarum*)¶
  - *Penicillium* (*P chrysogenum*, *P expansum*)¶
  - *Aspergillus fumigatus*¶
  - *Epicoccum nigrum*, *Drechslera* or *Bipolaris* type (eg, *Helminthosporium solani*)¶

*Compiled and selected in collaboration with the AAAAI Immunotherapy Committee Allergen Subcommittee for the identification of 35 key allergens of North America.
†Extensive cross-reaction of species within the genus.
‡Apart from regional prevalence, they are limited to local sites with substantial stands of these trees.
§Extensively cross-react with one another and bluegrass, orchard, red top, and sweet vernal.
‖Allergens for which standardized extracts are commercially available.
¶Species that are widely distributed and clinically important.

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.[79-82] 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.[83-85] Significant cross-reactivity between Betulaceae pollens and oak of the Fagaceae family has been demonstrated with percutaneous skin testing.[75] RAST inhibition studies have shown cross-inhibition between oaks and other *Fagales* species.[86] IgE immunoblot inhibition experiments have demonstrated that the *Fagales* species might be strongly inhibited by birch species.[87] The use of one of the locally prevalent members (eg, birch and alder) should be adequate.[88]

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.[89,90] Maple and box elder trees are found throughout the United States, except for the arid southwest. Although in the same genus as maple, *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,[91,92] and there are allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.[93]

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.[94] Similarly, Chenopod-Amaranth families have wide ranges in the western regions but are present throughout North America.[95] Current information on cross-reactivity of these families is limited.[96-98] 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.[99] The use of a single Amaranth extract should be sufficient to cover this family.[100,101] Similarly, *Atriplex* species (eg, saltbushes and scales) show near identity, and use of a single member is adequate. 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,

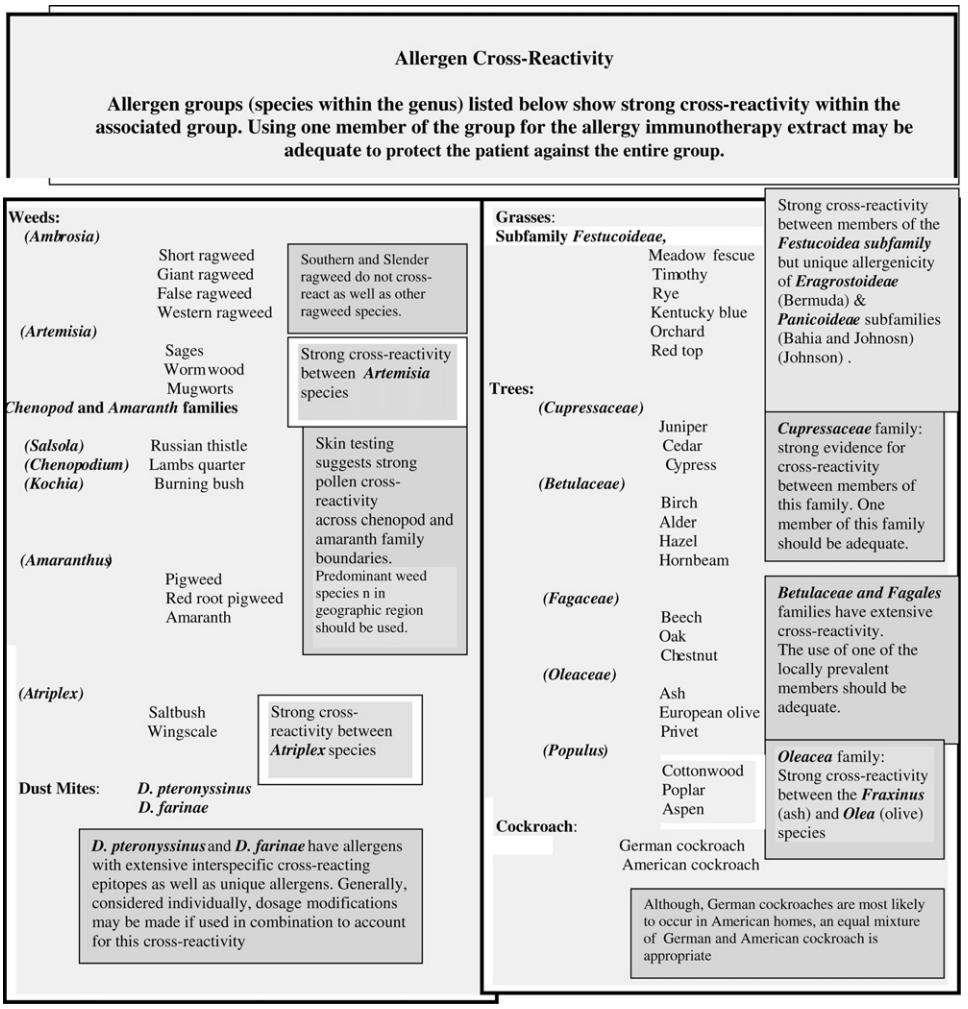


FIG 2. Patterns of allergen cross-reactivity.

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*).

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.[102,103] Stinging Hymenoptera insects occur throughout the United States; the fire ant is found only in Gulf Coast states, Texas, and some other southern and western states. Commercial venom extracts are available for some Hymenoptera species, except the fire ant, for which only whole-body extract is available.

EFFICACY OF IMMUNOTHERAPY

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity

Summary Statement 10: Immunotherapy is effective for 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.[104-111] Immunotherapy is effective for the treatment of allergic rhinitis[107] (including ocular symptoms[112,113]), allergic asthma,[104,109,111,114,115] and stinging insect hypersensitivity[108,116] and is effective in both adults and children.[117-124] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollens,[13,125-132] fungi,[133-138] animal allergens,[22,25,26,139-143] dust mite,[114,115,144-153] and cockroach.[154] There have been no controlled trials of fire ant whole-body extract, but it does appear to be effective in

TABLE IV. Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy

Outcome measure	House dust mite	Other allergens*†
Symptomatic improvement	2.7 (1.7-4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2-7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50)	5.5 (2.8-10.7)

Data are used with permission from Abramson et al.[104]
ND, Not done.
*Odds ratio (95% CI).
†Pollen, mold, or animal dander.

uncontrolled trials.[155-157] 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. A number of studies have also demonstrated a significant improvement in quality of life, as measured by using standardized questionnaires.[24,158-161] The magnitude of the effect depends on the outcome that is used (Table IV). For dust mite, the effect size ranges from a 2.7-fold improvement in symptoms to a 13.7-fold reduction in bronchial hyperresponsiveness. 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.[110] 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[107] and asthma[104,109,111] have been performed to deal with the issue of power. One review of 75 trials involving 3188 asthmatic patients found that, overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyperreactivity after immunotherapy, and it would have been necessary to treat 4 patients (95% CI, 3-5) with immunotherapy to avoid 1 deterioration in asthma symptoms and 5 (95% CI, 4-6) patients to avoid 1 requiring increased medication.[111] These meta-analyses strongly support the efficacy of allergen immunotherapy. Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued[13,162,163] and might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6,9,122,162-165] Allergen immunotherapy might also prevent the development of new allergen sensitivities in monosensitized patients.[120,166,167]

Food allergy, urticaria, and atopic dermatitis

Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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 use of allergen immunotherapy for individuals with the potential for IgE-mediated (anaphylaxis) reactions to foods should be regarded as investigational at this time.[168-171] There have been 2 investigational studies demonstrating efficacy in food hypersensitivity, the first using aqueous subcutaneous injections to peanut and the second using sublingual immunotherapy to hazelnut.[171-173]

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 a modified peanut extract is needed for clinical application of this method of treatment.[171] There is currently no FDA-approved formulation for sublingual immunotherapy, and this route of allergen immunotherapy is currently considered investigational at this time (see Summary Statement 73).

At the present time, there is not enough evidence to support food immunotherapy.

There is no evidence supporting the efficacy of immunotherapy for individuals with chronic urticaria, angioedema, or both.

There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[174-176] 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 ($P = .0379$) and topical corticosteroid use ($P = .0007$).[174]

The potential for benefit in symptoms related to oral allergy syndrome with the cross-reacting inhalant immunotherapy, which includes cross-reacting 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 subcutaneous immunotherapy directed against birch tree,[177] whereas another double-blind, double-dummy, placebo-controlled study comparing the effect of subcutaneous immunotherapy with sublingual immunotherapy 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, medication use, and decrease in IgE reactivity.[178] More investigation is required to substantiate the contention that benefits in oral symptoms will occur with immunotherapy.

Measures of efficacy

Summary Statement 12: 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. Objective measures, such as increase in allergen-specific IgG levels and decreased skin test reactivity, as measured by skin test titration, are changes generally associated with effective immunotherapy but, at present, are not practical for routine clinical use.[147] Nonquantitative skin testing or *in vitro* 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 are not very reliable given the strong placebo-like effect (Hawthorne effect) associated with any treatment. A more objective means for determining efficacy as validated in controlled clinical studies is the use of clinical symptom scores and the amount of medication required to control symptoms and maintain peak flow rates or pulmonary function tests within acceptable limits. Successful immunotherapy often results in a reduction in medication. Sequential measurement of disease-specific quality of life also might be helpful.

SAFETY OF IMMUNOTHERAPY

Reaction rates

Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Large local reactions associated with allergen immunotherapy are fairly common, with a frequency ranging from 26% to 86% of injections.[179] Two retrospective studies compared the effect of not adjusting immunotherapy dose based on large local reactions on the immunotherapy systemic reaction rate with dose-adjustment protocols.[179,180] There was a total of 12,464 injections administered with a dose-adjustment protocol in the 2 studies compared with 9542 injections administered with a no-dose-adjustment protocol. 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 for subsequent systemic reactions, 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 large local reactions, defined as 25 mm or larger, in patients who had experienced systemic reactions with age-, sex-, and allergen sensitivity–matched control subjects who had not had allergen immunotherapy systemic reactions found the rate of large local reactions was 4 times higher among the 258 patients who had subsequently experienced a systemic reaction compared with those who had never experienced a systemic reaction.[181] Patients who had experienced systemic reactions had 1573 large local reactions in 4460 visits (ie, 35.2% of visits) and 8081 injections (ie, 19.5% of injections) compared with the matched control group without systemic reactions who had 1388 large local reactions in 15,540 visits (8.9% per visit) and 26,259 injections (5.3% per injection; difference between groups, $P < .001$). Individual large local reactions were not predictive of future systemic reactions, but large local reactions preceded systemic reactions in approximately one third of the systemic reactions. These findings suggest that individuals with a greater frequency of large local reactions might be at greater risk for systemic reaction. Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy protocol modifications based on them are needed.

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

The prevalence of severe systemic reactions after allergen immunotherapy ranges from less than 1% of patients receiving conventional immunotherapy to greater than 36% of patients in some studies of patients receiving rush immunotherapy.[182,183]

In a recent survey of fatal and near-fatal reactions (NFRs) sent to physician members of the AAAAI, 273 of 646 respondents reported NFRs during the period of 1990-2001.[184]

The incidence of unconfirmed NFRs was 23 per year (5.4 events per million injections). Administration during the height of 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 angiotensin-converting enzyme 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 systemic reactions to subcutaneous immunotherapy over a 20-year period (1981-2000) during which 435,854 injections were administered to 4000 patients, 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.[185,186] In a prospective multicenter study there were 53 systemic reactions (0.3% of the doses) out of 17,526 administered doses in 18 (3.7%) of 423 patients.[187] 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 (21 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, there were 41 fatalities identified in the initial brief survey (20 directly reported and 17 with completed detailed questionnaire) from immunotherapy injections.[188] 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.[189,190] Therefore although severe systemic reactions to allergen immunotherapy are not common, serious systemic reactions (some fatal) can occur.

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

In the AAAAI survey of physician members on immunotherapy and skin testing, fatal reactions, and NFRs during the period of 1990-2001, 15 of the 17 fatalities had asthma, and in 9 patients asthma was considered the susceptibility factor that contributed to the fatal outcome.[188]

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.[184]

Administration during the peak pollen season (3 patients) and previous systemic reactions (4 patients) were cited as other contributing factors. Five fatalities occurred in outside medical facilities, and 2 fatalities occurred at home. No patients were receiving β-blockers; 1 patient was taking an angiotensin-converting enzyme inhibitor. In the most comprehensive evaluation of fatalities associated with allergen immunotherapy, from 1945-1987, there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[189] 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, with 73.3% of patients with an FEV_1 of less than 80% of predicted value experiencing 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 ($P < .0001$).[191] 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% of patients. These studies suggest that symptomatic asthma, severe asthma, or both might be a risk factor for immunotherapy.

In addition to symptomatic asthma and injections giving 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.[17] With the exception of dosing errors and 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 recent 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 or allergy symptom exacerbation, β-blocker use, change in health status (including pregnancy), or adverse reaction to previous allergen immunotherapy injection. The preinjection evaluation might also include a peak flow measurement to assess the airway function of asthmatic patients.

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 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

In a retrospective study the time to onset of a systemic reaction after an immunotherapy injection was less than 30 minutes in most cases.[189] A review of the literature indicates that 70% of systemic reactions occur within 30 minutes after an injection.[183] In the AAAAI 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.[184,188] 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.[190] 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 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.[192] In another prospective study 8% of systemic reactions occurred more than 2 hours after injection.[193]

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.[194]

Because most reactions that resulted from allergen immunotherapy occurred within 30 minutes after an injection, patients should remain in the physician's office for at least 30 minutes after receiving an injection, but longer waits are reasonable, as directed by the physician. In addition, patients who are at increased risk of a systemic reaction might need to carry injectable epinephrine. Such patients might also need to remain in the physician's office more than 30 minutes after an injection. 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.

β-Adrenergic blocking agents

Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

β-Blockade enhances pulmonary, cardiovascular, and dermatologic end-organ effects of mediators and increases mortality associated with experimental anaphylaxis induced by either immunologic or nonimmunologic mechanisms. Patients who are receiving β-adrenergic blocking medications might be at increased risk if they experience a systemic reaction to an allergen immunotherapy injection because the β-receptor blockade might attenuate the response to epinephrine.[195-202] Patients who are receiving β-blocking drugs were almost 9 times more likely to be hospitalized after an anaphylactoid reaction from radiocontrast media.[198] Although topical β-blockers have markedly less systemic β-antagonist effects than oral β-blockers, they still might exhibit some systemic β-antagonist effects. Whether topical β-blockers pose the same or a smaller risk than oral β-blockers in regard to the treatment of allergen immunotherapy–related systemic reactions is not known.

There have been very few studies that have examined the effect of β-blocker medications on allergen immunotherapy. A prospective 1-year study designed to determine whether patients taking β-blocker drugs were at increased risk of immunotherapy-induced systemic reactions found that there were 166 systemic reactions out of 56,105 injection visits in 3178 patients (68 were receiving a β-blocker).[203] The systemic reactions occurred in 144 (4.5%) patients, and only 1 of these patients was receiving a β-blocker medication. The authors calculated that by chance, 3.08 patients receiving the β-blocker medications drugs were expected to have had an systemic reaction and concluded that β-blocker medications did not increase the frequency of allergen immunotherapy systemic reactions ($P > .95$).

In another study of 1389 patients prescribed immunotherapy for Hymenoptera venom hypersensitivity who were followed for 34 months, there were 25 patients who received concomitant β-blocker medications.[204] Three (12%) of the 25 patients receiving β-blocker medications experienced systemic reactions during immunotherapy compared with 23 (16.7%) of 117 patients with cardiovascular disease not receiving β-blockers. Systemic reactions after a field sting or challenge occurred in 1 (14.3%) of 7 cardiovascular patients receiving β-blocker medications compared with 4 (13.8%) of 29 cardiovascular patients not receiving β-blocker medications. No severe reactions to immunotherapy or sting re-exposure were observed in patients receiving β-blockers medications.

Immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. In such cases, intravenous glucagon, which might reverse the refractory bronchospasm and hypotension by activating the adenyl cyclase directing and bypassing the β-adrenergic receptor, might be used if epinephrine has not been effective.[205,206] Prospective studies are necessary to clarify the magnitude of the risk of systemic reactions to allergens in patients who are receiving concomitant therapy with β-blockers, and a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy.

Contraindications

Summary Statement 18: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications

TABLE V. Actions to reduce the risk of anaphylaxis

- Assess the patient's general medical condition at the time of injection (eg, asthma exacerbation).
- Consider obtaining a PEFR before administration of the injection. If the PEFR is significantly less than the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.
- 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 with increased allergen sensitivity or those who have previously had a systemic reaction) might need to wait longer.
- Carefully evaluate any patient with a late reaction (eg, persistent large local reaction lasting >24 hours, systemic reaction occurring more than 30 minutes after the immunotherapy injection).
- 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.

PEFR, Peak expiratory flow rate measurement.

TABLE VI. Recommended equipment and medications to treat anaphylaxis

Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur. This should include at least the following equipment and medications:

- stethoscope and sphygmomanometer;
- tourniquet, syringes, hypodermic needles, and large-bore needles (14-gauge);
- aqueous epinephrine HCL 1:1000 wt/vol;
- equipment to administer oxygen by mask.
- intravenous fluid set-up;
- antihistamine for injection (second-line agents for anaphylaxis, but H_1 and H_2 antihistamines work better together than either one alone);
- corticosteroids for intravenous injection;
- vasopressor;
- equipment to maintain an airway appropriate for the supervising physician's expertise and skill.

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 venom hypersensitivity and cardiac disease being treated with β-blocker medications.

Reducing the risk of anaphylaxis to immunotherapy injections

Summary Statement 19: 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 extremely 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 or other health care professional appropriately trained in emergency treatment.

The 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. Epinephrine is the first-line treatment for anaphylaxis. 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.[12,207-213] It is important to administer epinephrine early in the management of anaphylaxis. 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 V and VI, respectively. Before allergen immunotherapy is chosen as a treatment, the physician should educate the patient about the benefits and risks of immunotherapy, as well as methods for minimizing risks. The patient also should be told that despite appropriate precautions, reactions might occur without warning signs or symptoms. Informed consent should include a discussion of the potential immunotherapy adverse reactions, and this discussion should be documented in the patient's medical record.

PATIENT SELECTION

Clinical indications

Summary Statement 20: Allergen immunotherapy should be considered for patients who have demonstrable

TABLE VII. Clinical indications for allergen immunotherapy

Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or both:
- symptoms of allergic rhinitis after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medications;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medication;
- coexisting allergic rhinitis and asthma;
- possible prevention of asthma in patients with allergic rhinitis

Symptoms of asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medication;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medications;
- coexisting allergic rhinitis and allergic asthma.

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);
- adults and children with a history of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.

evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic rhinitis.[107] Prospective, randomized, double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic asthma.[104,109,111]

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 proper identification and selection of component allergens on the basis of 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 (Table VII). The severity and duration of symptoms should also be considered in assessing the need for specific allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. In addition, specific allergen immunotherapy should be considered if the patient wishes to avoid long-term pharmacotherapy. Time lost from work, emergency department or physician's office visits, and responses to pharmacotherapy are important objective indicators of allergic disease severity.

Patients with allergic rhinitis who are unable to sleep because of symptoms or whose symptoms interfere with their work or school performance should be considered strong candidates for specific allergen immunotherapy. 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 considered. Unacceptable adverse effects of medications should also favor one's decision to initiate allergen immunotherapy. Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.[214]

Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued, and it might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6-9,122,162-165] These benefits of immunotherapy should be discussed with patients and might provide a clinical indication for immunotherapy for individual patients with allergic rhinitis.

Coexisting medical conditions should also be considered in the evaluation of a patient who might be a candidate for allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed with a combined aggressive regimen of allergen avoidance and pharmacotherapy and might also benefit from allergen immunotherapy.[215,216]

However, the patient's asthma must be stable before allergen immunotherapy is administered.[188,191]

Special precautions in patients with asthma

Summary Statement 21: 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 might be at increased risk for systemic reactions to immunotherapy injections.[182,188,191] Two surveys found that deaths from

immunotherapy were more common in symptomatic subjects with asthma.[188,189] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2,217]

Clinical indications for VIT

Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Systemic reactions to Hymenoptera stings, especially when associated with respiratory symptoms, cardiovascular symptoms, or both and positive skin test or *in vitro* test results for specific IgE antibodies, are a strong indication for allergen immunotherapy.[218] In the United States patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Several studies of patients with imported fire ant allergy have demonstrated the effectiveness of immunotherapy with whole-body extracts of fire ants.[155,156,219] 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. Patients younger than 16 years of age who present only with a cutaneous reaction to imported fire ant or Hymenoptera stings might not require immunotherapy.[218,220-222] In addition to allergen immunotherapy, patients with imported fire ant and Hymenoptera venom sensitivity should be instructed in how to best avoid insect stings, be prescribed epinephrine, and be taught how 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 the population that has not had a systemic reaction.[223] In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific IgE is recommended.[218] If the venom-specific IgE test result is also negative, it is recommended that the skin tests, venom-specific 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 IgE test result.[224] 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 re-stung. 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%).[225] 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 IgE test results who have had severe anaphylaxis to an insect sting.

Some patients who have negative venom skin test results and negative venom-specific IgE test results are reported to have had subsequent systemic reactions to stinging insects.[225-227] Controlled studies designed to evaluate the efficacy of immunotherapy in these patients have not been performed. There are very 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.[226] 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.

Summary Statement 23: 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.

ALLERGEN SELECTION AND HANDLING

Allergen selection

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

A careful history, noting environmental exposures and an understanding of the local and regional aerobiology of suspected allergens, such as pollen, fungi (mold), 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 skin or *in vitro* test results for specific IgE antibodies, provide good evidence that such exposures are relevant. Information concerning regional and local aerobiology is available on various Web sites or through the National Allergy Bureau at http://www.aaaai.org/nab. There are

no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma. 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 clinical history of an allergic disease.

There is no evidence to support the administration of immunotherapy based solely on results of specific *in vitro* 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.

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

The omission of clinically relevant allergens from an allergic patient's allergen immunotherapy extract contributes to decreased effectiveness of allergen immunotherapy. The 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 can make allergen immunotherapy less effective.

Knowledge of the total allergenic burden facing a patient and the realistic possibility of avoidance is important in determining whether allergen immunotherapy should be initiated. 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. Many individuals travel extensively for business or pleasure into different regions, and symptoms might worsen at these times. However, inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective. Determination of the significance of indoor allergens for a particular patient is harder because it is difficult to determine exposure in the home, school, and/or workplace. Historical factors, such as the presence of a furry animal in the home, a history of water damage and subsequent fungal exposure, or a history of insect infestation, might be helpful. However, such information is subjective and is often of uncertain reliability. In addition, some studies have demonstrated significant indoor levels of cat and dog allergen in households without pets[228] and significant levels of mouse allergen in suburban[229] and inner-city[230] homes 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 with increased asthma morbidity in inner-city children was found.[231] 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. Nevertheless, for most patients, determination of the clinical relevance of an allergen requires a strong correlation between the patient's history and evidence of allergen-specific IgE antibodies.

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted *in vitro* tests for specific IgE antibodies can also be used. **A**

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 the skin test results have demonstrated the efficacy of immunotherapy for relevant allergens.[25,26,112,130,134,135,140,141,149,154] 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 from skin testing in a highly sensitive individual.[232,233] In addition, skin tests might be difficult to perform in patients with dermatographism or atopic dermatitis. *In vitro* tests are particularly useful in such patients.

Studies indicate that skin testing is generally more sensitive than *in vitro* tests in detecting allergen-specific IgE.[234,235] Based on inhalation challenge test results, skin tests have shown specificity and sensitivity generally superior to those of *in vitro* tests. The comparability of skin tests and *in vitro* tests for specific IgE antibodies depends on the allergen being tested. For all of 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, prick testing is sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass[236] and cat,[237] are used. Intradermal/intracutaneous skin testing might be required for some allergen extracts. It is appropriate in some patients to use *in vitro* tests for specific IgE antibody as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. *In vitro* tests can also be used to define the allergens that should be used in allergen immunotherapy. If the allergy skin test result is negative and the *in vitro* test result is positive, a controlled challenge can be performed, and if the latter is positive, immunotherapy can be considered. 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 *in vitro* test results.

Specific allergens

Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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.[17,104,106,107,109] 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.[112,122] Because a particular pollen extract is a mixture of multiple glycoproteins, this suggests that mixing pollen allergens does not alter biologic activity.

Fungi (molds). Several studies with *Alternaria* and *Cladosporium* species suggest that allergen immunotherapy with fungi might be effective.[133-138] The allergen content of most mold extracts is highly variable.[238,239] However, there is evidence that proteolytic enzymes present in some mold extracts could digest other antigens, such as pollens, when combined in a mixture.[240] For this reason, it might be desirable to separate all pollen extracts from mold extracts when using mixtures.

Unfortunately, extracts for some potentially clinically important fungi are not available.[241] 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 distinguish 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.

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.

Because immunotherapy has been shown to be effective for cat[22,26,139-143,242] and dog,[25,141] the decision to include dog or cat allergen in an allergen immunotherapy extract should be considered in those circumstances in which there is exposure.

Dust mites and cockroach allergens. Crude house dust extract is generally an inappropriate substitute for house dust mite extract because the protein content measured is not restricted to dust mite allergens, nor does it necessarily guarantee inclusion of dust mite protein. Immunotherapy with standardized dust mite is generally more effective than that with crude house dust allergens. The house dust mites *D farinae* and *D 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, such as *Blomia tropicalis* and *Euroglyphus maynei*, partially cross-react with allergens from *Dermatophagoides* species. Only 50% of the projected amounts of each of the 2 house dust mites (*D pteronyssinus* and *D farinae*) need 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[144,147-149,151] 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. Dust mite hypersensitivity should particularly be considered in patients who have perennial symptoms exacerbated by a dusty environment at home, work, or both and periods of high humidity.

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. The major allergen of *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.[243] Immunotherapy with cockroach allergens is effective[154] and should 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.

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.[108,116,244] Efficacy has also been demonstrated with immunotherapy by using whole-body extracts of imported fire ants.[155,156]

Foods. Only a single clinical study accessing the efficacy and safety of subcutaneous immunotherapy with foods has been performed.[171,173] This study, which evaluated immunotherapy with peanut, found the incidence of systemic reactions, even during maintenance, was unacceptable. Thus there is no evidence to support the use of immunotherapy with food extracts. Currently, strict avoidance of the offending food is advisable, and subcutaneous immunotherapy for food allergy is not recommended.

Mixing of extracts

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Once the relevant allergens for each patient are identified, it is necessary to prepare a mixture that contains each of these allergens. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts. A number of 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 interactions between different types of allergens, when mixed, that could lead to degradation or unmasking of epitopes on exposure to proteolytic enzymes.

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Immunologic and 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.[71] 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 genera 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 the Allergen extract section, Fig 2, and the allergens and allergy diagnostic tests practice parameters).

Dose selection. Summary Statement 30: 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.[22-26,128,149,245] Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000 vol/vol).[28] A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy vaccine. Failure to do so might reduce the efficacy of immunotherapy. This occurs because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased (see the Immunotherapy schedules and doses section for further discussion and for recommended maintenance doses).

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as fungi (mold) and cockroach, from other extracts, such as pollens, is recommended. **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.[240,246,247] 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, and some weeds.[240,246,247] Cockroach had a similar deleterious effect on pollen extract potency.[246,248] Short ragweed appeared resistant to the effects of the proteolytic enzymes in one study,[240] 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.[247]

Dust mite extracts do not appear to have a deleterious effect on pollen extracts.[240,246,248] These studies suggest that pollen, dust mite, and cat extracts can be mixed together. 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. The evidence on mixing cockroach extract with other extracts is conflicting, and the clinical relevance of the changes is also unclear; therefore the clinician has the option of separating cockroach or not.

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 with lesser activities, such as pollen extracts.

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.

In this regard the number of separate injections that need to be given at each patient visit depends on whether all of the relevant extracts mixed into a single vial still deliver an optimal dose of each allergen. If mixing causes excessive dilution or if there are advantages to separating allergens into separate vials, then more than one vial might be necessary for successful immunotherapy.

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extracts are high-alert products that carry the risk for anaphylaxis. Policies, procedures, and processes intended for conventional drugs and medications might be highly 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 fatal anaphylactic reactions with allergenic products. 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. There are no reports of infection associated with allergen immunotherapy injections. Allergen vaccines are prepared by using sterile manufacturer's extracts and sterile diluents containing antibacterial constituents (usually phenol). A summary of the AAAAI/ACAAI/JCAAI proposed USP allergen immunotherapy extract preparation guidelines can be found in Table VIII.

TABLE VIII. AAAAI/ACAAI/JCAAI-proposed USP 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 below.*
   - 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.
2. **Physician responsibility**: A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in the preparation of immunotherapy using an aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files.
3. **Bacteriostasis**: Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if 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 the FDA-approved package insert 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 treatment with sanitizing agents containing alcohol and/or 70% isopropanol 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 the physical integrity of the vial.
10. **Labeling**: Immunotherapy vials are to be clearly labeled with the patient's name and 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.

*__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 media, such as from Valiteq (http://www.valiteq.com), 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.

Allergen immunotherapy extract handling

Storage. Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

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 a number of 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 extract, including reconstituted lyophilized extracts, should be stored at 4°C to minimize the rate of potency loss because storage at higher temperatures (eg, room temperature) can result in rapid deterioration.[249]

Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions (personal communication). These studies include actual shipments made by their carriers to places like

Phoenix in the summer and Alaska in the winter. 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.

Storing dilute extracts. Summary Statement 34a: More dilute concentrations of allergy immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than do more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: In determining the allergy vaccine expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of 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 allergen immunotherapy 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.[249,250]

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.[250] Phenol is a preservative added to extracts to prevent growth of microorganisms.

Phenol can denature proteins in allergen extracts.[251,252] Human serum albumin might protect against the deleterious effect of phenol on allergen extracts.[251] 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,[250,253] possibly through inhibition of the activity of proteolytic and glycosidic enzymes that are present in certain extracts. However, it is irritating when injected and should be diluted before beginning immunotherapy. Recommendations for extract stability are found in the manufacturers' product insert sheets. 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. The pain associated with glycerin increases in proportion to the glycerin concentration and injection volume, and the pain is proportional to the total injected dose of glycerin.[254] However, individual pain perception can vary substantially. Total glycerin doses of less than 0.05 mL rarely produce clinically important pain.

TABLE IX. Potency of selected manufacturer's extracts currently available

Extract	Potency
Cat hair and pelt	5000 and 10,000 BAU/mL
Dust mite	3000, 5000, 10,000, and 30,000 AU/mL
Bermuda grass	10,000 AU/mL
Short ragweed	1:10-1:20 wt/vol or 100,000 AU/mL
Other grasses*	10,000 and 100,000 BAU/mL
Other pollen	1:10 to 1:40 (wt/vol) or 10,000 PNU/mL
Molds	1:10 to 1:40 (wt/vol) or 20,000 to 100,000 PNU/mL

AU, Allergy unit; *BAU*, bioequivalent allergy unit; *PNU*, protein nitrogen unit.
*Perennial rye, Kentucky blue/June, timothy, sweet vernal, redtop, orchard, and meadow.

There have been few studies that have investigated the potency of dilutions of allergen extract mixture over time. Expiration dates for allergen extract dilutions are somewhat empiric and not strongly evidence based. A study undertaken by the AAAAI 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. Dust mite and cat at 1:10 and 1:100 vol/vol dilution were also stable in all conditions of storage over 12 months, as measured by an ELISA assay using 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.

IMMUNOTHERAPY SCHEDULES AND DOSES

Summary Statement 35: A customized individual 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 can be based on single or multiple allergens. **D**

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. Animal dander contains between 10 and 20 antigens,[255] house dust mites between 20 and 40 antigens,[256] and pollens between 30 and 50 antigens,[257,258] and fungal extract can contain as many as 80 antigens.[259]

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. This is designated as the patient's maintenance concentrate.

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. Standardized extracts are available with biologic potencies of 10,000 and 100,000 BAU for grasses; 5000 and 10,000 BAU for cat allergen; 5000, 10,000, or 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 wt/vol extracts (Table IX). 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.

Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

The highest concentration of an allergen extract mixture that is projected to be used as the therapeutically effective dose is called the maintenance concentrate. This should be prescribed individually for each patient by an allergist/immunologist. 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 individual manufacturer's extracts. Some patients might be unable to attain the projected therapeutically effective dose of the maintenance concentrate because of local reactions, systemic reactions, or both (eg, cat, 1000 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose]; see Table X for probable effective therapeutic dose range). Such patients might need weaker dilutions of their maintenance concentrate. Even so, 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 referred to as the maintenance dose. The consistent use of this nomenclature system is essential because errors in choosing the correct vial are a common cause of systemic reactions, especially when the patient transfers from one physician to another. Therefore it is important that standard terminology be adopted by all physicians who prescribe allergen immunotherapy.

Recommended doses

Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

The effective maintenance dose of immunotherapy for a particular patient must be individualized. To do this, the allergist/immunologist who prepares the allergen immunotherapy extract must balance the dose necessary to produce efficacy and the risk of reactions if such a dose is reached. The allergist/immunologist might need to prepare more than one maintenance concentrate to provide a therapeutic dose of each of the allergens for the polysensitized patient. Therapeutically effective doses for immunotherapy have been reported for some allergen extracts.[22,24,25,128,134,135,149,246,260,261] Effective doses have been determined for Hymenoptera venom, dust mite, cat allergen, dog, grass, and short ragweed (Table X).

Controlled studies demonstrate that the content of particular allergens in allergen immunotherapy extracts can be used to predict a therapeutic dose for those allergens, particularly when the extracts are standardized. For antigens 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. The therapeutically effective doses used in the most recent controlled clinical studies are the basis of the recommended dosage range of standardized extracts presented in Table X. 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 time that it is administered.[14]

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.[27] 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 risk of systemic reactions to immunotherapy injections with higher maintenance doses. The maintenance concentrate should be formulated to deliver a full therapeutic dose of each of its constituent components. However, some sensitive patients might not tolerate the targeted therapeutic dose, and their maintenance dose would be lower. Individuals 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 referred to as the maintenance dose.

Regardless of dose schedule, some patients are unable to progress to the predetermined maintenance dose because of large local or systemic reactions to the allergen

TABLE X. Probable effective dose range for allergen extracts US standardized units[a]

Antigen	Labeled potency or concentration[a,b]	Probable effective dose range
Dust mites: *D farinae* and *D pteronyssinus*[c]	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat[d]	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized[e]	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed[f]	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 μg of Amb a 1 1000-4000 AU Concentration of Amb a 1 is on the label of wt/vol extracts in FDA units[358]
Nonstandardized extract, dog[g]	1:10 to 1:100 wt/vol	15 μg of Can f 1
Nonstandardized extracts	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose

[a]Multiple studies have demonstrated that the efficacious dose for allergen immunotherapy is between 5 and 20 μg of the major allergen per injection. Only 2 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).

[b]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).

[c]There have been no dose-response studies with United States–licensed dust mite extracts, and dosing recommendations in AU value are extrapolated from published European studies that used aqueous[349] and alum-precipitated[149,151] extracts. 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.[149] The authors suggested the optimal maintenance dose was 7 μg of Der p 1. Corresponding doses were based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Extrapolating effective and safe doses in this manner might not be scientifically valid. *D farinae* and *D pteronyssinus* are similar in group 1 allergen content according to the FDA's current reference standards. 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*.

[d]The major cat allergen Fed d 1 is reported in FDA units, with 1 Fel d 1 unit equaling approximately 2 to 4 μg of Fel d 1.[55,58,59] The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 to 19.9 U/mL. One study demonstrated clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 dose in terms of decreased cat extract PD_{20}, titrated skin test results, and allergen-specific IgE and IgG levels.[350,351] In a recent study that investigated the efficacy in terms of immunologic changes of 3 doses of a United States–licensed cat extract (0.6, 3, and 15 μg) demonstrated that a significant effect on titrated skin prick test results, allergen-specific IgG4 levels, and $CD4^+$/IL-4 levels was only seen in the group treated with 15 μg of Fel d 1, although the 3-μg dose group did demonstrate a significant change in titrated skin test response and increase in cat-specific IgG4 levels.[22]

[e]There have been no dose-response studies with United States–licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,[130] alum-precipitated,[24,161] and calcium phosphate–precipitated grass pollen extracts.[352] One of these studies compared a dose of 2 μg with 20 μg of major timothy allergen (Phl p 5) and found clinical efficacy at both doses.[24] The efficacy was greater in the 20 μg of Phl p 5 dose, but the systemic reaction rate was also higher in the high-dose group. The package inserts for United States–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 BAU. Extrapolating effective and safe doses in this manner might not be scientifically valid. 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).

[f]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 suggested that 1 unit of Amb a 1 is equivalent to 1 μg of Amb a 1, and 350 Amb a 1 units/mL is equivalent to 100,000 BAU/mL.[60] The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2000 AU, with a range of 1000-4000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrated 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.[45] A ragweed dose-response study (0.6, 12.4, and 24.8 μg of Amb a 1) demonstrated efficacy, as measured by nasal challenge, at 12 and 24 μg of Amb a 1.[128] The efficacy of the 24-μg dose was not significantly better than the 12-μg dose, and the authors concluded that the optimal dose for ragweed extract was greater than 0.6 μg but not more than 12.4 μg of Amb a 1.

[g]Dog extracts are not standardized. However, one dose-response study with a United States–licensed acetone-precipitated dog extract investigated the efficacy of 3 doses (AP dog; Hollister-Stier, Spokane, Wash; 0.6, 3, and 15 μg) in terms of immunologic changes and found the dose of 15 μg of Can f 1 to be most efficacious.[25] 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 have assayed between 128 and 208 μg/mL (average Can f 1, 162 μg/mL [SD ± 26 μg/mL]; information provided by the extract manufacturer, Hollister-Stier).

immunotherapy extract. The evidence is not clear whether large local reactions are a potential risk for subsequent allergen immunotherapy systemic reactions.

Published studies do not indicate that an individual large local reaction is predictive of a subsequent systemic reaction.[179,180] However, one retrospective study found that individuals who have a history of repeated large local reactions (defined as >25 mm) might be at greater risk for a subsequent systemic reaction.[181]

The concept of highest tolerated dose does not apply for VIT, and all patients are expected to achieve the full recommended dose to achieve the necessary degree of protection. There are conflicting data over whether lower doses (50 μg) are less effective, but there are also data showing that 200 μg is more reliably effective.[245] In the case of VIT, patients are asked to tolerate more large local reactions to achieve the full dose, even though with inhalant immunotherapy the dose can be reduced for such large local reactions to minimize patient discomfort.

Effect of dilution on dose

Summary Statement 38: 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 vaccine, thereby limiting the ability to deliver a therapeutic effective dose for any given allergen.

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

Dilution from maintenance concentrate vaccine	Volume	Volume (mL)	Diluent volume (mL)	Final volume
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.

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 2000 BAU/mL, 2 mL of the manufacturer's extract (cat, 10,000 BAU/mL) can be added to 8 mL of diluent or 8 mL of other allergens, and the final concentration of cat will be 2000 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.

Dilutions of the maintenance concentrate

Summary Statement 39: 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 vol/vol 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, 1000 BAU or 100 BAU), but this system can be complicated if allergens with different potency units are used (eg, wt/vol, BAU, AU, or PNU) and make it difficult to easily interpret the vial label.

Instructions on how to prepare various allergen extracts 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.

Labeling dilutions

Summary Statement 40: 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, a number of 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 (vol/vol), a numbering system, a color-coding system, or an alphabetical system should be used. If this uniform labels 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.

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
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

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 3 and 4).

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 Appendix 2]).

Individualized treatment vials

Summary Statement 41: 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 (wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for 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). Labels on patient-specific vials can provide at least 2 patient identifiers (birth date and patient name), which would be consistent with the recommendations of the Joint Commission on Accreditation of Health Care Organizations National Patient Safety Goals: ''Goal 1: Improve the accuracy of patient identification by using at least two patient identifiers when providing care, treatment or services.''[5] 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 administration of the injection.[4,5]

In a survey of 1717 allergists endorsed by the AAAAI and JCAAI, 57% of the 476 respondents reported at least one wrong-patient injection, and 74% of the 473 respondents reported at least one wrong-dose injection.[4] 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 reasons why this might reduce incorrect injection errors. One reason was that patient-specific vials can be prepared in a quiet laboratory setting, which might provide substantially less distraction than the nurse in a room with a patient who is trying to concentrate only on drawing up the injection correctly. In addition, the specific components are mixed once with the preparation of individually prepared patient-labeled vials, whereas the mixing would be repeated on every injection visit if the allergen extract is withdrawn from different stock solutions, as it is in the off-the-board method. For safety reasons and to avoid cross-mixing of allergens removed from the manufacturer's extract, the mixing of antigens in the syringe (off the board) is not recommended.

Some allergists/immunologists prefer to administer immunotherapy doses drawn directly from a single stock dilution of individual allergens or common mixes (shared specific patient vials). In this way the immunotherapy dose is transferred to the patient without cross-contamination. If shared-patient (eg, mixed vespids and dust mite mix) vials are used, it is essential that policies and procedures are developed to verify that the correct dose from the correct vial is administered to the correct patient.

Starting doses

Summary Statement 42: The starting dose for build-up is usually a 1000- 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 slowly 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 1:1000 (vol/vol), although more diluted concentrations frequently are used for patients who are highly sensitive, as indicated by history or skin test reaction (see Appendix 3 for an example of a conventional immunotherapy schedule).

Frequency of build-up injections

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 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 2 times per week. 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 4 to 6 months, depending on the starting dilution and the occurrence of reactions. It is acceptable for patients to receive injections more frequently, provided there is adequate spacing between injections. The interval between injections is empiric but might be as short as 1 day without any increase in the occurrence of systemic reactions[262] if there is some urgency to achieve a maintenance dose (eg, allergy season is approaching) or for practical reasons (eg, patient's schedule). Alternatively, treatment schedules can be used that more rapidly achieve maintenance dosing. These cluster and rush dosing schedules are discussed in Summary Statements 47 through 49.

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 a number of 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).

Dose adjustments for systemic reactions

Summary Statement 44: 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 benefit/risk ratio justifies continuation of immunotherapy.

Reductions during periods of exacerbation of symptoms

Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Immunotherapy administered during periods of exacerbation of symptoms is considered a risk factor for immunotherapy.[17,184] Injections administered during periods when a patient is exposed to increased levels of allergen to which they are 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.[184] 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 sensitive, especially if their symptoms are poorly controlled.

Dose adjustments for late injections

Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

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 depends 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 Appendix 4 for an example of a dose-modification regimen for gaps in treatment).

Cluster schedules

Summary Statement 47: 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 (see Appendix 5).[22,26] 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. The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules.[145,263-266] The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.[267]

Rush schedules

Summary Statement 48: 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.[268] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.[191,269-272]

The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections over the course of 4 hours.[273] Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours.[274-276] 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 cluster[145,266] and rush[134,277] schedules.

Systemic reactions and rush schedules

Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

The advantages of rush immunotherapy come at a cost because there is an increased risk of local and systemic reactions. Systemic reaction rates have been reported to be

as high as 73% of patients, with the risk of such reactions reduced to 27% by premedication in one study.[272] Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing.[273]

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

Rush protocols for administration of Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions.[274-276,278,279]

Premedication and weekly immunotherapy

Summary Statement 50: Premedication can reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

There is concern that antihistamines taken before each injection with conventional immunotherapy might mask a minor reaction that would otherwise alert a physician to an impending systemic reaction. 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.[280] One study that compared terfenadine premedication with placebo premedication during rush VIT demonstrated greater clinical efficacy in the terfenadine-premedicated group in terms of subsequent responses to field stings or sting challenge.[281] There was also a significant difference in the systemic reaction rate between the 2 groups: 6 patients in the placebo-premedicated group had systemic reactions, whereas none of the patients in the terfenadine-premedicated group had systemic reactions ($P = .012$).

Unfortunately, patients might still have life-threatening anaphylaxis despite 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.

Premedication with cluster and rush immunotherapy

Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

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.[267] Premedication with a 3-day course of prednisone, an H_1 histamine receptor antagonist, and an H_2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.[272] In one study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on the safety and efficacy of rush immunotherapy, there was a 5-fold decrease in the risk of anaphylaxis in the group premedicated with omalizumab compared with the placebo premedication group.[282]

There are anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist, but there have been no published studies. Because the risk of a systemic reaction from rush VIT is relatively low, routine premedication before rush VIT is usually unnecessary.[274,276,278,279] In a study evaluating premedication with antihistamines and steroids for rush immunotherapy with imported fire ant venom, there was no statistically significant differences in the systemic reaction rates between the premedication and placebo premedication group (3.6% of the premedication group vs 6.7% of the placebo group, $P = .87$).[157]

Maintenance schedules

Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals 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 individuals might tolerate longer intervals between maintenance dose injections.

The interval between venom injections can be safely increased up to 8 weeks in some patients without loss of efficacy. 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.

Continuing care

Time course of improvement. Summary Statement 53: Clinical 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.[24,134,143,277] Improvement might not be observed for a number of reasons, including (1) failure to remove significant allergenic exposures (eg, a cat), (2) exposure to high levels of

allergen (eg, pollen or molds), (3) continued exposure to nonallergen triggers (eg, tobacco smoke), or (4) incomplete identification and treatment of clinically relevant allergens. 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 54: 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 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 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

The patient's response to immunotherapy should be evaluated on a regular basis. 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. 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.

There have been very 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 individuals.[283-285] However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported.[283,285] Nevertheless, systemic reactions to stings after discontinuing VIT were generally much milder than the pretreatment reactions and were rarely severe. Two studies did not find a difference in relapse rates between the patients treated for 3 years compared with those treated for 5 years,[283,286] but one of the studies noted that the small number of patients in the 3-year treatment group prevented them from making any conclusions about the risk of discontinuing treatment after 3 years.[283] However, one study found that patients who had experienced re-sting reactions after discontinuing VIT had received VIT for a significantly shorter duration (mean, 43.35 months) than those with continued protection (mean, 54.65 months; $P < .01$).[285] Another study reported that 5 years of VIT provided better immunologic and clinical outcomes than 2 to 4 years of treatment.[287]

Change in skin test reactivity did not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who experienced a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE.[286,288] Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment.[288] The relapse rate and the frequency of severe reactions were greater in patients who had a history of very severe reactions to stings before treatment, in patients who had systemic reactions during VIT (to a sting or a venom injection), in patients with honeybee allergy, and in those who had less than 5 years of treatment.

The duration of inhalant allergen immunotherapy efficacy has not been as extensively studied. Some studies have suggested 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 *(D pteronyssinus)* extract for 12 to 96 months.[14] 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.[13] There was a switch to placebo in half of 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. These studies demonstrate the uncertainty of the long-term benefit of inhalant immunotherapy after discontinuation.

Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained clinical remission after discontinuing inhalant immunotherapy, and 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 indication for continuation of immunotherapy can be found at http://www.aaaai.org or http://www.jcaai.org.

Documentation and record keeping. Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully 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 allergy immunotherapy and prescription forms can be found in the Appendix (Appendices 6-15), and these include examples of immunotherapy prescription and administration forms. These forms, along with examples of immunotherapy consent and instruction forms, can also be found at http://www.aaaai.org.

Injection techniques. Summary Statement 57: Allergen immunotherapy extract injections should be given using a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **C**

Immunotherapy should be given with a 26- to 27-gauge syringe with a half-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.[289-291]

If using shared specific patient vials (stock vials, such as mixed vespid or dust mite mix), a single dose should be drawn from each vial. Antigens from different vials should not be combined in a single syringe. Furthermore, extra care is needed to prevent using the wrong stock antigen.

Summary Statement 58: The injection should be given subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Each immunotherapy injection should be given in the posterior portion of the middle third of the upper 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.

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.

The syringe should be aspirated to check for blood return in the syringe before injecting. If blood is present, 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 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 syringe should be appropriately discarded. A fresh syringe and needle are necessary to determine whether a blood vessel has been entered.

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 could result in a local reaction.

LOCATION OF ALLERGEN IMMUNOTHERAPY ADMINISTRATION

Physician's office

Summary Statement 59: 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 to treat anaphylaxis should be in the immediate vicinity when immunotherapy injections are administered.

Summary Statement 60: 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.[292] 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.[184] 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 might be frequently necessary in the patient's immunotherapy schedule, as well as the patients total treatment program.

Other locations

Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **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.[292] The health care professional and staff 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, or allergy/asthma exacerbations at the time of allergen immunotherapy extract injection or poorly controlled asthma).

Appropriate adjustment of dose should be made as clinically indicated. The physician who prepared the patient's allergen immunotherapy extract should provide adequately labeled allergen immunotherapy extract vials, detailed directions regarding dosage schedule for build-up and maintenance, and instructions on adjustments that might be necessary under the following circumstances:

1. when providing patients with new vials;
2. during seasonal exposure to allergens that are in the patient's allergen vaccine, to which the patient is very sensitive, or both;
3. if the patient has missed injections; and
4. when reactions occur to the allergen immunotherapy extract.

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

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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 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 very 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 fully trained to administer the injection and to treat anaphylaxis if this should 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 supports (personnel, medications, supplies, and equipment) are more optimal for encouraging prompt recognition and treatment of anaphylaxis (Table V). 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.

Summary Statement 63: If a patient on 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for their immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extracts might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Patients often 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 brought from the previous physician (ie, an unchanged immunotherapy program) or one to be prepared by the current physician (ie, a new immunotherapy program).

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 full, clear, and detailed documentation of the patient's previous schedule and the contents of the allergen immunotherapy extract (see Appendices 7, 8, 11, 12, and 14 for examples of allergen immunotherapy prescription and administration forms and documentation guidelines for allergen immunotherapy forms). In addition, the patient's previous response to and compliance with this program 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 a schedule and the allergen immunotherapy extract, (2) the patient has shown significant improvement on this immunotherapy program, and (3) the contents of the allergen immunotherapy extract are appropriate for the area in which the patient is now living.

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, vaccine type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient's dose is not modified. This increased risk is due to the significant variability in content and potency of extracts and the variability in methods used by physicians to prepare the patient's maintenance concentrate and its dilutions. For example, the strength of a given concentration of nonstandardized extracts might vary significantly from vial to vial. The risk of systemic reactions in such a situation might be greater with nonstandardized extracts and allergen immunotherapy extracts that contain mixtures of allergens.

Therefore if the allergen immunotherapy extract is to be changed, the patient might need to be retested for specific IgE to the appropriate allergens 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 provided the interval of time since the last injection has not been too long. For lot changes from the same manufacturer, the physician can consider decreasing the dose by 50% to 90%. For changes in manufacturer and nonstandardized extracts, a greater decrease in dose might be necessary.

SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

Allergen immunotherapy in children

Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children

with allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Immunotherapy for children has been shown to be effective and often well tolerated,[137,242] although at least one study did not show efficacy.[293] 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.[294] In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (see the Patient selection section and Table VII). In recent studies children receiving allergen immunotherapy have demonstrated:

1. improvement in symptom control for asthma[117,119,121,122] and allergic rhinitis[118];
2. increased PC_{20} to histamine[121];
3. increased PC_{20} to cat and house dust mite allergens[121,149];
4. decreased risk of development of asthma[6,9,163-165];
5. decreased development of new sensitivities[120,166]; and
6. modification in release of mediators in children receiving immunotherapy that correlates with decreased clinical symptoms.[123]

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Although there is some disagreement about the role of allergen immunotherapy in children under the age of 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.[117,122] In children with allergic rhinitis, allergen immunotherapy might prevent the development of asthma.[6,9,163-165] However, allergen immunotherapy for inhalant allergens is usually not considered necessary in infants and toddlers because (1) there is 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 in pregnancy

Summary Statement 71: Allergen immunotherapy might be continued but is usually not initiated in the pregnant patient. **C**

The physician must be aware of the benefits and risks of immunotherapy in pregnant patients. The recommended precautions for prevention of adverse reactions are especially important in the pregnant patient. Allergen immunotherapy is effective in the pregnant patient. Thus allergen immunotherapy maintenance doses can be continued during pregnancy. Allergen immunotherapy is usually not initiated during pregnancy because of risks associated with systemic reactions and their treatment (ie, spontaneous abortion, premature labor, or fetal hypoxia). 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, and the patient is maintained on the dose that she is receiving at that time.

Immunotherapy in the elderly patient

Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy might be considered in the treatment of the elderly patient, but the benefit/risk assessment must be evaluated carefully in this population. Older 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. However, elderly patients may also benefit from allergen immunotherapy and age alone should not preclude the consideration of allergen immunotherapy.[295]

Immunotherapy in patients with immunodeficiency and autoimmune disorders

Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with immunodeficiency or autoimmune disorders. Therefore the decision to begin immunotherapy in patients with major humoral or cellular immune defects must be individualized. Concern about the increased risk of immunotherapy in such patients is largely hypothetical.

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

ALTERNATIVE ROUTES OF IMMUNOTHERAPY

Sublingual and oral immunotherapy

Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be

effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no FDA-approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **B**

Alternative routes of administration of allergen immunotherapy are ''a viable alternative to parenteral injection therapy'' in some cases.[106,296] Studies of oral immunotherapy have provided conflicting results for ragweed,[297] birch,[298] and cat[299] immunotherapy. The present dosage of oral immunotherapy extract is 20 to 200 times the parenteral injected dosage, which requires a cost assessment for this type of therapy. Furthermore, adverse effects have included gastrointestinal and oral reactions (50% in 1 study) that might preclude home therapy. Oral immunotherapy should be considered investigational at this time.

Optimal-dose (high-dose) sublingual swallow immunotherapy is effective in adults and children.[300-304] In a study of 855 patients with grass pollen allergy and allergic rhinitis randomized to placebo or one of 3 grass tablet doses, there was a significant reduction in symptom and medication scores in the highest-dose subgroup, who were treated for at least 8 weeks before the grass pollen season, compared with the placebo group (symptoms, 21%, $P = .0020$; medication use, 29%, $P = .0120$).[303]

Sublingual allergen studies have evaluated house dust, olive pollen, grass pollen, ragweed, birch, cat, latex, *Alternaria* species, and *Parietaria judaica*.[305-313] Sublingual immunotherapy has been shown to be effective in patients sensitized to 2 non–cross-reacting allergens, grass and birch.[314] It has been noted that the allergen is not degraded by saliva and that there is no direct sublingual absorption of allergen. Radiolabeled allergen has been detected after 48 hours in the sublingual region.[315,316] Alternative protocols, such as rush and ultra-rush (20 minutes) sublingual swallow[307,316,318] and no induction (build-up) phase,[301,303,317,319,320] have been studied. Several studies have suggested a relationship between dose and efficacy with sublingual immunotherapy,[303,310,321] but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. The majority of sublingual studies have demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both, but approximately 35% of the randomized, double-blind, placebo-controlled studies did not demonstrate efficacy in either parameter during the first year of treatment.[322] Further studies are needed to confirm the optimal dose for sublingual immunotherapy.

One of the potential advantages of sublingual immunotherapy is that it appears to be safe, even at very high doses (up to 500 times the usual monthly subcutaneous dose), and to be associated with a lower incidence of serious side effects.[310,320,323] This appears to apply to young children (<5 years), for whom there are prospective safety data[324,325] and a postmarketing survey.[326]



FIG 3. Sample of labels for allergen immunotherapy extract vials.

There have been no SLIT-related fatalities, but there have been 3 case reports of anaphylaxis caused by sublingual immunotherapy. One patient with latex hypersensitivity had anaphylactic shock 20 minutes after reaching the maximal dose on the fourth day of latex rush sublingual rush immunotherapy.[327]

The other 2 reported cases of SLIT anaphylaxis involved patients treated with multiple inhalant allergens. In one case a patient with allergic rhinitis and asthma who was prescribed a sublingual immunotherapy extract composed of multiple non–cross-reacting allergens (*Alternaria* species, dog, cat, ragweed mix, weed mix, and grass mix)[328] had generalized pruritis, followed by angioedema, shortness of breath, and dizziness, within a few minutes of administering 6 drops of the 1:100 vol/vol dilution on the third day of treatment. This episode was preceded by a milder systemic reaction the previous day (generalized pruritis). In the other case, a 13-year-old girl with allergic rhinitis and asthma had swelling of her lower lip 3 minutes after pollen drops, high fever, chest pain, nausea, and abdominal pain.[329] She was treated in the emergency department for anaphylaxis and hospitalized for observation. The reaction occurred 1 month after she had reached the maintenance dose during the peak of the spring season.

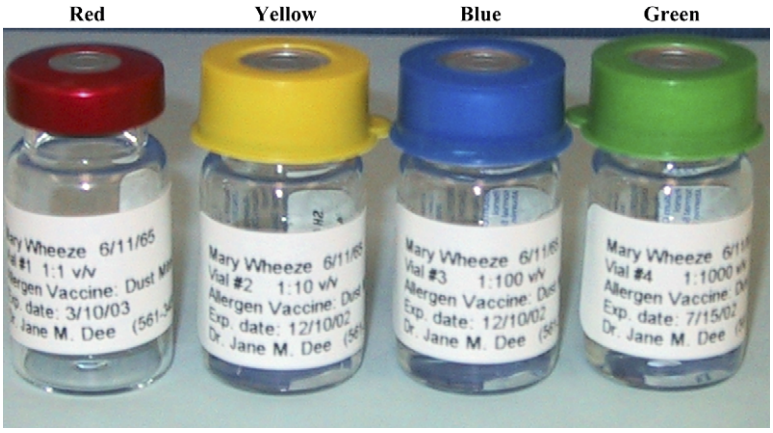


FIG 4. Sample set of color-coded vials of allergen vaccine.

There is currently no FDA-approved formulation for sublingual immunotherapy in the United States at this time, and this modality should be considered investigational. Current investigation of sublingual immunotherapy should not be confused with low-dose sublingual immunotherapy based on provocation neutralization testing or Rinkel-type skin testing.

Intranasal immunotherapy

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Based on controlled, well-designed studies, intranasal immunotherapy has been shown to improve the nasal symptoms of rhinitis.[330] Intranasal dry powder extract immunotherapy has been studied in grass,[330] birch,[331] *P judaica*,[332-334] and house dust mite[335] allergy. Clinical efficacy was noted in all of these studies. Nasal reactivity to allergen challenge was reduced, and only minor side effects were noted in 2 of the above studies. A 3-year study with *P judaica* reported to provide persistent benefits for up to 12 months after conclusion of allergen immunotherapy.[333] Local administration of nasal allergen in an aqueous solution for immunotherapy might be limited by the local side effects. Further studies in both pediatric and adult groups are needed. In human studies the antigen has been noted to appear in the serum within 15 to 30 minutes of administration, with a peak level occurring within 2 to 3 hours.[315] Some allergens have been reported to be retained in the nasal mucosa for up to 48 hours after administration. Intranasal immunotherapy is not currently available in the United States but has gained some acceptance in other parts of the world.

Immunotherapy techniques that are not recommended

Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

Low-dose regimens, including coseasonal low-dose immunotherapy for aeroallergens and the Rinkel low-dose titration techniques, are not effective.[27,28] Immunotherapy based on provocation–neutralization testing with food and aeroallergens and enzyme-potentiated desensitization is not effective.[336]

FUTURE TRENDS IN IMMUNOTHERAPY

Therapy with aeroallergen extracts will become more uniform (as is the current practice for insect venoms) as greater numbers of biologically standardized allergen extracts become available. The actual number of commercially available allergen extracts will be reduced based on consensus agreements about the regional prevalence of aeroallergens, their cross-allergenicity, and the relevance of their effect on human health in specific locales. Novel routes for more effective, convenient, and safer allergen immunotherapy are being investigated throughout the world.

For example, the sublingual route of administering allergen immunotherapy has been studied extensively in Europe. A meta-analysis confirmed its clinical effectiveness in allergic rhinitis,[302] and it has been reported to be effective in asthma as well.[337] Sublingual immunotherapy appears to have a very low risk of serious life-threatening systemic side effects, which might allow for home administration.[324,338] In some studies the clinical benefits of sublingual immunotherapy were not significant until the second year of treatment,[306,339] and comparisons suggest that the magnitude of the clinical benefit of sublingual immunotherapy might not be as great as that of subcutaneous immunotherapy.[311]

Trials with non–IgE-binding peptides containing T-cell stimulating peptides have been reported.[340] Site-directed mutagenesis has produced allergens with decreased IgE-binding capacity without decreased T-cell responses.[341,342]

Immunostimulatory sequences mimicking bacterial and viral DNA have been prepared that stimulate the innate immune system to direct T-cell responses toward

T_H1 rather than T_H2 phenotypes.[343] The results of clinical trials with a conjugate of the immunostimulatory sequence to the major allergen of ragweed, Amb a 1 (AIC), have been reported.[34,343] In a double-blind, placebo-controlled study of 25 adults who received 6 weekly injections of the AIC or placebo vaccine before ragweed season, the AIC group had better peak-season rhinitis scores on the visual analog scale ($P = .006$), peak-season daily nasal symptom diary scores ($P = .02$), and midseason overall quality-of-life scores ($P = .05$) than the placebo group during the first ragweed season, and this effect was observed in the subsequent ragweed season.[344]

Humanized anti-IgE mAb has been shown to have clinical effects in both allergic rhinitis and asthma.[345-348] Theoretically, this new therapeutic modality could be used as protective cover for clinical applications of rapid forms of immunotherapy. It is possible that preadministration of anti-IgE could provide a more effective protective effect than premedication with antihistamines and therefore permit a rush allergen immunotherapeutic regimen with reduced risk of serious systemic reactions.[282]

AUTHOR'S 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 2 systemic reaction grading systems (the European Academy of Allergy and Clinical Immunology's grading of severity for systemic side effects and the Portnoy method for numeric grading of reactions to allergen immunotherapy) can be found in the Appendix section. These forms can also be found along with examples of immunotherapy instruction and consent forms, preinjection health questionnaires, and indications for beginning and continuing immunotherapy forms at www.aaaai.org.

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352. Leynadier F, Banoun L, Dollois B, Terrier P, Epstein M, Guinnepain MT, 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.

APPENDIX 1. American College of Medical Quality's policy on the development and use of practice parameters for medical quality decision-making[1]

Practice parameters are strategies for patient management developed to assist health care professionals in clinical decision making. Practice parameters include standards, guidelines, and other patient management strategies. Standards are accepted principles for patient management. Guidelines are recommendations for patient management that identify a particular management strategy or a range of management strategies. Other strategies for patient management include practice policies and practice options. Practice parameters are to be used as screening tools to identify possible deviations from the applicable standards of care. Such parameters are not to be used as absolute standards or to profile or report on health care personnel. Parameters are designed to trigger a process in which possible deviations from the standard of care are identified as outlier practice patterns. Once a deviation from the parameter is identified, such a deviation should be referred to the appropriate qualified physician advisor or reviewer for a determination of medical necessity that conforms to the applicable standard of care. Parameters used in the day-to-day practice of clinical medicine should be clinically relevant. They should not be considered as substitutes for the standard of care but might contribute to its formulation.

Practice parameters must be developed, designed, and implemented only by board-certified, clinically practicing, specialty-matched physician advisors/reviewers with unrestricted medical licenses. Qualified nonphysicians might participate in the development of these parameters only in the areas in which their clinical expertise based on the standard of care is applicable. The health care personnel who develop these parameters should sign their names and date the final version as evidence of their participation and support. Practice parameters must be based on sound scientific research findings, professional literature, clinical experience and appropriate well-recognized methodologies and reflect professionally recognized national standards of care practiced in the clinical community of medicine. The development procedures followed, the participants involved, the evidence used, the assumptions and rationales accepted, and the analytic methods used should be meticulously documented, described, and made publicly available for national peer review. Parameters should be updated as needed.

Practice parameters are used as tools to enhance medical decision making but not as replacements for physicians' clinical judgment. They can be considered as means to enhance the performance of clinical and review personnel but not to replace them. It is below the standard of care of the medical review process to substitute qualified physician reviewer experts with unqualified reviewers who are using parameters.

APPENDIX 2. Examples of possible abbreviations for allergen immunotherapy extract 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

APPENDIX 3. 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

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

APPENDIX 4. Example of immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals (modification of the AAAAI skin testing and immunotherapy consent and instruction forms: immunotherapy administration instruction form, which can be found at http://www.aaaai.org)

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

- Up to 7 days, continue as scheduled (ie, if on weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection).
- Eight to 13 days after missed scheduled injection; repeat previous dose.
- Fourteen to 21 days after missed scheduled injection; reduce dose 25%.
- Twenty-one to 28 days after missed scheduled injection; reduce previous dose 50%.

Then increase dose each injection visit as directed on the immunotherapy schedule until therapeutic maintenance dose is reached.

This suggested approach to modification of doses of allergen immunotherapy because of gaps between treatment during the build-up phase is not based on retrospective or prospective published evidence, but it is presented as a sample for your consideration. The individual physician should use this or a similar protocol as a standard operating procedure for the specific clinical setting. A similar dose-reduction protocol should be developed for gaps in maintenance immunotherapy.

APPENDIX 5. Example of a cluster immunotherapy schedule[22,26]

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

APPENDIX 6. Recommended documentation for allergen immunotherapy prescription forms

The purpose of the allergen immunotherapy prescription form is to define the contents of the allergen immunotherapy extract in enough detail that it could be precisely duplicated. The following information should be on an immunotherapy prescription form:

Patient information:

- Patient name, patient number (if applicable), birth date, telephone number, and picture (if available) should be included.

Preparation information:

- Name of person and signature preparing the allergen immunotherapy extract should be included.
- Date of preparation should be recorded.
- Bottle name should be included (eg, trees and grass). If abbreviations are used, a 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 should be included.
- Volume of manufacturer's extract to add to achieve the projected effective concentration should be included. 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) should be included.
- Extract manufacturer should be included.
- Lot number should be included.
- Expiration date should be recorded and should not exceed the expiration date of any of the individual components.

APPENDIX 7. Allergen immunotherapy extract prescription 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:

_____
_____
_____
_____

_____ ____/____/____
Prescribing Physician Signature Date

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

APPENDIX 8. Maintenance concentrate prescription form

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: 6/10/06

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial **4** from Vial **1** on **8/30/06** Expiration date: **10/15/06**
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	Short ragweed	1:20 w/v G (150 Amb a1)	0.5ml	Greer	12345	1/01/08
2	Amaranthus Retroflexus	1:10 w/v G	0.5ml	H-S	6789	2/07/08
3	Ash	1:10 w/v G	0.5ml	Center	3333	3/17/08
4	Cat	10,000 BAU/ml G	2.00ml	ALO	9898	2/27/08
5	Timothy Grass	100,000 BAU/ml G	0.4ml	ALK	56789	7/09/08
6	Johnson Grass	1:10 w/v G	0.5ml	Greer	2434	7/20/08
7						
8						
9						
10						
Diluent	HSA		0.6ml	ALK	68597	12/08
Total Volume			5.00 ml			6/10/07

*** Components of mixes listed on a separate sheet**
**** Assumes 0.5 ml injection as target maintenance dose**

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

Specific Instructions:

_____

_____

Prescribing Physician Signature

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

APPENDIX 9. Labels for allergen immunotherapy extracts

Each vial of allergen immunotherapy extract should be labeled in a way that permits easy identification. Each label should include the following information (example in Figs 3 and 4):

- Appropriate patient identifiers might include the patient's name, patient's number, patient's picture, and birth date.
- The contents of the allergen immunotherapy extract in a general way should be included. The detail with which this can be identified depends on the size of the label and the number of allergens in the vial. Ideally, allergens should be identified as trees, grasses, weeds, mold, dust mite, cockroach, cat, and dog. Because of space limitations, it might be necessary to abbreviate the antigens (eg, T, G, W, M, DM, Cr, C, and D respectively [see Appendix 2]). A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate (vol/vol) should be recorded. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- The expiration date should be included.

APPENDIX 10. Allergen immunotherapy administration form recommended documentation

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

Patient information:

- Patient's name, date of birth, telephone number, and patient's picture (optional but helpful).

Allergen immunotherapy extract information:

- Allergen immunotherapy extract name and dilution from maintenance in vol/vol bottle letter (eg, A and B), bottle color, or number, if used.
- Expiration date of all dilutions.

Administration information in separate columns:

- Date of injection.
- Arm administered injection, which might facilitate determination of exact cause of local reaction.
- Projected build-up schedule.
- Delivered volume reported in milliliters.
- Description of any reactions. The details of any treatment given in response to a reaction would be documented elsewhere in the medical record and referenced on the administration form.
- *Patient's health before injection*. This can be performed through a verbal or written interview of the patient before administering the immunotherapy injection. The patient should be questioned about increased asthma or allergy symptoms, β-blocker use, change in health status (including pregnancy and recent infections), or an adverse reaction to a previous injection (including delayed large local reactions persisting through the next day). Patients with significant systemic illness generally should not receive an injection.
- *Antihistamine use*. Antihistamines are frequently a component of an allergy medication regimen, and it would be important to note whether a patient is taking an antihistamine on the day he or she receives his or her immunotherapy injection. For consistency in interpretation of reactions, it might be desirable for a patient to either take or avoid antihistamines on a regular basis on the days he or she receives immunotherapy. The physician should note on the form whether he or she recommends the patient consistently take an antihistamine on immunotherapy treatment days.
- *Peak flow reading*. Consider obtaining a peak expiratory flow rate measurement before administering an immunotherapy injection to asthmatic patients. Poorly controlled asthma is considered a risk factor for immunotherapy. Obtaining a peak expiratory flow rate measurement before the immunotherapy injection might help identify patients with symptomatic asthma. The patient's baseline peak expiratory flow rate should be provided on the form as a reference. Health care professionals administering immunotherapy injections should be provided with specific guidelines about the peak expiratory flow rate measurement for when an immunotherapy injection should be withheld and the patient referred for clinical evaluation.
- **Baseline blood pressure**. It might be useful to record the patient's blood pressure as a baseline for future reference.

APPENDIX 11. Allergen immunotherapy administration form

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 allergy or 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

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

Date to reorder: __/__/__

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 allergy or 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**	

APPENDIX 12. 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: _____
_____
Staff action taken (if any): _____

APPENDIX 13. 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.

APPENDIX 14. Allergen immunotherapy systemic reaction/anaphylaxis 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
__Epinephrine IM into 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	

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:
_____
_____
_____
_____

Clinical impression: True SR Questionable SR No SR

Systemic reaction severity classification: EAACI_____ **Portnoy** _____

Dosage adjustment? _____

Signatures_____ **RN** _____**MD/DO**

APPENDIX 15. Grading severity of allergen immunotherapy reactions: Two methods

1. **The European Academy of Allergy and Clinical Immunology grading of severity for systemic side effects***

Classification of systemic reactions

0 = No symptoms or nonspecific symptoms

I = Mild systemic reactions: symptoms—localized urticaria, rhinitis, or mild asthma (PF <20% decrease from baseline).

II = Moderate systemic reaction: symptoms—slow onset (>15 minutes) of generalized urticaria, moderate asthma, or both (PF < 40% decrease from baseline).

III = Severe (non–life-threatening) systemic reactions: symptoms—rapid onset (<15 minutes) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).

IV = Anaphylactic shock: symptoms—immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, and hypotension, for example.

2. **Portnoy method for numeric grading of reactions to allergen immunotherapy†**

Local

0+ = No significant reaction or small area of erythema less than the size of a half dollar without swelling or wheal formation

1+ = Erythema greater than the size of a half dollar, swelling or wheal formation, or both

Systemic

2+ = Systemic reactions: cutaneous only—might consist of a cutaneous eruption, such as urticaria

3+ = Systemic reaction: generalized pruritus, sneezing, or both—might consist of increased allergy symptoms, such as nasal congestion, sneezing, or pruritus, especially in the mouth or throat

4+ = Systemic reaction: pulmonary—consists of wheezing, shortness of breath, and tightness. Might be associated with decreased pulmonary function tests

5+ = Systemic reaction: anaphylaxis—a sensation of not feeling right is a frequent prelude; might consist of hypotension, laryngeal edema, severe wheezing, and cramping

6+ = Cardiopulmonary arrest

PF, Peak expiratory flow.

*Subcutaneous immunotherapy. Allergy 2006;61(suppl 82):5-13.

†Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80.

Allergen immunotherapy: A practice parameter second update

Supplement Editor: **Linda Cox, MD**
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These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology.

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the "Allergen immunotherapy: a practice parameter second 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 and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
5. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
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11. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999;83(suppl): S665–S700.
12. Diagnosis and management of urticaria: a practice parameter. Ann Allergy 2000;85(suppl):S521-S544.
13. Allergen immunotherapy: a practice parameter. Ann Allergy 2003;90(suppl):SI-S540.
14. Symptom severity assessment of allergic rhinitis: part I. Ann Allergy 2003;91:105-14.
15. Disease management of atopic dermatitis: an updated practice parameter. Ann Allergy 2004;93(suppl): S1-S21.
16. Stinging insect hypersensitivity: a practice parameter update. J Allergy Clin Immunol 2004;114:869-86.
17. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol 2005;115(suppl):S483-S523.

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22. Contact dermatitis: a practice parameter. Ann Allergy Asthma Immunol 2006;97(suppl 2):S1-S38.

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

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Allergen immunotherapy: A practice parameter second update

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PREFACE

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

The objective of ''Allergen immunotherapy: A practice parameter second update'' is to optimize the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. 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's ''Policy on development and use of practice parameters for medical quality decision-making'' (Appendix 1).[1]

This document builds on the previous Joint Task Force document, ''Allergen immunotherapy: a practice parameter'' published in the *Annals of Allergy, Asthma and Immunology* in 2003.[2] The updated practice parameters draft was prepared by Drs Linda Cox, James Li, Hal Nelson, and Richard Lockey. The Joint Task Force reworked the initial draft into a working draft of the document. The project was exclusively funded by the 3 allergy and immunology societies noted above.

In preparation for the 2003 ''Allergen immunotherapy: a practice parameter'' and the second update, a comprehensive search of the medical literature was conducted with various search engines, including PubMed; *immunotherapy*, *allergic rhinitis*, *asthma*, *stinging insect allergy*, and related search terms were used. 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 second update'' was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the ACAAI, AAAAI, and JCAAI. In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for review and comments from members of the sponsoring organizations. 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 allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. This document also contains recommendations for the safe practice of allergen immunotherapy, including specific recommendations on the prevention and management of 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 or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. Symptoms of allergic conjunctivitis (eg, itchy watery eyes) are often considered part of allergic rhinitis or are included in the diagnosis of rhinoconjunctivitis. Particularly good candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures, those in whom it is important to avoid the potential adverse effects of medications, and those who wish to reduce the long-term use of medications. Immunotherapy is recommended for patients with a history of systemic reaction to Hymenoptera stings and specific IgE antibodies to Hymenoptera venom.

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.[3]

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. 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 *maintenance concentrate* should be used to identify the allergen immunotherapy extract that contains a therapeutic effective dose for each of its individual constituents (see the Immunotherapy schedules and doses section).

The term *manufacturer's extract* refers to the allergy extract purchased from the manufacturer. The terms *stock*, *full-strength*, and *concentrate* are ambiguous and should not be used. 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).

Allergen immunotherapy is effective when appropriate doses of the allergens are administered. ''Allergen immunotherapy: A practice parameter'' recommends that vials of allergen immunotherapy extracts should be prepared individually for each patient to enhance the individualization of therapy, reduce the risk of allergen cross-contamination, and reduce the risk of error in administration.[4,5] This parameter recommends the use of standardized allergen immunotherapy prescription and administration forms to improve the safety, uniformity, and standardization of allergen immunotherapy practice.[4,5] The suggested forms are found in the Appendix (Appendices 7, 8, 11, 12, and 14) and in the members' section of the www.aaaai.org Web site. The routine use of these standardized forms should improve the quality of immunotherapy practice.

Members' feedback comments on the recommended allergen extract dilution dating in the 2003 ''Allergen immunotherapy: A practice parameter'' led to an allergen immunotherapy extract dilution stability study designed by the AAAAI Immunotherapy and Allergy Diagnostics Committee and funded by the AAAAI Board of Directors. The study was designed to investigate the effect of time, temperature, and dilution of standardized allergen extract potency, and the results of this study were considered in this update.

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 3 years after publication. Requests for information about or an interpretation of these practice parameters should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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. Allergen immunotherapy

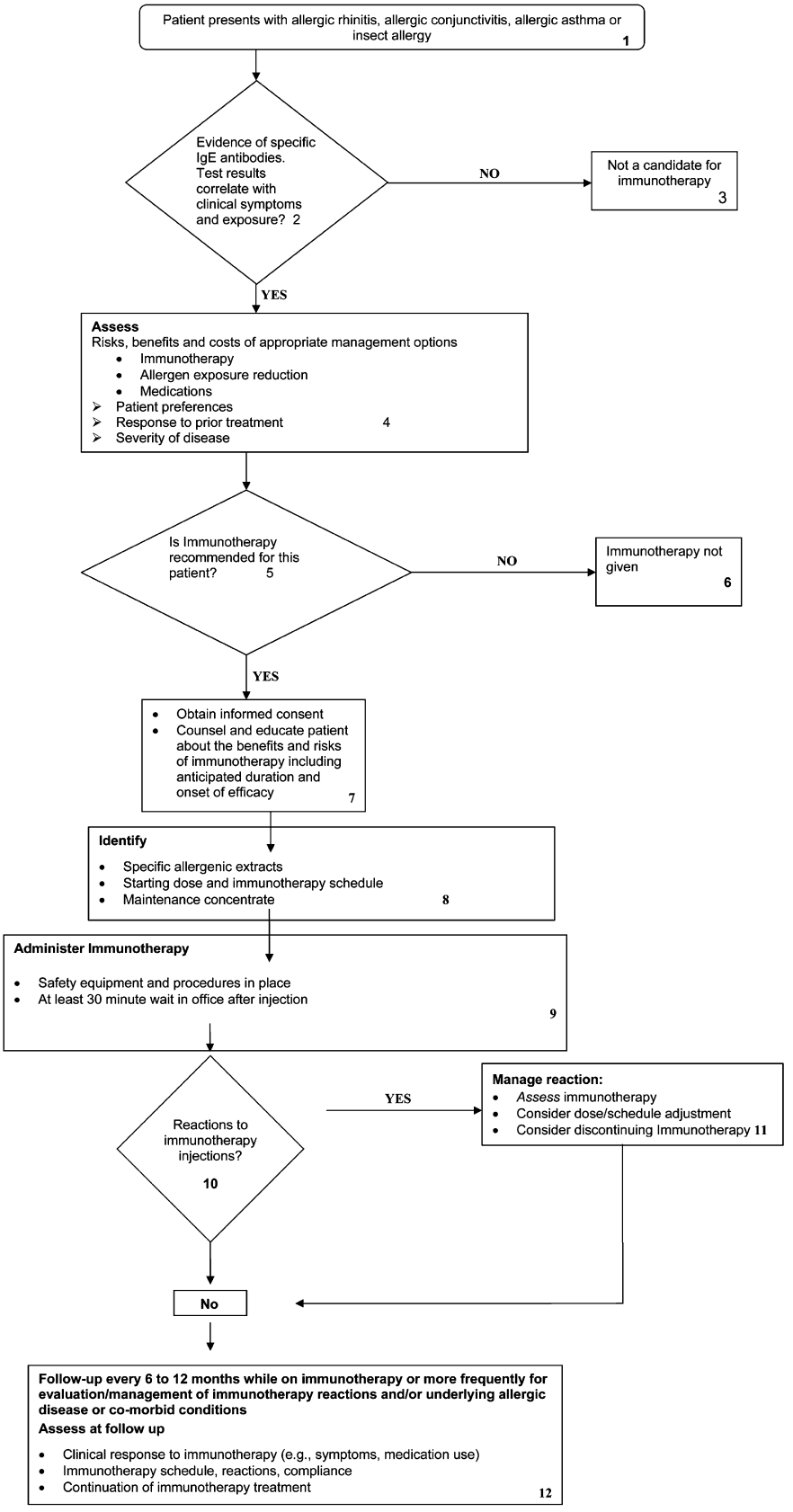


FIG 1. Algorithm for allergen immunotherapy.

might prevent the development of asthma in individuals with allergic rhinitis.[6-9] Evaluation of a patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic conjunctivitis, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for specific IgE antibody).[10]

Box 2

Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although *in vitro* testing for 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

Management of complex medical conditions, such as allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity, should include the careful evaluation of management 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 patient 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. On the basis of clinical considerations and patient 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 good candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy (VIT).

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 on the basis of 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 (see the Immunotherapy schedules and doses section). In general, the starting immunotherapy dose is 1000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 1000 to 4000 arbitrary units (AU; eg, for dust mite) or bioequivalent allergy units (BAU; eg, for grass) 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 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 referred to as *up-dosing*, *induction*, or the *dose-increase phase*) entails administration of gradually increasing doses during a period of approximately 14 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 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, in particular anaphylaxis. Patients should wait at the physician's office for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly, if they occur.

In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring 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. Some physicians recommend providing certain patients with epinephrine for self-administration in case of severe late reactions to immunotherapy injections.

Box 10

Injections of allergen immunotherapy extract can cause local or systemic reactions. Most severe reactions develop within 30 minutes after the immunotherapy injection, but reactions can occur after this time.

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 (anaphylaxis). Epinephrine is the treatment of choice in anaphylaxis, preferably when administered intramuscularly,[11] although subcutaneous administration is acceptable.[12]

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, see the practice parameters for anaphylaxis.[12]

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. After a severe systemic reaction, careful evaluation by the prescribing physician is recommended. For some patients, the immunotherapy maintenance dose might need to be reduced because of repeated systemic reactions to immunotherapy injections. The decision to continue immunotherapy should be re-evaluated after severe or repeated systemic reactions to allergen immunotherapy extracts.

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 doses, 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,[13] but others might experience a recurrence of their symptoms after discontinuation of allergen immunotherapy.[14] 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, and 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 on the basis of the patient's clinical response, disease severity, immunotherapy reaction history, and patient preference.

IMMUNOTHERAPY GLOSSARY

For more information on immunotherapy definitions, see the article by Kao.[15]

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 (pigments and salts; see the Allergen selection and handling section). Other terms used to describe the allergen immunotherapy extract include *allergen product*,[16] *allergy serum*, *allergen vaccine*,[17] 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.[18] Other terms that have been used for allergen immunotherapy include *hyposensitization*, *allergen-specific desensitization*, and the lay terms *allergy shots* or *allergy injections*.[15]

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

TABLE II. Allergen immunotherapy dose-calculation table

- Express weight per volume as a fraction: $\frac{1}{N}$ or 1:*N*.
- Calculate concentration of individual allergens in mixtures. If a mixture is made of equal amounts of N individual allergens to make a total concentration (C), the final concentration of an individual allergen (Ca) can be calculated by using the following equation:

$Ca = C \times \frac{1}{N} = \frac{C}{N}$ or *C*:*N*.

For example, if a mixture of equal amounts of 5 (N) allergens has a total concentration (C) of 100,000 BAU/mL, then the final concentration of each individual allergen (Ca) is: $Ca = \frac{C}{N} = \frac{100{,}000}{5} = 20{,}000\ BAU/mL$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{C}{N} = \frac{1/10}{5} = \frac{0.1}{5} = 0.02$ or $\frac{1}{50}$ or 1:50.

- Dilution of individual allergen: If an initial volume, Vi (in milliliters), of an individual antigen with concentration, Ci, is added to an allergen extract to make a final volume of Vf (in milliliters), the final allergen concentration (Ca) in the allergen extract mixture will be: $Ca = Ci \times \frac{Vi}{Vf}$.
- Final concentration of an allergen in a mixture of mixtures is determined by multiplying the initial concentration by the dilution factors from each mixing step.

For example, consider a mixture containing equal amounts of 5 (N) allergens with a total concentration (C) of 100,000 BAU/mL (first dilution). If an initial volume (Vi) of 0.5 mL of this mixture is further mixed with other components and diluent to make a final allergen extract mixture volume (Vf) of 5.0 mL (second dilution), the final concentration of an individual allergen (Ca) will be:

$$Ca = C \times \underbrace{\frac{1}{N}}_{\text{Mixture dilution}} \times \underbrace{\frac{Vi}{Vf}}_{\text{Allergen extract dilution}} = 100{,}000 \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{100{,}000}{50} = 2000\ BAU/mL$$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{1}{10} \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{1}{500}$ or 1:500.

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).

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 to 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-medicated 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 multiplied by volume of administered dose (see Table II for a dose-calculation table).

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, cat, 1000 BAU, [highest tolerated dose] vs 2000 BAU [projected effective dose]).

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 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 by a variety of immunologic transformations. Early definitions of the term immunotherapy included active and passive immunization for the purpose of improving 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 by means of induction of clonal deletion, anergy, immune tolerance, or immune deviation.

The *maintenance concentrate* is a preparation that contains individual 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 may not be the initially calculated projected effective dose.

The *maintenance goal* (or projected effective dose) is the allergen dose projected to provide therapeutic efficacy. The maintenance goal is based on published studies, but a projected effective dose has not been established for allergens. 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 the 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 large local reaction causing discomfort). The intervals between maintenance immunotherapy injections generally ranges 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 by means of immunoblotting or crossed allergoimmunoelectrophoresis.

For a definition of *projected effective dose*, see 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 test responses), and premedication with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similar high incidence of systemic reactions.

Off the board into one syringe is a phrase that describes a method of allergen immunotherapy preparation and administration that involves specifically mixing the patient's allergen immunotherapy injection in a single syringe, which is not recommended. This syringe might be inserted into more than one allergen extract vial, and this poses a risk of cross-contamination of the allergen extracts and might dull the needle with repeated penetration of the rubber stopper.

Shared specific patient vials is a method of allergen immunotherapy preparation and administration in which the allergy immunotherapy extract is withdrawn from a shared vial (eg, mixed vespids or dust mite mix). This is sometimes referred to as off the board, but it is distinct from the method of off the board into one syringe in that the syringe enters only one allergen extract vial.

INTRODUCTION

Immunity has been defined as protection against certain diseases. The initial immunotherapeutic interventions, which included the use of preventive vaccines and xenogenic 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 the field of allergen immunotherapy. From its humble empiric emergence in 1900, when ragweed injections were proposed as therapy for autumnal hay fever, allergen immunotherapy has progressed in both theory and practice from the passive immunologic approach to the active immunologic procedures pioneered by Noon[19] and Freeman.[20,21] 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 10 years. Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Some studies have suggested that allergen immunotherapy might prevent the development of asthma in individuals with allergic rhinitis.[6-9]

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,[22-26] and it should be differentiated from unproved methods, such as neutralization-provocation therapy and low-dose subcutaneous regimens based on the Rinkel technique, which have been found to ineffective in a double-blind placebo-controlled study.[27,28]

SUMMARY STATEMENTS

Mechanisms of immunotherapy

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, defined as a relative decrease in allergen-specific responsiveness and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

Allergen extracts

Summary Statement 6: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. **A**

Summary Statement 7: Nonstandardized extracts might vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Summary Statement 8: 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**

Cross-reactivity of allergen extract. Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

Efficacy of immunotherapy

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Summary Statement 10: Immunotherapy is effective for 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**

Food allergy, urticaria, and atopic dermatitis. Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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**

Measures of efficacy. Summary Statement 12: 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**

Safety of immunotherapy

Reaction rates. Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

Timing of anaphylactic reactions to immunotherapy injections. Summary Statement 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

β-*Adrenergic blocking agents.* Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

Contraindications. Summary Statement 18: 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**

Reducing the risk of anaphylaxis to immunotherapy injections. Summary Statement 19: 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**

Patient selection

Clinical indications. Summary Statement 20: 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 depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Special precautions in patients with asthma. Summary Statement 21: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. **C**

Clinical indications for VIT. Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Summary Statement 23: Patients selected for immunotherapy should be cooperative and compliant. **D**

Allergen selection and handling

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted in vitro tests for specific IgE antibodies can also be used. **A**

Specific allergens. Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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, supported by the presence of specific IgE antibodies. **A**

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Dose selection. Summary Statement 30: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. **A**

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens, is recommended. **B**

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extract handling

STORAGE

Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

STORING DILUTE EXTRACTS

Summary Statement 34a: More dilute concentrations of allergen immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: 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 a number of 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. **B**

Immunotherapy schedules and doses

Summary Statement 35: A customized individual 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 be based on single or multiple allergens. **D**

Maintenance concentrate. Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

Recommended doses. Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

Effect of dilution on dose. Summary Statement 38: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. **A**

Dilutions of the maintenance concentrate. Summary Statement 39: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. **D**

Labeling dilutions. Summary Statement 40: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. **D**

Individualized treatment vials. Summary Statement 41: 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. The mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. **C**

Starting doses. Summary Statement 42: The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. **D**

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

Dose adjustments for systemic reactions. Summary Statement 44: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. **D**

Reductions during periods of exacerbation of symptoms. Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Dose adjustments for late injections. Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

Cluster schedules. Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. **C**

Rush schedules. Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. **A**

Systemic reactions and rush schedules. Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

Premedication and weekly immunotherapy. Summary Statement 50: Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

Premedication with cluster and rush immunotherapy. Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

Maintenance schedules. Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. **A**

Continuing care

TIME COURSE OF IMPROVEMENT

Summary Statement 53: Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **A**

FOLLOW-UP VISITS

Summary Statement 54: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. **D**

DURATION OF TREATMENT

Summary Statement 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

DOCUMENTATION AND RECORD KEEPING

Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. **D**

INJECTION TECHNIQUES

Summary Statement 57: Allergen immunotherapy extract injections should be administered with a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **D**

Summary Statement 58: The injection should be administered subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Location of allergen immunotherapy administration

Physician's office. Summary Statement 59: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Summary Statement 60: 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**

Other locations. Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **D**

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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**

Summary Statement 63: 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for his or her immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extract might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Special considerations in immunotherapy

Allergen immunotherapy in children. Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Pregnancy. Summary Statement 71: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. **C**

Immunotherapy in the elderly patient. Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy in patients with immunodeficiency and autoimmune disorders. Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

Alternative routes of immunotherapy

Sublingual and oral immunotherapy. Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no US Food and Drug Administration (FDA)–approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **A**

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Immunotherapy techniques that are not recommended. Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

MECHANISMS OF IMMUNOTHERAPY

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, which is defined as a relative decrease in allergen-specific responsiveness, and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

The immunologic changes associated with immunotherapy are complex, and the exact mechanism or mechanisms responsible for its' clinical efficacy are continually being elucidated. Data support the concept that successful immunotherapy is associated with a change to a T_H1 $CD4^+$ cytokine profile.[29-34] Data indicate that increased production of IL-12, a strong inducer of T_H1 responses, contributes to this shift.[33] Clinically successful immunotherapy has been reported to be associated with immunologic tolerance, which is defined as a relative decrease in antigen-specific responsiveness, immune deviation, or anergy. For example, lymphoproliferative responses to allergen are reduced with immunotherapy.[32] Successful immunotherapy results in generation of a population of T regulatory cells, which are $CD4^+CD25^+$ T lymphocytes producing IL-10, TGF-β, or both.[35-39] Regulatory T-cell release has been described in allergen immunotherapy with Hymenoptera venom,[35] grass pollen extract,[37] and house dust mites.[38] IL-10 reduces B-cell antigen-specific IgE and increases IgG4 levels; reduces proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicits tolerance in T cells by means of selective inhibition of the CD28 costimulatory pathway.[36,37]

Allergen immunotherapy has been shown to block both the immediate and late-phase allergic response.[40] Allergen immunotherapy has been shown to decrease the recruitment of mast cells, basophils, and eosinophils in the skin, nose, eye, and bronchial mucosa after provocation or natural exposure to allergens.[41]

In patients receiving immunotherapy, initially there is an increase in specific IgE antibody levels, followed by a gradual decrease to a level that is still higher than that present before treatment. Clinical improvement in many patients develops before decreases in their IgE antibody levels occur or in other patients whose IgE antibody levels never decrease, thereby demonstrating that efficacy is not dependent on reductions in specific IgE levels.[42,43] Immunotherapy does diminish the seasonal increase in specific IgE levels.[44] Despite the persistence of significant levels of specific IgE antibody levels, immunotherapy usually causes a reduction in 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.[45-48]

An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, has also been associated with immunotherapy. The properties of allergen-specific IgA have yet to be determined, and there is a weak correlation between the increase in allergen-specific IgG levels and immunotherapy's clinical efficacy.[30,49,50]

Immunotherapy might alter the affinity and specificity of allergen-specific IgG.[51,52] During the initial phase of ultrarush VIT, a change in IgG specificity (ie, a change in the set of epitopes dominantly recognized by IgG on wasp venom antigens) occurred concomitantly with early clinical tolerance and was seen within 12 hours of ultrarush VIT ($P < .001$).[51] 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 individuals.[52] This change in IgG specificity preceded the increase in IgG titers and was sustained for up to 6 months.[52]

Allergen-specific IgG induced from immunotherapy can block IgE-dependent histamine release and subsequent IgE-mediated antigen presentation to T cells.[53] This effect might be dependent on IgE, allergen concentration, and CD23, the low-affinity receptor for IgE.

Whereas 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.[37,53]

The relationship between these immunologic changes and immunotherapy efficacy is not completely understood.

ALLERGEN EXTRACTS

Summary Statement 6: 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 has 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.[2,18,54-56] 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.

United States–licensed extracts can be obtained in aqueous, glycerinated, lyophilized, and acetone-precipitated and alum-precipitated formulations. Some commonly used allergens are standardized. These include extracts for cat hair, cat pelt, *Dermatophagoides pteronyssinus*, *Dermatophagoides 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.[57] 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.

Most standardized extracts are labeled in BAU. Short ragweed potency units were originally based on the content of the major allergen Amb a 1. Ragweed potency is reported in FDA units and BAU. One FDA unit of Amb a 1 equals 1 μg of Amb a 1, and 350 units of Amb a 1/mL is equivalent to 100,000 BAU/mL. Cat extracts were also originally standardized based on the content of major allergen (Fel d 1), with 100,000 arbitrary units (AU) per milliliter containing between 10 to 19.9 FDA units of Fel d 1 per milliliter (1 FDA unit of Fel d 1 equals 2 to 4 μg of Fel d 1).[55,58,59] Subsequently, $ID_{50}EAL$ testing suggested that 100,000 AU/mL was equal to 10,000 BAU/mL.[60] Approximately 22% of individuals with cat allergy have specific IgE antibodies to cat albumin.[61] Cat pelt extracts have a greater amount of albumin than cat hair extracts.[60]

Dust mites were originally standardized in AU by means of inhibition radioimmunoassay (RIA), and subsequent $ID_{50}EAL$ testing indicated that the AU was bioequivalent to the BAU, and the original AU nomenclature was kept. Dust mite extracts are still labeled in AU.

Summary Statement 7: Nonstandardized extracts can vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Nonstandardized extracts are labeled as wt/vol, which expresses weight in grams per volume in milliliters; that is, a potency of 1:100 indicates that 1 g 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 with a particular wt/vol or PNU potency can have widely varying biologic activities.[62-64] Therefore they should not be considered equipotent.

Summary Statement 8: 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**

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. The major clinically relevant aeroallergens of North America are listed in Table III. Furthermore, nonrelevant allergens in such mixtures could act as sensitizers rather than as tolerogens.[65,66] The physician must therefore select only those aeroallergens for testing and treatment that are clinically relevant in a particular geographic area.

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, dog), insect (cockroach), and Hymenoptera venom source materials.

Cross-reactivity of allergen extract

Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

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. A summary of cross-reactivity patterns of the clinically relevant North American aeroallergens can be found in Fig 2. 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,[67] inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[68-75] Grasses in other subfamilies (eg, Bermuda, Bahia, and Johnson) show greater diversity and should be evaluated separately.[76-78] Bermuda and Johnson grasses are increasingly important in the South,

TABLE III. The major clinically relevant aeroallergens of North America*

- Tree pollen
  - Chinese elm *(Ulmus parvifolia)*†‡; Siberian elm *(Ulmus pumila)*†‡; American elm *(Ulmus Americana)*†‡
  - Red oak *(Quercus rubra)*†; White oak *(Quercus alba)*†
  - Paper birch *(Betula papyrifera)*
  - Alder *(Alnus rubra)*
  - Box elder *(Acer negundo)*†; Red maple *(Acer rubra)*†
  - Eastern cottonwood *(Populus deltoides)*
  - Sycamore *(Platanus occidentalis)*
  - White ash *(Fraxinus americana)*†; Olive *(Olea europaea)*†‡
  - Black walnut *(Juglans nigra)*
  - Mulberry *(Morus rubra)*
  - Mountain cedar *(Juniperus ashei)*
  - Pecan *(Carya illinoensis)*
- Grass pollen
  - Rye *(Lolium perenne)*§‖
  - Timothy *(Phleum pratense)*§‖
  - Meadow fescue *(Festuca elatior)*§‖
  - Bermuda *(Cynodon dactylon)*‖
  - Johnson *(Holcus halepensis)*
  - Bahia *(Paspalum notatum)*
- Weed pollen
  - Short ragweed *(Ambrosia artemisiifolia)*‖
  - English (narrow leaf) plantain *(Plantago lanceolata)*
  - Mugwort *(Artemisia vulgaris)*
  - Russian thistle *(Salsola kali)*
  - Burning bush *(Kochia scoparia)*
  - Sheet (red) sorrel *(Rumex asetosella)*
  - Red root pigweed *(Amaranthus retroflexus)*
- Indoor aeroallergens
  - Cat epithelium *(Felis domesticus)*‖
  - Dog epithelium *(Canis familiaris)*
  - Arthropods (domestic mites: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*)‖
  - Insects (German cockroach: *Blattella germanica*)
- Fungi
  - *Alternaria alternata*¶
  - *Cladosporium* (*C cladosporioides*, *C herbarum*)¶
  - *Penicillium* (*P chrysogenum*, *P expansum*)¶
  - *Aspergillus fumigatus*¶
  - *Epicoccum nigrum*, *Drechslera* or *Bipolaris* type (eg, *Helminthosporium solani*)¶

*Compiled and selected in collaboration with the AAAAI Immunotherapy Committee Allergen Subcommittee for the identification of 35 key allergens of North America.
†Extensive cross-reaction of species within the genus.
‡Apart from regional prevalence, they are limited to local sites with substantial stands of these trees.
§Extensively cross-react with one another and bluegrass, orchard, red top, and sweet vernal.
‖Allergens for which standardized extracts are commercially available.
¶Species that are widely distributed and clinically important.

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.[79-82] 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.[83-85] Significant cross-reactivity between Betulaceae pollens and oak of the Fagaceae family has been demonstrated with percutaneous skin testing.[75] RAST inhibition studies have shown cross-inhibition between oaks and other *Fagales* species.[86] IgE immunoblot inhibition experiments have demonstrated that the *Fagales* species might be strongly inhibited by birch species.[87] The use of one of the locally prevalent members (eg, birch and alder) should be adequate.[88]

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.[89,90] Maple and box elder trees are found throughout the United States, except for the arid southwest. Although in the same genus as maple, *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,[91,92] and there are allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.[93]

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.[94] Similarly, Chenopod-Amaranth families have wide ranges in the western regions but are present throughout North America.[95] Current information on cross-reactivity of these families is limited.[96-98] 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.[99] The use of a single Amaranth extract should be sufficient to cover this family.[100,101] Similarly, *Atriplex* species (eg, saltbushes and scales) show near identity, and use of a single member is adequate. 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,

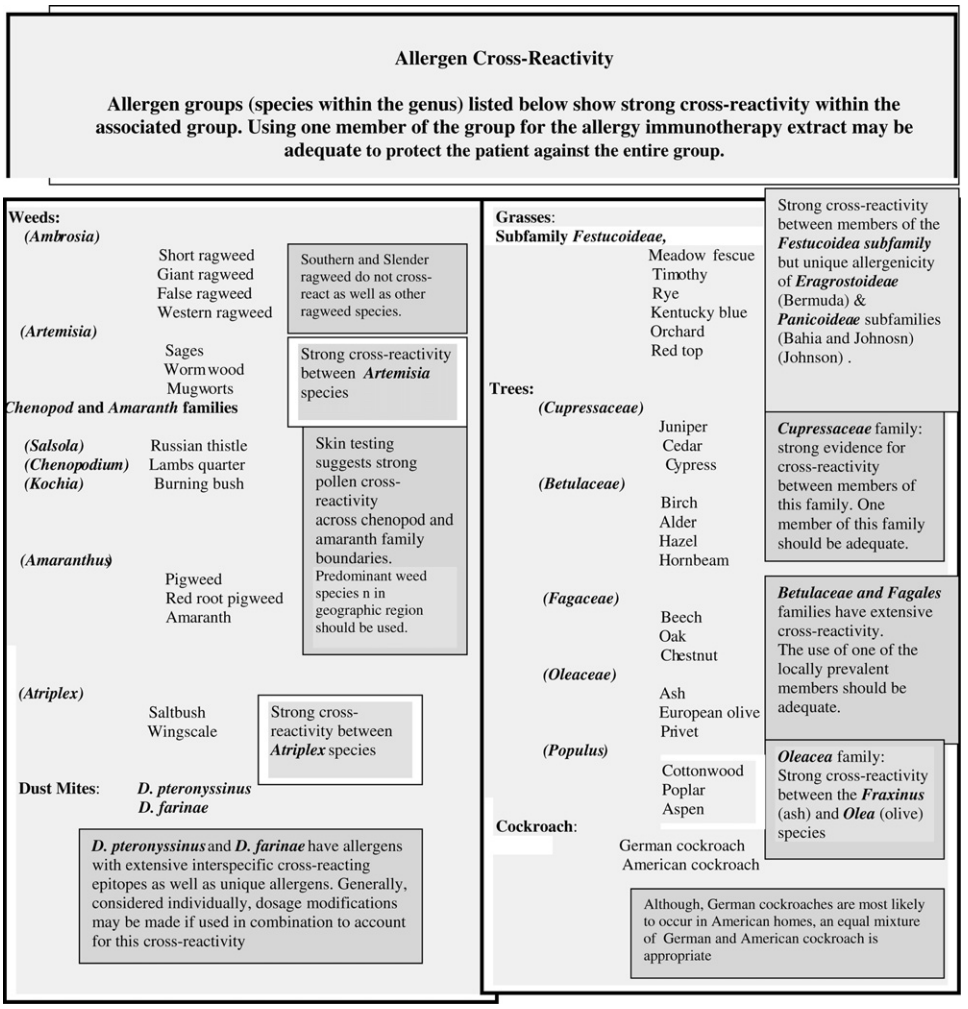


FIG 2. Patterns of allergen cross-reactivity.

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*).

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.[102,103] Stinging Hymenoptera insects occur throughout the United States; the fire ant is found only in Gulf Coast states, Texas, and some other southern and western states. Commercial venom extracts are available for some Hymenoptera species, except the fire ant, for which only whole-body extract is available.

EFFICACY OF IMMUNOTHERAPY

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity

Summary Statement 10: Immunotherapy is effective for 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.[104-111] Immunotherapy is effective for the treatment of allergic rhinitis[107] (including ocular symptoms[112,113]), allergic asthma,[104,109,111,114,115] and stinging insect hypersensitivity[108,116] and is effective in both adults and children.[117-124] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollens,[13,125-132] fungi,[133-138] animal allergens,[22,25,26,139-143] dust mite,[114,115,144-153] and cockroach.[154] There have been no controlled trials of fire ant whole-body extract, but it does appear to be effective in

TABLE IV. Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy

Outcome measure	House dust mite	Other allergens*†
Symptomatic improvement	2.7 (1.7-4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2-7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50)	5.5 (2.8-10.7)

Data are used with permission from Abramson et al.[104]
ND, Not done.
*Odds ratio (95% CI).
†Pollen, mold, or animal dander.

uncontrolled trials.[155-157] 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. A number of studies have also demonstrated a significant improvement in quality of life, as measured by using standardized questionnaires.[24,158-161] The magnitude of the effect depends on the outcome that is used (Table IV). For dust mite, the effect size ranges from a 2.7-fold improvement in symptoms to a 13.7-fold reduction in bronchial hyperresponsiveness. 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.[110] 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[107] and asthma[104,109,111] have been performed to deal with the issue of power. One review of 75 trials involving 3188 asthmatic patients found that, overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyperreactivity after immunotherapy, and it would have been necessary to treat 4 patients (95% CI, 3-5) with immunotherapy to avoid 1 deterioration in asthma symptoms and 5 (95% CI, 4-6) patients to avoid 1 requiring increased medication.[111] These meta-analyses strongly support the efficacy of allergen immunotherapy. Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued[13,162,163] and might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6,9,122,162-165] Allergen immunotherapy might also prevent the development of new allergen sensitivities in monosensitized patients.[120,166,167]

Food allergy, urticaria, and atopic dermatitis

Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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 use of allergen immunotherapy for individuals with the potential for IgE-mediated (anaphylaxis) reactions to foods should be regarded as investigational at this time.[168-171] There have been 2 investigational studies demonstrating efficacy in food hypersensitivity, the first using aqueous subcutaneous injections to peanut and the second using sublingual immunotherapy to hazelnut.[171-173]

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 a modified peanut extract is needed for clinical application of this method of treatment.[171] There is currently no FDA-approved formulation for sublingual immunotherapy, and this route of allergen immunotherapy is currently considered investigational at this time (see Summary Statement 73).

At the present time, there is not enough evidence to support food immunotherapy.

There is no evidence supporting the efficacy of immunotherapy for individuals with chronic urticaria, angioedema, or both.

There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[174-176] 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 ($P = .0379$) and topical corticosteroid use ($P = .0007$).[174]

The potential for benefit in symptoms related to oral allergy syndrome with the cross-reacting inhalant immunotherapy, which includes cross-reacting 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 subcutaneous immunotherapy directed against birch tree,[177] whereas another double-blind, double-dummy, placebo-controlled study comparing the effect of subcutaneous immunotherapy with sublingual immunotherapy 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, medication use, and decrease in IgE reactivity.[178] More investigation is required to substantiate the contention that benefits in oral symptoms will occur with immunotherapy.

Measures of efficacy

Summary Statement 12: 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. Objective measures, such as increase in allergen-specific IgG levels and decreased skin test reactivity, as measured by skin test titration, are changes generally associated with effective immunotherapy but, at present, are not practical for routine clinical use.[147] Nonquantitative skin testing or *in vitro* 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 are not very reliable given the strong placebo-like effect (Hawthorne effect) associated with any treatment. A more objective means for determining efficacy as validated in controlled clinical studies is the use of clinical symptom scores and the amount of medication required to control symptoms and maintain peak flow rates or pulmonary function tests within acceptable limits. Successful immunotherapy often results in a reduction in medication. Sequential measurement of disease-specific quality of life also might be helpful.

SAFETY OF IMMUNOTHERAPY

Reaction rates

Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Large local reactions associated with allergen immunotherapy are fairly common, with a frequency ranging from 26% to 86% of injections.[179] Two retrospective studies compared the effect of not adjusting immunotherapy dose based on large local reactions on the immunotherapy systemic reaction rate with dose-adjustment protocols.[179,180] There was a total of 12,464 injections administered with a dose-adjustment protocol in the 2 studies compared with 9542 injections administered with a no-dose-adjustment protocol. 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 for subsequent systemic reactions, 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 large local reactions, defined as 25 mm or larger, in patients who had experienced systemic reactions with age-, sex-, and allergen sensitivity–matched control subjects who had not had allergen immunotherapy systemic reactions found the rate of large local reactions was 4 times higher among the 258 patients who had subsequently experienced a systemic reaction compared with those who had never experienced a systemic reaction.[181] Patients who had experienced systemic reactions had 1573 large local reactions in 4460 visits (ie, 35.2% of visits) and 8081 injections (ie, 19.5% of injections) compared with the matched control group without systemic reactions who had 1388 large local reactions in 15,540 visits (8.9% per visit) and 26,259 injections (5.3% per injection; difference between groups, $P < .001$). Individual large local reactions were not predictive of future systemic reactions, but large local reactions preceded systemic reactions in approximately one third of the systemic reactions. These findings suggest that individuals with a greater frequency of large local reactions might be at greater risk for systemic reaction. Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy protocol modifications based on them are needed.

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

The prevalence of severe systemic reactions after allergen immunotherapy ranges from less than 1% of patients receiving conventional immunotherapy to greater than 36% of patients in some studies of patients receiving rush immunotherapy.[182,183]

In a recent survey of fatal and near-fatal reactions (NFRs) sent to physician members of the AAAAI, 273 of 646 respondents reported NFRs during the period of 1990-2001.[184]

The incidence of unconfirmed NFRs was 23 per year (5.4 events per million injections). Administration during the height of 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 angiotensin-converting enzyme 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 systemic reactions to subcutaneous immunotherapy over a 20-year period (1981-2000) during which 435,854 injections were administered to 4000 patients, 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.[185,186] In a prospective multicenter study there were 53 systemic reactions (0.3% of the doses) out of 17,526 administered doses in 18 (3.7%) of 423 patients.[187] 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 (21 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, there were 41 fatalities identified in the initial brief survey (20 directly reported and 17 with completed detailed questionnaire) from immunotherapy injections.[188] 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.[189,190] Therefore although severe systemic reactions to allergen immunotherapy are not common, serious systemic reactions (some fatal) can occur.

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

In the AAAAI survey of physician members on immunotherapy and skin testing, fatal reactions, and NFRs during the period of 1990-2001, 15 of the 17 fatalities had asthma, and in 9 patients asthma was considered the susceptibility factor that contributed to the fatal outcome.[188]

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.[184]

Administration during the peak pollen season (3 patients) and previous systemic reactions (4 patients) were cited as other contributing factors. Five fatalities occurred in outside medical facilities, and 2 fatalities occurred at home. No patients were receiving β-blockers; 1 patient was taking an angiotensin-converting enzyme inhibitor. In the most comprehensive evaluation of fatalities associated with allergen immunotherapy, from 1945-1987, there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[189] 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, with 73.3% of patients with an FEV_1 of less than 80% of predicted value experiencing 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 ($P < .0001$).[191] 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% of patients. These studies suggest that symptomatic asthma, severe asthma, or both might be a risk factor for immunotherapy.

In addition to symptomatic asthma and injections giving 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.[17] With the exception of dosing errors and 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 recent 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 or allergy symptom exacerbation, β-blocker use, change in health status (including pregnancy), or adverse reaction to previous allergen immunotherapy injection. The preinjection evaluation might also include a peak flow measurement to assess the airway function of asthmatic patients.

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 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

In a retrospective study the time to onset of a systemic reaction after an immunotherapy injection was less than 30 minutes in most cases.[189] A review of the literature indicates that 70% of systemic reactions occur within 30 minutes after an injection.[183] In the AAAAI 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.[184,188] 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.[190] 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 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.[192] In another prospective study 8% of systemic reactions occurred more than 2 hours after injection.[193]

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.[194]

Because most reactions that resulted from allergen immunotherapy occurred within 30 minutes after an injection, patients should remain in the physician's office for at least 30 minutes after receiving an injection, but longer waits are reasonable, as directed by the physician. In addition, patients who are at increased risk of a systemic reaction might need to carry injectable epinephrine. Such patients might also need to remain in the physician's office more than 30 minutes after an injection. 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.

β-Adrenergic blocking agents

Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

β-Blockade enhances pulmonary, cardiovascular, and dermatologic end-organ effects of mediators and increases mortality associated with experimental anaphylaxis induced by either immunologic or nonimmunologic mechanisms. Patients who are receiving β-adrenergic blocking medications might be at increased risk if they experience a systemic reaction to an allergen immunotherapy injection because the β-receptor blockade might attenuate the response to epinephrine.[195-202] Patients who are receiving β-blocking drugs were almost 9 times more likely to be hospitalized after an anaphylactoid reaction from radiocontrast media.[198] Although topical β-blockers have markedly less systemic β-antagonist effects than oral β-blockers, they still might exhibit some systemic β-antagonist effects. Whether topical β-blockers pose the same or a smaller risk than oral β-blockers in regard to the treatment of allergen immunotherapy–related systemic reactions is not known.

There have been very few studies that have examined the effect of β-blocker medications on allergen immunotherapy. A prospective 1-year study designed to determine whether patients taking β-blocker drugs were at increased risk of immunotherapy-induced systemic reactions found that there were 166 systemic reactions out of 56,105 injection visits in 3178 patients (68 were receiving a β-blocker).[203] The systemic reactions occurred in 144 (4.5%) patients, and only 1 of these patients was receiving a β-blocker medication. The authors calculated that by chance, 3.08 patients receiving the β-blocker medications drugs were expected to have had an systemic reaction and concluded that β-blocker medications did not increase the frequency of allergen immunotherapy systemic reactions ($P > .95$).

In another study of 1389 patients prescribed immunotherapy for Hymenoptera venom hypersensitivity who were followed for 34 months, there were 25 patients who received concomitant β-blocker medications.[204] Three (12%) of the 25 patients receiving β-blocker medications experienced systemic reactions during immunotherapy compared with 23 (16.7%) of 117 patients with cardiovascular disease not receiving β-blockers. Systemic reactions after a field sting or challenge occurred in 1 (14.3%) of 7 cardiovascular patients receiving β-blocker medications compared with 4 (13.8%) of 29 cardiovascular patients not receiving β-blocker medications. No severe reactions to immunotherapy or sting re-exposure were observed in patients receiving β-blockers medications.

Immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. In such cases, intravenous glucagon, which might reverse the refractory bronchospasm and hypotension by activating the adenyl cyclase directing and bypassing the β-adrenergic receptor, might be used if epinephrine has not been effective.[205,206] Prospective studies are necessary to clarify the magnitude of the risk of systemic reactions to allergens in patients who are receiving concomitant therapy with β-blockers, and a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy.

Contraindications

Summary Statement 18: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications

TABLE V. Actions to reduce the risk of anaphylaxis

- Assess the patient's general medical condition at the time of injection (eg, asthma exacerbation).
- Consider obtaining a PEFR before administration of the injection. If the PEFR is significantly less than the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.
- 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 with increased allergen sensitivity or those who have previously had a systemic reaction) might need to wait longer.
- Carefully evaluate any patient with a late reaction (eg, persistent large local reaction lasting >24 hours, systemic reaction occurring more than 30 minutes after the immunotherapy injection).
- 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.

PEFR, Peak expiratory flow rate measurement.

TABLE VI. Recommended equipment and medications to treat anaphylaxis

Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur. This should include at least the following equipment and medications:

- stethoscope and sphygmomanometer;
- tourniquet, syringes, hypodermic needles, and large-bore needles (14-gauge);
- aqueous epinephrine HCL 1:1000 wt/vol;
- equipment to administer oxygen by mask.
- intravenous fluid set-up;
- antihistamine for injection (second-line agents for anaphylaxis, but H_1 and H_2 antihistamines work better together than either one alone);
- corticosteroids for intravenous injection;
- vasopressor;
- equipment to maintain an airway appropriate for the supervising physician's expertise and skill.

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 venom hypersensitivity and cardiac disease being treated with β-blocker medications.

Reducing the risk of anaphylaxis to immunotherapy injections

Summary Statement 19: 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 extremely 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 or other health care professional appropriately trained in emergency treatment.

The 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. Epinephrine is the first-line treatment for anaphylaxis. 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.[12,207-213] It is important to administer epinephrine early in the management of anaphylaxis. 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 V and VI, respectively. Before allergen immunotherapy is chosen as a treatment, the physician should educate the patient about the benefits and risks of immunotherapy, as well as methods for minimizing risks. The patient also should be told that despite appropriate precautions, reactions might occur without warning signs or symptoms. Informed consent should include a discussion of the potential immunotherapy adverse reactions, and this discussion should be documented in the patient's medical record.

PATIENT SELECTION

Clinical indications

Summary Statement 20: Allergen immunotherapy should be considered for patients who have demonstrable

TABLE VII. Clinical indications for allergen immunotherapy

Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or both:
- symptoms of allergic rhinitis after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medications;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medication;
- coexisting allergic rhinitis and asthma;
- possible prevention of asthma in patients with allergic rhinitis

Symptoms of asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medication;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medications;
- coexisting allergic rhinitis and allergic asthma.

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);
- adults and children with a history of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.

evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic rhinitis.[107] Prospective, randomized, double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic asthma.[104,109,111]

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 proper identification and selection of component allergens on the basis of 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 (Table VII). The severity and duration of symptoms should also be considered in assessing the need for specific allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. In addition, specific allergen immunotherapy should be considered if the patient wishes to avoid long-term pharmacotherapy. Time lost from work, emergency department or physician's office visits, and responses to pharmacotherapy are important objective indicators of allergic disease severity.

Patients with allergic rhinitis who are unable to sleep because of symptoms or whose symptoms interfere with their work or school performance should be considered strong candidates for specific allergen immunotherapy. 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 considered. Unacceptable adverse effects of medications should also favor one's decision to initiate allergen immunotherapy. Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.[214]

Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued, and it might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6-9,122,162-165] These benefits of immunotherapy should be discussed with patients and might provide a clinical indication for immunotherapy for individual patients with allergic rhinitis.

Coexisting medical conditions should also be considered in the evaluation of a patient who might be a candidate for allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed with a combined aggressive regimen of allergen avoidance and pharmacotherapy and might also benefit from allergen immunotherapy.[215,216]

However, the patient's asthma must be stable before allergen immunotherapy is administered.[188,191]

Special precautions in patients with asthma

Summary Statement 21: 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 might be at increased risk for systemic reactions to immunotherapy injections.[182,188,191] Two surveys found that deaths from

immunotherapy were more common in symptomatic subjects with asthma.[188,189] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2,217]

Clinical indications for VIT

Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Systemic reactions to Hymenoptera stings, especially when associated with respiratory symptoms, cardiovascular symptoms, or both and positive skin test or *in vitro* test results for specific IgE antibodies, are a strong indication for allergen immunotherapy.[218] In the United States patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Several studies of patients with imported fire ant allergy have demonstrated the effectiveness of immunotherapy with whole-body extracts of fire ants.[155,156,219] 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. Patients younger than 16 years of age who present only with a cutaneous reaction to imported fire ant or Hymenoptera stings might not require immunotherapy.[218,220-222] In addition to allergen immunotherapy, patients with imported fire ant and Hymenoptera venom sensitivity should be instructed in how to best avoid insect stings, be prescribed epinephrine, and be taught how 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 the population that has not had a systemic reaction.[223] In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific IgE is recommended.[218] If the venom-specific IgE test result is also negative, it is recommended that the skin tests, venom-specific 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 IgE test result.[224] 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 re-stung. 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%).[225] 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 IgE test results who have had severe anaphylaxis to an insect sting.

Some patients who have negative venom skin test results and negative venom-specific IgE test results are reported to have had subsequent systemic reactions to stinging insects.[225-227] Controlled studies designed to evaluate the efficacy of immunotherapy in these patients have not been performed. There are very 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.[226] 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.

Summary Statement 23: 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.

ALLERGEN SELECTION AND HANDLING

Allergen selection

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

A careful history, noting environmental exposures and an understanding of the local and regional aerobiology of suspected allergens, such as pollen, fungi (mold), 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 skin or *in vitro* test results for specific IgE antibodies, provide good evidence that such exposures are relevant. Information concerning regional and local aerobiology is available on various Web sites or through the National Allergy Bureau at http://www.aaaai.org/nab. There are

no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma. 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 clinical history of an allergic disease.

There is no evidence to support the administration of immunotherapy based solely on results of specific *in vitro* 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.

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

The omission of clinically relevant allergens from an allergic patient's allergen immunotherapy extract contributes to decreased effectiveness of allergen immunotherapy. The 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 can make allergen immunotherapy less effective.

Knowledge of the total allergenic burden facing a patient and the realistic possibility of avoidance is important in determining whether allergen immunotherapy should be initiated. 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. Many individuals travel extensively for business or pleasure into different regions, and symptoms might worsen at these times. However, inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective. Determination of the significance of indoor allergens for a particular patient is harder because it is difficult to determine exposure in the home, school, and/or workplace. Historical factors, such as the presence of a furry animal in the home, a history of water damage and subsequent fungal exposure, or a history of insect infestation, might be helpful. However, such information is subjective and is often of uncertain reliability. In addition, some studies have demonstrated significant indoor levels of cat and dog allergen in households without pets[228] and significant levels of mouse allergen in suburban[229] and inner-city[230] homes 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 with increased asthma morbidity in inner-city children was found.[231] 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. Nevertheless, for most patients, determination of the clinical relevance of an allergen requires a strong correlation between the patient's history and evidence of allergen-specific IgE antibodies.

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted *in vitro* tests for specific IgE antibodies can also be used. **A**

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 the skin test results have demonstrated the efficacy of immunotherapy for relevant allergens.[25,26,112,130,134,135,140,141,149,154] 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 from skin testing in a highly sensitive individual.[232,233] In addition, skin tests might be difficult to perform in patients with dermatographism or atopic dermatitis. *In vitro* tests are particularly useful in such patients.

Studies indicate that skin testing is generally more sensitive than *in vitro* tests in detecting allergen-specific IgE.[234,235] Based on inhalation challenge test results, skin tests have shown specificity and sensitivity generally superior to those of *in vitro* tests. The comparability of skin tests and *in vitro* tests for specific IgE antibodies depends on the allergen being tested. For all of 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, prick testing is sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass[236] and cat,[237] are used. Intradermal/intracutaneous skin testing might be required for some allergen extracts. It is appropriate in some patients to use *in vitro* tests for specific IgE antibody as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. *In vitro* tests can also be used to define the allergens that should be used in allergen immunotherapy. If the allergy skin test result is negative and the *in vitro* test result is positive, a controlled challenge can be performed, and if the latter is positive, immunotherapy can be considered. 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 *in vitro* test results.

Specific allergens

Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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.[17,104,106,107,109] 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.[112,122] Because a particular pollen extract is a mixture of multiple glycoproteins, this suggests that mixing pollen allergens does not alter biologic activity.

Fungi (molds). Several studies with *Alternaria* and *Cladosporium* species suggest that allergen immunotherapy with fungi might be effective.[133-138] The allergen content of most mold extracts is highly variable.[238,239] However, there is evidence that proteolytic enzymes present in some mold extracts could digest other antigens, such as pollens, when combined in a mixture.[240] For this reason, it might be desirable to separate all pollen extracts from mold extracts when using mixtures.

Unfortunately, extracts for some potentially clinically important fungi are not available.[241] 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 distinguish 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.

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.

Because immunotherapy has been shown to be effective for cat[22,26,139-143,242] and dog,[25,141] the decision to include dog or cat allergen in an allergen immunotherapy extract should be considered in those circumstances in which there is exposure.

Dust mites and cockroach allergens. Crude house dust extract is generally an inappropriate substitute for house dust mite extract because the protein content measured is not restricted to dust mite allergens, nor does it necessarily guarantee inclusion of dust mite protein. Immunotherapy with standardized dust mite is generally more effective than that with crude house dust allergens. The house dust mites *D farinae* and *D 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, such as *Blomia tropicalis* and *Euroglyphus maynei*, partially cross-react with allergens from *Dermatophagoides* species. Only 50% of the projected amounts of each of the 2 house dust mites (*D pteronyssinus* and *D farinae*) need 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[144,147-149,151] 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. Dust mite hypersensitivity should particularly be considered in patients who have perennial symptoms exacerbated by a dusty environment at home, work, or both and periods of high humidity.

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. The major allergen of *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.[243] Immunotherapy with cockroach allergens is effective[154] and should 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.

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.[108,116,244] Efficacy has also been demonstrated with immunotherapy by using whole-body extracts of imported fire ants.[155,156]

Foods. Only a single clinical study accessing the efficacy and safety of subcutaneous immunotherapy with foods has been performed.[171,173] This study, which evaluated immunotherapy with peanut, found the incidence of systemic reactions, even during maintenance, was unacceptable. Thus there is no evidence to support the use of immunotherapy with food extracts. Currently, strict avoidance of the offending food is advisable, and subcutaneous immunotherapy for food allergy is not recommended.

Mixing of extracts

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Once the relevant allergens for each patient are identified, it is necessary to prepare a mixture that contains each of these allergens. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts. A number of 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 interactions between different types of allergens, when mixed, that could lead to degradation or unmasking of epitopes on exposure to proteolytic enzymes.

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Immunologic and 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.[71] 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 genera 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 the Allergen extract section, Fig 2, and the allergens and allergy diagnostic tests practice parameters).

Dose selection. Summary Statement 30: 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.[22-26,128,149,245] Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000 vol/vol).[28] A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy vaccine. Failure to do so might reduce the efficacy of immunotherapy. This occurs because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased (see the Immunotherapy schedules and doses section for further discussion and for recommended maintenance doses).

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as fungi (mold) and cockroach, from other extracts, such as pollens, is recommended. **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.[240,246,247] 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, and some weeds.[240,246,247] Cockroach had a similar deleterious effect on pollen extract potency.[246,248] Short ragweed appeared resistant to the effects of the proteolytic enzymes in one study,[240] 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.[247]

Dust mite extracts do not appear to have a deleterious effect on pollen extracts.[240,246,248] These studies suggest that pollen, dust mite, and cat extracts can be mixed together. 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. The evidence on mixing cockroach extract with other extracts is conflicting, and the clinical relevance of the changes is also unclear; therefore the clinician has the option of separating cockroach or not.

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 with lesser activities, such as pollen extracts.

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.

In this regard the number of separate injections that need to be given at each patient visit depends on whether all of the relevant extracts mixed into a single vial still deliver an optimal dose of each allergen. If mixing causes excessive dilution or if there are advantages to separating allergens into separate vials, then more than one vial might be necessary for successful immunotherapy.

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extracts are high-alert products that carry the risk for anaphylaxis. Policies, procedures, and processes intended for conventional drugs and medications might be highly 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 fatal anaphylactic reactions with allergenic products. 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. There are no reports of infection associated with allergen immunotherapy injections. Allergen vaccines are prepared by using sterile manufacturer's extracts and sterile diluents containing antibacterial constituents (usually phenol). A summary of the AAAAI/ACAAI/JCAAI proposed USP allergen immunotherapy extract preparation guidelines can be found in Table VIII.

TABLE VIII. AAAAI/ACAAI/JCAAI-proposed USP 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 below.*
   - 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.
2. **Physician responsibility**: A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in the preparation of immunotherapy using an aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files.
3. **Bacteriostasis**: Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if 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 the FDA-approved package insert 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 treatment with sanitizing agents containing alcohol and/or 70% isopropanol 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 the physical integrity of the vial.
10. **Labeling**: Immunotherapy vials are to be clearly labeled with the patient's name and 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.

*__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 media, such as from Valiteq (http://www.valiteq.com), 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.

Allergen immunotherapy extract handling

Storage. Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

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 a number of 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 extract, including reconstituted lyophilized extracts, should be stored at 4°C to minimize the rate of potency loss because storage at higher temperatures (eg, room temperature) can result in rapid deterioration.[249]

Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions (personal communication). These studies include actual shipments made by their carriers to places like

Phoenix in the summer and Alaska in the winter. 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.

Storing dilute extracts. Summary Statement 34a: More dilute concentrations of allergy immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than do more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: In determining the allergy vaccine expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of 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 allergen immunotherapy 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.[249,250]

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.[250] Phenol is a preservative added to extracts to prevent growth of microorganisms.

Phenol can denature proteins in allergen extracts.[251,252] Human serum albumin might protect against the deleterious effect of phenol on allergen extracts.[251] 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,[250,253] possibly through inhibition of the activity of proteolytic and glycosidic enzymes that are present in certain extracts. However, it is irritating when injected and should be diluted before beginning immunotherapy. Recommendations for extract stability are found in the manufacturers' product insert sheets. 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. The pain associated with glycerin increases in proportion to the glycerin concentration and injection volume, and the pain is proportional to the total injected dose of glycerin.[254] However, individual pain perception can vary substantially. Total glycerin doses of less than 0.05 mL rarely produce clinically important pain.

TABLE IX. Potency of selected manufacturer's extracts currently available

Extract	Potency
Cat hair and pelt	5000 and 10,000 BAU/mL
Dust mite	3000, 5000, 10,000, and 30,000 AU/mL
Bermuda grass	10,000 AU/mL
Short ragweed	1:10-1:20 wt/vol or 100,000 AU/mL
Other grasses*	10,000 and 100,000 BAU/mL
Other pollen	1:10 to 1:40 (wt/vol) or 10,000 PNU/mL
Molds	1:10 to 1:40 (wt/vol) or 20,000 to 100,000 PNU/mL

AU, Allergy unit; *BAU*, bioequivalent allergy unit; *PNU*, protein nitrogen unit.
*Perennial rye, Kentucky blue/June, timothy, sweet vernal, redtop, orchard, and meadow.

There have been few studies that have investigated the potency of dilutions of allergen extract mixture over time. Expiration dates for allergen extract dilutions are somewhat empiric and not strongly evidence based. A study undertaken by the AAAAI 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. Dust mite and cat at 1:10 and 1:100 vol/vol dilution were also stable in all conditions of storage over 12 months, as measured by an ELISA assay using 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.

IMMUNOTHERAPY SCHEDULES AND DOSES

Summary Statement 35: A customized individual 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 can be based on single or multiple allergens. **D**

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. Animal dander contains between 10 and 20 antigens,[255] house dust mites between 20 and 40 antigens,[256] and pollens between 30 and 50 antigens,[257,258] and fungal extract can contain as many as 80 antigens.[259]

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. This is designated as the patient's maintenance concentrate.

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. Standardized extracts are available with biologic potencies of 10,000 and 100,000 BAU for grasses; 5000 and 10,000 BAU for cat allergen; 5000, 10,000, or 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 wt/vol extracts (Table IX). 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.

Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

The highest concentration of an allergen extract mixture that is projected to be used as the therapeutically effective dose is called the maintenance concentrate. This should be prescribed individually for each patient by an allergist/immunologist. 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 individual manufacturer's extracts. Some patients might be unable to attain the projected therapeutically effective dose of the maintenance concentrate because of local reactions, systemic reactions, or both (eg, cat, 1000 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose]; see Table X for probable effective therapeutic dose range). Such patients might need weaker dilutions of their maintenance concentrate. Even so, 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 referred to as the maintenance dose. The consistent use of this nomenclature system is essential because errors in choosing the correct vial are a common cause of systemic reactions, especially when the patient transfers from one physician to another. Therefore it is important that standard terminology be adopted by all physicians who prescribe allergen immunotherapy.

Recommended doses

Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

The effective maintenance dose of immunotherapy for a particular patient must be individualized. To do this, the allergist/immunologist who prepares the allergen immunotherapy extract must balance the dose necessary to produce efficacy and the risk of reactions if such a dose is reached. The allergist/immunologist might need to prepare more than one maintenance concentrate to provide a therapeutic dose of each of the allergens for the polysensitized patient. Therapeutically effective doses for immunotherapy have been reported for some allergen extracts.[22,24,25,128,134,135,149,246,260,261] Effective doses have been determined for Hymenoptera venom, dust mite, cat allergen, dog, grass, and short ragweed (Table X).

Controlled studies demonstrate that the content of particular allergens in allergen immunotherapy extracts can be used to predict a therapeutic dose for those allergens, particularly when the extracts are standardized. For antigens 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. The therapeutically effective doses used in the most recent controlled clinical studies are the basis of the recommended dosage range of standardized extracts presented in Table X. 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 time that it is administered.[14]

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.[27] 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 risk of systemic reactions to immunotherapy injections with higher maintenance doses. The maintenance concentrate should be formulated to deliver a full therapeutic dose of each of its constituent components. However, some sensitive patients might not tolerate the targeted therapeutic dose, and their maintenance dose would be lower. Individuals 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 referred to as the maintenance dose.

Regardless of dose schedule, some patients are unable to progress to the predetermined maintenance dose because of large local or systemic reactions to the allergen

TABLE X. Probable effective dose range for allergen extracts US standardized units[a]

Antigen	Labeled potency or concentration[a,b]	Probable effective dose range
Dust mites: *D farinae* and *D pteronyssinus*[c]	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat[d]	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized[e]	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed[f]	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 μg of Amb a 1 1000-4000 AU Concentration of Amb a 1 is on the label of wt/vol extracts in FDA units[358]
Nonstandardized extract, dog[g]	1:10 to 1:100 wt/vol	15 μg of Can f 1
Nonstandardized extracts	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose

[a]Multiple studies have demonstrated that the efficacious dose for allergen immunotherapy is between 5 and 20 μg of the major allergen per injection. Only 2 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).

[b]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).

[c]There have been no dose-response studies with United States–licensed dust mite extracts, and dosing recommendations in AU value are extrapolated from published European studies that used aqueous[349] and alum-precipitated[149,151] extracts. 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.[149] The authors suggested the optimal maintenance dose was 7 μg of Der p 1. Corresponding doses were based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Extrapolating effective and safe doses in this manner might not be scientifically valid. *D farinae* and *D pteronyssinus* are similar in group 1 allergen content according to the FDA's current reference standards. 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*.

[d]The major cat allergen Fed d 1 is reported in FDA units, with 1 Fel d 1 unit equaling approximately 2 to 4 μg of Fel d 1.[55,58,59] The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 to 19.9 U/mL. One study demonstrated clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 dose in terms of decreased cat extract PD_{20}, titrated skin test results, and allergen-specific IgE and IgG levels.[350,351] In a recent study that investigated the efficacy in terms of immunologic changes of 3 doses of a United States–licensed cat extract (0.6, 3, and 15 μg) demonstrated that a significant effect on titrated skin prick test results, allergen-specific IgG4 levels, and $CD4^+$/IL-4 levels was only seen in the group treated with 15 μg of Fel d 1, although the 3-μg dose group did demonstrate a significant change in titrated skin test response and increase in cat-specific IgG4 levels.[22]

[e]There have been no dose-response studies with United States–licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,[130] alum-precipitated,[24,161] and calcium phosphate–precipitated grass pollen extracts.[352] One of these studies compared a dose of 2 μg with 20 μg of major timothy allergen (Phl p 5) and found clinical efficacy at both doses.[24] The efficacy was greater in the 20 μg of Phl p 5 dose, but the systemic reaction rate was also higher in the high-dose group. The package inserts for United States–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 BAU. Extrapolating effective and safe doses in this manner might not be scientifically valid. 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).

[f]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 suggested that 1 unit of Amb a 1 is equivalent to 1 μg of Amb a 1, and 350 Amb a 1 units/mL is equivalent to 100,000 BAU/mL.[60] The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2000 AU, with a range of 1000-4000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrated 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.[45] A ragweed dose-response study (0.6, 12.4, and 24.8 μg of Amb a 1) demonstrated efficacy, as measured by nasal challenge, at 12 and 24 μg of Amb a 1.[128] The efficacy of the 24-μg dose was not significantly better than the 12-μg dose, and the authors concluded that the optimal dose for ragweed extract was greater than 0.6 μg but not more than 12.4 μg of Amb a 1.

[g]Dog extracts are not standardized. However, one dose-response study with a United States–licensed acetone-precipitated dog extract investigated the efficacy of 3 doses (AP dog; Hollister-Stier, Spokane, Wash; 0.6, 3, and 15 μg) in terms of immunologic changes and found the dose of 15 μg of Can f 1 to be most efficacious.[25] 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 have assayed between 128 and 208 μg/mL (average Can f 1, 162 μg/mL [SD ± 26 μg/mL]; information provided by the extract manufacturer, Hollister-Stier).

immunotherapy extract. The evidence is not clear whether large local reactions are a potential risk for subsequent allergen immunotherapy systemic reactions.

Published studies do not indicate that an individual large local reaction is predictive of a subsequent systemic reaction.[179,180] However, one retrospective study found that individuals who have a history of repeated large local reactions (defined as >25 mm) might be at greater risk for a subsequent systemic reaction.[181]

The concept of highest tolerated dose does not apply for VIT, and all patients are expected to achieve the full recommended dose to achieve the necessary degree of protection. There are conflicting data over whether lower doses (50 μg) are less effective, but there are also data showing that 200 μg is more reliably effective.[245] In the case of VIT, patients are asked to tolerate more large local reactions to achieve the full dose, even though with inhalant immunotherapy the dose can be reduced for such large local reactions to minimize patient discomfort.

Effect of dilution on dose

Summary Statement 38: 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 vaccine, thereby limiting the ability to deliver a therapeutic effective dose for any given allergen.

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

Dilution from maintenance concentrate vaccine	Volume	Volume (mL)	Diluent volume (mL)	Final volume
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.

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 2000 BAU/mL, 2 mL of the manufacturer's extract (cat, 10,000 BAU/mL) can be added to 8 mL of diluent or 8 mL of other allergens, and the final concentration of cat will be 2000 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.

Dilutions of the maintenance concentrate

Summary Statement 39: 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 vol/vol 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, 1000 BAU or 100 BAU), but this system can be complicated if allergens with different potency units are used (eg, wt/vol, BAU, AU, or PNU) and make it difficult to easily interpret the vial label.

Instructions on how to prepare various allergen extracts 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.

Labeling dilutions

Summary Statement 40: 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, a number of 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 (vol/vol), a numbering system, a color-coding system, or an alphabetical system should be used. If this uniform labels 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.

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
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

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 3 and 4).

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 Appendix 2]).

Individualized treatment vials

Summary Statement 41: 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 (wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for 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). Labels on patient-specific vials can provide at least 2 patient identifiers (birth date and patient name), which would be consistent with the recommendations of the Joint Commission on Accreditation of Health Care Organizations National Patient Safety Goals: ''Goal 1: Improve the accuracy of patient identification by using at least two patient identifiers when providing care, treatment or services.''[5] 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 administration of the injection.[4,5]

In a survey of 1717 allergists endorsed by the AAAAI and JCAAI, 57% of the 476 respondents reported at least one wrong-patient injection, and 74% of the 473 respondents reported at least one wrong-dose injection.[4] 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 reasons why this might reduce incorrect injection errors. One reason was that patient-specific vials can be prepared in a quiet laboratory setting, which might provide substantially less distraction than the nurse in a room with a patient who is trying to concentrate only on drawing up the injection correctly. In addition, the specific components are mixed once with the preparation of individually prepared patient-labeled vials, whereas the mixing would be repeated on every injection visit if the allergen extract is withdrawn from different stock solutions, as it is in the off-the-board method. For safety reasons and to avoid cross-mixing of allergens removed from the manufacturer's extract, the mixing of antigens in the syringe (off the board) is not recommended.

Some allergists/immunologists prefer to administer immunotherapy doses drawn directly from a single stock dilution of individual allergens or common mixes (shared specific patient vials). In this way the immunotherapy dose is transferred to the patient without cross-contamination. If shared-patient (eg, mixed vespids and dust mite mix) vials are used, it is essential that policies and procedures are developed to verify that the correct dose from the correct vial is administered to the correct patient.

Starting doses

Summary Statement 42: The starting dose for build-up is usually a 1000- 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 slowly 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 1:1000 (vol/vol), although more diluted concentrations frequently are used for patients who are highly sensitive, as indicated by history or skin test reaction (see Appendix 3 for an example of a conventional immunotherapy schedule).

Frequency of build-up injections

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 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 2 times per week. 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 4 to 6 months, depending on the starting dilution and the occurrence of reactions. It is acceptable for patients to receive injections more frequently, provided there is adequate spacing between injections. The interval between injections is empiric but might be as short as 1 day without any increase in the occurrence of systemic reactions[262] if there is some urgency to achieve a maintenance dose (eg, allergy season is approaching) or for practical reasons (eg, patient's schedule). Alternatively, treatment schedules can be used that more rapidly achieve maintenance dosing. These cluster and rush dosing schedules are discussed in Summary Statements 47 through 49.

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 a number of 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).

Dose adjustments for systemic reactions

Summary Statement 44: 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 benefit/risk ratio justifies continuation of immunotherapy.

Reductions during periods of exacerbation of symptoms

Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Immunotherapy administered during periods of exacerbation of symptoms is considered a risk factor for immunotherapy.[17,184] Injections administered during periods when a patient is exposed to increased levels of allergen to which they are 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.[184] 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 sensitive, especially if their symptoms are poorly controlled.

Dose adjustments for late injections

Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

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 depends 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 Appendix 4 for an example of a dose-modification regimen for gaps in treatment).

Cluster schedules

Summary Statement 47: 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 (see Appendix 5).[22,26] 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. The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules.[145,263-266] The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.[267]

Rush schedules

Summary Statement 48: 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.[268] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.[191,269-272]

The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections over the course of 4 hours.[273] Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours.[274-276] 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 cluster[145,266] and rush[134,277] schedules.

Systemic reactions and rush schedules

Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

The advantages of rush immunotherapy come at a cost because there is an increased risk of local and systemic reactions. Systemic reaction rates have been reported to be

as high as 73% of patients, with the risk of such reactions reduced to 27% by premedication in one study.[272] Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing.[273]

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

Rush protocols for administration of Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions.[274-276,278,279]

Premedication and weekly immunotherapy

Summary Statement 50: Premedication can reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

There is concern that antihistamines taken before each injection with conventional immunotherapy might mask a minor reaction that would otherwise alert a physician to an impending systemic reaction. 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.[280] One study that compared terfenadine premedication with placebo premedication during rush VIT demonstrated greater clinical efficacy in the terfenadine-premedicated group in terms of subsequent responses to field stings or sting challenge.[281] There was also a significant difference in the systemic reaction rate between the 2 groups: 6 patients in the placebo-premedicated group had systemic reactions, whereas none of the patients in the terfenadine-premedicated group had systemic reactions ($P = .012$).

Unfortunately, patients might still have life-threatening anaphylaxis despite 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.

Premedication with cluster and rush immunotherapy

Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

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.[267] Premedication with a 3-day course of prednisone, an H_1 histamine receptor antagonist, and an H_2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.[272] In one study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on the safety and efficacy of rush immunotherapy, there was a 5-fold decrease in the risk of anaphylaxis in the group premedicated with omalizumab compared with the placebo premedication group.[282]

There are anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist, but there have been no published studies. Because the risk of a systemic reaction from rush VIT is relatively low, routine premedication before rush VIT is usually unnecessary.[274,276,278,279] In a study evaluating premedication with antihistamines and steroids for rush immunotherapy with imported fire ant venom, there was no statistically significant differences in the systemic reaction rates between the premedication and placebo premedication group (3.6% of the premedication group vs 6.7% of the placebo group, $P = .87$).[157]

Maintenance schedules

Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals 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 individuals might tolerate longer intervals between maintenance dose injections.

The interval between venom injections can be safely increased up to 8 weeks in some patients without loss of efficacy. 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.

Continuing care

Time course of improvement. Summary Statement 53: Clinical 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.[24,134,143,277] Improvement might not be observed for a number of reasons, including (1) failure to remove significant allergenic exposures (eg, a cat), (2) exposure to high levels of

allergen (eg, pollen or molds), (3) continued exposure to nonallergen triggers (eg, tobacco smoke), or (4) incomplete identification and treatment of clinically relevant allergens. 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 54: 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 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 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

The patient's response to immunotherapy should be evaluated on a regular basis. 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. 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.

There have been very 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 individuals.[283-285] However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported.[283,285] Nevertheless, systemic reactions to stings after discontinuing VIT were generally much milder than the pretreatment reactions and were rarely severe. Two studies did not find a difference in relapse rates between the patients treated for 3 years compared with those treated for 5 years,[283,286] but one of the studies noted that the small number of patients in the 3-year treatment group prevented them from making any conclusions about the risk of discontinuing treatment after 3 years.[283] However, one study found that patients who had experienced re-sting reactions after discontinuing VIT had received VIT for a significantly shorter duration (mean, 43.35 months) than those with continued protection (mean, 54.65 months; $P < .01$).[285] Another study reported that 5 years of VIT provided better immunologic and clinical outcomes than 2 to 4 years of treatment.[287]

Change in skin test reactivity did not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who experienced a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE.[286,288] Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment.[288] The relapse rate and the frequency of severe reactions were greater in patients who had a history of very severe reactions to stings before treatment, in patients who had systemic reactions during VIT (to a sting or a venom injection), in patients with honeybee allergy, and in those who had less than 5 years of treatment.

The duration of inhalant allergen immunotherapy efficacy has not been as extensively studied. Some studies have suggested 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 *(D pteronyssinus)* extract for 12 to 96 months.[14] 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.[13] There was a switch to placebo in half of 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. These studies demonstrate the uncertainty of the long-term benefit of inhalant immunotherapy after discontinuation.

Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained clinical remission after discontinuing inhalant immunotherapy, and 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 indication for continuation of immunotherapy can be found at http://www.aaaai.org or http://www.jcaai.org.

Documentation and record keeping. Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully 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 allergy immunotherapy and prescription forms can be found in the Appendix (Appendices 6-15), and these include examples of immunotherapy prescription and administration forms. These forms, along with examples of immunotherapy consent and instruction forms, can also be found at http://www.aaaai.org.

Injection techniques. Summary Statement 57: Allergen immunotherapy extract injections should be given using a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **C**

Immunotherapy should be given with a 26- to 27-gauge syringe with a half-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.[289-291]

If using shared specific patient vials (stock vials, such as mixed vespid or dust mite mix), a single dose should be drawn from each vial. Antigens from different vials should not be combined in a single syringe. Furthermore, extra care is needed to prevent using the wrong stock antigen.

Summary Statement 58: The injection should be given subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Each immunotherapy injection should be given in the posterior portion of the middle third of the upper 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.

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.

The syringe should be aspirated to check for blood return in the syringe before injecting. If blood is present, 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 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 syringe should be appropriately discarded. A fresh syringe and needle are necessary to determine whether a blood vessel has been entered.

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 could result in a local reaction.

LOCATION OF ALLERGEN IMMUNOTHERAPY ADMINISTRATION

Physician's office

Summary Statement 59: 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 to treat anaphylaxis should be in the immediate vicinity when immunotherapy injections are administered.

Summary Statement 60: 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.[292] 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.[184] 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 might be frequently necessary in the patient's immunotherapy schedule, as well as the patients total treatment program.

Other locations

Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **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.[292] The health care professional and staff 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, or allergy/asthma exacerbations at the time of allergen immunotherapy extract injection or poorly controlled asthma).

Appropriate adjustment of dose should be made as clinically indicated. The physician who prepared the patient's allergen immunotherapy extract should provide adequately labeled allergen immunotherapy extract vials, detailed directions regarding dosage schedule for build-up and maintenance, and instructions on adjustments that might be necessary under the following circumstances:

1. when providing patients with new vials;
2. during seasonal exposure to allergens that are in the patient's allergen vaccine, to which the patient is very sensitive, or both;
3. if the patient has missed injections; and
4. when reactions occur to the allergen immunotherapy extract.

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

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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 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 very 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 fully trained to administer the injection and to treat anaphylaxis if this should 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 supports (personnel, medications, supplies, and equipment) are more optimal for encouraging prompt recognition and treatment of anaphylaxis (Table V). 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.

Summary Statement 63: If a patient on 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for their immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extracts might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Patients often 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 brought from the previous physician (ie, an unchanged immunotherapy program) or one to be prepared by the current physician (ie, a new immunotherapy program).

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 full, clear, and detailed documentation of the patient's previous schedule and the contents of the allergen immunotherapy extract (see Appendices 7, 8, 11, 12, and 14 for examples of allergen immunotherapy prescription and administration forms and documentation guidelines for allergen immunotherapy forms). In addition, the patient's previous response to and compliance with this program 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 a schedule and the allergen immunotherapy extract, (2) the patient has shown significant improvement on this immunotherapy program, and (3) the contents of the allergen immunotherapy extract are appropriate for the area in which the patient is now living.

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, vaccine type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient's dose is not modified. This increased risk is due to the significant variability in content and potency of extracts and the variability in methods used by physicians to prepare the patient's maintenance concentrate and its dilutions. For example, the strength of a given concentration of nonstandardized extracts might vary significantly from vial to vial. The risk of systemic reactions in such a situation might be greater with nonstandardized extracts and allergen immunotherapy extracts that contain mixtures of allergens.

Therefore if the allergen immunotherapy extract is to be changed, the patient might need to be retested for specific IgE to the appropriate allergens 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 provided the interval of time since the last injection has not been too long. For lot changes from the same manufacturer, the physician can consider decreasing the dose by 50% to 90%. For changes in manufacturer and nonstandardized extracts, a greater decrease in dose might be necessary.

SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

Allergen immunotherapy in children

Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children

with allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Immunotherapy for children has been shown to be effective and often well tolerated,[137,242] although at least one study did not show efficacy.[293] 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.[294] In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (see the Patient selection section and Table VII). In recent studies children receiving allergen immunotherapy have demonstrated:

1. improvement in symptom control for asthma[117,119,121,122] and allergic rhinitis[118];
2. increased PC_{20} to histamine[121];
3. increased PC_{20} to cat and house dust mite allergens[121,149];
4. decreased risk of development of asthma[6,9,163-165];
5. decreased development of new sensitivities[120,166]; and
6. modification in release of mediators in children receiving immunotherapy that correlates with decreased clinical symptoms.[123]

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Although there is some disagreement about the role of allergen immunotherapy in children under the age of 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.[117,122] In children with allergic rhinitis, allergen immunotherapy might prevent the development of asthma.[6,9,163-165] However, allergen immunotherapy for inhalant allergens is usually not considered necessary in infants and toddlers because (1) there is 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 in pregnancy

Summary Statement 71: Allergen immunotherapy might be continued but is usually not initiated in the pregnant patient. **C**

The physician must be aware of the benefits and risks of immunotherapy in pregnant patients. The recommended precautions for prevention of adverse reactions are especially important in the pregnant patient. Allergen immunotherapy is effective in the pregnant patient. Thus allergen immunotherapy maintenance doses can be continued during pregnancy. Allergen immunotherapy is usually not initiated during pregnancy because of risks associated with systemic reactions and their treatment (ie, spontaneous abortion, premature labor, or fetal hypoxia). 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, and the patient is maintained on the dose that she is receiving at that time.

Immunotherapy in the elderly patient

Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy might be considered in the treatment of the elderly patient, but the benefit/risk assessment must be evaluated carefully in this population. Older 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. However, elderly patients may also benefit from allergen immunotherapy and age alone should not preclude the consideration of allergen immunotherapy.[295]

Immunotherapy in patients with immunodeficiency and autoimmune disorders

Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with immunodeficiency or autoimmune disorders. Therefore the decision to begin immunotherapy in patients with major humoral or cellular immune defects must be individualized. Concern about the increased risk of immunotherapy in such patients is largely hypothetical.

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

ALTERNATIVE ROUTES OF IMMUNOTHERAPY

Sublingual and oral immunotherapy

Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be

effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no FDA-approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **B**

Alternative routes of administration of allergen immunotherapy are ''a viable alternative to parenteral injection therapy'' in some cases.[106,296] Studies of oral immunotherapy have provided conflicting results for ragweed,[297] birch,[298] and cat[299] immunotherapy. The present dosage of oral immunotherapy extract is 20 to 200 times the parenteral injected dosage, which requires a cost assessment for this type of therapy. Furthermore, adverse effects have included gastrointestinal and oral reactions (50% in 1 study) that might preclude home therapy. Oral immunotherapy should be considered investigational at this time.

Optimal-dose (high-dose) sublingual swallow immunotherapy is effective in adults and children.[300-304] In a study of 855 patients with grass pollen allergy and allergic rhinitis randomized to placebo or one of 3 grass tablet doses, there was a significant reduction in symptom and medication scores in the highest-dose subgroup, who were treated for at least 8 weeks before the grass pollen season, compared with the placebo group (symptoms, 21%, $P = .0020$; medication use, 29%, $P = .0120$).[303]

Sublingual allergen studies have evaluated house dust, olive pollen, grass pollen, ragweed, birch, cat, latex, *Alternaria* species, and *Parietaria judaica*.[305-313] Sublingual immunotherapy has been shown to be effective in patients sensitized to 2 non–cross-reacting allergens, grass and birch.[314] It has been noted that the allergen is not degraded by saliva and that there is no direct sublingual absorption of allergen. Radiolabeled allergen has been detected after 48 hours in the sublingual region.[315,316] Alternative protocols, such as rush and ultra-rush (20 minutes) sublingual swallow[307,316,318] and no induction (build-up) phase,[301,303,317,319,320] have been studied. Several studies have suggested a relationship between dose and efficacy with sublingual immunotherapy,[303,310,321] but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. The majority of sublingual studies have demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both, but approximately 35% of the randomized, double-blind, placebo-controlled studies did not demonstrate efficacy in either parameter during the first year of treatment.[322] Further studies are needed to confirm the optimal dose for sublingual immunotherapy.

One of the potential advantages of sublingual immunotherapy is that it appears to be safe, even at very high doses (up to 500 times the usual monthly subcutaneous dose), and to be associated with a lower incidence of serious side effects.[310,320,323] This appears to apply to young children (<5 years), for whom there are prospective safety data[324,325] and a postmarketing survey.[326]



FIG 3. Sample of labels for allergen immunotherapy extract vials.

There have been no SLIT-related fatalities, but there have been 3 case reports of anaphylaxis caused by sublingual immunotherapy. One patient with latex hypersensitivity had anaphylactic shock 20 minutes after reaching the maximal dose on the fourth day of latex rush sublingual rush immunotherapy.[327]

The other 2 reported cases of SLIT anaphylaxis involved patients treated with multiple inhalant allergens. In one case a patient with allergic rhinitis and asthma who was prescribed a sublingual immunotherapy extract composed of multiple non–cross-reacting allergens (*Alternaria* species, dog, cat, ragweed mix, weed mix, and grass mix)[328] had generalized pruritis, followed by angioedema, shortness of breath, and dizziness, within a few minutes of administering 6 drops of the 1:100 vol/vol dilution on the third day of treatment. This episode was preceded by a milder systemic reaction the previous day (generalized pruritis). In the other case, a 13-year-old girl with allergic rhinitis and asthma had swelling of her lower lip 3 minutes after pollen drops, high fever, chest pain, nausea, and abdominal pain.[329] She was treated in the emergency department for anaphylaxis and hospitalized for observation. The reaction occurred 1 month after she had reached the maintenance dose during the peak of the spring season.

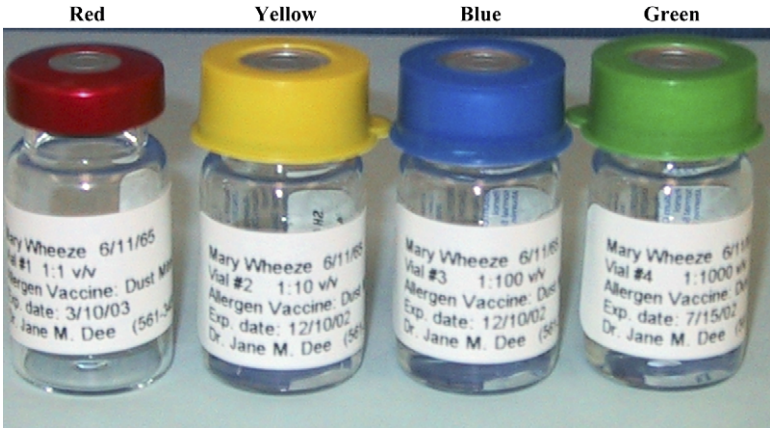


FIG 4. Sample set of color-coded vials of allergen vaccine.

There is currently no FDA-approved formulation for sublingual immunotherapy in the United States at this time, and this modality should be considered investigational. Current investigation of sublingual immunotherapy should not be confused with low-dose sublingual immunotherapy based on provocation neutralization testing or Rinkel-type skin testing.

Intranasal immunotherapy

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Based on controlled, well-designed studies, intranasal immunotherapy has been shown to improve the nasal symptoms of rhinitis.[330] Intranasal dry powder extract immunotherapy has been studied in grass,[330] birch,[331] *P judaica*,[332-334] and house dust mite[335] allergy. Clinical efficacy was noted in all of these studies. Nasal reactivity to allergen challenge was reduced, and only minor side effects were noted in 2 of the above studies. A 3-year study with *P judaica* reported to provide persistent benefits for up to 12 months after conclusion of allergen immunotherapy.[333] Local administration of nasal allergen in an aqueous solution for immunotherapy might be limited by the local side effects. Further studies in both pediatric and adult groups are needed. In human studies the antigen has been noted to appear in the serum within 15 to 30 minutes of administration, with a peak level occurring within 2 to 3 hours.[315] Some allergens have been reported to be retained in the nasal mucosa for up to 48 hours after administration. Intranasal immunotherapy is not currently available in the United States but has gained some acceptance in other parts of the world.

Immunotherapy techniques that are not recommended

Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

Low-dose regimens, including coseasonal low-dose immunotherapy for aeroallergens and the Rinkel low-dose titration techniques, are not effective.[27,28] Immunotherapy based on provocation–neutralization testing with food and aeroallergens and enzyme-potentiated desensitization is not effective.[336]

FUTURE TRENDS IN IMMUNOTHERAPY

Therapy with aeroallergen extracts will become more uniform (as is the current practice for insect venoms) as greater numbers of biologically standardized allergen extracts become available. The actual number of commercially available allergen extracts will be reduced based on consensus agreements about the regional prevalence of aeroallergens, their cross-allergenicity, and the relevance of their effect on human health in specific locales. Novel routes for more effective, convenient, and safer allergen immunotherapy are being investigated throughout the world.

For example, the sublingual route of administering allergen immunotherapy has been studied extensively in Europe. A meta-analysis confirmed its clinical effectiveness in allergic rhinitis,[302] and it has been reported to be effective in asthma as well.[337] Sublingual immunotherapy appears to have a very low risk of serious life-threatening systemic side effects, which might allow for home administration.[324,338] In some studies the clinical benefits of sublingual immunotherapy were not significant until the second year of treatment,[306,339] and comparisons suggest that the magnitude of the clinical benefit of sublingual immunotherapy might not be as great as that of subcutaneous immunotherapy.[311]

Trials with non–IgE-binding peptides containing T-cell stimulating peptides have been reported.[340] Site-directed mutagenesis has produced allergens with decreased IgE-binding capacity without decreased T-cell responses.[341,342]

Immunostimulatory sequences mimicking bacterial and viral DNA have been prepared that stimulate the innate immune system to direct T-cell responses toward

T_H1 rather than T_H2 phenotypes.[343] The results of clinical trials with a conjugate of the immunostimulatory sequence to the major allergen of ragweed, Amb a 1 (AIC), have been reported.[34,343] In a double-blind, placebo-controlled study of 25 adults who received 6 weekly injections of the AIC or placebo vaccine before ragweed season, the AIC group had better peak-season rhinitis scores on the visual analog scale ($P = .006$), peak-season daily nasal symptom diary scores ($P = .02$), and midseason overall quality-of-life scores ($P = .05$) than the placebo group during the first ragweed season, and this effect was observed in the subsequent ragweed season.[344]

Humanized anti-IgE mAb has been shown to have clinical effects in both allergic rhinitis and asthma.[345-348] Theoretically, this new therapeutic modality could be used as protective cover for clinical applications of rapid forms of immunotherapy. It is possible that preadministration of anti-IgE could provide a more effective protective effect than premedication with antihistamines and therefore permit a rush allergen immunotherapeutic regimen with reduced risk of serious systemic reactions.[282]

AUTHOR'S 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 2 systemic reaction grading systems (the European Academy of Allergy and Clinical Immunology's grading of severity for systemic side effects and the Portnoy method for numeric grading of reactions to allergen immunotherapy) can be found in the Appendix section. These forms can also be found along with examples of immunotherapy instruction and consent forms, preinjection health questionnaires, and indications for beginning and continuing immunotherapy forms at www.aaaai.org.

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APPENDIX 1. American College of Medical Quality's policy on the development and use of practice parameters for medical quality decision-making[1]

Practice parameters are strategies for patient management developed to assist health care professionals in clinical decision making. Practice parameters include standards, guidelines, and other patient management strategies. Standards are accepted principles for patient management. Guidelines are recommendations for patient management that identify a particular management strategy or a range of management strategies. Other strategies for patient management include practice policies and practice options. Practice parameters are to be used as screening tools to identify possible deviations from the applicable standards of care. Such parameters are not to be used as absolute standards or to profile or report on health care personnel. Parameters are designed to trigger a process in which possible deviations from the standard of care are identified as outlier practice patterns. Once a deviation from the parameter is identified, such a deviation should be referred to the appropriate qualified physician advisor or reviewer for a determination of medical necessity that conforms to the applicable standard of care. Parameters used in the day-to-day practice of clinical medicine should be clinically relevant. They should not be considered as substitutes for the standard of care but might contribute to its formulation.

Practice parameters must be developed, designed, and implemented only by board-certified, clinically practicing, specialty-matched physician advisors/reviewers with unrestricted medical licenses. Qualified nonphysicians might participate in the development of these parameters only in the areas in which their clinical expertise based on the standard of care is applicable. The health care personnel who develop these parameters should sign their names and date the final version as evidence of their participation and support. Practice parameters must be based on sound scientific research findings, professional literature, clinical experience and appropriate well-recognized methodologies and reflect professionally recognized national standards of care practiced in the clinical community of medicine. The development procedures followed, the participants involved, the evidence used, the assumptions and rationales accepted, and the analytic methods used should be meticulously documented, described, and made publicly available for national peer review. Parameters should be updated as needed.

Practice parameters are used as tools to enhance medical decision making but not as replacements for physicians' clinical judgment. They can be considered as means to enhance the performance of clinical and review personnel but not to replace them. It is below the standard of care of the medical review process to substitute qualified physician reviewer experts with unqualified reviewers who are using parameters.

APPENDIX 2. Examples of possible abbreviations for allergen immunotherapy extract 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

APPENDIX 3. 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

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

APPENDIX 4. Example of immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals (modification of the AAAAI skin testing and immunotherapy consent and instruction forms: immunotherapy administration instruction form, which can be found at http://www.aaaai.org)

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

- Up to 7 days, continue as scheduled (ie, if on weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection).
- Eight to 13 days after missed scheduled injection; repeat previous dose.
- Fourteen to 21 days after missed scheduled injection; reduce dose 25%.
- Twenty-one to 28 days after missed scheduled injection; reduce previous dose 50%.

Then increase dose each injection visit as directed on the immunotherapy schedule until therapeutic maintenance dose is reached.

This suggested approach to modification of doses of allergen immunotherapy because of gaps between treatment during the build-up phase is not based on retrospective or prospective published evidence, but it is presented as a sample for your consideration. The individual physician should use this or a similar protocol as a standard operating procedure for the specific clinical setting. A similar dose-reduction protocol should be developed for gaps in maintenance immunotherapy.

APPENDIX 5. Example of a cluster immunotherapy schedule[22,26]

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

APPENDIX 6. Recommended documentation for allergen immunotherapy prescription forms

The purpose of the allergen immunotherapy prescription form is to define the contents of the allergen immunotherapy extract in enough detail that it could be precisely duplicated. The following information should be on an immunotherapy prescription form:

Patient information:

- Patient name, patient number (if applicable), birth date, telephone number, and picture (if available) should be included.

Preparation information:

- Name of person and signature preparing the allergen immunotherapy extract should be included.
- Date of preparation should be recorded.
- Bottle name should be included (eg, trees and grass). If abbreviations are used, a 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 should be included.
- Volume of manufacturer's extract to add to achieve the projected effective concentration should be included. 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) should be included.
- Extract manufacturer should be included.
- Lot number should be included.
- Expiration date should be recorded and should not exceed the expiration date of any of the individual components.

APPENDIX 7. Allergen immunotherapy extract prescription 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:

_____
_____
_____
_____

_____ ____/____/____
Prescribing Physician Signature Date

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

APPENDIX 8. Maintenance concentrate prescription form

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: 6/10/06

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial **4** from Vial **1** on **8/30/06** Expiration date: **10/15/06**
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	Short ragweed	1:20 w/v G (150 Amb a1)	0.5ml	Greer	12345	1/01/08
2	Amaranthus Retroflexus	1:10 w/v G	0.5ml	H-S	6789	2/07/08
3	Ash	1:10 w/v G	0.5ml	Center	3333	3/17/08
4	Cat	10,000 BAU/ml G	2.00ml	ALO	9898	2/27/08
5	Timothy Grass	100,000 BAU/ml G	0.4ml	ALK	56789	7/09/08
6	Johnson Grass	1:10 w/v G	0.5ml	Greer	2434	7/20/08
7						
8						
9						
10						
Diluent	HSA		0.6ml	ALK	68597	12/08
Total Volume			5.00 ml			6/10/07

*** Components of mixes listed on a separate sheet**
**** Assumes 0.5 ml injection as target maintenance dose**

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

Specific Instructions:

_____

_____

Prescribing Physician Signature

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

APPENDIX 9. Labels for allergen immunotherapy extracts

Each vial of allergen immunotherapy extract should be labeled in a way that permits easy identification. Each label should include the following information (example in Figs 3 and 4):

- Appropriate patient identifiers might include the patient's name, patient's number, patient's picture, and birth date.
- The contents of the allergen immunotherapy extract in a general way should be included. The detail with which this can be identified depends on the size of the label and the number of allergens in the vial. Ideally, allergens should be identified as trees, grasses, weeds, mold, dust mite, cockroach, cat, and dog. Because of space limitations, it might be necessary to abbreviate the antigens (eg, T, G, W, M, DM, Cr, C, and D respectively [see Appendix 2]). A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate (vol/vol) should be recorded. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- The expiration date should be included.

APPENDIX 10. Allergen immunotherapy administration form recommended documentation

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

Patient information:

- Patient's name, date of birth, telephone number, and patient's picture (optional but helpful).

Allergen immunotherapy extract information:

- Allergen immunotherapy extract name and dilution from maintenance in vol/vol bottle letter (eg, A and B), bottle color, or number, if used.
- Expiration date of all dilutions.

Administration information in separate columns:

- Date of injection.
- Arm administered injection, which might facilitate determination of exact cause of local reaction.
- Projected build-up schedule.
- Delivered volume reported in milliliters.
- Description of any reactions. The details of any treatment given in response to a reaction would be documented elsewhere in the medical record and referenced on the administration form.
- *Patient's health before injection*. This can be performed through a verbal or written interview of the patient before administering the immunotherapy injection. The patient should be questioned about increased asthma or allergy symptoms, β-blocker use, change in health status (including pregnancy and recent infections), or an adverse reaction to a previous injection (including delayed large local reactions persisting through the next day). Patients with significant systemic illness generally should not receive an injection.
- *Antihistamine use*. Antihistamines are frequently a component of an allergy medication regimen, and it would be important to note whether a patient is taking an antihistamine on the day he or she receives his or her immunotherapy injection. For consistency in interpretation of reactions, it might be desirable for a patient to either take or avoid antihistamines on a regular basis on the days he or she receives immunotherapy. The physician should note on the form whether he or she recommends the patient consistently take an antihistamine on immunotherapy treatment days.
- *Peak flow reading*. Consider obtaining a peak expiratory flow rate measurement before administering an immunotherapy injection to asthmatic patients. Poorly controlled asthma is considered a risk factor for immunotherapy. Obtaining a peak expiratory flow rate measurement before the immunotherapy injection might help identify patients with symptomatic asthma. The patient's baseline peak expiratory flow rate should be provided on the form as a reference. Health care professionals administering immunotherapy injections should be provided with specific guidelines about the peak expiratory flow rate measurement for when an immunotherapy injection should be withheld and the patient referred for clinical evaluation.
- **Baseline blood pressure**. It might be useful to record the patient's blood pressure as a baseline for future reference.

APPENDIX 11. Allergen immunotherapy administration form

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 allergy or 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

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

Date to reorder: __/__/__

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 allergy or 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**	

APPENDIX 12. 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: _____
_____
Staff action taken (if any): _____

APPENDIX 13. 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.

APPENDIX 14. Allergen immunotherapy systemic reaction/anaphylaxis 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
__Epinephrine IM into 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	

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:
_____
_____
_____
_____

Clinical impression: True SR Questionable SR No SR

Systemic reaction severity classification: EAACI_____ **Portnoy** _____

Dosage adjustment? _____

Signatures_____ **RN** _____**MD/DO**

APPENDIX 15. Grading severity of allergen immunotherapy reactions: Two methods

1. **The European Academy of Allergy and Clinical Immunology grading of severity for systemic side effects***

Classification of systemic reactions

0 = No symptoms or nonspecific symptoms

I = Mild systemic reactions: symptoms—localized urticaria, rhinitis, or mild asthma (PF <20% decrease from baseline).

II = Moderate systemic reaction: symptoms—slow onset (>15 minutes) of generalized urticaria, moderate asthma, or both (PF < 40% decrease from baseline).

III = Severe (non–life-threatening) systemic reactions: symptoms—rapid onset (<15 minutes) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).

IV = Anaphylactic shock: symptoms—immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, and hypotension, for example.

2. **Portnoy method for numeric grading of reactions to allergen immunotherapy†**

Local

0+ = No significant reaction or small area of erythema less than the size of a half dollar without swelling or wheal formation

1+ = Erythema greater than the size of a half dollar, swelling or wheal formation, or both

Systemic

2+ = Systemic reactions: cutaneous only—might consist of a cutaneous eruption, such as urticaria

3+ = Systemic reaction: generalized pruritus, sneezing, or both—might consist of increased allergy symptoms, such as nasal congestion, sneezing, or pruritus, especially in the mouth or throat

4+ = Systemic reaction: pulmonary—consists of wheezing, shortness of breath, and tightness. Might be associated with decreased pulmonary function tests

5+ = Systemic reaction: anaphylaxis—a sensation of not feeling right is a frequent prelude; might consist of hypotension, laryngeal edema, severe wheezing, and cramping

6+ = Cardiopulmonary arrest

PF, Peak expiratory flow.

*Subcutaneous immunotherapy. Allergy 2006;61(suppl 82):5-13.

†Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80.

Allergen immunotherapy: A practice parameter second update

Supplement Editor: **Linda Cox, MD**
Co-editors: **James T. Li, MD, Harold Nelson, MD, and Richard Lockey, MD**

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

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the "Allergen immunotherapy: a practice parameter second 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 and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
5. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
6. The diagnosis and management of anaphylaxis. J Allergy Clin Immunol 1998;101(suppl):S465-S528.
7. Algorithm for the diagnosis and management of asthma: a practice parameter update. Ann Allergy 1998;81:415-20.
8. Diagnosis and management of rhinitis: parameter documents of the Joint Task Force on Practice parameters in Allergy, Asthma and Immunology. Ann Allergy 1998;81(suppl):S463-S518.
9. Parameters for the diagnosis and management of sinusitis. J Allergy Clin Immunol 1998;102(suppl): S107-S144.
10. Stinging insect hypersensitivity: a practice parameter. J Allergy Clin Immunol 1999;103:963-80.
11. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999;83(suppl): S665–S700.
12. Diagnosis and management of urticaria: a practice parameter. Ann Allergy 2000;85(suppl):S521-S544.
13. Allergen immunotherapy: a practice parameter. Ann Allergy 2003;90(suppl):SI-S540.
14. Symptom severity assessment of allergic rhinitis: part I. Ann Allergy 2003;91:105-14.
15. Disease management of atopic dermatitis: an updated practice parameter. Ann Allergy 2004;93(suppl): S1-S21.
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These parameters are also available on the internet at http://www.jcaai.org.

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PREFACE

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

The objective of ''Allergen immunotherapy: A practice parameter second update'' is to optimize the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. 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's ''Policy on development and use of practice parameters for medical quality decision-making'' (Appendix 1).[1]

This document builds on the previous Joint Task Force document, ''Allergen immunotherapy: a practice parameter'' published in the *Annals of Allergy, Asthma and Immunology* in 2003.[2] The updated practice parameters draft was prepared by Drs Linda Cox, James Li, Hal Nelson, and Richard Lockey. The Joint Task Force reworked the initial draft into a working draft of the document. The project was exclusively funded by the 3 allergy and immunology societies noted above.

In preparation for the 2003 ''Allergen immunotherapy: a practice parameter'' and the second update, a comprehensive search of the medical literature was conducted with various search engines, including PubMed; *immunotherapy*, *allergic rhinitis*, *asthma*, *stinging insect allergy*, and related search terms were used. 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 second update'' was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the ACAAI, AAAAI, and JCAAI. In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for review and comments from members of the sponsoring organizations. 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 allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. This document also contains recommendations for the safe practice of allergen immunotherapy, including specific recommendations on the prevention and management of 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 or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. Symptoms of allergic conjunctivitis (eg, itchy watery eyes) are often considered part of allergic rhinitis or are included in the diagnosis of rhinoconjunctivitis. Particularly good candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures, those in whom it is important to avoid the potential adverse effects of medications, and those who wish to reduce the long-term use of medications. Immunotherapy is recommended for patients with a history of systemic reaction to Hymenoptera stings and specific IgE antibodies to Hymenoptera venom.

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.[3]

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. 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 *maintenance concentrate* should be used to identify the allergen immunotherapy extract that contains a therapeutic effective dose for each of its individual constituents (see the Immunotherapy schedules and doses section).

The term *manufacturer's extract* refers to the allergy extract purchased from the manufacturer. The terms *stock*, *full-strength*, and *concentrate* are ambiguous and should not be used. 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).

Allergen immunotherapy is effective when appropriate doses of the allergens are administered. ''Allergen immunotherapy: A practice parameter'' recommends that vials of allergen immunotherapy extracts should be prepared individually for each patient to enhance the individualization of therapy, reduce the risk of allergen cross-contamination, and reduce the risk of error in administration.[4,5] This parameter recommends the use of standardized allergen immunotherapy prescription and administration forms to improve the safety, uniformity, and standardization of allergen immunotherapy practice.[4,5] The suggested forms are found in the Appendix (Appendices 7, 8, 11, 12, and 14) and in the members' section of the www.aaaai.org Web site. The routine use of these standardized forms should improve the quality of immunotherapy practice.

Members' feedback comments on the recommended allergen extract dilution dating in the 2003 ''Allergen immunotherapy: A practice parameter'' led to an allergen immunotherapy extract dilution stability study designed by the AAAAI Immunotherapy and Allergy Diagnostics Committee and funded by the AAAAI Board of Directors. The study was designed to investigate the effect of time, temperature, and dilution of standardized allergen extract potency, and the results of this study were considered in this update.

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 3 years after publication. Requests for information about or an interpretation of these practice parameters should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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. Allergen immunotherapy

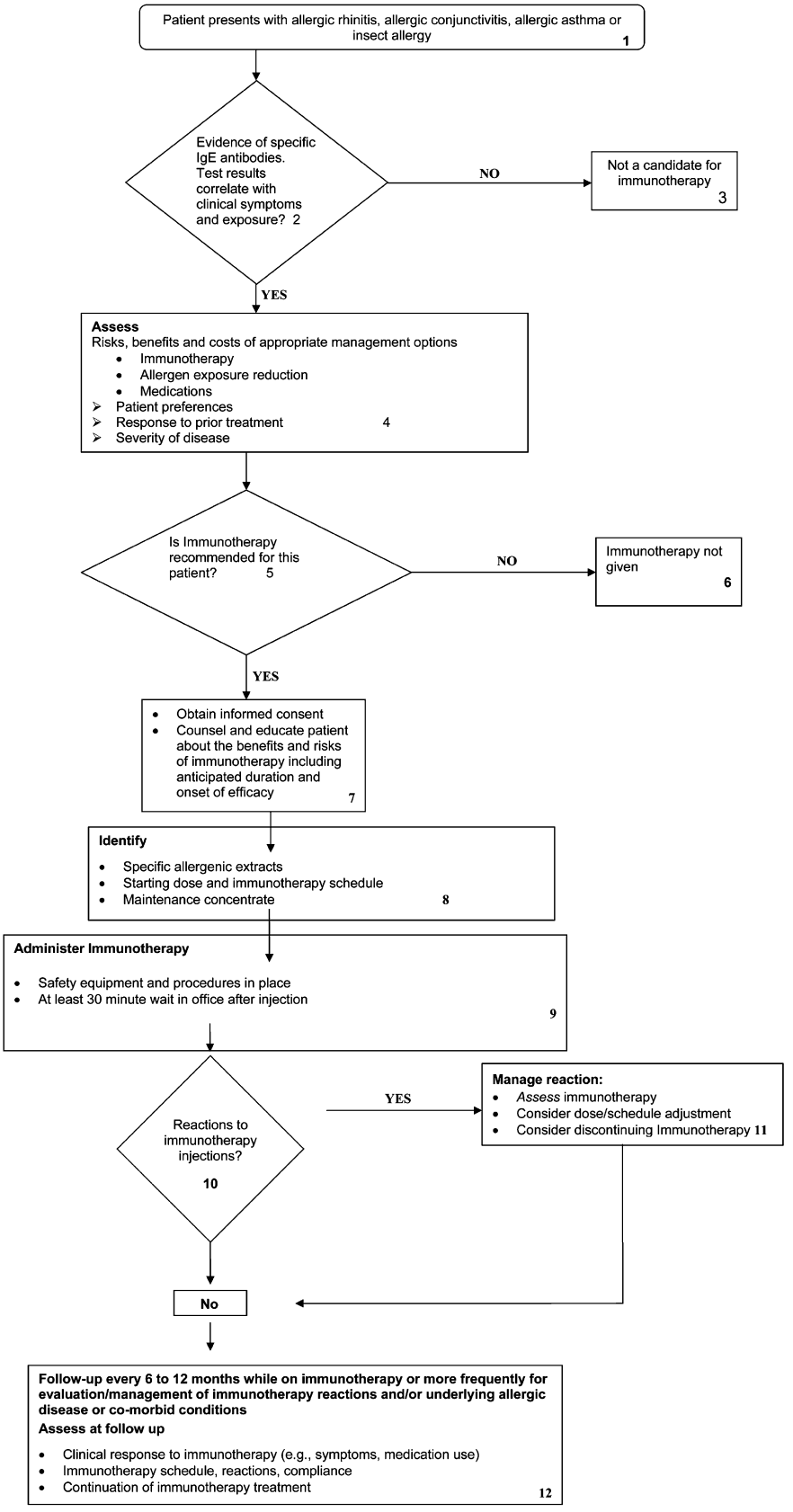


FIG 1. Algorithm for allergen immunotherapy.

might prevent the development of asthma in individuals with allergic rhinitis.[6-9] Evaluation of a patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic conjunctivitis, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for specific IgE antibody).[10]

Box 2

Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although *in vitro* testing for 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

Management of complex medical conditions, such as allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity, should include the careful evaluation of management 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 patient 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. On the basis of clinical considerations and patient 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 good candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy (VIT).

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 on the basis of 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 (see the Immunotherapy schedules and doses section). In general, the starting immunotherapy dose is 1000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 1000 to 4000 arbitrary units (AU; eg, for dust mite) or bioequivalent allergy units (BAU; eg, for grass) 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 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 referred to as *up-dosing*, *induction*, or the *dose-increase phase*) entails administration of gradually increasing doses during a period of approximately 14 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 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, in particular anaphylaxis. Patients should wait at the physician's office for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly, if they occur.

In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring 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. Some physicians recommend providing certain patients with epinephrine for self-administration in case of severe late reactions to immunotherapy injections.

Box 10

Injections of allergen immunotherapy extract can cause local or systemic reactions. Most severe reactions develop within 30 minutes after the immunotherapy injection, but reactions can occur after this time.

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 (anaphylaxis). Epinephrine is the treatment of choice in anaphylaxis, preferably when administered intramuscularly,[11] although subcutaneous administration is acceptable.[12]

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, see the practice parameters for anaphylaxis.[12]

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. After a severe systemic reaction, careful evaluation by the prescribing physician is recommended. For some patients, the immunotherapy maintenance dose might need to be reduced because of repeated systemic reactions to immunotherapy injections. The decision to continue immunotherapy should be re-evaluated after severe or repeated systemic reactions to allergen immunotherapy extracts.

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 doses, 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,[13] but others might experience a recurrence of their symptoms after discontinuation of allergen immunotherapy.[14] 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, and 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 on the basis of the patient's clinical response, disease severity, immunotherapy reaction history, and patient preference.

IMMUNOTHERAPY GLOSSARY

For more information on immunotherapy definitions, see the article by Kao.[15]

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 (pigments and salts; see the Allergen selection and handling section). Other terms used to describe the allergen immunotherapy extract include *allergen product*,[16] *allergy serum*, *allergen vaccine*,[17] 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.[18] Other terms that have been used for allergen immunotherapy include *hyposensitization*, *allergen-specific desensitization*, and the lay terms *allergy shots* or *allergy injections*.[15]

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

TABLE II. Allergen immunotherapy dose-calculation table

- Express weight per volume as a fraction: $\frac{1}{N}$ or 1:*N*.
- Calculate concentration of individual allergens in mixtures. If a mixture is made of equal amounts of N individual allergens to make a total concentration (C), the final concentration of an individual allergen (Ca) can be calculated by using the following equation:

$Ca = C \times \frac{1}{N} = \frac{C}{N}$ or *C*:*N*.

For example, if a mixture of equal amounts of 5 (N) allergens has a total concentration (C) of 100,000 BAU/mL, then the final concentration of each individual allergen (Ca) is: $Ca = \frac{C}{N} = \frac{100{,}000}{5} = 20{,}000\ BAU/mL$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{C}{N} = \frac{1/10}{5} = \frac{0.1}{5} = 0.02$ or $\frac{1}{50}$ or 1:50.

- Dilution of individual allergen: If an initial volume, Vi (in milliliters), of an individual antigen with concentration, Ci, is added to an allergen extract to make a final volume of Vf (in milliliters), the final allergen concentration (Ca) in the allergen extract mixture will be: $Ca = Ci \times \frac{Vi}{Vf}$.
- Final concentration of an allergen in a mixture of mixtures is determined by multiplying the initial concentration by the dilution factors from each mixing step.

For example, consider a mixture containing equal amounts of 5 (N) allergens with a total concentration (C) of 100,000 BAU/mL (first dilution). If an initial volume (Vi) of 0.5 mL of this mixture is further mixed with other components and diluent to make a final allergen extract mixture volume (Vf) of 5.0 mL (second dilution), the final concentration of an individual allergen (Ca) will be:

$$Ca = C \times \underbrace{\frac{1}{N}}_{\text{Mixture dilution}} \times \underbrace{\frac{Vi}{Vf}}_{\text{Allergen extract dilution}} = 100{,}000 \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{100{,}000}{50} = 2000\ BAU/mL$$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{1}{10} \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{1}{500}$ or 1:500.

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).

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 to 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-medicated 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 multiplied by volume of administered dose (see Table II for a dose-calculation table).

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, cat, 1000 BAU, [highest tolerated dose] vs 2000 BAU [projected effective dose]).

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 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 by a variety of immunologic transformations. Early definitions of the term immunotherapy included active and passive immunization for the purpose of improving 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 by means of induction of clonal deletion, anergy, immune tolerance, or immune deviation.

The *maintenance concentrate* is a preparation that contains individual 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 may not be the initially calculated projected effective dose.

The *maintenance goal* (or projected effective dose) is the allergen dose projected to provide therapeutic efficacy. The maintenance goal is based on published studies, but a projected effective dose has not been established for allergens. 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 the 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 large local reaction causing discomfort). The intervals between maintenance immunotherapy injections generally ranges 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 by means of immunoblotting or crossed allergoimmunoelectrophoresis.

For a definition of *projected effective dose*, see 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 test responses), and premedication with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similar high incidence of systemic reactions.

Off the board into one syringe is a phrase that describes a method of allergen immunotherapy preparation and administration that involves specifically mixing the patient's allergen immunotherapy injection in a single syringe, which is not recommended. This syringe might be inserted into more than one allergen extract vial, and this poses a risk of cross-contamination of the allergen extracts and might dull the needle with repeated penetration of the rubber stopper.

Shared specific patient vials is a method of allergen immunotherapy preparation and administration in which the allergy immunotherapy extract is withdrawn from a shared vial (eg, mixed vespids or dust mite mix). This is sometimes referred to as off the board, but it is distinct from the method of off the board into one syringe in that the syringe enters only one allergen extract vial.

INTRODUCTION

Immunity has been defined as protection against certain diseases. The initial immunotherapeutic interventions, which included the use of preventive vaccines and xenogenic 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 the field of allergen immunotherapy. From its humble empiric emergence in 1900, when ragweed injections were proposed as therapy for autumnal hay fever, allergen immunotherapy has progressed in both theory and practice from the passive immunologic approach to the active immunologic procedures pioneered by Noon[19] and Freeman.[20,21] 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 10 years. Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Some studies have suggested that allergen immunotherapy might prevent the development of asthma in individuals with allergic rhinitis.[6-9]

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,[22-26] and it should be differentiated from unproved methods, such as neutralization-provocation therapy and low-dose subcutaneous regimens based on the Rinkel technique, which have been found to ineffective in a double-blind placebo-controlled study.[27,28]

SUMMARY STATEMENTS

Mechanisms of immunotherapy

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, defined as a relative decrease in allergen-specific responsiveness and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

Allergen extracts

Summary Statement 6: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. **A**

Summary Statement 7: Nonstandardized extracts might vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Summary Statement 8: 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**

Cross-reactivity of allergen extract. Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

Efficacy of immunotherapy

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Summary Statement 10: Immunotherapy is effective for 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**

Food allergy, urticaria, and atopic dermatitis. Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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**

Measures of efficacy. Summary Statement 12: 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**

Safety of immunotherapy

Reaction rates. Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

Timing of anaphylactic reactions to immunotherapy injections. Summary Statement 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

β-*Adrenergic blocking agents.* Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

Contraindications. Summary Statement 18: 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**

Reducing the risk of anaphylaxis to immunotherapy injections. Summary Statement 19: 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**

Patient selection

Clinical indications. Summary Statement 20: 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 depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Special precautions in patients with asthma. Summary Statement 21: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. **C**

Clinical indications for VIT. Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Summary Statement 23: Patients selected for immunotherapy should be cooperative and compliant. **D**

Allergen selection and handling

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted in vitro tests for specific IgE antibodies can also be used. **A**

Specific allergens. Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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, supported by the presence of specific IgE antibodies. **A**

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Dose selection. Summary Statement 30: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. **A**

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens, is recommended. **B**

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extract handling

STORAGE

Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

STORING DILUTE EXTRACTS

Summary Statement 34a: More dilute concentrations of allergen immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: 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 a number of 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. **B**

Immunotherapy schedules and doses

Summary Statement 35: A customized individual 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 be based on single or multiple allergens. **D**

Maintenance concentrate. Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

Recommended doses. Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

Effect of dilution on dose. Summary Statement 38: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. **A**

Dilutions of the maintenance concentrate. Summary Statement 39: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. **D**

Labeling dilutions. Summary Statement 40: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. **D**

Individualized treatment vials. Summary Statement 41: 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. The mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. **C**

Starting doses. Summary Statement 42: The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. **D**

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

Dose adjustments for systemic reactions. Summary Statement 44: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. **D**

Reductions during periods of exacerbation of symptoms. Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Dose adjustments for late injections. Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

Cluster schedules. Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. **C**

Rush schedules. Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. **A**

Systemic reactions and rush schedules. Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

Premedication and weekly immunotherapy. Summary Statement 50: Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

Premedication with cluster and rush immunotherapy. Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

Maintenance schedules. Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. **A**

Continuing care

TIME COURSE OF IMPROVEMENT

Summary Statement 53: Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **A**

FOLLOW-UP VISITS

Summary Statement 54: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. **D**

DURATION OF TREATMENT

Summary Statement 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

DOCUMENTATION AND RECORD KEEPING

Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. **D**

INJECTION TECHNIQUES

Summary Statement 57: Allergen immunotherapy extract injections should be administered with a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **D**

Summary Statement 58: The injection should be administered subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Location of allergen immunotherapy administration

Physician's office. Summary Statement 59: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Summary Statement 60: 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**

Other locations. Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **D**

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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**

Summary Statement 63: 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for his or her immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extract might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Special considerations in immunotherapy

Allergen immunotherapy in children. Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Pregnancy. Summary Statement 71: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. **C**

Immunotherapy in the elderly patient. Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy in patients with immunodeficiency and autoimmune disorders. Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

Alternative routes of immunotherapy

Sublingual and oral immunotherapy. Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no US Food and Drug Administration (FDA)–approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **A**

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Immunotherapy techniques that are not recommended. Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

MECHANISMS OF IMMUNOTHERAPY

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, which is defined as a relative decrease in allergen-specific responsiveness, and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

The immunologic changes associated with immunotherapy are complex, and the exact mechanism or mechanisms responsible for its' clinical efficacy are continually being elucidated. Data support the concept that successful immunotherapy is associated with a change to a T_H1 $CD4^+$ cytokine profile.[29-34] Data indicate that increased production of IL-12, a strong inducer of T_H1 responses, contributes to this shift.[33] Clinically successful immunotherapy has been reported to be associated with immunologic tolerance, which is defined as a relative decrease in antigen-specific responsiveness, immune deviation, or anergy. For example, lymphoproliferative responses to allergen are reduced with immunotherapy.[32] Successful immunotherapy results in generation of a population of T regulatory cells, which are $CD4^+CD25^+$ T lymphocytes producing IL-10, TGF-β, or both.[35-39] Regulatory T-cell release has been described in allergen immunotherapy with Hymenoptera venom,[35] grass pollen extract,[37] and house dust mites.[38] IL-10 reduces B-cell antigen-specific IgE and increases IgG4 levels; reduces proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicits tolerance in T cells by means of selective inhibition of the CD28 costimulatory pathway.[36,37]

Allergen immunotherapy has been shown to block both the immediate and late-phase allergic response.[40] Allergen immunotherapy has been shown to decrease the recruitment of mast cells, basophils, and eosinophils in the skin, nose, eye, and bronchial mucosa after provocation or natural exposure to allergens.[41]

In patients receiving immunotherapy, initially there is an increase in specific IgE antibody levels, followed by a gradual decrease to a level that is still higher than that present before treatment. Clinical improvement in many patients develops before decreases in their IgE antibody levels occur or in other patients whose IgE antibody levels never decrease, thereby demonstrating that efficacy is not dependent on reductions in specific IgE levels.[42,43] Immunotherapy does diminish the seasonal increase in specific IgE levels.[44] Despite the persistence of significant levels of specific IgE antibody levels, immunotherapy usually causes a reduction in 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.[45-48]

An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, has also been associated with immunotherapy. The properties of allergen-specific IgA have yet to be determined, and there is a weak correlation between the increase in allergen-specific IgG levels and immunotherapy's clinical efficacy.[30,49,50]

Immunotherapy might alter the affinity and specificity of allergen-specific IgG.[51,52] During the initial phase of ultrarush VIT, a change in IgG specificity (ie, a change in the set of epitopes dominantly recognized by IgG on wasp venom antigens) occurred concomitantly with early clinical tolerance and was seen within 12 hours of ultrarush VIT ($P < .001$).[51] 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 individuals.[52] This change in IgG specificity preceded the increase in IgG titers and was sustained for up to 6 months.[52]

Allergen-specific IgG induced from immunotherapy can block IgE-dependent histamine release and subsequent IgE-mediated antigen presentation to T cells.[53] This effect might be dependent on IgE, allergen concentration, and CD23, the low-affinity receptor for IgE.

Whereas 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.[37,53]

The relationship between these immunologic changes and immunotherapy efficacy is not completely understood.

ALLERGEN EXTRACTS

Summary Statement 6: 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 has 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.[2,18,54-56] 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.

United States–licensed extracts can be obtained in aqueous, glycerinated, lyophilized, and acetone-precipitated and alum-precipitated formulations. Some commonly used allergens are standardized. These include extracts for cat hair, cat pelt, *Dermatophagoides pteronyssinus*, *Dermatophagoides 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.[57] 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.

Most standardized extracts are labeled in BAU. Short ragweed potency units were originally based on the content of the major allergen Amb a 1. Ragweed potency is reported in FDA units and BAU. One FDA unit of Amb a 1 equals 1 μg of Amb a 1, and 350 units of Amb a 1/mL is equivalent to 100,000 BAU/mL. Cat extracts were also originally standardized based on the content of major allergen (Fel d 1), with 100,000 arbitrary units (AU) per milliliter containing between 10 to 19.9 FDA units of Fel d 1 per milliliter (1 FDA unit of Fel d 1 equals 2 to 4 μg of Fel d 1).[55,58,59] Subsequently, $ID_{50}EAL$ testing suggested that 100,000 AU/mL was equal to 10,000 BAU/mL.[60] Approximately 22% of individuals with cat allergy have specific IgE antibodies to cat albumin.[61] Cat pelt extracts have a greater amount of albumin than cat hair extracts.[60]

Dust mites were originally standardized in AU by means of inhibition radioimmunoassay (RIA), and subsequent $ID_{50}EAL$ testing indicated that the AU was bioequivalent to the BAU, and the original AU nomenclature was kept. Dust mite extracts are still labeled in AU.

Summary Statement 7: Nonstandardized extracts can vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Nonstandardized extracts are labeled as wt/vol, which expresses weight in grams per volume in milliliters; that is, a potency of 1:100 indicates that 1 g 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 with a particular wt/vol or PNU potency can have widely varying biologic activities.[62-64] Therefore they should not be considered equipotent.

Summary Statement 8: 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**

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. The major clinically relevant aeroallergens of North America are listed in Table III. Furthermore, nonrelevant allergens in such mixtures could act as sensitizers rather than as tolerogens.[65,66] The physician must therefore select only those aeroallergens for testing and treatment that are clinically relevant in a particular geographic area.

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, dog), insect (cockroach), and Hymenoptera venom source materials.

Cross-reactivity of allergen extract

Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

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. A summary of cross-reactivity patterns of the clinically relevant North American aeroallergens can be found in Fig 2. 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,[67] inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[68-75] Grasses in other subfamilies (eg, Bermuda, Bahia, and Johnson) show greater diversity and should be evaluated separately.[76-78] Bermuda and Johnson grasses are increasingly important in the South,

TABLE III. The major clinically relevant aeroallergens of North America*

- Tree pollen
  - Chinese elm *(Ulmus parvifolia)*†‡; Siberian elm *(Ulmus pumila)*†‡; American elm *(Ulmus Americana)*†‡
  - Red oak *(Quercus rubra)*†; White oak *(Quercus alba)*†
  - Paper birch *(Betula papyrifera)*
  - Alder *(Alnus rubra)*
  - Box elder *(Acer negundo)*†; Red maple *(Acer rubra)*†
  - Eastern cottonwood *(Populus deltoides)*
  - Sycamore *(Platanus occidentalis)*
  - White ash *(Fraxinus americana)*†; Olive *(Olea europaea)*†‡
  - Black walnut *(Juglans nigra)*
  - Mulberry *(Morus rubra)*
  - Mountain cedar *(Juniperus ashei)*
  - Pecan *(Carya illinoensis)*
- Grass pollen
  - Rye *(Lolium perenne)*§‖
  - Timothy *(Phleum pratense)*§‖
  - Meadow fescue *(Festuca elatior)*§‖
  - Bermuda *(Cynodon dactylon)*‖
  - Johnson *(Holcus halepensis)*
  - Bahia *(Paspalum notatum)*
- Weed pollen
  - Short ragweed *(Ambrosia artemisiifolia)*‖
  - English (narrow leaf) plantain *(Plantago lanceolata)*
  - Mugwort *(Artemisia vulgaris)*
  - Russian thistle *(Salsola kali)*
  - Burning bush *(Kochia scoparia)*
  - Sheet (red) sorrel *(Rumex asetosella)*
  - Red root pigweed *(Amaranthus retroflexus)*
- Indoor aeroallergens
  - Cat epithelium *(Felis domesticus)*‖
  - Dog epithelium *(Canis familiaris)*
  - Arthropods (domestic mites: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*)‖
  - Insects (German cockroach: *Blattella germanica*)
- Fungi
  - *Alternaria alternata*¶
  - *Cladosporium* (*C cladosporioides*, *C herbarum*)¶
  - *Penicillium* (*P chrysogenum*, *P expansum*)¶
  - *Aspergillus fumigatus*¶
  - *Epicoccum nigrum*, *Drechslera* or *Bipolaris* type (eg, *Helminthosporium solani*)¶

*Compiled and selected in collaboration with the AAAAI Immunotherapy Committee Allergen Subcommittee for the identification of 35 key allergens of North America.
†Extensive cross-reaction of species within the genus.
‡Apart from regional prevalence, they are limited to local sites with substantial stands of these trees.
§Extensively cross-react with one another and bluegrass, orchard, red top, and sweet vernal.
‖Allergens for which standardized extracts are commercially available.
¶Species that are widely distributed and clinically important.

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.[79-82] 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.[83-85] Significant cross-reactivity between Betulaceae pollens and oak of the Fagaceae family has been demonstrated with percutaneous skin testing.[75] RAST inhibition studies have shown cross-inhibition between oaks and other *Fagales* species.[86] IgE immunoblot inhibition experiments have demonstrated that the *Fagales* species might be strongly inhibited by birch species.[87] The use of one of the locally prevalent members (eg, birch and alder) should be adequate.[88]

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.[89,90] Maple and box elder trees are found throughout the United States, except for the arid southwest. Although in the same genus as maple, *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,[91,92] and there are allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.[93]

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.[94] Similarly, Chenopod-Amaranth families have wide ranges in the western regions but are present throughout North America.[95] Current information on cross-reactivity of these families is limited.[96-98] 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.[99] The use of a single Amaranth extract should be sufficient to cover this family.[100,101] Similarly, *Atriplex* species (eg, saltbushes and scales) show near identity, and use of a single member is adequate. 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,

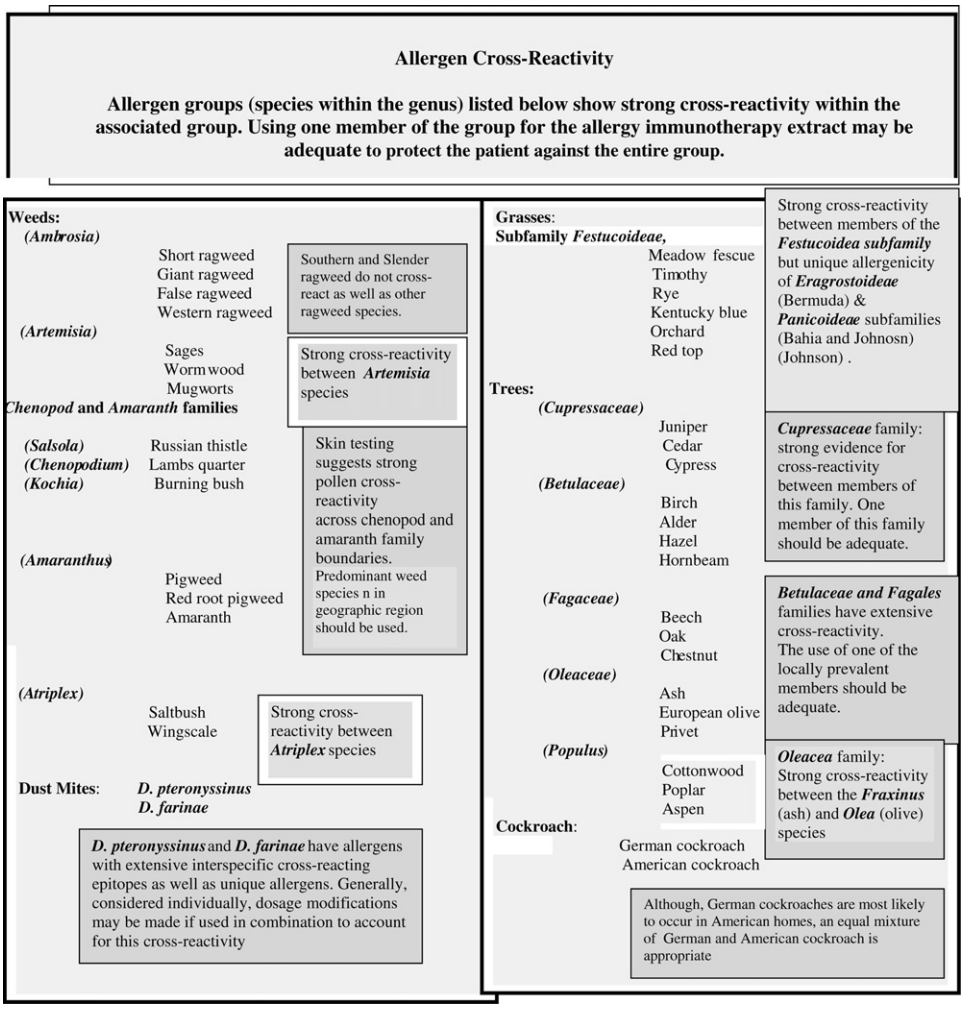


FIG 2. Patterns of allergen cross-reactivity.

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*).

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.[102,103] Stinging Hymenoptera insects occur throughout the United States; the fire ant is found only in Gulf Coast states, Texas, and some other southern and western states. Commercial venom extracts are available for some Hymenoptera species, except the fire ant, for which only whole-body extract is available.

EFFICACY OF IMMUNOTHERAPY

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity

Summary Statement 10: Immunotherapy is effective for 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.[104-111] Immunotherapy is effective for the treatment of allergic rhinitis[107] (including ocular symptoms[112,113]), allergic asthma,[104,109,111,114,115] and stinging insect hypersensitivity[108,116] and is effective in both adults and children.[117-124] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollens,[13,125-132] fungi,[133-138] animal allergens,[22,25,26,139-143] dust mite,[114,115,144-153] and cockroach.[154] There have been no controlled trials of fire ant whole-body extract, but it does appear to be effective in

TABLE IV. Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy

Outcome measure	House dust mite	Other allergens*†
Symptomatic improvement	2.7 (1.7-4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2-7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50)	5.5 (2.8-10.7)

Data are used with permission from Abramson et al.[104]
ND, Not done.
*Odds ratio (95% CI).
†Pollen, mold, or animal dander.

uncontrolled trials.[155-157] 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. A number of studies have also demonstrated a significant improvement in quality of life, as measured by using standardized questionnaires.[24,158-161] The magnitude of the effect depends on the outcome that is used (Table IV). For dust mite, the effect size ranges from a 2.7-fold improvement in symptoms to a 13.7-fold reduction in bronchial hyperresponsiveness. 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.[110] 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[107] and asthma[104,109,111] have been performed to deal with the issue of power. One review of 75 trials involving 3188 asthmatic patients found that, overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyperreactivity after immunotherapy, and it would have been necessary to treat 4 patients (95% CI, 3-5) with immunotherapy to avoid 1 deterioration in asthma symptoms and 5 (95% CI, 4-6) patients to avoid 1 requiring increased medication.[111] These meta-analyses strongly support the efficacy of allergen immunotherapy. Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued[13,162,163] and might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6,9,122,162-165] Allergen immunotherapy might also prevent the development of new allergen sensitivities in monosensitized patients.[120,166,167]

Food allergy, urticaria, and atopic dermatitis

Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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 use of allergen immunotherapy for individuals with the potential for IgE-mediated (anaphylaxis) reactions to foods should be regarded as investigational at this time.[168-171] There have been 2 investigational studies demonstrating efficacy in food hypersensitivity, the first using aqueous subcutaneous injections to peanut and the second using sublingual immunotherapy to hazelnut.[171-173]

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 a modified peanut extract is needed for clinical application of this method of treatment.[171] There is currently no FDA-approved formulation for sublingual immunotherapy, and this route of allergen immunotherapy is currently considered investigational at this time (see Summary Statement 73).

At the present time, there is not enough evidence to support food immunotherapy.

There is no evidence supporting the efficacy of immunotherapy for individuals with chronic urticaria, angioedema, or both.

There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[174-176] 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 ($P = .0379$) and topical corticosteroid use ($P = .0007$).[174]

The potential for benefit in symptoms related to oral allergy syndrome with the cross-reacting inhalant immunotherapy, which includes cross-reacting 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 subcutaneous immunotherapy directed against birch tree,[177] whereas another double-blind, double-dummy, placebo-controlled study comparing the effect of subcutaneous immunotherapy with sublingual immunotherapy 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, medication use, and decrease in IgE reactivity.[178] More investigation is required to substantiate the contention that benefits in oral symptoms will occur with immunotherapy.

Measures of efficacy

Summary Statement 12: 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. Objective measures, such as increase in allergen-specific IgG levels and decreased skin test reactivity, as measured by skin test titration, are changes generally associated with effective immunotherapy but, at present, are not practical for routine clinical use.[147] Nonquantitative skin testing or *in vitro* 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 are not very reliable given the strong placebo-like effect (Hawthorne effect) associated with any treatment. A more objective means for determining efficacy as validated in controlled clinical studies is the use of clinical symptom scores and the amount of medication required to control symptoms and maintain peak flow rates or pulmonary function tests within acceptable limits. Successful immunotherapy often results in a reduction in medication. Sequential measurement of disease-specific quality of life also might be helpful.

SAFETY OF IMMUNOTHERAPY

Reaction rates

Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Large local reactions associated with allergen immunotherapy are fairly common, with a frequency ranging from 26% to 86% of injections.[179] Two retrospective studies compared the effect of not adjusting immunotherapy dose based on large local reactions on the immunotherapy systemic reaction rate with dose-adjustment protocols.[179,180] There was a total of 12,464 injections administered with a dose-adjustment protocol in the 2 studies compared with 9542 injections administered with a no-dose-adjustment protocol. 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 for subsequent systemic reactions, 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 large local reactions, defined as 25 mm or larger, in patients who had experienced systemic reactions with age-, sex-, and allergen sensitivity–matched control subjects who had not had allergen immunotherapy systemic reactions found the rate of large local reactions was 4 times higher among the 258 patients who had subsequently experienced a systemic reaction compared with those who had never experienced a systemic reaction.[181] Patients who had experienced systemic reactions had 1573 large local reactions in 4460 visits (ie, 35.2% of visits) and 8081 injections (ie, 19.5% of injections) compared with the matched control group without systemic reactions who had 1388 large local reactions in 15,540 visits (8.9% per visit) and 26,259 injections (5.3% per injection; difference between groups, $P < .001$). Individual large local reactions were not predictive of future systemic reactions, but large local reactions preceded systemic reactions in approximately one third of the systemic reactions. These findings suggest that individuals with a greater frequency of large local reactions might be at greater risk for systemic reaction. Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy protocol modifications based on them are needed.

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

The prevalence of severe systemic reactions after allergen immunotherapy ranges from less than 1% of patients receiving conventional immunotherapy to greater than 36% of patients in some studies of patients receiving rush immunotherapy.[182,183]

In a recent survey of fatal and near-fatal reactions (NFRs) sent to physician members of the AAAAI, 273 of 646 respondents reported NFRs during the period of 1990-2001.[184]

The incidence of unconfirmed NFRs was 23 per year (5.4 events per million injections). Administration during the height of 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 angiotensin-converting enzyme 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 systemic reactions to subcutaneous immunotherapy over a 20-year period (1981-2000) during which 435,854 injections were administered to 4000 patients, 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.[185,186] In a prospective multicenter study there were 53 systemic reactions (0.3% of the doses) out of 17,526 administered doses in 18 (3.7%) of 423 patients.[187] 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 (21 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, there were 41 fatalities identified in the initial brief survey (20 directly reported and 17 with completed detailed questionnaire) from immunotherapy injections.[188] 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.[189,190] Therefore although severe systemic reactions to allergen immunotherapy are not common, serious systemic reactions (some fatal) can occur.

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

In the AAAAI survey of physician members on immunotherapy and skin testing, fatal reactions, and NFRs during the period of 1990-2001, 15 of the 17 fatalities had asthma, and in 9 patients asthma was considered the susceptibility factor that contributed to the fatal outcome.[188]

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.[184]

Administration during the peak pollen season (3 patients) and previous systemic reactions (4 patients) were cited as other contributing factors. Five fatalities occurred in outside medical facilities, and 2 fatalities occurred at home. No patients were receiving β-blockers; 1 patient was taking an angiotensin-converting enzyme inhibitor. In the most comprehensive evaluation of fatalities associated with allergen immunotherapy, from 1945-1987, there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[189] 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, with 73.3% of patients with an FEV_1 of less than 80% of predicted value experiencing 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 ($P < .0001$).[191] 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% of patients. These studies suggest that symptomatic asthma, severe asthma, or both might be a risk factor for immunotherapy.

In addition to symptomatic asthma and injections giving 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.[17] With the exception of dosing errors and 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 recent 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 or allergy symptom exacerbation, β-blocker use, change in health status (including pregnancy), or adverse reaction to previous allergen immunotherapy injection. The preinjection evaluation might also include a peak flow measurement to assess the airway function of asthmatic patients.

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 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

In a retrospective study the time to onset of a systemic reaction after an immunotherapy injection was less than 30 minutes in most cases.[189] A review of the literature indicates that 70% of systemic reactions occur within 30 minutes after an injection.[183] In the AAAAI 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.[184,188] 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.[190] 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 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.[192] In another prospective study 8% of systemic reactions occurred more than 2 hours after injection.[193]

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.[194]

Because most reactions that resulted from allergen immunotherapy occurred within 30 minutes after an injection, patients should remain in the physician's office for at least 30 minutes after receiving an injection, but longer waits are reasonable, as directed by the physician. In addition, patients who are at increased risk of a systemic reaction might need to carry injectable epinephrine. Such patients might also need to remain in the physician's office more than 30 minutes after an injection. 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.

β-Adrenergic blocking agents

Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

β-Blockade enhances pulmonary, cardiovascular, and dermatologic end-organ effects of mediators and increases mortality associated with experimental anaphylaxis induced by either immunologic or nonimmunologic mechanisms. Patients who are receiving β-adrenergic blocking medications might be at increased risk if they experience a systemic reaction to an allergen immunotherapy injection because the β-receptor blockade might attenuate the response to epinephrine.[195-202] Patients who are receiving β-blocking drugs were almost 9 times more likely to be hospitalized after an anaphylactoid reaction from radiocontrast media.[198] Although topical β-blockers have markedly less systemic β-antagonist effects than oral β-blockers, they still might exhibit some systemic β-antagonist effects. Whether topical β-blockers pose the same or a smaller risk than oral β-blockers in regard to the treatment of allergen immunotherapy–related systemic reactions is not known.

There have been very few studies that have examined the effect of β-blocker medications on allergen immunotherapy. A prospective 1-year study designed to determine whether patients taking β-blocker drugs were at increased risk of immunotherapy-induced systemic reactions found that there were 166 systemic reactions out of 56,105 injection visits in 3178 patients (68 were receiving a β-blocker).[203] The systemic reactions occurred in 144 (4.5%) patients, and only 1 of these patients was receiving a β-blocker medication. The authors calculated that by chance, 3.08 patients receiving the β-blocker medications drugs were expected to have had an systemic reaction and concluded that β-blocker medications did not increase the frequency of allergen immunotherapy systemic reactions ($P > .95$).

In another study of 1389 patients prescribed immunotherapy for Hymenoptera venom hypersensitivity who were followed for 34 months, there were 25 patients who received concomitant β-blocker medications.[204] Three (12%) of the 25 patients receiving β-blocker medications experienced systemic reactions during immunotherapy compared with 23 (16.7%) of 117 patients with cardiovascular disease not receiving β-blockers. Systemic reactions after a field sting or challenge occurred in 1 (14.3%) of 7 cardiovascular patients receiving β-blocker medications compared with 4 (13.8%) of 29 cardiovascular patients not receiving β-blocker medications. No severe reactions to immunotherapy or sting re-exposure were observed in patients receiving β-blockers medications.

Immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. In such cases, intravenous glucagon, which might reverse the refractory bronchospasm and hypotension by activating the adenyl cyclase directing and bypassing the β-adrenergic receptor, might be used if epinephrine has not been effective.[205,206] Prospective studies are necessary to clarify the magnitude of the risk of systemic reactions to allergens in patients who are receiving concomitant therapy with β-blockers, and a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy.

Contraindications

Summary Statement 18: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications

TABLE V. Actions to reduce the risk of anaphylaxis

- Assess the patient's general medical condition at the time of injection (eg, asthma exacerbation).
- Consider obtaining a PEFR before administration of the injection. If the PEFR is significantly less than the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.
- 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 with increased allergen sensitivity or those who have previously had a systemic reaction) might need to wait longer.
- Carefully evaluate any patient with a late reaction (eg, persistent large local reaction lasting >24 hours, systemic reaction occurring more than 30 minutes after the immunotherapy injection).
- 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.

PEFR, Peak expiratory flow rate measurement.

TABLE VI. Recommended equipment and medications to treat anaphylaxis

Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur. This should include at least the following equipment and medications:

- stethoscope and sphygmomanometer;
- tourniquet, syringes, hypodermic needles, and large-bore needles (14-gauge);
- aqueous epinephrine HCL 1:1000 wt/vol;
- equipment to administer oxygen by mask.
- intravenous fluid set-up;
- antihistamine for injection (second-line agents for anaphylaxis, but H_1 and H_2 antihistamines work better together than either one alone);
- corticosteroids for intravenous injection;
- vasopressor;
- equipment to maintain an airway appropriate for the supervising physician's expertise and skill.

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 venom hypersensitivity and cardiac disease being treated with β-blocker medications.

Reducing the risk of anaphylaxis to immunotherapy injections

Summary Statement 19: 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 extremely 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 or other health care professional appropriately trained in emergency treatment.

The 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. Epinephrine is the first-line treatment for anaphylaxis. 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.[12,207-213] It is important to administer epinephrine early in the management of anaphylaxis. 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 V and VI, respectively. Before allergen immunotherapy is chosen as a treatment, the physician should educate the patient about the benefits and risks of immunotherapy, as well as methods for minimizing risks. The patient also should be told that despite appropriate precautions, reactions might occur without warning signs or symptoms. Informed consent should include a discussion of the potential immunotherapy adverse reactions, and this discussion should be documented in the patient's medical record.

PATIENT SELECTION

Clinical indications

Summary Statement 20: Allergen immunotherapy should be considered for patients who have demonstrable

TABLE VII. Clinical indications for allergen immunotherapy

Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or both:
- symptoms of allergic rhinitis after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medications;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medication;
- coexisting allergic rhinitis and asthma;
- possible prevention of asthma in patients with allergic rhinitis

Symptoms of asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medication;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medications;
- coexisting allergic rhinitis and allergic asthma.

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);
- adults and children with a history of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.

evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic rhinitis.[107] Prospective, randomized, double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic asthma.[104,109,111]

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 proper identification and selection of component allergens on the basis of 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 (Table VII). The severity and duration of symptoms should also be considered in assessing the need for specific allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. In addition, specific allergen immunotherapy should be considered if the patient wishes to avoid long-term pharmacotherapy. Time lost from work, emergency department or physician's office visits, and responses to pharmacotherapy are important objective indicators of allergic disease severity.

Patients with allergic rhinitis who are unable to sleep because of symptoms or whose symptoms interfere with their work or school performance should be considered strong candidates for specific allergen immunotherapy. 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 considered. Unacceptable adverse effects of medications should also favor one's decision to initiate allergen immunotherapy. Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.[214]

Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued, and it might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6-9,122,162-165] These benefits of immunotherapy should be discussed with patients and might provide a clinical indication for immunotherapy for individual patients with allergic rhinitis.

Coexisting medical conditions should also be considered in the evaluation of a patient who might be a candidate for allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed with a combined aggressive regimen of allergen avoidance and pharmacotherapy and might also benefit from allergen immunotherapy.[215,216]

However, the patient's asthma must be stable before allergen immunotherapy is administered.[188,191]

Special precautions in patients with asthma

Summary Statement 21: 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 might be at increased risk for systemic reactions to immunotherapy injections.[182,188,191] Two surveys found that deaths from

immunotherapy were more common in symptomatic subjects with asthma.[188,189] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2,217]

Clinical indications for VIT

Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Systemic reactions to Hymenoptera stings, especially when associated with respiratory symptoms, cardiovascular symptoms, or both and positive skin test or *in vitro* test results for specific IgE antibodies, are a strong indication for allergen immunotherapy.[218] In the United States patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Several studies of patients with imported fire ant allergy have demonstrated the effectiveness of immunotherapy with whole-body extracts of fire ants.[155,156,219] 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. Patients younger than 16 years of age who present only with a cutaneous reaction to imported fire ant or Hymenoptera stings might not require immunotherapy.[218,220-222] In addition to allergen immunotherapy, patients with imported fire ant and Hymenoptera venom sensitivity should be instructed in how to best avoid insect stings, be prescribed epinephrine, and be taught how 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 the population that has not had a systemic reaction.[223] In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific IgE is recommended.[218] If the venom-specific IgE test result is also negative, it is recommended that the skin tests, venom-specific 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 IgE test result.[224] 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 re-stung. 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%).[225] 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 IgE test results who have had severe anaphylaxis to an insect sting.

Some patients who have negative venom skin test results and negative venom-specific IgE test results are reported to have had subsequent systemic reactions to stinging insects.[225-227] Controlled studies designed to evaluate the efficacy of immunotherapy in these patients have not been performed. There are very 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.[226] 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.

Summary Statement 23: 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.

ALLERGEN SELECTION AND HANDLING

Allergen selection

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

A careful history, noting environmental exposures and an understanding of the local and regional aerobiology of suspected allergens, such as pollen, fungi (mold), 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 skin or *in vitro* test results for specific IgE antibodies, provide good evidence that such exposures are relevant. Information concerning regional and local aerobiology is available on various Web sites or through the National Allergy Bureau at http://www.aaaai.org/nab. There are

no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma. 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 clinical history of an allergic disease.

There is no evidence to support the administration of immunotherapy based solely on results of specific *in vitro* 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.

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

The omission of clinically relevant allergens from an allergic patient's allergen immunotherapy extract contributes to decreased effectiveness of allergen immunotherapy. The 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 can make allergen immunotherapy less effective.

Knowledge of the total allergenic burden facing a patient and the realistic possibility of avoidance is important in determining whether allergen immunotherapy should be initiated. 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. Many individuals travel extensively for business or pleasure into different regions, and symptoms might worsen at these times. However, inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective. Determination of the significance of indoor allergens for a particular patient is harder because it is difficult to determine exposure in the home, school, and/or workplace. Historical factors, such as the presence of a furry animal in the home, a history of water damage and subsequent fungal exposure, or a history of insect infestation, might be helpful. However, such information is subjective and is often of uncertain reliability. In addition, some studies have demonstrated significant indoor levels of cat and dog allergen in households without pets[228] and significant levels of mouse allergen in suburban[229] and inner-city[230] homes 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 with increased asthma morbidity in inner-city children was found.[231] 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. Nevertheless, for most patients, determination of the clinical relevance of an allergen requires a strong correlation between the patient's history and evidence of allergen-specific IgE antibodies.

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted *in vitro* tests for specific IgE antibodies can also be used. **A**

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 the skin test results have demonstrated the efficacy of immunotherapy for relevant allergens.[25,26,112,130,134,135,140,141,149,154] 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 from skin testing in a highly sensitive individual.[232,233] In addition, skin tests might be difficult to perform in patients with dermatographism or atopic dermatitis. *In vitro* tests are particularly useful in such patients.

Studies indicate that skin testing is generally more sensitive than *in vitro* tests in detecting allergen-specific IgE.[234,235] Based on inhalation challenge test results, skin tests have shown specificity and sensitivity generally superior to those of *in vitro* tests. The comparability of skin tests and *in vitro* tests for specific IgE antibodies depends on the allergen being tested. For all of 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, prick testing is sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass[236] and cat,[237] are used. Intradermal/intracutaneous skin testing might be required for some allergen extracts. It is appropriate in some patients to use *in vitro* tests for specific IgE antibody as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. *In vitro* tests can also be used to define the allergens that should be used in allergen immunotherapy. If the allergy skin test result is negative and the *in vitro* test result is positive, a controlled challenge can be performed, and if the latter is positive, immunotherapy can be considered. 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 *in vitro* test results.

Specific allergens

Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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.[17,104,106,107,109] 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.[112,122] Because a particular pollen extract is a mixture of multiple glycoproteins, this suggests that mixing pollen allergens does not alter biologic activity.

Fungi (molds). Several studies with *Alternaria* and *Cladosporium* species suggest that allergen immunotherapy with fungi might be effective.[133-138] The allergen content of most mold extracts is highly variable.[238,239] However, there is evidence that proteolytic enzymes present in some mold extracts could digest other antigens, such as pollens, when combined in a mixture.[240] For this reason, it might be desirable to separate all pollen extracts from mold extracts when using mixtures.

Unfortunately, extracts for some potentially clinically important fungi are not available.[241] 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 distinguish 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.

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.

Because immunotherapy has been shown to be effective for cat[22,26,139-143,242] and dog,[25,141] the decision to include dog or cat allergen in an allergen immunotherapy extract should be considered in those circumstances in which there is exposure.

Dust mites and cockroach allergens. Crude house dust extract is generally an inappropriate substitute for house dust mite extract because the protein content measured is not restricted to dust mite allergens, nor does it necessarily guarantee inclusion of dust mite protein. Immunotherapy with standardized dust mite is generally more effective than that with crude house dust allergens. The house dust mites *D farinae* and *D 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, such as *Blomia tropicalis* and *Euroglyphus maynei*, partially cross-react with allergens from *Dermatophagoides* species. Only 50% of the projected amounts of each of the 2 house dust mites (*D pteronyssinus* and *D farinae*) need 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[144,147-149,151] 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. Dust mite hypersensitivity should particularly be considered in patients who have perennial symptoms exacerbated by a dusty environment at home, work, or both and periods of high humidity.

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. The major allergen of *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.[243] Immunotherapy with cockroach allergens is effective[154] and should 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.

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.[108,116,244] Efficacy has also been demonstrated with immunotherapy by using whole-body extracts of imported fire ants.[155,156]

Foods. Only a single clinical study accessing the efficacy and safety of subcutaneous immunotherapy with foods has been performed.[171,173] This study, which evaluated immunotherapy with peanut, found the incidence of systemic reactions, even during maintenance, was unacceptable. Thus there is no evidence to support the use of immunotherapy with food extracts. Currently, strict avoidance of the offending food is advisable, and subcutaneous immunotherapy for food allergy is not recommended.

Mixing of extracts

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Once the relevant allergens for each patient are identified, it is necessary to prepare a mixture that contains each of these allergens. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts. A number of 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 interactions between different types of allergens, when mixed, that could lead to degradation or unmasking of epitopes on exposure to proteolytic enzymes.

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Immunologic and 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.[71] 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 genera 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 the Allergen extract section, Fig 2, and the allergens and allergy diagnostic tests practice parameters).

Dose selection. Summary Statement 30: 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.[22-26,128,149,245] Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000 vol/vol).[28] A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy vaccine. Failure to do so might reduce the efficacy of immunotherapy. This occurs because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased (see the Immunotherapy schedules and doses section for further discussion and for recommended maintenance doses).

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as fungi (mold) and cockroach, from other extracts, such as pollens, is recommended. **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.[240,246,247] 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, and some weeds.[240,246,247] Cockroach had a similar deleterious effect on pollen extract potency.[246,248] Short ragweed appeared resistant to the effects of the proteolytic enzymes in one study,[240] 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.[247]

Dust mite extracts do not appear to have a deleterious effect on pollen extracts.[240,246,248] These studies suggest that pollen, dust mite, and cat extracts can be mixed together. 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. The evidence on mixing cockroach extract with other extracts is conflicting, and the clinical relevance of the changes is also unclear; therefore the clinician has the option of separating cockroach or not.

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 with lesser activities, such as pollen extracts.

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.

In this regard the number of separate injections that need to be given at each patient visit depends on whether all of the relevant extracts mixed into a single vial still deliver an optimal dose of each allergen. If mixing causes excessive dilution or if there are advantages to separating allergens into separate vials, then more than one vial might be necessary for successful immunotherapy.

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extracts are high-alert products that carry the risk for anaphylaxis. Policies, procedures, and processes intended for conventional drugs and medications might be highly 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 fatal anaphylactic reactions with allergenic products. 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. There are no reports of infection associated with allergen immunotherapy injections. Allergen vaccines are prepared by using sterile manufacturer's extracts and sterile diluents containing antibacterial constituents (usually phenol). A summary of the AAAAI/ACAAI/JCAAI proposed USP allergen immunotherapy extract preparation guidelines can be found in Table VIII.

TABLE VIII. AAAAI/ACAAI/JCAAI-proposed USP 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 below.*
   - 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.
2. **Physician responsibility**: A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in the preparation of immunotherapy using an aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files.
3. **Bacteriostasis**: Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if 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 the FDA-approved package insert 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 treatment with sanitizing agents containing alcohol and/or 70% isopropanol 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 the physical integrity of the vial.
10. **Labeling**: Immunotherapy vials are to be clearly labeled with the patient's name and 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.

*__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 media, such as from Valiteq (http://www.valiteq.com), 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.

Allergen immunotherapy extract handling

Storage. Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

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 a number of 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 extract, including reconstituted lyophilized extracts, should be stored at 4°C to minimize the rate of potency loss because storage at higher temperatures (eg, room temperature) can result in rapid deterioration.[249]

Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions (personal communication). These studies include actual shipments made by their carriers to places like

Phoenix in the summer and Alaska in the winter. 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.

Storing dilute extracts. Summary Statement 34a: More dilute concentrations of allergy immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than do more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: In determining the allergy vaccine expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of 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 allergen immunotherapy 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.[249,250]

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.[250] Phenol is a preservative added to extracts to prevent growth of microorganisms.

Phenol can denature proteins in allergen extracts.[251,252] Human serum albumin might protect against the deleterious effect of phenol on allergen extracts.[251] 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,[250,253] possibly through inhibition of the activity of proteolytic and glycosidic enzymes that are present in certain extracts. However, it is irritating when injected and should be diluted before beginning immunotherapy. Recommendations for extract stability are found in the manufacturers' product insert sheets. 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. The pain associated with glycerin increases in proportion to the glycerin concentration and injection volume, and the pain is proportional to the total injected dose of glycerin.[254] However, individual pain perception can vary substantially. Total glycerin doses of less than 0.05 mL rarely produce clinically important pain.

TABLE IX. Potency of selected manufacturer's extracts currently available

Extract	Potency
Cat hair and pelt	5000 and 10,000 BAU/mL
Dust mite	3000, 5000, 10,000, and 30,000 AU/mL
Bermuda grass	10,000 AU/mL
Short ragweed	1:10-1:20 wt/vol or 100,000 AU/mL
Other grasses*	10,000 and 100,000 BAU/mL
Other pollen	1:10 to 1:40 (wt/vol) or 10,000 PNU/mL
Molds	1:10 to 1:40 (wt/vol) or 20,000 to 100,000 PNU/mL

AU, Allergy unit; *BAU*, bioequivalent allergy unit; *PNU*, protein nitrogen unit.
*Perennial rye, Kentucky blue/June, timothy, sweet vernal, redtop, orchard, and meadow.

There have been few studies that have investigated the potency of dilutions of allergen extract mixture over time. Expiration dates for allergen extract dilutions are somewhat empiric and not strongly evidence based. A study undertaken by the AAAAI 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. Dust mite and cat at 1:10 and 1:100 vol/vol dilution were also stable in all conditions of storage over 12 months, as measured by an ELISA assay using 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.

IMMUNOTHERAPY SCHEDULES AND DOSES

Summary Statement 35: A customized individual 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 can be based on single or multiple allergens. **D**

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. Animal dander contains between 10 and 20 antigens,[255] house dust mites between 20 and 40 antigens,[256] and pollens between 30 and 50 antigens,[257,258] and fungal extract can contain as many as 80 antigens.[259]

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. This is designated as the patient's maintenance concentrate.

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. Standardized extracts are available with biologic potencies of 10,000 and 100,000 BAU for grasses; 5000 and 10,000 BAU for cat allergen; 5000, 10,000, or 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 wt/vol extracts (Table IX). 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.

Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

The highest concentration of an allergen extract mixture that is projected to be used as the therapeutically effective dose is called the maintenance concentrate. This should be prescribed individually for each patient by an allergist/immunologist. 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 individual manufacturer's extracts. Some patients might be unable to attain the projected therapeutically effective dose of the maintenance concentrate because of local reactions, systemic reactions, or both (eg, cat, 1000 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose]; see Table X for probable effective therapeutic dose range). Such patients might need weaker dilutions of their maintenance concentrate. Even so, 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 referred to as the maintenance dose. The consistent use of this nomenclature system is essential because errors in choosing the correct vial are a common cause of systemic reactions, especially when the patient transfers from one physician to another. Therefore it is important that standard terminology be adopted by all physicians who prescribe allergen immunotherapy.

Recommended doses

Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

The effective maintenance dose of immunotherapy for a particular patient must be individualized. To do this, the allergist/immunologist who prepares the allergen immunotherapy extract must balance the dose necessary to produce efficacy and the risk of reactions if such a dose is reached. The allergist/immunologist might need to prepare more than one maintenance concentrate to provide a therapeutic dose of each of the allergens for the polysensitized patient. Therapeutically effective doses for immunotherapy have been reported for some allergen extracts.[22,24,25,128,134,135,149,246,260,261] Effective doses have been determined for Hymenoptera venom, dust mite, cat allergen, dog, grass, and short ragweed (Table X).

Controlled studies demonstrate that the content of particular allergens in allergen immunotherapy extracts can be used to predict a therapeutic dose for those allergens, particularly when the extracts are standardized. For antigens 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. The therapeutically effective doses used in the most recent controlled clinical studies are the basis of the recommended dosage range of standardized extracts presented in Table X. 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 time that it is administered.[14]

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.[27] 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 risk of systemic reactions to immunotherapy injections with higher maintenance doses. The maintenance concentrate should be formulated to deliver a full therapeutic dose of each of its constituent components. However, some sensitive patients might not tolerate the targeted therapeutic dose, and their maintenance dose would be lower. Individuals 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 referred to as the maintenance dose.

Regardless of dose schedule, some patients are unable to progress to the predetermined maintenance dose because of large local or systemic reactions to the allergen

TABLE X. Probable effective dose range for allergen extracts US standardized units[a]

Antigen	Labeled potency or concentration[a,b]	Probable effective dose range
Dust mites: *D farinae* and *D pteronyssinus*[c]	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat[d]	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized[e]	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed[f]	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 μg of Amb a 1 1000-4000 AU Concentration of Amb a 1 is on the label of wt/vol extracts in FDA units[358]
Nonstandardized extract, dog[g]	1:10 to 1:100 wt/vol	15 μg of Can f 1
Nonstandardized extracts	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose

[a]Multiple studies have demonstrated that the efficacious dose for allergen immunotherapy is between 5 and 20 μg of the major allergen per injection. Only 2 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).

[b]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).

[c]There have been no dose-response studies with United States–licensed dust mite extracts, and dosing recommendations in AU value are extrapolated from published European studies that used aqueous[349] and alum-precipitated[149,151] extracts. 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.[149] The authors suggested the optimal maintenance dose was 7 μg of Der p 1. Corresponding doses were based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Extrapolating effective and safe doses in this manner might not be scientifically valid. *D farinae* and *D pteronyssinus* are similar in group 1 allergen content according to the FDA's current reference standards. 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*.

[d]The major cat allergen Fed d 1 is reported in FDA units, with 1 Fel d 1 unit equaling approximately 2 to 4 μg of Fel d 1.[55,58,59] The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 to 19.9 U/mL. One study demonstrated clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 dose in terms of decreased cat extract PD_{20}, titrated skin test results, and allergen-specific IgE and IgG levels.[350,351] In a recent study that investigated the efficacy in terms of immunologic changes of 3 doses of a United States–licensed cat extract (0.6, 3, and 15 μg) demonstrated that a significant effect on titrated skin prick test results, allergen-specific IgG4 levels, and $CD4^+$/IL-4 levels was only seen in the group treated with 15 μg of Fel d 1, although the 3-μg dose group did demonstrate a significant change in titrated skin test response and increase in cat-specific IgG4 levels.[22]

[e]There have been no dose-response studies with United States–licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,[130] alum-precipitated,[24,161] and calcium phosphate–precipitated grass pollen extracts.[352] One of these studies compared a dose of 2 μg with 20 μg of major timothy allergen (Phl p 5) and found clinical efficacy at both doses.[24] The efficacy was greater in the 20 μg of Phl p 5 dose, but the systemic reaction rate was also higher in the high-dose group. The package inserts for United States–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 BAU. Extrapolating effective and safe doses in this manner might not be scientifically valid. 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).

[f]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 suggested that 1 unit of Amb a 1 is equivalent to 1 μg of Amb a 1, and 350 Amb a 1 units/mL is equivalent to 100,000 BAU/mL.[60] The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2000 AU, with a range of 1000-4000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrated 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.[45] A ragweed dose-response study (0.6, 12.4, and 24.8 μg of Amb a 1) demonstrated efficacy, as measured by nasal challenge, at 12 and 24 μg of Amb a 1.[128] The efficacy of the 24-μg dose was not significantly better than the 12-μg dose, and the authors concluded that the optimal dose for ragweed extract was greater than 0.6 μg but not more than 12.4 μg of Amb a 1.

[g]Dog extracts are not standardized. However, one dose-response study with a United States–licensed acetone-precipitated dog extract investigated the efficacy of 3 doses (AP dog; Hollister-Stier, Spokane, Wash; 0.6, 3, and 15 μg) in terms of immunologic changes and found the dose of 15 μg of Can f 1 to be most efficacious.[25] 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 have assayed between 128 and 208 μg/mL (average Can f 1, 162 μg/mL [SD ± 26 μg/mL]; information provided by the extract manufacturer, Hollister-Stier).

immunotherapy extract. The evidence is not clear whether large local reactions are a potential risk for subsequent allergen immunotherapy systemic reactions.

Published studies do not indicate that an individual large local reaction is predictive of a subsequent systemic reaction.[179,180] However, one retrospective study found that individuals who have a history of repeated large local reactions (defined as >25 mm) might be at greater risk for a subsequent systemic reaction.[181]

The concept of highest tolerated dose does not apply for VIT, and all patients are expected to achieve the full recommended dose to achieve the necessary degree of protection. There are conflicting data over whether lower doses (50 μg) are less effective, but there are also data showing that 200 μg is more reliably effective.[245] In the case of VIT, patients are asked to tolerate more large local reactions to achieve the full dose, even though with inhalant immunotherapy the dose can be reduced for such large local reactions to minimize patient discomfort.

Effect of dilution on dose

Summary Statement 38: 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 vaccine, thereby limiting the ability to deliver a therapeutic effective dose for any given allergen.

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

Dilution from maintenance concentrate vaccine	Volume	Volume (mL)	Diluent volume (mL)	Final volume
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.

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 2000 BAU/mL, 2 mL of the manufacturer's extract (cat, 10,000 BAU/mL) can be added to 8 mL of diluent or 8 mL of other allergens, and the final concentration of cat will be 2000 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.

Dilutions of the maintenance concentrate

Summary Statement 39: 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 vol/vol 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, 1000 BAU or 100 BAU), but this system can be complicated if allergens with different potency units are used (eg, wt/vol, BAU, AU, or PNU) and make it difficult to easily interpret the vial label.

Instructions on how to prepare various allergen extracts 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.

Labeling dilutions

Summary Statement 40: 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, a number of 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 (vol/vol), a numbering system, a color-coding system, or an alphabetical system should be used. If this uniform labels 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.

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
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

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 3 and 4).

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 Appendix 2]).

Individualized treatment vials

Summary Statement 41: 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 (wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for 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). Labels on patient-specific vials can provide at least 2 patient identifiers (birth date and patient name), which would be consistent with the recommendations of the Joint Commission on Accreditation of Health Care Organizations National Patient Safety Goals: ''Goal 1: Improve the accuracy of patient identification by using at least two patient identifiers when providing care, treatment or services.''[5] 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 administration of the injection.[4,5]

In a survey of 1717 allergists endorsed by the AAAAI and JCAAI, 57% of the 476 respondents reported at least one wrong-patient injection, and 74% of the 473 respondents reported at least one wrong-dose injection.[4] 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 reasons why this might reduce incorrect injection errors. One reason was that patient-specific vials can be prepared in a quiet laboratory setting, which might provide substantially less distraction than the nurse in a room with a patient who is trying to concentrate only on drawing up the injection correctly. In addition, the specific components are mixed once with the preparation of individually prepared patient-labeled vials, whereas the mixing would be repeated on every injection visit if the allergen extract is withdrawn from different stock solutions, as it is in the off-the-board method. For safety reasons and to avoid cross-mixing of allergens removed from the manufacturer's extract, the mixing of antigens in the syringe (off the board) is not recommended.

Some allergists/immunologists prefer to administer immunotherapy doses drawn directly from a single stock dilution of individual allergens or common mixes (shared specific patient vials). In this way the immunotherapy dose is transferred to the patient without cross-contamination. If shared-patient (eg, mixed vespids and dust mite mix) vials are used, it is essential that policies and procedures are developed to verify that the correct dose from the correct vial is administered to the correct patient.

Starting doses

Summary Statement 42: The starting dose for build-up is usually a 1000- 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 slowly 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 1:1000 (vol/vol), although more diluted concentrations frequently are used for patients who are highly sensitive, as indicated by history or skin test reaction (see Appendix 3 for an example of a conventional immunotherapy schedule).

Frequency of build-up injections

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 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 2 times per week. 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 4 to 6 months, depending on the starting dilution and the occurrence of reactions. It is acceptable for patients to receive injections more frequently, provided there is adequate spacing between injections. The interval between injections is empiric but might be as short as 1 day without any increase in the occurrence of systemic reactions[262] if there is some urgency to achieve a maintenance dose (eg, allergy season is approaching) or for practical reasons (eg, patient's schedule). Alternatively, treatment schedules can be used that more rapidly achieve maintenance dosing. These cluster and rush dosing schedules are discussed in Summary Statements 47 through 49.

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 a number of 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).

Dose adjustments for systemic reactions

Summary Statement 44: 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 benefit/risk ratio justifies continuation of immunotherapy.

Reductions during periods of exacerbation of symptoms

Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Immunotherapy administered during periods of exacerbation of symptoms is considered a risk factor for immunotherapy.[17,184] Injections administered during periods when a patient is exposed to increased levels of allergen to which they are 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.[184] 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 sensitive, especially if their symptoms are poorly controlled.

Dose adjustments for late injections

Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

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 depends 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 Appendix 4 for an example of a dose-modification regimen for gaps in treatment).

Cluster schedules

Summary Statement 47: 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 (see Appendix 5).[22,26] 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. The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules.[145,263-266] The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.[267]

Rush schedules

Summary Statement 48: 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.[268] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.[191,269-272]

The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections over the course of 4 hours.[273] Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours.[274-276] 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 cluster[145,266] and rush[134,277] schedules.

Systemic reactions and rush schedules

Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

The advantages of rush immunotherapy come at a cost because there is an increased risk of local and systemic reactions. Systemic reaction rates have been reported to be

as high as 73% of patients, with the risk of such reactions reduced to 27% by premedication in one study.[272] Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing.[273]

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

Rush protocols for administration of Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions.[274-276,278,279]

Premedication and weekly immunotherapy

Summary Statement 50: Premedication can reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

There is concern that antihistamines taken before each injection with conventional immunotherapy might mask a minor reaction that would otherwise alert a physician to an impending systemic reaction. 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.[280] One study that compared terfenadine premedication with placebo premedication during rush VIT demonstrated greater clinical efficacy in the terfenadine-premedicated group in terms of subsequent responses to field stings or sting challenge.[281] There was also a significant difference in the systemic reaction rate between the 2 groups: 6 patients in the placebo-premedicated group had systemic reactions, whereas none of the patients in the terfenadine-premedicated group had systemic reactions ($P = .012$).

Unfortunately, patients might still have life-threatening anaphylaxis despite 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.

Premedication with cluster and rush immunotherapy

Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

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.[267] Premedication with a 3-day course of prednisone, an H_1 histamine receptor antagonist, and an H_2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.[272] In one study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on the safety and efficacy of rush immunotherapy, there was a 5-fold decrease in the risk of anaphylaxis in the group premedicated with omalizumab compared with the placebo premedication group.[282]

There are anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist, but there have been no published studies. Because the risk of a systemic reaction from rush VIT is relatively low, routine premedication before rush VIT is usually unnecessary.[274,276,278,279] In a study evaluating premedication with antihistamines and steroids for rush immunotherapy with imported fire ant venom, there was no statistically significant differences in the systemic reaction rates between the premedication and placebo premedication group (3.6% of the premedication group vs 6.7% of the placebo group, $P = .87$).[157]

Maintenance schedules

Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals 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 individuals might tolerate longer intervals between maintenance dose injections.

The interval between venom injections can be safely increased up to 8 weeks in some patients without loss of efficacy. 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.

Continuing care

Time course of improvement. Summary Statement 53: Clinical 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.[24,134,143,277] Improvement might not be observed for a number of reasons, including (1) failure to remove significant allergenic exposures (eg, a cat), (2) exposure to high levels of

allergen (eg, pollen or molds), (3) continued exposure to nonallergen triggers (eg, tobacco smoke), or (4) incomplete identification and treatment of clinically relevant allergens. 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 54: 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 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 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

The patient's response to immunotherapy should be evaluated on a regular basis. 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. 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.

There have been very 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 individuals.[283-285] However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported.[283,285] Nevertheless, systemic reactions to stings after discontinuing VIT were generally much milder than the pretreatment reactions and were rarely severe. Two studies did not find a difference in relapse rates between the patients treated for 3 years compared with those treated for 5 years,[283,286] but one of the studies noted that the small number of patients in the 3-year treatment group prevented them from making any conclusions about the risk of discontinuing treatment after 3 years.[283] However, one study found that patients who had experienced re-sting reactions after discontinuing VIT had received VIT for a significantly shorter duration (mean, 43.35 months) than those with continued protection (mean, 54.65 months; $P < .01$).[285] Another study reported that 5 years of VIT provided better immunologic and clinical outcomes than 2 to 4 years of treatment.[287]

Change in skin test reactivity did not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who experienced a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE.[286,288] Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment.[288] The relapse rate and the frequency of severe reactions were greater in patients who had a history of very severe reactions to stings before treatment, in patients who had systemic reactions during VIT (to a sting or a venom injection), in patients with honeybee allergy, and in those who had less than 5 years of treatment.

The duration of inhalant allergen immunotherapy efficacy has not been as extensively studied. Some studies have suggested 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 *(D pteronyssinus)* extract for 12 to 96 months.[14] 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.[13] There was a switch to placebo in half of 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. These studies demonstrate the uncertainty of the long-term benefit of inhalant immunotherapy after discontinuation.

Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained clinical remission after discontinuing inhalant immunotherapy, and 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 indication for continuation of immunotherapy can be found at http://www.aaaai.org or http://www.jcaai.org.

Documentation and record keeping. Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully 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 allergy immunotherapy and prescription forms can be found in the Appendix (Appendices 6-15), and these include examples of immunotherapy prescription and administration forms. These forms, along with examples of immunotherapy consent and instruction forms, can also be found at http://www.aaaai.org.

Injection techniques. Summary Statement 57: Allergen immunotherapy extract injections should be given using a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **C**

Immunotherapy should be given with a 26- to 27-gauge syringe with a half-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.[289-291]

If using shared specific patient vials (stock vials, such as mixed vespid or dust mite mix), a single dose should be drawn from each vial. Antigens from different vials should not be combined in a single syringe. Furthermore, extra care is needed to prevent using the wrong stock antigen.

Summary Statement 58: The injection should be given subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Each immunotherapy injection should be given in the posterior portion of the middle third of the upper 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.

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.

The syringe should be aspirated to check for blood return in the syringe before injecting. If blood is present, 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 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 syringe should be appropriately discarded. A fresh syringe and needle are necessary to determine whether a blood vessel has been entered.

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 could result in a local reaction.

LOCATION OF ALLERGEN IMMUNOTHERAPY ADMINISTRATION

Physician's office

Summary Statement 59: 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 to treat anaphylaxis should be in the immediate vicinity when immunotherapy injections are administered.

Summary Statement 60: 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.[292] 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.[184] 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 might be frequently necessary in the patient's immunotherapy schedule, as well as the patients total treatment program.

Other locations

Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **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.[292] The health care professional and staff 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, or allergy/asthma exacerbations at the time of allergen immunotherapy extract injection or poorly controlled asthma).

Appropriate adjustment of dose should be made as clinically indicated. The physician who prepared the patient's allergen immunotherapy extract should provide adequately labeled allergen immunotherapy extract vials, detailed directions regarding dosage schedule for build-up and maintenance, and instructions on adjustments that might be necessary under the following circumstances:

1. when providing patients with new vials;
2. during seasonal exposure to allergens that are in the patient's allergen vaccine, to which the patient is very sensitive, or both;
3. if the patient has missed injections; and
4. when reactions occur to the allergen immunotherapy extract.

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

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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 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 very 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 fully trained to administer the injection and to treat anaphylaxis if this should 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 supports (personnel, medications, supplies, and equipment) are more optimal for encouraging prompt recognition and treatment of anaphylaxis (Table V). 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.

Summary Statement 63: If a patient on 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for their immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extracts might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Patients often 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 brought from the previous physician (ie, an unchanged immunotherapy program) or one to be prepared by the current physician (ie, a new immunotherapy program).

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 full, clear, and detailed documentation of the patient's previous schedule and the contents of the allergen immunotherapy extract (see Appendices 7, 8, 11, 12, and 14 for examples of allergen immunotherapy prescription and administration forms and documentation guidelines for allergen immunotherapy forms). In addition, the patient's previous response to and compliance with this program 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 a schedule and the allergen immunotherapy extract, (2) the patient has shown significant improvement on this immunotherapy program, and (3) the contents of the allergen immunotherapy extract are appropriate for the area in which the patient is now living.

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, vaccine type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient's dose is not modified. This increased risk is due to the significant variability in content and potency of extracts and the variability in methods used by physicians to prepare the patient's maintenance concentrate and its dilutions. For example, the strength of a given concentration of nonstandardized extracts might vary significantly from vial to vial. The risk of systemic reactions in such a situation might be greater with nonstandardized extracts and allergen immunotherapy extracts that contain mixtures of allergens.

Therefore if the allergen immunotherapy extract is to be changed, the patient might need to be retested for specific IgE to the appropriate allergens 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 provided the interval of time since the last injection has not been too long. For lot changes from the same manufacturer, the physician can consider decreasing the dose by 50% to 90%. For changes in manufacturer and nonstandardized extracts, a greater decrease in dose might be necessary.

SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

Allergen immunotherapy in children

Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children

with allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Immunotherapy for children has been shown to be effective and often well tolerated,[137,242] although at least one study did not show efficacy.[293] 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.[294] In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (see the Patient selection section and Table VII). In recent studies children receiving allergen immunotherapy have demonstrated:

1. improvement in symptom control for asthma[117,119,121,122] and allergic rhinitis[118];
2. increased PC_{20} to histamine[121];
3. increased PC_{20} to cat and house dust mite allergens[121,149];
4. decreased risk of development of asthma[6,9,163-165];
5. decreased development of new sensitivities[120,166]; and
6. modification in release of mediators in children receiving immunotherapy that correlates with decreased clinical symptoms.[123]

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Although there is some disagreement about the role of allergen immunotherapy in children under the age of 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.[117,122] In children with allergic rhinitis, allergen immunotherapy might prevent the development of asthma.[6,9,163-165] However, allergen immunotherapy for inhalant allergens is usually not considered necessary in infants and toddlers because (1) there is 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 in pregnancy

Summary Statement 71: Allergen immunotherapy might be continued but is usually not initiated in the pregnant patient. **C**

The physician must be aware of the benefits and risks of immunotherapy in pregnant patients. The recommended precautions for prevention of adverse reactions are especially important in the pregnant patient. Allergen immunotherapy is effective in the pregnant patient. Thus allergen immunotherapy maintenance doses can be continued during pregnancy. Allergen immunotherapy is usually not initiated during pregnancy because of risks associated with systemic reactions and their treatment (ie, spontaneous abortion, premature labor, or fetal hypoxia). 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, and the patient is maintained on the dose that she is receiving at that time.

Immunotherapy in the elderly patient

Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy might be considered in the treatment of the elderly patient, but the benefit/risk assessment must be evaluated carefully in this population. Older 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. However, elderly patients may also benefit from allergen immunotherapy and age alone should not preclude the consideration of allergen immunotherapy.[295]

Immunotherapy in patients with immunodeficiency and autoimmune disorders

Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with immunodeficiency or autoimmune disorders. Therefore the decision to begin immunotherapy in patients with major humoral or cellular immune defects must be individualized. Concern about the increased risk of immunotherapy in such patients is largely hypothetical.

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

ALTERNATIVE ROUTES OF IMMUNOTHERAPY

Sublingual and oral immunotherapy

Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be

effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no FDA-approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **B**

Alternative routes of administration of allergen immunotherapy are ''a viable alternative to parenteral injection therapy'' in some cases.[106,296] Studies of oral immunotherapy have provided conflicting results for ragweed,[297] birch,[298] and cat[299] immunotherapy. The present dosage of oral immunotherapy extract is 20 to 200 times the parenteral injected dosage, which requires a cost assessment for this type of therapy. Furthermore, adverse effects have included gastrointestinal and oral reactions (50% in 1 study) that might preclude home therapy. Oral immunotherapy should be considered investigational at this time.

Optimal-dose (high-dose) sublingual swallow immunotherapy is effective in adults and children.[300-304] In a study of 855 patients with grass pollen allergy and allergic rhinitis randomized to placebo or one of 3 grass tablet doses, there was a significant reduction in symptom and medication scores in the highest-dose subgroup, who were treated for at least 8 weeks before the grass pollen season, compared with the placebo group (symptoms, 21%, $P = .0020$; medication use, 29%, $P = .0120$).[303]

Sublingual allergen studies have evaluated house dust, olive pollen, grass pollen, ragweed, birch, cat, latex, *Alternaria* species, and *Parietaria judaica*.[305-313] Sublingual immunotherapy has been shown to be effective in patients sensitized to 2 non–cross-reacting allergens, grass and birch.[314] It has been noted that the allergen is not degraded by saliva and that there is no direct sublingual absorption of allergen. Radiolabeled allergen has been detected after 48 hours in the sublingual region.[315,316] Alternative protocols, such as rush and ultra-rush (20 minutes) sublingual swallow[307,316,318] and no induction (build-up) phase,[301,303,317,319,320] have been studied. Several studies have suggested a relationship between dose and efficacy with sublingual immunotherapy,[303,310,321] but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. The majority of sublingual studies have demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both, but approximately 35% of the randomized, double-blind, placebo-controlled studies did not demonstrate efficacy in either parameter during the first year of treatment.[322] Further studies are needed to confirm the optimal dose for sublingual immunotherapy.

One of the potential advantages of sublingual immunotherapy is that it appears to be safe, even at very high doses (up to 500 times the usual monthly subcutaneous dose), and to be associated with a lower incidence of serious side effects.[310,320,323] This appears to apply to young children (<5 years), for whom there are prospective safety data[324,325] and a postmarketing survey.[326]



FIG 3. Sample of labels for allergen immunotherapy extract vials.

There have been no SLIT-related fatalities, but there have been 3 case reports of anaphylaxis caused by sublingual immunotherapy. One patient with latex hypersensitivity had anaphylactic shock 20 minutes after reaching the maximal dose on the fourth day of latex rush sublingual rush immunotherapy.[327]

The other 2 reported cases of SLIT anaphylaxis involved patients treated with multiple inhalant allergens. In one case a patient with allergic rhinitis and asthma who was prescribed a sublingual immunotherapy extract composed of multiple non–cross-reacting allergens (*Alternaria* species, dog, cat, ragweed mix, weed mix, and grass mix)[328] had generalized pruritis, followed by angioedema, shortness of breath, and dizziness, within a few minutes of administering 6 drops of the 1:100 vol/vol dilution on the third day of treatment. This episode was preceded by a milder systemic reaction the previous day (generalized pruritis). In the other case, a 13-year-old girl with allergic rhinitis and asthma had swelling of her lower lip 3 minutes after pollen drops, high fever, chest pain, nausea, and abdominal pain.[329] She was treated in the emergency department for anaphylaxis and hospitalized for observation. The reaction occurred 1 month after she had reached the maintenance dose during the peak of the spring season.

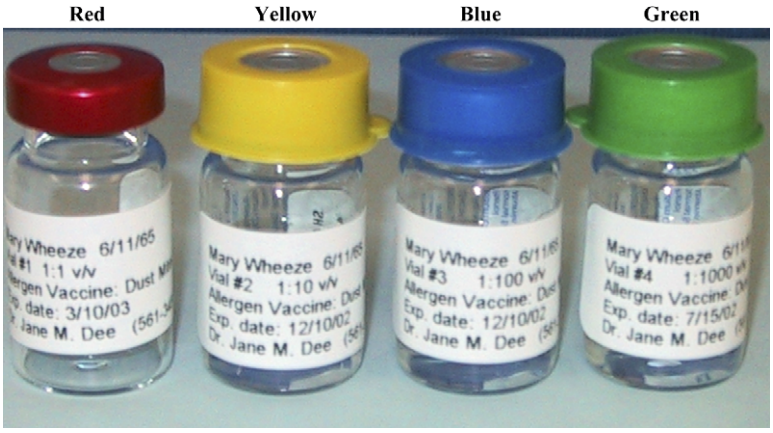


FIG 4. Sample set of color-coded vials of allergen vaccine.

There is currently no FDA-approved formulation for sublingual immunotherapy in the United States at this time, and this modality should be considered investigational. Current investigation of sublingual immunotherapy should not be confused with low-dose sublingual immunotherapy based on provocation neutralization testing or Rinkel-type skin testing.

Intranasal immunotherapy

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Based on controlled, well-designed studies, intranasal immunotherapy has been shown to improve the nasal symptoms of rhinitis.[330] Intranasal dry powder extract immunotherapy has been studied in grass,[330] birch,[331] *P judaica*,[332-334] and house dust mite[335] allergy. Clinical efficacy was noted in all of these studies. Nasal reactivity to allergen challenge was reduced, and only minor side effects were noted in 2 of the above studies. A 3-year study with *P judaica* reported to provide persistent benefits for up to 12 months after conclusion of allergen immunotherapy.[333] Local administration of nasal allergen in an aqueous solution for immunotherapy might be limited by the local side effects. Further studies in both pediatric and adult groups are needed. In human studies the antigen has been noted to appear in the serum within 15 to 30 minutes of administration, with a peak level occurring within 2 to 3 hours.[315] Some allergens have been reported to be retained in the nasal mucosa for up to 48 hours after administration. Intranasal immunotherapy is not currently available in the United States but has gained some acceptance in other parts of the world.

Immunotherapy techniques that are not recommended

Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

Low-dose regimens, including coseasonal low-dose immunotherapy for aeroallergens and the Rinkel low-dose titration techniques, are not effective.[27,28] Immunotherapy based on provocation–neutralization testing with food and aeroallergens and enzyme-potentiated desensitization is not effective.[336]

FUTURE TRENDS IN IMMUNOTHERAPY

Therapy with aeroallergen extracts will become more uniform (as is the current practice for insect venoms) as greater numbers of biologically standardized allergen extracts become available. The actual number of commercially available allergen extracts will be reduced based on consensus agreements about the regional prevalence of aeroallergens, their cross-allergenicity, and the relevance of their effect on human health in specific locales. Novel routes for more effective, convenient, and safer allergen immunotherapy are being investigated throughout the world.

For example, the sublingual route of administering allergen immunotherapy has been studied extensively in Europe. A meta-analysis confirmed its clinical effectiveness in allergic rhinitis,[302] and it has been reported to be effective in asthma as well.[337] Sublingual immunotherapy appears to have a very low risk of serious life-threatening systemic side effects, which might allow for home administration.[324,338] In some studies the clinical benefits of sublingual immunotherapy were not significant until the second year of treatment,[306,339] and comparisons suggest that the magnitude of the clinical benefit of sublingual immunotherapy might not be as great as that of subcutaneous immunotherapy.[311]

Trials with non–IgE-binding peptides containing T-cell stimulating peptides have been reported.[340] Site-directed mutagenesis has produced allergens with decreased IgE-binding capacity without decreased T-cell responses.[341,342]

Immunostimulatory sequences mimicking bacterial and viral DNA have been prepared that stimulate the innate immune system to direct T-cell responses toward

T_H1 rather than T_H2 phenotypes.[343] The results of clinical trials with a conjugate of the immunostimulatory sequence to the major allergen of ragweed, Amb a 1 (AIC), have been reported.[34,343] In a double-blind, placebo-controlled study of 25 adults who received 6 weekly injections of the AIC or placebo vaccine before ragweed season, the AIC group had better peak-season rhinitis scores on the visual analog scale ($P = .006$), peak-season daily nasal symptom diary scores ($P = .02$), and midseason overall quality-of-life scores ($P = .05$) than the placebo group during the first ragweed season, and this effect was observed in the subsequent ragweed season.[344]

Humanized anti-IgE mAb has been shown to have clinical effects in both allergic rhinitis and asthma.[345-348] Theoretically, this new therapeutic modality could be used as protective cover for clinical applications of rapid forms of immunotherapy. It is possible that preadministration of anti-IgE could provide a more effective protective effect than premedication with antihistamines and therefore permit a rush allergen immunotherapeutic regimen with reduced risk of serious systemic reactions.[282]

AUTHOR'S 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 2 systemic reaction grading systems (the European Academy of Allergy and Clinical Immunology's grading of severity for systemic side effects and the Portnoy method for numeric grading of reactions to allergen immunotherapy) can be found in the Appendix section. These forms can also be found along with examples of immunotherapy instruction and consent forms, preinjection health questionnaires, and indications for beginning and continuing immunotherapy forms at www.aaaai.org.

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APPENDIX 1. American College of Medical Quality's policy on the development and use of practice parameters for medical quality decision-making[1]

Practice parameters are strategies for patient management developed to assist health care professionals in clinical decision making. Practice parameters include standards, guidelines, and other patient management strategies. Standards are accepted principles for patient management. Guidelines are recommendations for patient management that identify a particular management strategy or a range of management strategies. Other strategies for patient management include practice policies and practice options. Practice parameters are to be used as screening tools to identify possible deviations from the applicable standards of care. Such parameters are not to be used as absolute standards or to profile or report on health care personnel. Parameters are designed to trigger a process in which possible deviations from the standard of care are identified as outlier practice patterns. Once a deviation from the parameter is identified, such a deviation should be referred to the appropriate qualified physician advisor or reviewer for a determination of medical necessity that conforms to the applicable standard of care. Parameters used in the day-to-day practice of clinical medicine should be clinically relevant. They should not be considered as substitutes for the standard of care but might contribute to its formulation.

Practice parameters must be developed, designed, and implemented only by board-certified, clinically practicing, specialty-matched physician advisors/reviewers with unrestricted medical licenses. Qualified nonphysicians might participate in the development of these parameters only in the areas in which their clinical expertise based on the standard of care is applicable. The health care personnel who develop these parameters should sign their names and date the final version as evidence of their participation and support. Practice parameters must be based on sound scientific research findings, professional literature, clinical experience and appropriate well-recognized methodologies and reflect professionally recognized national standards of care practiced in the clinical community of medicine. The development procedures followed, the participants involved, the evidence used, the assumptions and rationales accepted, and the analytic methods used should be meticulously documented, described, and made publicly available for national peer review. Parameters should be updated as needed.

Practice parameters are used as tools to enhance medical decision making but not as replacements for physicians' clinical judgment. They can be considered as means to enhance the performance of clinical and review personnel but not to replace them. It is below the standard of care of the medical review process to substitute qualified physician reviewer experts with unqualified reviewers who are using parameters.

APPENDIX 2. Examples of possible abbreviations for allergen immunotherapy extract 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

APPENDIX 3. 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

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

APPENDIX 4. Example of immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals (modification of the AAAAI skin testing and immunotherapy consent and instruction forms: immunotherapy administration instruction form, which can be found at http://www.aaaai.org)

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

- Up to 7 days, continue as scheduled (ie, if on weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection).
- Eight to 13 days after missed scheduled injection; repeat previous dose.
- Fourteen to 21 days after missed scheduled injection; reduce dose 25%.
- Twenty-one to 28 days after missed scheduled injection; reduce previous dose 50%.

Then increase dose each injection visit as directed on the immunotherapy schedule until therapeutic maintenance dose is reached.

This suggested approach to modification of doses of allergen immunotherapy because of gaps between treatment during the build-up phase is not based on retrospective or prospective published evidence, but it is presented as a sample for your consideration. The individual physician should use this or a similar protocol as a standard operating procedure for the specific clinical setting. A similar dose-reduction protocol should be developed for gaps in maintenance immunotherapy.

APPENDIX 5. Example of a cluster immunotherapy schedule[22,26]

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

APPENDIX 6. Recommended documentation for allergen immunotherapy prescription forms

The purpose of the allergen immunotherapy prescription form is to define the contents of the allergen immunotherapy extract in enough detail that it could be precisely duplicated. The following information should be on an immunotherapy prescription form:

Patient information:

- Patient name, patient number (if applicable), birth date, telephone number, and picture (if available) should be included.

Preparation information:

- Name of person and signature preparing the allergen immunotherapy extract should be included.
- Date of preparation should be recorded.
- Bottle name should be included (eg, trees and grass). If abbreviations are used, a 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 should be included.
- Volume of manufacturer's extract to add to achieve the projected effective concentration should be included. 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) should be included.
- Extract manufacturer should be included.
- Lot number should be included.
- Expiration date should be recorded and should not exceed the expiration date of any of the individual components.

APPENDIX 7. Allergen immunotherapy extract prescription 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:

_____
_____
_____
_____

_____ ____/____/____
Prescribing Physician Signature Date

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

APPENDIX 8. Maintenance concentrate prescription form

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: 6/10/06

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial **4** from Vial **1** on **8/30/06** Expiration date: **10/15/06**
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	Short ragweed	1:20 w/v G (150 Amb a1)	0.5ml	Greer	12345	1/01/08
2	Amaranthus Retroflexus	1:10 w/v G	0.5ml	H-S	6789	2/07/08
3	Ash	1:10 w/v G	0.5ml	Center	3333	3/17/08
4	Cat	10,000 BAU/ml G	2.00ml	ALO	9898	2/27/08
5	Timothy Grass	100,000 BAU/ml G	0.4ml	ALK	56789	7/09/08
6	Johnson Grass	1:10 w/v G	0.5ml	Greer	2434	7/20/08
7						
8						
9						
10						
Diluent	HSA		0.6ml	ALK	68597	12/08
Total Volume			5.00 ml			6/10/07

*** Components of mixes listed on a separate sheet**
**** Assumes 0.5 ml injection as target maintenance dose**

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

Specific Instructions:

_____

_____

Prescribing Physician Signature

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

APPENDIX 9. Labels for allergen immunotherapy extracts

Each vial of allergen immunotherapy extract should be labeled in a way that permits easy identification. Each label should include the following information (example in Figs 3 and 4):

- Appropriate patient identifiers might include the patient's name, patient's number, patient's picture, and birth date.
- The contents of the allergen immunotherapy extract in a general way should be included. The detail with which this can be identified depends on the size of the label and the number of allergens in the vial. Ideally, allergens should be identified as trees, grasses, weeds, mold, dust mite, cockroach, cat, and dog. Because of space limitations, it might be necessary to abbreviate the antigens (eg, T, G, W, M, DM, Cr, C, and D respectively [see Appendix 2]). A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate (vol/vol) should be recorded. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- The expiration date should be included.

APPENDIX 10. Allergen immunotherapy administration form recommended documentation

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

Patient information:

- Patient's name, date of birth, telephone number, and patient's picture (optional but helpful).

Allergen immunotherapy extract information:

- Allergen immunotherapy extract name and dilution from maintenance in vol/vol bottle letter (eg, A and B), bottle color, or number, if used.
- Expiration date of all dilutions.

Administration information in separate columns:

- Date of injection.
- Arm administered injection, which might facilitate determination of exact cause of local reaction.
- Projected build-up schedule.
- Delivered volume reported in milliliters.
- Description of any reactions. The details of any treatment given in response to a reaction would be documented elsewhere in the medical record and referenced on the administration form.
- *Patient's health before injection*. This can be performed through a verbal or written interview of the patient before administering the immunotherapy injection. The patient should be questioned about increased asthma or allergy symptoms, β-blocker use, change in health status (including pregnancy and recent infections), or an adverse reaction to a previous injection (including delayed large local reactions persisting through the next day). Patients with significant systemic illness generally should not receive an injection.
- *Antihistamine use*. Antihistamines are frequently a component of an allergy medication regimen, and it would be important to note whether a patient is taking an antihistamine on the day he or she receives his or her immunotherapy injection. For consistency in interpretation of reactions, it might be desirable for a patient to either take or avoid antihistamines on a regular basis on the days he or she receives immunotherapy. The physician should note on the form whether he or she recommends the patient consistently take an antihistamine on immunotherapy treatment days.
- *Peak flow reading*. Consider obtaining a peak expiratory flow rate measurement before administering an immunotherapy injection to asthmatic patients. Poorly controlled asthma is considered a risk factor for immunotherapy. Obtaining a peak expiratory flow rate measurement before the immunotherapy injection might help identify patients with symptomatic asthma. The patient's baseline peak expiratory flow rate should be provided on the form as a reference. Health care professionals administering immunotherapy injections should be provided with specific guidelines about the peak expiratory flow rate measurement for when an immunotherapy injection should be withheld and the patient referred for clinical evaluation.
- **Baseline blood pressure**. It might be useful to record the patient's blood pressure as a baseline for future reference.

APPENDIX 11. Allergen immunotherapy administration form

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 allergy or 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

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

Date to reorder: __/__/__

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 allergy or 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**	

APPENDIX 12. 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: _____
_____
Staff action taken (if any): _____

APPENDIX 13. 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.

APPENDIX 14. Allergen immunotherapy systemic reaction/anaphylaxis 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
__Epinephrine IM into 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	

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:
_____
_____
_____
_____

Clinical impression: True SR Questionable SR No SR

Systemic reaction severity classification: EAACI_____ **Portnoy** _____

Dosage adjustment? _____

Signatures_____ **RN** _____**MD/DO**

APPENDIX 15. Grading severity of allergen immunotherapy reactions: Two methods

1. **The European Academy of Allergy and Clinical Immunology grading of severity for systemic side effects***

Classification of systemic reactions

0 = No symptoms or nonspecific symptoms

I = Mild systemic reactions: symptoms—localized urticaria, rhinitis, or mild asthma (PF <20% decrease from baseline).

II = Moderate systemic reaction: symptoms—slow onset (>15 minutes) of generalized urticaria, moderate asthma, or both (PF < 40% decrease from baseline).

III = Severe (non–life-threatening) systemic reactions: symptoms—rapid onset (<15 minutes) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).

IV = Anaphylactic shock: symptoms—immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, and hypotension, for example.

2. **Portnoy method for numeric grading of reactions to allergen immunotherapy†**

Local

0+ = No significant reaction or small area of erythema less than the size of a half dollar without swelling or wheal formation

1+ = Erythema greater than the size of a half dollar, swelling or wheal formation, or both

Systemic

2+ = Systemic reactions: cutaneous only—might consist of a cutaneous eruption, such as urticaria

3+ = Systemic reaction: generalized pruritus, sneezing, or both—might consist of increased allergy symptoms, such as nasal congestion, sneezing, or pruritus, especially in the mouth or throat

4+ = Systemic reaction: pulmonary—consists of wheezing, shortness of breath, and tightness. Might be associated with decreased pulmonary function tests

5+ = Systemic reaction: anaphylaxis—a sensation of not feeling right is a frequent prelude; might consist of hypotension, laryngeal edema, severe wheezing, and cramping

6+ = Cardiopulmonary arrest

PF, Peak expiratory flow.

*Subcutaneous immunotherapy. Allergy 2006;61(suppl 82):5-13.

†Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80.

Allergen immunotherapy: A practice parameter second update

Supplement Editor: **Linda Cox, MD**
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These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology.

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the "Allergen immunotherapy: a practice parameter second 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 and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
5. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
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These parameters are also available on the internet at http://www.jcaai.org.

CONTRIBUTORS

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Allergen immunotherapy: A practice parameter second update

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PREFACE

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

The objective of ''Allergen immunotherapy: A practice parameter second update'' is to optimize the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. 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's ''Policy on development and use of practice parameters for medical quality decision-making'' (Appendix 1).[1]

This document builds on the previous Joint Task Force document, ''Allergen immunotherapy: a practice parameter'' published in the *Annals of Allergy, Asthma and Immunology* in 2003.[2] The updated practice parameters draft was prepared by Drs Linda Cox, James Li, Hal Nelson, and Richard Lockey. The Joint Task Force reworked the initial draft into a working draft of the document. The project was exclusively funded by the 3 allergy and immunology societies noted above.

In preparation for the 2003 ''Allergen immunotherapy: a practice parameter'' and the second update, a comprehensive search of the medical literature was conducted with various search engines, including PubMed; *immunotherapy*, *allergic rhinitis*, *asthma*, *stinging insect allergy*, and related search terms were used. 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 second update'' was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the ACAAI, AAAAI, and JCAAI. In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for review and comments from members of the sponsoring organizations. 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 allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. This document also contains recommendations for the safe practice of allergen immunotherapy, including specific recommendations on the prevention and management of 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 or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. Symptoms of allergic conjunctivitis (eg, itchy watery eyes) are often considered part of allergic rhinitis or are included in the diagnosis of rhinoconjunctivitis. Particularly good candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures, those in whom it is important to avoid the potential adverse effects of medications, and those who wish to reduce the long-term use of medications. Immunotherapy is recommended for patients with a history of systemic reaction to Hymenoptera stings and specific IgE antibodies to Hymenoptera venom.

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.[3]

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. 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 *maintenance concentrate* should be used to identify the allergen immunotherapy extract that contains a therapeutic effective dose for each of its individual constituents (see the Immunotherapy schedules and doses section).

The term *manufacturer's extract* refers to the allergy extract purchased from the manufacturer. The terms *stock*, *full-strength*, and *concentrate* are ambiguous and should not be used. 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).

Allergen immunotherapy is effective when appropriate doses of the allergens are administered. ''Allergen immunotherapy: A practice parameter'' recommends that vials of allergen immunotherapy extracts should be prepared individually for each patient to enhance the individualization of therapy, reduce the risk of allergen cross-contamination, and reduce the risk of error in administration.[4,5] This parameter recommends the use of standardized allergen immunotherapy prescription and administration forms to improve the safety, uniformity, and standardization of allergen immunotherapy practice.[4,5] The suggested forms are found in the Appendix (Appendices 7, 8, 11, 12, and 14) and in the members' section of the www.aaaai.org Web site. The routine use of these standardized forms should improve the quality of immunotherapy practice.

Members' feedback comments on the recommended allergen extract dilution dating in the 2003 ''Allergen immunotherapy: A practice parameter'' led to an allergen immunotherapy extract dilution stability study designed by the AAAAI Immunotherapy and Allergy Diagnostics Committee and funded by the AAAAI Board of Directors. The study was designed to investigate the effect of time, temperature, and dilution of standardized allergen extract potency, and the results of this study were considered in this update.

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 3 years after publication. Requests for information about or an interpretation of these practice parameters should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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. Allergen immunotherapy

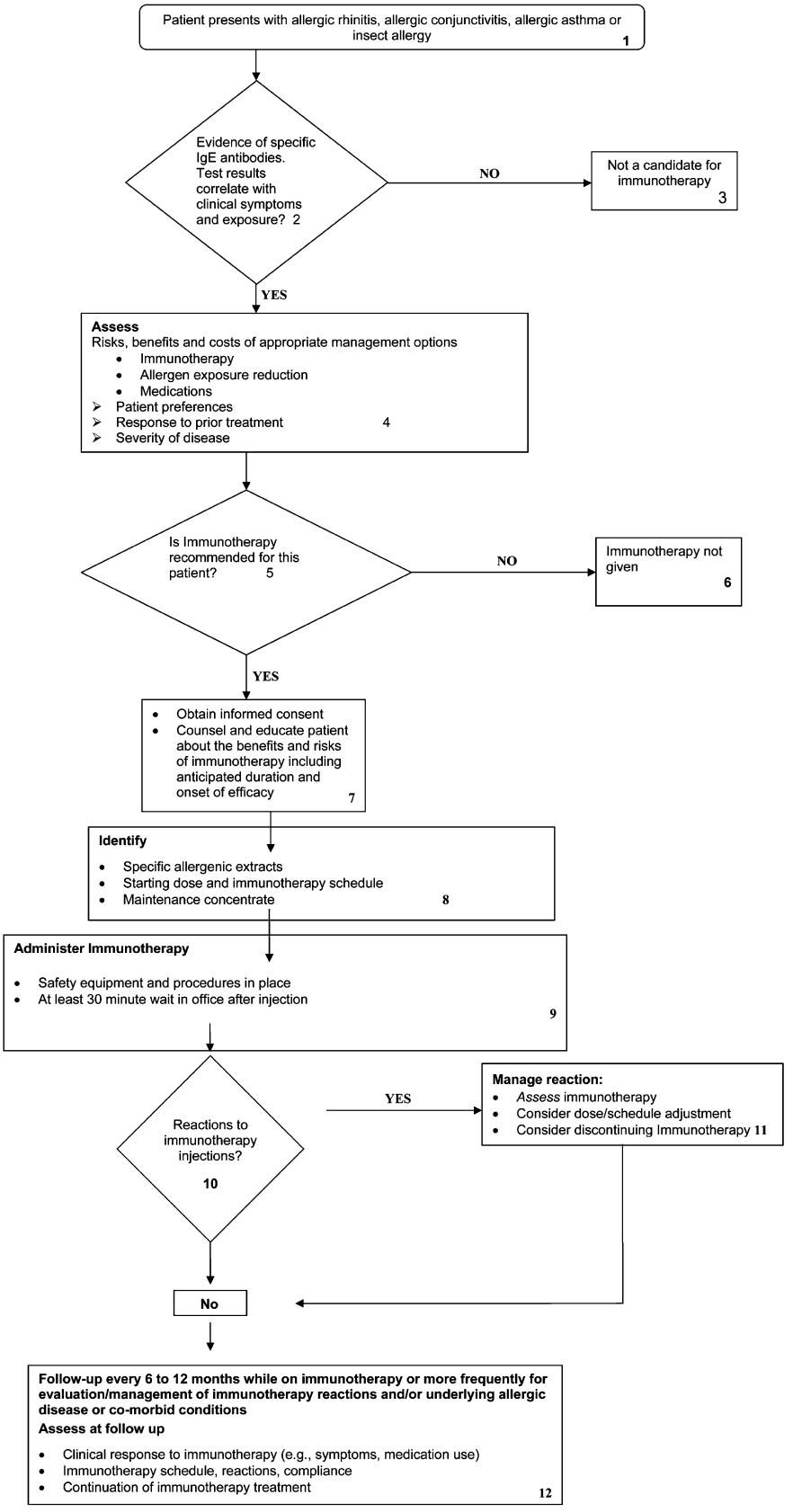


FIG 1. Algorithm for allergen immunotherapy.

might prevent the development of asthma in individuals with allergic rhinitis.[6-9] Evaluation of a patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic conjunctivitis, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for specific IgE antibody).[10]

Box 2

Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although *in vitro* testing for 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

Management of complex medical conditions, such as allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity, should include the careful evaluation of management 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 patient 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. On the basis of clinical considerations and patient 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 good candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy (VIT).

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 on the basis of 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 (see the Immunotherapy schedules and doses section). In general, the starting immunotherapy dose is 1000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 1000 to 4000 arbitrary units (AU; eg, for dust mite) or bioequivalent allergy units (BAU; eg, for grass) 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 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 referred to as *up-dosing*, *induction*, or the *dose-increase phase*) entails administration of gradually increasing doses during a period of approximately 14 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 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, in particular anaphylaxis. Patients should wait at the physician's office for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly, if they occur.

In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring 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. Some physicians recommend providing certain patients with epinephrine for self-administration in case of severe late reactions to immunotherapy injections.

Box 10

Injections of allergen immunotherapy extract can cause local or systemic reactions. Most severe reactions develop within 30 minutes after the immunotherapy injection, but reactions can occur after this time.

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 (anaphylaxis). Epinephrine is the treatment of choice in anaphylaxis, preferably when administered intramuscularly,[11] although subcutaneous administration is acceptable.[12]

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, see the practice parameters for anaphylaxis.[12]

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. After a severe systemic reaction, careful evaluation by the prescribing physician is recommended. For some patients, the immunotherapy maintenance dose might need to be reduced because of repeated systemic reactions to immunotherapy injections. The decision to continue immunotherapy should be re-evaluated after severe or repeated systemic reactions to allergen immunotherapy extracts.

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 doses, 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,[13] but others might experience a recurrence of their symptoms after discontinuation of allergen immunotherapy.[14] 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, and 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 on the basis of the patient's clinical response, disease severity, immunotherapy reaction history, and patient preference.

IMMUNOTHERAPY GLOSSARY

For more information on immunotherapy definitions, see the article by Kao.[15]

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 (pigments and salts; see the Allergen selection and handling section). Other terms used to describe the allergen immunotherapy extract include *allergen product*,[16] *allergy serum*, *allergen vaccine*,[17] 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.[18] Other terms that have been used for allergen immunotherapy include *hyposensitization*, *allergen-specific desensitization*, and the lay terms *allergy shots* or *allergy injections*.[15]

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

TABLE II. Allergen immunotherapy dose-calculation table

- Express weight per volume as a fraction: $\frac{1}{N}$ or 1:*N*.
- Calculate concentration of individual allergens in mixtures. If a mixture is made of equal amounts of N individual allergens to make a total concentration (C), the final concentration of an individual allergen (Ca) can be calculated by using the following equation:

$Ca = C \times \frac{1}{N} = \frac{C}{N}$ or *C*:*N*.

For example, if a mixture of equal amounts of 5 (N) allergens has a total concentration (C) of 100,000 BAU/mL, then the final concentration of each individual allergen (Ca) is: $Ca = \frac{C}{N} = \frac{100{,}000}{5} = 20{,}000\ BAU/mL$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{C}{N} = \frac{1/10}{5} = \frac{0.1}{5} = 0.02$ or $\frac{1}{50}$ or 1:50.

- Dilution of individual allergen: If an initial volume, Vi (in milliliters), of an individual antigen with concentration, Ci, is added to an allergen extract to make a final volume of Vf (in milliliters), the final allergen concentration (Ca) in the allergen extract mixture will be: $Ca = Ci \times \frac{Vi}{Vf}$.
- Final concentration of an allergen in a mixture of mixtures is determined by multiplying the initial concentration by the dilution factors from each mixing step.

For example, consider a mixture containing equal amounts of 5 (N) allergens with a total concentration (C) of 100,000 BAU/mL (first dilution). If an initial volume (Vi) of 0.5 mL of this mixture is further mixed with other components and diluent to make a final allergen extract mixture volume (Vf) of 5.0 mL (second dilution), the final concentration of an individual allergen (Ca) will be:

$$Ca = C \times \underbrace{\frac{1}{N}}_{\text{Mixture dilution}} \times \underbrace{\frac{Vi}{Vf}}_{\text{Allergen extract dilution}} = 100{,}000 \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{100{,}000}{50} = 2000\ BAU/mL$$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{1}{10} \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{1}{500}$ or 1:500.

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).

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 to 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-medicated 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 multiplied by volume of administered dose (see Table II for a dose-calculation table).

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, cat, 1000 BAU, [highest tolerated dose] vs 2000 BAU [projected effective dose]).

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 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 by a variety of immunologic transformations. Early definitions of the term immunotherapy included active and passive immunization for the purpose of improving 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 by means of induction of clonal deletion, anergy, immune tolerance, or immune deviation.

The *maintenance concentrate* is a preparation that contains individual 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 may not be the initially calculated projected effective dose.

The *maintenance goal* (or projected effective dose) is the allergen dose projected to provide therapeutic efficacy. The maintenance goal is based on published studies, but a projected effective dose has not been established for allergens. 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 the 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 large local reaction causing discomfort). The intervals between maintenance immunotherapy injections generally ranges 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 by means of immunoblotting or crossed allergoimmunoelectrophoresis.

For a definition of *projected effective dose*, see 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 test responses), and premedication with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similar high incidence of systemic reactions.

Off the board into one syringe is a phrase that describes a method of allergen immunotherapy preparation and administration that involves specifically mixing the patient's allergen immunotherapy injection in a single syringe, which is not recommended. This syringe might be inserted into more than one allergen extract vial, and this poses a risk of cross-contamination of the allergen extracts and might dull the needle with repeated penetration of the rubber stopper.

Shared specific patient vials is a method of allergen immunotherapy preparation and administration in which the allergy immunotherapy extract is withdrawn from a shared vial (eg, mixed vespids or dust mite mix). This is sometimes referred to as off the board, but it is distinct from the method of off the board into one syringe in that the syringe enters only one allergen extract vial.

INTRODUCTION

Immunity has been defined as protection against certain diseases. The initial immunotherapeutic interventions, which included the use of preventive vaccines and xenogenic 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 the field of allergen immunotherapy. From its humble empiric emergence in 1900, when ragweed injections were proposed as therapy for autumnal hay fever, allergen immunotherapy has progressed in both theory and practice from the passive immunologic approach to the active immunologic procedures pioneered by Noon[19] and Freeman.[20,21] 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 10 years. Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Some studies have suggested that allergen immunotherapy might prevent the development of asthma in individuals with allergic rhinitis.[6-9]

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,[22-26] and it should be differentiated from unproved methods, such as neutralization-provocation therapy and low-dose subcutaneous regimens based on the Rinkel technique, which have been found to ineffective in a double-blind placebo-controlled study.[27,28]

SUMMARY STATEMENTS

Mechanisms of immunotherapy

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, defined as a relative decrease in allergen-specific responsiveness and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

Allergen extracts

Summary Statement 6: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. **A**

Summary Statement 7: Nonstandardized extracts might vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Summary Statement 8: 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**

Cross-reactivity of allergen extract. Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

Efficacy of immunotherapy

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Summary Statement 10: Immunotherapy is effective for 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**

Food allergy, urticaria, and atopic dermatitis. Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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**

Measures of efficacy. Summary Statement 12: 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**

Safety of immunotherapy

Reaction rates. Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

Timing of anaphylactic reactions to immunotherapy injections. Summary Statement 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

β-*Adrenergic blocking agents.* Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

Contraindications. Summary Statement 18: 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**

Reducing the risk of anaphylaxis to immunotherapy injections. Summary Statement 19: 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**

Patient selection

Clinical indications. Summary Statement 20: 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 depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Special precautions in patients with asthma. Summary Statement 21: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. **C**

Clinical indications for VIT. Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Summary Statement 23: Patients selected for immunotherapy should be cooperative and compliant. **D**

Allergen selection and handling

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted in vitro tests for specific IgE antibodies can also be used. **A**

Specific allergens. Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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, supported by the presence of specific IgE antibodies. **A**

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Dose selection. Summary Statement 30: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. **A**

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens, is recommended. **B**

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extract handling

STORAGE

Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

STORING DILUTE EXTRACTS

Summary Statement 34a: More dilute concentrations of allergen immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: 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 a number of 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. **B**

Immunotherapy schedules and doses

Summary Statement 35: A customized individual 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 be based on single or multiple allergens. **D**

Maintenance concentrate. Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

Recommended doses. Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

Effect of dilution on dose. Summary Statement 38: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. **A**

Dilutions of the maintenance concentrate. Summary Statement 39: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. **D**

Labeling dilutions. Summary Statement 40: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. **D**

Individualized treatment vials. Summary Statement 41: 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. The mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. **C**

Starting doses. Summary Statement 42: The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. **D**

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

Dose adjustments for systemic reactions. Summary Statement 44: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. **D**

Reductions during periods of exacerbation of symptoms. Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Dose adjustments for late injections. Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

Cluster schedules. Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. **C**

Rush schedules. Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. **A**

Systemic reactions and rush schedules. Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

Premedication and weekly immunotherapy. Summary Statement 50: Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

Premedication with cluster and rush immunotherapy. Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

Maintenance schedules. Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. **A**

Continuing care

TIME COURSE OF IMPROVEMENT

Summary Statement 53: Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **A**

FOLLOW-UP VISITS

Summary Statement 54: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. **D**

DURATION OF TREATMENT

Summary Statement 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

DOCUMENTATION AND RECORD KEEPING

Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. **D**

INJECTION TECHNIQUES

Summary Statement 57: Allergen immunotherapy extract injections should be administered with a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **D**

Summary Statement 58: The injection should be administered subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Location of allergen immunotherapy administration

Physician's office. Summary Statement 59: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Summary Statement 60: 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**

Other locations. Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **D**

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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**

Summary Statement 63: 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for his or her immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extract might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Special considerations in immunotherapy

Allergen immunotherapy in children. Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Pregnancy. Summary Statement 71: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. **C**

Immunotherapy in the elderly patient. Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy in patients with immunodeficiency and autoimmune disorders. Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

Alternative routes of immunotherapy

Sublingual and oral immunotherapy. Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no US Food and Drug Administration (FDA)–approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **A**

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Immunotherapy techniques that are not recommended. Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

MECHANISMS OF IMMUNOTHERAPY

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, which is defined as a relative decrease in allergen-specific responsiveness, and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

The immunologic changes associated with immunotherapy are complex, and the exact mechanism or mechanisms responsible for its' clinical efficacy are continually being elucidated. Data support the concept that successful immunotherapy is associated with a change to a T_H1 $CD4^+$ cytokine profile.[29-34] Data indicate that increased production of IL-12, a strong inducer of T_H1 responses, contributes to this shift.[33] Clinically successful immunotherapy has been reported to be associated with immunologic tolerance, which is defined as a relative decrease in antigen-specific responsiveness, immune deviation, or anergy. For example, lymphoproliferative responses to allergen are reduced with immunotherapy.[32] Successful immunotherapy results in generation of a population of T regulatory cells, which are $CD4^+CD25^+$ T lymphocytes producing IL-10, TGF-β, or both.[35-39] Regulatory T-cell release has been described in allergen immunotherapy with Hymenoptera venom,[35] grass pollen extract,[37] and house dust mites.[38] IL-10 reduces B-cell antigen-specific IgE and increases IgG4 levels; reduces proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicits tolerance in T cells by means of selective inhibition of the CD28 costimulatory pathway.[36,37]

Allergen immunotherapy has been shown to block both the immediate and late-phase allergic response.[40] Allergen immunotherapy has been shown to decrease the recruitment of mast cells, basophils, and eosinophils in the skin, nose, eye, and bronchial mucosa after provocation or natural exposure to allergens.[41]

In patients receiving immunotherapy, initially there is an increase in specific IgE antibody levels, followed by a gradual decrease to a level that is still higher than that present before treatment. Clinical improvement in many patients develops before decreases in their IgE antibody levels occur or in other patients whose IgE antibody levels never decrease, thereby demonstrating that efficacy is not dependent on reductions in specific IgE levels.[42,43] Immunotherapy does diminish the seasonal increase in specific IgE levels.[44] Despite the persistence of significant levels of specific IgE antibody levels, immunotherapy usually causes a reduction in 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.[45-48]

An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, has also been associated with immunotherapy. The properties of allergen-specific IgA have yet to be determined, and there is a weak correlation between the increase in allergen-specific IgG levels and immunotherapy's clinical efficacy.[30,49,50]

Immunotherapy might alter the affinity and specificity of allergen-specific IgG.[51,52] During the initial phase of ultrarush VIT, a change in IgG specificity (ie, a change in the set of epitopes dominantly recognized by IgG on wasp venom antigens) occurred concomitantly with early clinical tolerance and was seen within 12 hours of ultrarush VIT ($P < .001$).[51] 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 individuals.[52] This change in IgG specificity preceded the increase in IgG titers and was sustained for up to 6 months.[52]

Allergen-specific IgG induced from immunotherapy can block IgE-dependent histamine release and subsequent IgE-mediated antigen presentation to T cells.[53] This effect might be dependent on IgE, allergen concentration, and CD23, the low-affinity receptor for IgE.

Whereas 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.[37,53]

The relationship between these immunologic changes and immunotherapy efficacy is not completely understood.

ALLERGEN EXTRACTS

Summary Statement 6: 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 has 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.[2,18,54-56] 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.

United States–licensed extracts can be obtained in aqueous, glycerinated, lyophilized, and acetone-precipitated and alum-precipitated formulations. Some commonly used allergens are standardized. These include extracts for cat hair, cat pelt, *Dermatophagoides pteronyssinus*, *Dermatophagoides 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.[57] 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.

Most standardized extracts are labeled in BAU. Short ragweed potency units were originally based on the content of the major allergen Amb a 1. Ragweed potency is reported in FDA units and BAU. One FDA unit of Amb a 1 equals 1 μg of Amb a 1, and 350 units of Amb a 1/mL is equivalent to 100,000 BAU/mL. Cat extracts were also originally standardized based on the content of major allergen (Fel d 1), with 100,000 arbitrary units (AU) per milliliter containing between 10 to 19.9 FDA units of Fel d 1 per milliliter (1 FDA unit of Fel d 1 equals 2 to 4 μg of Fel d 1).[55,58,59] Subsequently, $ID_{50}EAL$ testing suggested that 100,000 AU/mL was equal to 10,000 BAU/mL.[60] Approximately 22% of individuals with cat allergy have specific IgE antibodies to cat albumin.[61] Cat pelt extracts have a greater amount of albumin than cat hair extracts.[60]

Dust mites were originally standardized in AU by means of inhibition radioimmunoassay (RIA), and subsequent $ID_{50}EAL$ testing indicated that the AU was bioequivalent to the BAU, and the original AU nomenclature was kept. Dust mite extracts are still labeled in AU.

Summary Statement 7: Nonstandardized extracts can vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Nonstandardized extracts are labeled as wt/vol, which expresses weight in grams per volume in milliliters; that is, a potency of 1:100 indicates that 1 g 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 with a particular wt/vol or PNU potency can have widely varying biologic activities.[62-64] Therefore they should not be considered equipotent.

Summary Statement 8: 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**

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. The major clinically relevant aeroallergens of North America are listed in Table III. Furthermore, nonrelevant allergens in such mixtures could act as sensitizers rather than as tolerogens.[65,66] The physician must therefore select only those aeroallergens for testing and treatment that are clinically relevant in a particular geographic area.

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, dog), insect (cockroach), and Hymenoptera venom source materials.

Cross-reactivity of allergen extract

Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

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. A summary of cross-reactivity patterns of the clinically relevant North American aeroallergens can be found in Fig 2. 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,[67] inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[68-75] Grasses in other subfamilies (eg, Bermuda, Bahia, and Johnson) show greater diversity and should be evaluated separately.[76-78] Bermuda and Johnson grasses are increasingly important in the South,

TABLE III. The major clinically relevant aeroallergens of North America*

- Tree pollen
  - Chinese elm *(Ulmus parvifolia)*†‡; Siberian elm *(Ulmus pumila)*†‡; American elm *(Ulmus Americana)*†‡
  - Red oak *(Quercus rubra)*†; White oak *(Quercus alba)*†
  - Paper birch *(Betula papyrifera)*
  - Alder *(Alnus rubra)*
  - Box elder *(Acer negundo)*†; Red maple *(Acer rubra)*†
  - Eastern cottonwood *(Populus deltoides)*
  - Sycamore *(Platanus occidentalis)*
  - White ash *(Fraxinus americana)*†; Olive *(Olea europaea)*†‡
  - Black walnut *(Juglans nigra)*
  - Mulberry *(Morus rubra)*
  - Mountain cedar *(Juniperus ashei)*
  - Pecan *(Carya illinoensis)*
- Grass pollen
  - Rye *(Lolium perenne)*§‖
  - Timothy *(Phleum pratense)*§‖
  - Meadow fescue *(Festuca elatior)*§‖
  - Bermuda *(Cynodon dactylon)*‖
  - Johnson *(Holcus halepensis)*
  - Bahia *(Paspalum notatum)*
- Weed pollen
  - Short ragweed *(Ambrosia artemisiifolia)*‖
  - English (narrow leaf) plantain *(Plantago lanceolata)*
  - Mugwort *(Artemisia vulgaris)*
  - Russian thistle *(Salsola kali)*
  - Burning bush *(Kochia scoparia)*
  - Sheet (red) sorrel *(Rumex asetosella)*
  - Red root pigweed *(Amaranthus retroflexus)*
- Indoor aeroallergens
  - Cat epithelium *(Felis domesticus)*‖
  - Dog epithelium *(Canis familiaris)*
  - Arthropods (domestic mites: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*)‖
  - Insects (German cockroach: *Blattella germanica*)
- Fungi
  - *Alternaria alternata*¶
  - *Cladosporium* (*C cladosporioides*, *C herbarum*)¶
  - *Penicillium* (*P chrysogenum*, *P expansum*)¶
  - *Aspergillus fumigatus*¶
  - *Epicoccum nigrum*, *Drechslera* or *Bipolaris* type (eg, *Helminthosporium solani*)¶

*Compiled and selected in collaboration with the AAAAI Immunotherapy Committee Allergen Subcommittee for the identification of 35 key allergens of North America.
†Extensive cross-reaction of species within the genus.
‡Apart from regional prevalence, they are limited to local sites with substantial stands of these trees.
§Extensively cross-react with one another and bluegrass, orchard, red top, and sweet vernal.
‖Allergens for which standardized extracts are commercially available.
¶Species that are widely distributed and clinically important.

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.[79-82] 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.[83-85] Significant cross-reactivity between Betulaceae pollens and oak of the Fagaceae family has been demonstrated with percutaneous skin testing.[75] RAST inhibition studies have shown cross-inhibition between oaks and other *Fagales* species.[86] IgE immunoblot inhibition experiments have demonstrated that the *Fagales* species might be strongly inhibited by birch species.[87] The use of one of the locally prevalent members (eg, birch and alder) should be adequate.[88]

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.[89,90] Maple and box elder trees are found throughout the United States, except for the arid southwest. Although in the same genus as maple, *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,[91,92] and there are allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.[93]

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.[94] Similarly, Chenopod-Amaranth families have wide ranges in the western regions but are present throughout North America.[95] Current information on cross-reactivity of these families is limited.[96-98] 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.[99] The use of a single Amaranth extract should be sufficient to cover this family.[100,101] Similarly, *Atriplex* species (eg, saltbushes and scales) show near identity, and use of a single member is adequate. 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,

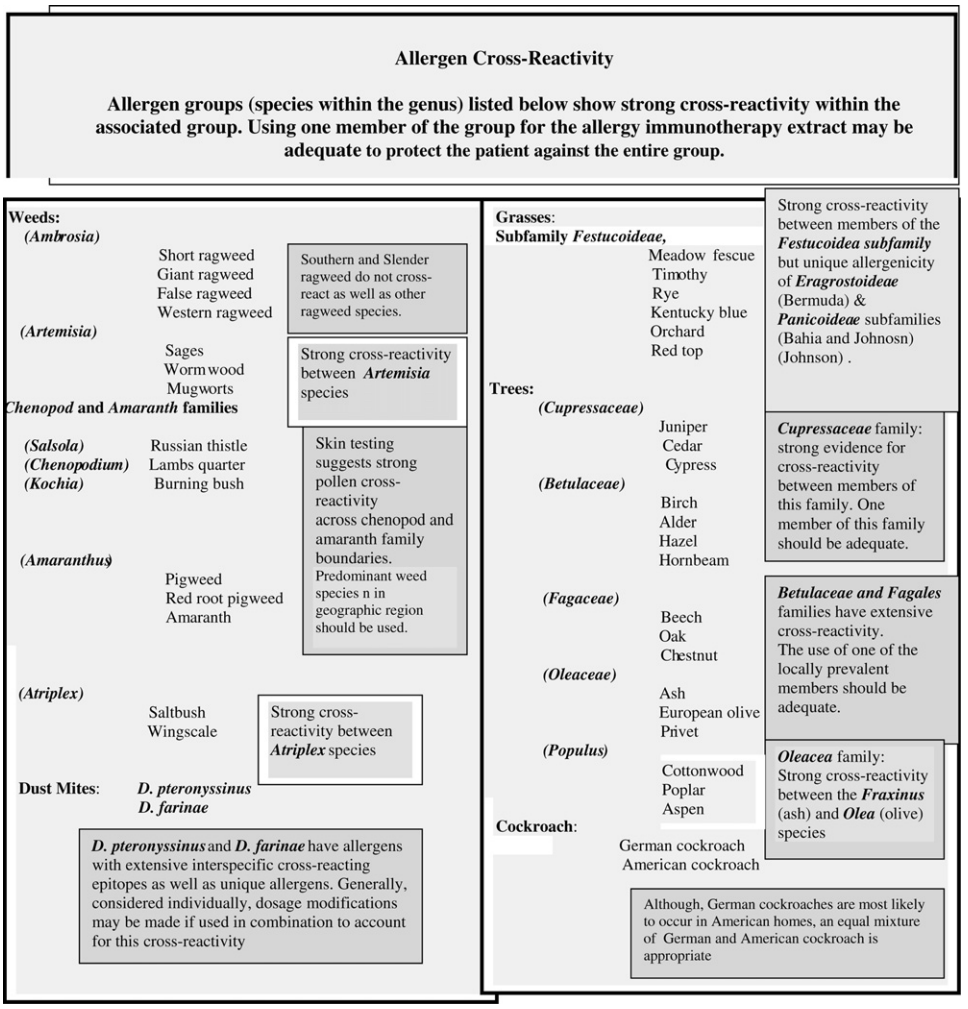


FIG 2. Patterns of allergen cross-reactivity.

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*).

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.[102,103] Stinging Hymenoptera insects occur throughout the United States; the fire ant is found only in Gulf Coast states, Texas, and some other southern and western states. Commercial venom extracts are available for some Hymenoptera species, except the fire ant, for which only whole-body extract is available.

EFFICACY OF IMMUNOTHERAPY

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity

Summary Statement 10: Immunotherapy is effective for 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.[104-111] Immunotherapy is effective for the treatment of allergic rhinitis[107] (including ocular symptoms[112,113]), allergic asthma,[104,109,111,114,115] and stinging insect hypersensitivity[108,116] and is effective in both adults and children.[117-124] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollens,[13,125-132] fungi,[133-138] animal allergens,[22,25,26,139-143] dust mite,[114,115,144-153] and cockroach.[154] There have been no controlled trials of fire ant whole-body extract, but it does appear to be effective in

TABLE IV. Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy

Outcome measure	House dust mite	Other allergens*†
Symptomatic improvement	2.7 (1.7-4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2-7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50)	5.5 (2.8-10.7)

Data are used with permission from Abramson et al.[104]
ND, Not done.
*Odds ratio (95% CI).
†Pollen, mold, or animal dander.

uncontrolled trials.[155-157] 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. A number of studies have also demonstrated a significant improvement in quality of life, as measured by using standardized questionnaires.[24,158-161] The magnitude of the effect depends on the outcome that is used (Table IV). For dust mite, the effect size ranges from a 2.7-fold improvement in symptoms to a 13.7-fold reduction in bronchial hyperresponsiveness. 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.[110] 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[107] and asthma[104,109,111] have been performed to deal with the issue of power. One review of 75 trials involving 3188 asthmatic patients found that, overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyperreactivity after immunotherapy, and it would have been necessary to treat 4 patients (95% CI, 3-5) with immunotherapy to avoid 1 deterioration in asthma symptoms and 5 (95% CI, 4-6) patients to avoid 1 requiring increased medication.[111] These meta-analyses strongly support the efficacy of allergen immunotherapy. Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued[13,162,163] and might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6,9,122,162-165] Allergen immunotherapy might also prevent the development of new allergen sensitivities in monosensitized patients.[120,166,167]

Food allergy, urticaria, and atopic dermatitis

Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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 use of allergen immunotherapy for individuals with the potential for IgE-mediated (anaphylaxis) reactions to foods should be regarded as investigational at this time.[168-171] There have been 2 investigational studies demonstrating efficacy in food hypersensitivity, the first using aqueous subcutaneous injections to peanut and the second using sublingual immunotherapy to hazelnut.[171-173]

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 a modified peanut extract is needed for clinical application of this method of treatment.[171] There is currently no FDA-approved formulation for sublingual immunotherapy, and this route of allergen immunotherapy is currently considered investigational at this time (see Summary Statement 73).

At the present time, there is not enough evidence to support food immunotherapy.

There is no evidence supporting the efficacy of immunotherapy for individuals with chronic urticaria, angioedema, or both.

There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[174-176] 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 ($P = .0379$) and topical corticosteroid use ($P = .0007$).[174]

The potential for benefit in symptoms related to oral allergy syndrome with the cross-reacting inhalant immunotherapy, which includes cross-reacting 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 subcutaneous immunotherapy directed against birch tree,[177] whereas another double-blind, double-dummy, placebo-controlled study comparing the effect of subcutaneous immunotherapy with sublingual immunotherapy 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, medication use, and decrease in IgE reactivity.[178] More investigation is required to substantiate the contention that benefits in oral symptoms will occur with immunotherapy.

Measures of efficacy

Summary Statement 12: 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. Objective measures, such as increase in allergen-specific IgG levels and decreased skin test reactivity, as measured by skin test titration, are changes generally associated with effective immunotherapy but, at present, are not practical for routine clinical use.[147] Nonquantitative skin testing or *in vitro* 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 are not very reliable given the strong placebo-like effect (Hawthorne effect) associated with any treatment. A more objective means for determining efficacy as validated in controlled clinical studies is the use of clinical symptom scores and the amount of medication required to control symptoms and maintain peak flow rates or pulmonary function tests within acceptable limits. Successful immunotherapy often results in a reduction in medication. Sequential measurement of disease-specific quality of life also might be helpful.

SAFETY OF IMMUNOTHERAPY

Reaction rates

Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Large local reactions associated with allergen immunotherapy are fairly common, with a frequency ranging from 26% to 86% of injections.[179] Two retrospective studies compared the effect of not adjusting immunotherapy dose based on large local reactions on the immunotherapy systemic reaction rate with dose-adjustment protocols.[179,180] There was a total of 12,464 injections administered with a dose-adjustment protocol in the 2 studies compared with 9542 injections administered with a no-dose-adjustment protocol. 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 for subsequent systemic reactions, 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 large local reactions, defined as 25 mm or larger, in patients who had experienced systemic reactions with age-, sex-, and allergen sensitivity–matched control subjects who had not had allergen immunotherapy systemic reactions found the rate of large local reactions was 4 times higher among the 258 patients who had subsequently experienced a systemic reaction compared with those who had never experienced a systemic reaction.[181] Patients who had experienced systemic reactions had 1573 large local reactions in 4460 visits (ie, 35.2% of visits) and 8081 injections (ie, 19.5% of injections) compared with the matched control group without systemic reactions who had 1388 large local reactions in 15,540 visits (8.9% per visit) and 26,259 injections (5.3% per injection; difference between groups, $P < .001$). Individual large local reactions were not predictive of future systemic reactions, but large local reactions preceded systemic reactions in approximately one third of the systemic reactions. These findings suggest that individuals with a greater frequency of large local reactions might be at greater risk for systemic reaction. Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy protocol modifications based on them are needed.

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

The prevalence of severe systemic reactions after allergen immunotherapy ranges from less than 1% of patients receiving conventional immunotherapy to greater than 36% of patients in some studies of patients receiving rush immunotherapy.[182,183]

In a recent survey of fatal and near-fatal reactions (NFRs) sent to physician members of the AAAAI, 273 of 646 respondents reported NFRs during the period of 1990-2001.[184]

The incidence of unconfirmed NFRs was 23 per year (5.4 events per million injections). Administration during the height of 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 angiotensin-converting enzyme 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 systemic reactions to subcutaneous immunotherapy over a 20-year period (1981-2000) during which 435,854 injections were administered to 4000 patients, 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.[185,186] In a prospective multicenter study there were 53 systemic reactions (0.3% of the doses) out of 17,526 administered doses in 18 (3.7%) of 423 patients.[187] 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 (21 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, there were 41 fatalities identified in the initial brief survey (20 directly reported and 17 with completed detailed questionnaire) from immunotherapy injections.[188] 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.[189,190] Therefore although severe systemic reactions to allergen immunotherapy are not common, serious systemic reactions (some fatal) can occur.

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

In the AAAAI survey of physician members on immunotherapy and skin testing, fatal reactions, and NFRs during the period of 1990-2001, 15 of the 17 fatalities had asthma, and in 9 patients asthma was considered the susceptibility factor that contributed to the fatal outcome.[188]

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.[184]

Administration during the peak pollen season (3 patients) and previous systemic reactions (4 patients) were cited as other contributing factors. Five fatalities occurred in outside medical facilities, and 2 fatalities occurred at home. No patients were receiving β-blockers; 1 patient was taking an angiotensin-converting enzyme inhibitor. In the most comprehensive evaluation of fatalities associated with allergen immunotherapy, from 1945-1987, there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[189] 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, with 73.3% of patients with an FEV_1 of less than 80% of predicted value experiencing 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 ($P < .0001$).[191] 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% of patients. These studies suggest that symptomatic asthma, severe asthma, or both might be a risk factor for immunotherapy.

In addition to symptomatic asthma and injections giving 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.[17] With the exception of dosing errors and 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 recent 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 or allergy symptom exacerbation, β-blocker use, change in health status (including pregnancy), or adverse reaction to previous allergen immunotherapy injection. The preinjection evaluation might also include a peak flow measurement to assess the airway function of asthmatic patients.

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 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

In a retrospective study the time to onset of a systemic reaction after an immunotherapy injection was less than 30 minutes in most cases.[189] A review of the literature indicates that 70% of systemic reactions occur within 30 minutes after an injection.[183] In the AAAAI 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.[184,188] 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.[190] 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 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.[192] In another prospective study 8% of systemic reactions occurred more than 2 hours after injection.[193]

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.[194]

Because most reactions that resulted from allergen immunotherapy occurred within 30 minutes after an injection, patients should remain in the physician's office for at least 30 minutes after receiving an injection, but longer waits are reasonable, as directed by the physician. In addition, patients who are at increased risk of a systemic reaction might need to carry injectable epinephrine. Such patients might also need to remain in the physician's office more than 30 minutes after an injection. 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.

β-Adrenergic blocking agents

Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

β-Blockade enhances pulmonary, cardiovascular, and dermatologic end-organ effects of mediators and increases mortality associated with experimental anaphylaxis induced by either immunologic or nonimmunologic mechanisms. Patients who are receiving β-adrenergic blocking medications might be at increased risk if they experience a systemic reaction to an allergen immunotherapy injection because the β-receptor blockade might attenuate the response to epinephrine.[195-202] Patients who are receiving β-blocking drugs were almost 9 times more likely to be hospitalized after an anaphylactoid reaction from radiocontrast media.[198] Although topical β-blockers have markedly less systemic β-antagonist effects than oral β-blockers, they still might exhibit some systemic β-antagonist effects. Whether topical β-blockers pose the same or a smaller risk than oral β-blockers in regard to the treatment of allergen immunotherapy–related systemic reactions is not known.

There have been very few studies that have examined the effect of β-blocker medications on allergen immunotherapy. A prospective 1-year study designed to determine whether patients taking β-blocker drugs were at increased risk of immunotherapy-induced systemic reactions found that there were 166 systemic reactions out of 56,105 injection visits in 3178 patients (68 were receiving a β-blocker).[203] The systemic reactions occurred in 144 (4.5%) patients, and only 1 of these patients was receiving a β-blocker medication. The authors calculated that by chance, 3.08 patients receiving the β-blocker medications drugs were expected to have had an systemic reaction and concluded that β-blocker medications did not increase the frequency of allergen immunotherapy systemic reactions ($P > .95$).

In another study of 1389 patients prescribed immunotherapy for Hymenoptera venom hypersensitivity who were followed for 34 months, there were 25 patients who received concomitant β-blocker medications.[204] Three (12%) of the 25 patients receiving β-blocker medications experienced systemic reactions during immunotherapy compared with 23 (16.7%) of 117 patients with cardiovascular disease not receiving β-blockers. Systemic reactions after a field sting or challenge occurred in 1 (14.3%) of 7 cardiovascular patients receiving β-blocker medications compared with 4 (13.8%) of 29 cardiovascular patients not receiving β-blocker medications. No severe reactions to immunotherapy or sting re-exposure were observed in patients receiving β-blockers medications.

Immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. In such cases, intravenous glucagon, which might reverse the refractory bronchospasm and hypotension by activating the adenyl cyclase directing and bypassing the β-adrenergic receptor, might be used if epinephrine has not been effective.[205,206] Prospective studies are necessary to clarify the magnitude of the risk of systemic reactions to allergens in patients who are receiving concomitant therapy with β-blockers, and a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy.

Contraindications

Summary Statement 18: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications

TABLE V. Actions to reduce the risk of anaphylaxis

- Assess the patient's general medical condition at the time of injection (eg, asthma exacerbation).
- Consider obtaining a PEFR before administration of the injection. If the PEFR is significantly less than the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.
- 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 with increased allergen sensitivity or those who have previously had a systemic reaction) might need to wait longer.
- Carefully evaluate any patient with a late reaction (eg, persistent large local reaction lasting >24 hours, systemic reaction occurring more than 30 minutes after the immunotherapy injection).
- 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.

PEFR, Peak expiratory flow rate measurement.

TABLE VI. Recommended equipment and medications to treat anaphylaxis

Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur. This should include at least the following equipment and medications:

- stethoscope and sphygmomanometer;
- tourniquet, syringes, hypodermic needles, and large-bore needles (14-gauge);
- aqueous epinephrine HCL 1:1000 wt/vol;
- equipment to administer oxygen by mask.
- intravenous fluid set-up;
- antihistamine for injection (second-line agents for anaphylaxis, but H_1 and H_2 antihistamines work better together than either one alone);
- corticosteroids for intravenous injection;
- vasopressor;
- equipment to maintain an airway appropriate for the supervising physician's expertise and skill.

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 venom hypersensitivity and cardiac disease being treated with β-blocker medications.

Reducing the risk of anaphylaxis to immunotherapy injections

Summary Statement 19: 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 extremely 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 or other health care professional appropriately trained in emergency treatment.

The 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. Epinephrine is the first-line treatment for anaphylaxis. 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.[12,207-213] It is important to administer epinephrine early in the management of anaphylaxis. 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 V and VI, respectively. Before allergen immunotherapy is chosen as a treatment, the physician should educate the patient about the benefits and risks of immunotherapy, as well as methods for minimizing risks. The patient also should be told that despite appropriate precautions, reactions might occur without warning signs or symptoms. Informed consent should include a discussion of the potential immunotherapy adverse reactions, and this discussion should be documented in the patient's medical record.

PATIENT SELECTION

Clinical indications

Summary Statement 20: Allergen immunotherapy should be considered for patients who have demonstrable

TABLE VII. Clinical indications for allergen immunotherapy

Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or both:
- symptoms of allergic rhinitis after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medications;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medication;
- coexisting allergic rhinitis and asthma;
- possible prevention of asthma in patients with allergic rhinitis

Symptoms of asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medication;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medications;
- coexisting allergic rhinitis and allergic asthma.

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);
- adults and children with a history of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.

evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic rhinitis.[107] Prospective, randomized, double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic asthma.[104,109,111]

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 proper identification and selection of component allergens on the basis of 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 (Table VII). The severity and duration of symptoms should also be considered in assessing the need for specific allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. In addition, specific allergen immunotherapy should be considered if the patient wishes to avoid long-term pharmacotherapy. Time lost from work, emergency department or physician's office visits, and responses to pharmacotherapy are important objective indicators of allergic disease severity.

Patients with allergic rhinitis who are unable to sleep because of symptoms or whose symptoms interfere with their work or school performance should be considered strong candidates for specific allergen immunotherapy. 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 considered. Unacceptable adverse effects of medications should also favor one's decision to initiate allergen immunotherapy. Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.[214]

Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued, and it might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6-9,122,162-165] These benefits of immunotherapy should be discussed with patients and might provide a clinical indication for immunotherapy for individual patients with allergic rhinitis.

Coexisting medical conditions should also be considered in the evaluation of a patient who might be a candidate for allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed with a combined aggressive regimen of allergen avoidance and pharmacotherapy and might also benefit from allergen immunotherapy.[215,216]

However, the patient's asthma must be stable before allergen immunotherapy is administered.[188,191]

Special precautions in patients with asthma

Summary Statement 21: 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 might be at increased risk for systemic reactions to immunotherapy injections.[182,188,191] Two surveys found that deaths from

immunotherapy were more common in symptomatic subjects with asthma.[188,189] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2,217]

Clinical indications for VIT

Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Systemic reactions to Hymenoptera stings, especially when associated with respiratory symptoms, cardiovascular symptoms, or both and positive skin test or *in vitro* test results for specific IgE antibodies, are a strong indication for allergen immunotherapy.[218] In the United States patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Several studies of patients with imported fire ant allergy have demonstrated the effectiveness of immunotherapy with whole-body extracts of fire ants.[155,156,219] 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. Patients younger than 16 years of age who present only with a cutaneous reaction to imported fire ant or Hymenoptera stings might not require immunotherapy.[218,220-222] In addition to allergen immunotherapy, patients with imported fire ant and Hymenoptera venom sensitivity should be instructed in how to best avoid insect stings, be prescribed epinephrine, and be taught how 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 the population that has not had a systemic reaction.[223] In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific IgE is recommended.[218] If the venom-specific IgE test result is also negative, it is recommended that the skin tests, venom-specific 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 IgE test result.[224] 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 re-stung. 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%).[225] 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 IgE test results who have had severe anaphylaxis to an insect sting.

Some patients who have negative venom skin test results and negative venom-specific IgE test results are reported to have had subsequent systemic reactions to stinging insects.[225-227] Controlled studies designed to evaluate the efficacy of immunotherapy in these patients have not been performed. There are very 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.[226] 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.

Summary Statement 23: 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.

ALLERGEN SELECTION AND HANDLING

Allergen selection

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

A careful history, noting environmental exposures and an understanding of the local and regional aerobiology of suspected allergens, such as pollen, fungi (mold), 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 skin or *in vitro* test results for specific IgE antibodies, provide good evidence that such exposures are relevant. Information concerning regional and local aerobiology is available on various Web sites or through the National Allergy Bureau at http://www.aaaai.org/nab. There are

no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma. 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 clinical history of an allergic disease.

There is no evidence to support the administration of immunotherapy based solely on results of specific *in vitro* 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.

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

The omission of clinically relevant allergens from an allergic patient's allergen immunotherapy extract contributes to decreased effectiveness of allergen immunotherapy. The 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 can make allergen immunotherapy less effective.

Knowledge of the total allergenic burden facing a patient and the realistic possibility of avoidance is important in determining whether allergen immunotherapy should be initiated. 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. Many individuals travel extensively for business or pleasure into different regions, and symptoms might worsen at these times. However, inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective. Determination of the significance of indoor allergens for a particular patient is harder because it is difficult to determine exposure in the home, school, and/or workplace. Historical factors, such as the presence of a furry animal in the home, a history of water damage and subsequent fungal exposure, or a history of insect infestation, might be helpful. However, such information is subjective and is often of uncertain reliability. In addition, some studies have demonstrated significant indoor levels of cat and dog allergen in households without pets[228] and significant levels of mouse allergen in suburban[229] and inner-city[230] homes 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 with increased asthma morbidity in inner-city children was found.[231] 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. Nevertheless, for most patients, determination of the clinical relevance of an allergen requires a strong correlation between the patient's history and evidence of allergen-specific IgE antibodies.

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted *in vitro* tests for specific IgE antibodies can also be used. **A**

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 the skin test results have demonstrated the efficacy of immunotherapy for relevant allergens.[25,26,112,130,134,135,140,141,149,154] 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 from skin testing in a highly sensitive individual.[232,233] In addition, skin tests might be difficult to perform in patients with dermatographism or atopic dermatitis. *In vitro* tests are particularly useful in such patients.

Studies indicate that skin testing is generally more sensitive than *in vitro* tests in detecting allergen-specific IgE.[234,235] Based on inhalation challenge test results, skin tests have shown specificity and sensitivity generally superior to those of *in vitro* tests. The comparability of skin tests and *in vitro* tests for specific IgE antibodies depends on the allergen being tested. For all of 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, prick testing is sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass[236] and cat,[237] are used. Intradermal/intracutaneous skin testing might be required for some allergen extracts. It is appropriate in some patients to use *in vitro* tests for specific IgE antibody as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. *In vitro* tests can also be used to define the allergens that should be used in allergen immunotherapy. If the allergy skin test result is negative and the *in vitro* test result is positive, a controlled challenge can be performed, and if the latter is positive, immunotherapy can be considered. 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 *in vitro* test results.

Specific allergens

Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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.[17,104,106,107,109] 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.[112,122] Because a particular pollen extract is a mixture of multiple glycoproteins, this suggests that mixing pollen allergens does not alter biologic activity.

Fungi (molds). Several studies with *Alternaria* and *Cladosporium* species suggest that allergen immunotherapy with fungi might be effective.[133-138] The allergen content of most mold extracts is highly variable.[238,239] However, there is evidence that proteolytic enzymes present in some mold extracts could digest other antigens, such as pollens, when combined in a mixture.[240] For this reason, it might be desirable to separate all pollen extracts from mold extracts when using mixtures.

Unfortunately, extracts for some potentially clinically important fungi are not available.[241] 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 distinguish 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.

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.

Because immunotherapy has been shown to be effective for cat[22,26,139-143,242] and dog,[25,141] the decision to include dog or cat allergen in an allergen immunotherapy extract should be considered in those circumstances in which there is exposure.

Dust mites and cockroach allergens. Crude house dust extract is generally an inappropriate substitute for house dust mite extract because the protein content measured is not restricted to dust mite allergens, nor does it necessarily guarantee inclusion of dust mite protein. Immunotherapy with standardized dust mite is generally more effective than that with crude house dust allergens. The house dust mites *D farinae* and *D 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, such as *Blomia tropicalis* and *Euroglyphus maynei*, partially cross-react with allergens from *Dermatophagoides* species. Only 50% of the projected amounts of each of the 2 house dust mites (*D pteronyssinus* and *D farinae*) need 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[144,147-149,151] 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. Dust mite hypersensitivity should particularly be considered in patients who have perennial symptoms exacerbated by a dusty environment at home, work, or both and periods of high humidity.

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. The major allergen of *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.[243] Immunotherapy with cockroach allergens is effective[154] and should 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.

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.[108,116,244] Efficacy has also been demonstrated with immunotherapy by using whole-body extracts of imported fire ants.[155,156]

Foods. Only a single clinical study accessing the efficacy and safety of subcutaneous immunotherapy with foods has been performed.[171,173] This study, which evaluated immunotherapy with peanut, found the incidence of systemic reactions, even during maintenance, was unacceptable. Thus there is no evidence to support the use of immunotherapy with food extracts. Currently, strict avoidance of the offending food is advisable, and subcutaneous immunotherapy for food allergy is not recommended.

Mixing of extracts

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Once the relevant allergens for each patient are identified, it is necessary to prepare a mixture that contains each of these allergens. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts. A number of 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 interactions between different types of allergens, when mixed, that could lead to degradation or unmasking of epitopes on exposure to proteolytic enzymes.

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Immunologic and 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.[71] 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 genera 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 the Allergen extract section, Fig 2, and the allergens and allergy diagnostic tests practice parameters).

Dose selection. Summary Statement 30: 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.[22-26,128,149,245] Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000 vol/vol).[28] A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy vaccine. Failure to do so might reduce the efficacy of immunotherapy. This occurs because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased (see the Immunotherapy schedules and doses section for further discussion and for recommended maintenance doses).

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as fungi (mold) and cockroach, from other extracts, such as pollens, is recommended. **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.[240,246,247] 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, and some weeds.[240,246,247] Cockroach had a similar deleterious effect on pollen extract potency.[246,248] Short ragweed appeared resistant to the effects of the proteolytic enzymes in one study,[240] 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.[247]

Dust mite extracts do not appear to have a deleterious effect on pollen extracts.[240,246,248] These studies suggest that pollen, dust mite, and cat extracts can be mixed together. 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. The evidence on mixing cockroach extract with other extracts is conflicting, and the clinical relevance of the changes is also unclear; therefore the clinician has the option of separating cockroach or not.

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 with lesser activities, such as pollen extracts.

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.

In this regard the number of separate injections that need to be given at each patient visit depends on whether all of the relevant extracts mixed into a single vial still deliver an optimal dose of each allergen. If mixing causes excessive dilution or if there are advantages to separating allergens into separate vials, then more than one vial might be necessary for successful immunotherapy.

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extracts are high-alert products that carry the risk for anaphylaxis. Policies, procedures, and processes intended for conventional drugs and medications might be highly 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 fatal anaphylactic reactions with allergenic products. 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. There are no reports of infection associated with allergen immunotherapy injections. Allergen vaccines are prepared by using sterile manufacturer's extracts and sterile diluents containing antibacterial constituents (usually phenol). A summary of the AAAAI/ACAAI/JCAAI proposed USP allergen immunotherapy extract preparation guidelines can be found in Table VIII.

TABLE VIII. AAAAI/ACAAI/JCAAI-proposed USP 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 below.*
   - 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.
2. **Physician responsibility**: A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in the preparation of immunotherapy using an aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files.
3. **Bacteriostasis**: Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if 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 the FDA-approved package insert 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 treatment with sanitizing agents containing alcohol and/or 70% isopropanol 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 the physical integrity of the vial.
10. **Labeling**: Immunotherapy vials are to be clearly labeled with the patient's name and 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.

*__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 media, such as from Valiteq (http://www.valiteq.com), 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.

Allergen immunotherapy extract handling

Storage. Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

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 a number of 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 extract, including reconstituted lyophilized extracts, should be stored at 4°C to minimize the rate of potency loss because storage at higher temperatures (eg, room temperature) can result in rapid deterioration.[249]

Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions (personal communication). These studies include actual shipments made by their carriers to places like

Phoenix in the summer and Alaska in the winter. 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.

Storing dilute extracts. Summary Statement 34a: More dilute concentrations of allergy immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than do more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: In determining the allergy vaccine expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of 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 allergen immunotherapy 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.[249,250]

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.[250] Phenol is a preservative added to extracts to prevent growth of microorganisms.

Phenol can denature proteins in allergen extracts.[251,252] Human serum albumin might protect against the deleterious effect of phenol on allergen extracts.[251] 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,[250,253] possibly through inhibition of the activity of proteolytic and glycosidic enzymes that are present in certain extracts. However, it is irritating when injected and should be diluted before beginning immunotherapy. Recommendations for extract stability are found in the manufacturers' product insert sheets. 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. The pain associated with glycerin increases in proportion to the glycerin concentration and injection volume, and the pain is proportional to the total injected dose of glycerin.[254] However, individual pain perception can vary substantially. Total glycerin doses of less than 0.05 mL rarely produce clinically important pain.

TABLE IX. Potency of selected manufacturer's extracts currently available

Extract	Potency
Cat hair and pelt	5000 and 10,000 BAU/mL
Dust mite	3000, 5000, 10,000, and 30,000 AU/mL
Bermuda grass	10,000 AU/mL
Short ragweed	1:10-1:20 wt/vol or 100,000 AU/mL
Other grasses*	10,000 and 100,000 BAU/mL
Other pollen	1:10 to 1:40 (wt/vol) or 10,000 PNU/mL
Molds	1:10 to 1:40 (wt/vol) or 20,000 to 100,000 PNU/mL

AU, Allergy unit; *BAU*, bioequivalent allergy unit; *PNU*, protein nitrogen unit.
*Perennial rye, Kentucky blue/June, timothy, sweet vernal, redtop, orchard, and meadow.

There have been few studies that have investigated the potency of dilutions of allergen extract mixture over time. Expiration dates for allergen extract dilutions are somewhat empiric and not strongly evidence based. A study undertaken by the AAAAI 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. Dust mite and cat at 1:10 and 1:100 vol/vol dilution were also stable in all conditions of storage over 12 months, as measured by an ELISA assay using 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.

IMMUNOTHERAPY SCHEDULES AND DOSES

Summary Statement 35: A customized individual 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 can be based on single or multiple allergens. **D**

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. Animal dander contains between 10 and 20 antigens,[255] house dust mites between 20 and 40 antigens,[256] and pollens between 30 and 50 antigens,[257,258] and fungal extract can contain as many as 80 antigens.[259]

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. This is designated as the patient's maintenance concentrate.

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. Standardized extracts are available with biologic potencies of 10,000 and 100,000 BAU for grasses; 5000 and 10,000 BAU for cat allergen; 5000, 10,000, or 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 wt/vol extracts (Table IX). 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.

Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

The highest concentration of an allergen extract mixture that is projected to be used as the therapeutically effective dose is called the maintenance concentrate. This should be prescribed individually for each patient by an allergist/immunologist. 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 individual manufacturer's extracts. Some patients might be unable to attain the projected therapeutically effective dose of the maintenance concentrate because of local reactions, systemic reactions, or both (eg, cat, 1000 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose]; see Table X for probable effective therapeutic dose range). Such patients might need weaker dilutions of their maintenance concentrate. Even so, 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 referred to as the maintenance dose. The consistent use of this nomenclature system is essential because errors in choosing the correct vial are a common cause of systemic reactions, especially when the patient transfers from one physician to another. Therefore it is important that standard terminology be adopted by all physicians who prescribe allergen immunotherapy.

Recommended doses

Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

The effective maintenance dose of immunotherapy for a particular patient must be individualized. To do this, the allergist/immunologist who prepares the allergen immunotherapy extract must balance the dose necessary to produce efficacy and the risk of reactions if such a dose is reached. The allergist/immunologist might need to prepare more than one maintenance concentrate to provide a therapeutic dose of each of the allergens for the polysensitized patient. Therapeutically effective doses for immunotherapy have been reported for some allergen extracts.[22,24,25,128,134,135,149,246,260,261] Effective doses have been determined for Hymenoptera venom, dust mite, cat allergen, dog, grass, and short ragweed (Table X).

Controlled studies demonstrate that the content of particular allergens in allergen immunotherapy extracts can be used to predict a therapeutic dose for those allergens, particularly when the extracts are standardized. For antigens 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. The therapeutically effective doses used in the most recent controlled clinical studies are the basis of the recommended dosage range of standardized extracts presented in Table X. 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 time that it is administered.[14]

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.[27] 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 risk of systemic reactions to immunotherapy injections with higher maintenance doses. The maintenance concentrate should be formulated to deliver a full therapeutic dose of each of its constituent components. However, some sensitive patients might not tolerate the targeted therapeutic dose, and their maintenance dose would be lower. Individuals 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 referred to as the maintenance dose.

Regardless of dose schedule, some patients are unable to progress to the predetermined maintenance dose because of large local or systemic reactions to the allergen

TABLE X. Probable effective dose range for allergen extracts US standardized units[a]

Antigen	Labeled potency or concentration[a,b]	Probable effective dose range
Dust mites: *D farinae* and *D pteronyssinus*[c]	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat[d]	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized[e]	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed[f]	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 μg of Amb a 1 1000-4000 AU Concentration of Amb a 1 is on the label of wt/vol extracts in FDA units[358]
Nonstandardized extract, dog[g]	1:10 to 1:100 wt/vol	15 μg of Can f 1
Nonstandardized extracts	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose

[a]Multiple studies have demonstrated that the efficacious dose for allergen immunotherapy is between 5 and 20 μg of the major allergen per injection. Only 2 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).

[b]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).

[c]There have been no dose-response studies with United States–licensed dust mite extracts, and dosing recommendations in AU value are extrapolated from published European studies that used aqueous[349] and alum-precipitated[149,151] extracts. 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.[149] The authors suggested the optimal maintenance dose was 7 μg of Der p 1. Corresponding doses were based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Extrapolating effective and safe doses in this manner might not be scientifically valid. *D farinae* and *D pteronyssinus* are similar in group 1 allergen content according to the FDA's current reference standards. 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*.

[d]The major cat allergen Fed d 1 is reported in FDA units, with 1 Fel d 1 unit equaling approximately 2 to 4 μg of Fel d 1.[55,58,59] The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 to 19.9 U/mL. One study demonstrated clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 dose in terms of decreased cat extract PD_{20}, titrated skin test results, and allergen-specific IgE and IgG levels.[350,351] In a recent study that investigated the efficacy in terms of immunologic changes of 3 doses of a United States–licensed cat extract (0.6, 3, and 15 μg) demonstrated that a significant effect on titrated skin prick test results, allergen-specific IgG4 levels, and $CD4^+$/IL-4 levels was only seen in the group treated with 15 μg of Fel d 1, although the 3-μg dose group did demonstrate a significant change in titrated skin test response and increase in cat-specific IgG4 levels.[22]

[e]There have been no dose-response studies with United States–licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,[130] alum-precipitated,[24,161] and calcium phosphate–precipitated grass pollen extracts.[352] One of these studies compared a dose of 2 μg with 20 μg of major timothy allergen (Phl p 5) and found clinical efficacy at both doses.[24] The efficacy was greater in the 20 μg of Phl p 5 dose, but the systemic reaction rate was also higher in the high-dose group. The package inserts for United States–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 BAU. Extrapolating effective and safe doses in this manner might not be scientifically valid. 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).

[f]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 suggested that 1 unit of Amb a 1 is equivalent to 1 μg of Amb a 1, and 350 Amb a 1 units/mL is equivalent to 100,000 BAU/mL.[60] The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2000 AU, with a range of 1000-4000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrated 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.[45] A ragweed dose-response study (0.6, 12.4, and 24.8 μg of Amb a 1) demonstrated efficacy, as measured by nasal challenge, at 12 and 24 μg of Amb a 1.[128] The efficacy of the 24-μg dose was not significantly better than the 12-μg dose, and the authors concluded that the optimal dose for ragweed extract was greater than 0.6 μg but not more than 12.4 μg of Amb a 1.

[g]Dog extracts are not standardized. However, one dose-response study with a United States–licensed acetone-precipitated dog extract investigated the efficacy of 3 doses (AP dog; Hollister-Stier, Spokane, Wash; 0.6, 3, and 15 μg) in terms of immunologic changes and found the dose of 15 μg of Can f 1 to be most efficacious.[25] 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 have assayed between 128 and 208 μg/mL (average Can f 1, 162 μg/mL [SD ± 26 μg/mL]; information provided by the extract manufacturer, Hollister-Stier).

immunotherapy extract. The evidence is not clear whether large local reactions are a potential risk for subsequent allergen immunotherapy systemic reactions.

Published studies do not indicate that an individual large local reaction is predictive of a subsequent systemic reaction.[179,180] However, one retrospective study found that individuals who have a history of repeated large local reactions (defined as >25 mm) might be at greater risk for a subsequent systemic reaction.[181]

The concept of highest tolerated dose does not apply for VIT, and all patients are expected to achieve the full recommended dose to achieve the necessary degree of protection. There are conflicting data over whether lower doses (50 μg) are less effective, but there are also data showing that 200 μg is more reliably effective.[245] In the case of VIT, patients are asked to tolerate more large local reactions to achieve the full dose, even though with inhalant immunotherapy the dose can be reduced for such large local reactions to minimize patient discomfort.

Effect of dilution on dose

Summary Statement 38: 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 vaccine, thereby limiting the ability to deliver a therapeutic effective dose for any given allergen.

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

Dilution from maintenance concentrate vaccine	Volume	Volume (mL)	Diluent volume (mL)	Final volume
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.

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 2000 BAU/mL, 2 mL of the manufacturer's extract (cat, 10,000 BAU/mL) can be added to 8 mL of diluent or 8 mL of other allergens, and the final concentration of cat will be 2000 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.

Dilutions of the maintenance concentrate

Summary Statement 39: 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 vol/vol 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, 1000 BAU or 100 BAU), but this system can be complicated if allergens with different potency units are used (eg, wt/vol, BAU, AU, or PNU) and make it difficult to easily interpret the vial label.

Instructions on how to prepare various allergen extracts 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.

Labeling dilutions

Summary Statement 40: 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, a number of 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 (vol/vol), a numbering system, a color-coding system, or an alphabetical system should be used. If this uniform labels 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.

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
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

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 3 and 4).

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 Appendix 2]).

Individualized treatment vials

Summary Statement 41: 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 (wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for 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). Labels on patient-specific vials can provide at least 2 patient identifiers (birth date and patient name), which would be consistent with the recommendations of the Joint Commission on Accreditation of Health Care Organizations National Patient Safety Goals: ''Goal 1: Improve the accuracy of patient identification by using at least two patient identifiers when providing care, treatment or services.''[5] 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 administration of the injection.[4,5]

In a survey of 1717 allergists endorsed by the AAAAI and JCAAI, 57% of the 476 respondents reported at least one wrong-patient injection, and 74% of the 473 respondents reported at least one wrong-dose injection.[4] 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 reasons why this might reduce incorrect injection errors. One reason was that patient-specific vials can be prepared in a quiet laboratory setting, which might provide substantially less distraction than the nurse in a room with a patient who is trying to concentrate only on drawing up the injection correctly. In addition, the specific components are mixed once with the preparation of individually prepared patient-labeled vials, whereas the mixing would be repeated on every injection visit if the allergen extract is withdrawn from different stock solutions, as it is in the off-the-board method. For safety reasons and to avoid cross-mixing of allergens removed from the manufacturer's extract, the mixing of antigens in the syringe (off the board) is not recommended.

Some allergists/immunologists prefer to administer immunotherapy doses drawn directly from a single stock dilution of individual allergens or common mixes (shared specific patient vials). In this way the immunotherapy dose is transferred to the patient without cross-contamination. If shared-patient (eg, mixed vespids and dust mite mix) vials are used, it is essential that policies and procedures are developed to verify that the correct dose from the correct vial is administered to the correct patient.

Starting doses

Summary Statement 42: The starting dose for build-up is usually a 1000- 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 slowly 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 1:1000 (vol/vol), although more diluted concentrations frequently are used for patients who are highly sensitive, as indicated by history or skin test reaction (see Appendix 3 for an example of a conventional immunotherapy schedule).

Frequency of build-up injections

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 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 2 times per week. 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 4 to 6 months, depending on the starting dilution and the occurrence of reactions. It is acceptable for patients to receive injections more frequently, provided there is adequate spacing between injections. The interval between injections is empiric but might be as short as 1 day without any increase in the occurrence of systemic reactions[262] if there is some urgency to achieve a maintenance dose (eg, allergy season is approaching) or for practical reasons (eg, patient's schedule). Alternatively, treatment schedules can be used that more rapidly achieve maintenance dosing. These cluster and rush dosing schedules are discussed in Summary Statements 47 through 49.

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 a number of 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).

Dose adjustments for systemic reactions

Summary Statement 44: 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 benefit/risk ratio justifies continuation of immunotherapy.

Reductions during periods of exacerbation of symptoms

Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Immunotherapy administered during periods of exacerbation of symptoms is considered a risk factor for immunotherapy.[17,184] Injections administered during periods when a patient is exposed to increased levels of allergen to which they are 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.[184] 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 sensitive, especially if their symptoms are poorly controlled.

Dose adjustments for late injections

Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

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 depends 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 Appendix 4 for an example of a dose-modification regimen for gaps in treatment).

Cluster schedules

Summary Statement 47: 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 (see Appendix 5).[22,26] 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. The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules.[145,263-266] The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.[267]

Rush schedules

Summary Statement 48: 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.[268] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.[191,269-272]

The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections over the course of 4 hours.[273] Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours.[274-276] 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 cluster[145,266] and rush[134,277] schedules.

Systemic reactions and rush schedules

Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

The advantages of rush immunotherapy come at a cost because there is an increased risk of local and systemic reactions. Systemic reaction rates have been reported to be

as high as 73% of patients, with the risk of such reactions reduced to 27% by premedication in one study.[272] Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing.[273]

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

Rush protocols for administration of Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions.[274-276,278,279]

Premedication and weekly immunotherapy

Summary Statement 50: Premedication can reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

There is concern that antihistamines taken before each injection with conventional immunotherapy might mask a minor reaction that would otherwise alert a physician to an impending systemic reaction. 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.[280] One study that compared terfenadine premedication with placebo premedication during rush VIT demonstrated greater clinical efficacy in the terfenadine-premedicated group in terms of subsequent responses to field stings or sting challenge.[281] There was also a significant difference in the systemic reaction rate between the 2 groups: 6 patients in the placebo-premedicated group had systemic reactions, whereas none of the patients in the terfenadine-premedicated group had systemic reactions ($P = .012$).

Unfortunately, patients might still have life-threatening anaphylaxis despite 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.

Premedication with cluster and rush immunotherapy

Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

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.[267] Premedication with a 3-day course of prednisone, an H_1 histamine receptor antagonist, and an H_2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.[272] In one study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on the safety and efficacy of rush immunotherapy, there was a 5-fold decrease in the risk of anaphylaxis in the group premedicated with omalizumab compared with the placebo premedication group.[282]

There are anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist, but there have been no published studies. Because the risk of a systemic reaction from rush VIT is relatively low, routine premedication before rush VIT is usually unnecessary.[274,276,278,279] In a study evaluating premedication with antihistamines and steroids for rush immunotherapy with imported fire ant venom, there was no statistically significant differences in the systemic reaction rates between the premedication and placebo premedication group (3.6% of the premedication group vs 6.7% of the placebo group, $P = .87$).[157]

Maintenance schedules

Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals 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 individuals might tolerate longer intervals between maintenance dose injections.

The interval between venom injections can be safely increased up to 8 weeks in some patients without loss of efficacy. 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.

Continuing care

Time course of improvement. Summary Statement 53: Clinical 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.[24,134,143,277] Improvement might not be observed for a number of reasons, including (1) failure to remove significant allergenic exposures (eg, a cat), (2) exposure to high levels of

allergen (eg, pollen or molds), (3) continued exposure to nonallergen triggers (eg, tobacco smoke), or (4) incomplete identification and treatment of clinically relevant allergens. 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 54: 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 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 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

The patient's response to immunotherapy should be evaluated on a regular basis. 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. 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.

There have been very 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 individuals.[283-285] However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported.[283,285] Nevertheless, systemic reactions to stings after discontinuing VIT were generally much milder than the pretreatment reactions and were rarely severe. Two studies did not find a difference in relapse rates between the patients treated for 3 years compared with those treated for 5 years,[283,286] but one of the studies noted that the small number of patients in the 3-year treatment group prevented them from making any conclusions about the risk of discontinuing treatment after 3 years.[283] However, one study found that patients who had experienced re-sting reactions after discontinuing VIT had received VIT for a significantly shorter duration (mean, 43.35 months) than those with continued protection (mean, 54.65 months; $P < .01$).[285] Another study reported that 5 years of VIT provided better immunologic and clinical outcomes than 2 to 4 years of treatment.[287]

Change in skin test reactivity did not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who experienced a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE.[286,288] Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment.[288] The relapse rate and the frequency of severe reactions were greater in patients who had a history of very severe reactions to stings before treatment, in patients who had systemic reactions during VIT (to a sting or a venom injection), in patients with honeybee allergy, and in those who had less than 5 years of treatment.

The duration of inhalant allergen immunotherapy efficacy has not been as extensively studied. Some studies have suggested 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 *(D pteronyssinus)* extract for 12 to 96 months.[14] 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.[13] There was a switch to placebo in half of 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. These studies demonstrate the uncertainty of the long-term benefit of inhalant immunotherapy after discontinuation.

Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained clinical remission after discontinuing inhalant immunotherapy, and 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 indication for continuation of immunotherapy can be found at http://www.aaaai.org or http://www.jcaai.org.

Documentation and record keeping. Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully 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 allergy immunotherapy and prescription forms can be found in the Appendix (Appendices 6-15), and these include examples of immunotherapy prescription and administration forms. These forms, along with examples of immunotherapy consent and instruction forms, can also be found at http://www.aaaai.org.

Injection techniques. Summary Statement 57: Allergen immunotherapy extract injections should be given using a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **C**

Immunotherapy should be given with a 26- to 27-gauge syringe with a half-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.[289-291]

If using shared specific patient vials (stock vials, such as mixed vespid or dust mite mix), a single dose should be drawn from each vial. Antigens from different vials should not be combined in a single syringe. Furthermore, extra care is needed to prevent using the wrong stock antigen.

Summary Statement 58: The injection should be given subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Each immunotherapy injection should be given in the posterior portion of the middle third of the upper 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.

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.

The syringe should be aspirated to check for blood return in the syringe before injecting. If blood is present, 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 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 syringe should be appropriately discarded. A fresh syringe and needle are necessary to determine whether a blood vessel has been entered.

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 could result in a local reaction.

LOCATION OF ALLERGEN IMMUNOTHERAPY ADMINISTRATION

Physician's office

Summary Statement 59: 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 to treat anaphylaxis should be in the immediate vicinity when immunotherapy injections are administered.

Summary Statement 60: 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.[292] 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.[184] 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 might be frequently necessary in the patient's immunotherapy schedule, as well as the patients total treatment program.

Other locations

Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **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.[292] The health care professional and staff 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, or allergy/asthma exacerbations at the time of allergen immunotherapy extract injection or poorly controlled asthma).

Appropriate adjustment of dose should be made as clinically indicated. The physician who prepared the patient's allergen immunotherapy extract should provide adequately labeled allergen immunotherapy extract vials, detailed directions regarding dosage schedule for build-up and maintenance, and instructions on adjustments that might be necessary under the following circumstances:

1. when providing patients with new vials;
2. during seasonal exposure to allergens that are in the patient's allergen vaccine, to which the patient is very sensitive, or both;
3. if the patient has missed injections; and
4. when reactions occur to the allergen immunotherapy extract.

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

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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 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 very 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 fully trained to administer the injection and to treat anaphylaxis if this should 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 supports (personnel, medications, supplies, and equipment) are more optimal for encouraging prompt recognition and treatment of anaphylaxis (Table V). 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.

Summary Statement 63: If a patient on 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for their immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extracts might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Patients often 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 brought from the previous physician (ie, an unchanged immunotherapy program) or one to be prepared by the current physician (ie, a new immunotherapy program).

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 full, clear, and detailed documentation of the patient's previous schedule and the contents of the allergen immunotherapy extract (see Appendices 7, 8, 11, 12, and 14 for examples of allergen immunotherapy prescription and administration forms and documentation guidelines for allergen immunotherapy forms). In addition, the patient's previous response to and compliance with this program 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 a schedule and the allergen immunotherapy extract, (2) the patient has shown significant improvement on this immunotherapy program, and (3) the contents of the allergen immunotherapy extract are appropriate for the area in which the patient is now living.

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, vaccine type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient's dose is not modified. This increased risk is due to the significant variability in content and potency of extracts and the variability in methods used by physicians to prepare the patient's maintenance concentrate and its dilutions. For example, the strength of a given concentration of nonstandardized extracts might vary significantly from vial to vial. The risk of systemic reactions in such a situation might be greater with nonstandardized extracts and allergen immunotherapy extracts that contain mixtures of allergens.

Therefore if the allergen immunotherapy extract is to be changed, the patient might need to be retested for specific IgE to the appropriate allergens 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 provided the interval of time since the last injection has not been too long. For lot changes from the same manufacturer, the physician can consider decreasing the dose by 50% to 90%. For changes in manufacturer and nonstandardized extracts, a greater decrease in dose might be necessary.

SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

Allergen immunotherapy in children

Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children

with allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Immunotherapy for children has been shown to be effective and often well tolerated,[137,242] although at least one study did not show efficacy.[293] 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.[294] In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (see the Patient selection section and Table VII). In recent studies children receiving allergen immunotherapy have demonstrated:

1. improvement in symptom control for asthma[117,119,121,122] and allergic rhinitis[118];
2. increased PC_{20} to histamine[121];
3. increased PC_{20} to cat and house dust mite allergens[121,149];
4. decreased risk of development of asthma[6,9,163-165];
5. decreased development of new sensitivities[120,166]; and
6. modification in release of mediators in children receiving immunotherapy that correlates with decreased clinical symptoms.[123]

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Although there is some disagreement about the role of allergen immunotherapy in children under the age of 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.[117,122] In children with allergic rhinitis, allergen immunotherapy might prevent the development of asthma.[6,9,163-165] However, allergen immunotherapy for inhalant allergens is usually not considered necessary in infants and toddlers because (1) there is 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 in pregnancy

Summary Statement 71: Allergen immunotherapy might be continued but is usually not initiated in the pregnant patient. **C**

The physician must be aware of the benefits and risks of immunotherapy in pregnant patients. The recommended precautions for prevention of adverse reactions are especially important in the pregnant patient. Allergen immunotherapy is effective in the pregnant patient. Thus allergen immunotherapy maintenance doses can be continued during pregnancy. Allergen immunotherapy is usually not initiated during pregnancy because of risks associated with systemic reactions and their treatment (ie, spontaneous abortion, premature labor, or fetal hypoxia). 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, and the patient is maintained on the dose that she is receiving at that time.

Immunotherapy in the elderly patient

Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy might be considered in the treatment of the elderly patient, but the benefit/risk assessment must be evaluated carefully in this population. Older 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. However, elderly patients may also benefit from allergen immunotherapy and age alone should not preclude the consideration of allergen immunotherapy.[295]

Immunotherapy in patients with immunodeficiency and autoimmune disorders

Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with immunodeficiency or autoimmune disorders. Therefore the decision to begin immunotherapy in patients with major humoral or cellular immune defects must be individualized. Concern about the increased risk of immunotherapy in such patients is largely hypothetical.

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

ALTERNATIVE ROUTES OF IMMUNOTHERAPY

Sublingual and oral immunotherapy

Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be

effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no FDA-approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **B**

Alternative routes of administration of allergen immunotherapy are ''a viable alternative to parenteral injection therapy'' in some cases.[106,296] Studies of oral immunotherapy have provided conflicting results for ragweed,[297] birch,[298] and cat[299] immunotherapy. The present dosage of oral immunotherapy extract is 20 to 200 times the parenteral injected dosage, which requires a cost assessment for this type of therapy. Furthermore, adverse effects have included gastrointestinal and oral reactions (50% in 1 study) that might preclude home therapy. Oral immunotherapy should be considered investigational at this time.

Optimal-dose (high-dose) sublingual swallow immunotherapy is effective in adults and children.[300-304] In a study of 855 patients with grass pollen allergy and allergic rhinitis randomized to placebo or one of 3 grass tablet doses, there was a significant reduction in symptom and medication scores in the highest-dose subgroup, who were treated for at least 8 weeks before the grass pollen season, compared with the placebo group (symptoms, 21%, $P = .0020$; medication use, 29%, $P = .0120$).[303]

Sublingual allergen studies have evaluated house dust, olive pollen, grass pollen, ragweed, birch, cat, latex, *Alternaria* species, and *Parietaria judaica*.[305-313] Sublingual immunotherapy has been shown to be effective in patients sensitized to 2 non–cross-reacting allergens, grass and birch.[314] It has been noted that the allergen is not degraded by saliva and that there is no direct sublingual absorption of allergen. Radiolabeled allergen has been detected after 48 hours in the sublingual region.[315,316] Alternative protocols, such as rush and ultra-rush (20 minutes) sublingual swallow[307,316,318] and no induction (build-up) phase,[301,303,317,319,320] have been studied. Several studies have suggested a relationship between dose and efficacy with sublingual immunotherapy,[303,310,321] but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. The majority of sublingual studies have demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both, but approximately 35% of the randomized, double-blind, placebo-controlled studies did not demonstrate efficacy in either parameter during the first year of treatment.[322] Further studies are needed to confirm the optimal dose for sublingual immunotherapy.

One of the potential advantages of sublingual immunotherapy is that it appears to be safe, even at very high doses (up to 500 times the usual monthly subcutaneous dose), and to be associated with a lower incidence of serious side effects.[310,320,323] This appears to apply to young children (<5 years), for whom there are prospective safety data[324,325] and a postmarketing survey.[326]



FIG 3. Sample of labels for allergen immunotherapy extract vials.

There have been no SLIT-related fatalities, but there have been 3 case reports of anaphylaxis caused by sublingual immunotherapy. One patient with latex hypersensitivity had anaphylactic shock 20 minutes after reaching the maximal dose on the fourth day of latex rush sublingual rush immunotherapy.[327]

The other 2 reported cases of SLIT anaphylaxis involved patients treated with multiple inhalant allergens. In one case a patient with allergic rhinitis and asthma who was prescribed a sublingual immunotherapy extract composed of multiple non–cross-reacting allergens (*Alternaria* species, dog, cat, ragweed mix, weed mix, and grass mix)[328] had generalized pruritis, followed by angioedema, shortness of breath, and dizziness, within a few minutes of administering 6 drops of the 1:100 vol/vol dilution on the third day of treatment. This episode was preceded by a milder systemic reaction the previous day (generalized pruritis). In the other case, a 13-year-old girl with allergic rhinitis and asthma had swelling of her lower lip 3 minutes after pollen drops, high fever, chest pain, nausea, and abdominal pain.[329] She was treated in the emergency department for anaphylaxis and hospitalized for observation. The reaction occurred 1 month after she had reached the maintenance dose during the peak of the spring season.

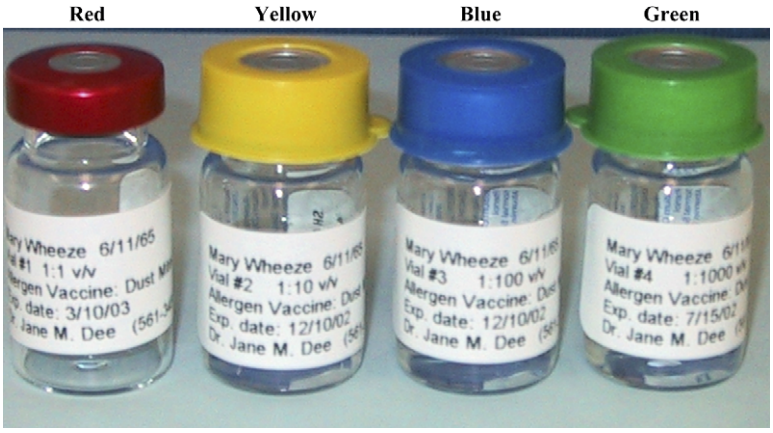


FIG 4. Sample set of color-coded vials of allergen vaccine.

There is currently no FDA-approved formulation for sublingual immunotherapy in the United States at this time, and this modality should be considered investigational. Current investigation of sublingual immunotherapy should not be confused with low-dose sublingual immunotherapy based on provocation neutralization testing or Rinkel-type skin testing.

Intranasal immunotherapy

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Based on controlled, well-designed studies, intranasal immunotherapy has been shown to improve the nasal symptoms of rhinitis.[330] Intranasal dry powder extract immunotherapy has been studied in grass,[330] birch,[331] *P judaica*,[332-334] and house dust mite[335] allergy. Clinical efficacy was noted in all of these studies. Nasal reactivity to allergen challenge was reduced, and only minor side effects were noted in 2 of the above studies. A 3-year study with *P judaica* reported to provide persistent benefits for up to 12 months after conclusion of allergen immunotherapy.[333] Local administration of nasal allergen in an aqueous solution for immunotherapy might be limited by the local side effects. Further studies in both pediatric and adult groups are needed. In human studies the antigen has been noted to appear in the serum within 15 to 30 minutes of administration, with a peak level occurring within 2 to 3 hours.[315] Some allergens have been reported to be retained in the nasal mucosa for up to 48 hours after administration. Intranasal immunotherapy is not currently available in the United States but has gained some acceptance in other parts of the world.

Immunotherapy techniques that are not recommended

Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

Low-dose regimens, including coseasonal low-dose immunotherapy for aeroallergens and the Rinkel low-dose titration techniques, are not effective.[27,28] Immunotherapy based on provocation–neutralization testing with food and aeroallergens and enzyme-potentiated desensitization is not effective.[336]

FUTURE TRENDS IN IMMUNOTHERAPY

Therapy with aeroallergen extracts will become more uniform (as is the current practice for insect venoms) as greater numbers of biologically standardized allergen extracts become available. The actual number of commercially available allergen extracts will be reduced based on consensus agreements about the regional prevalence of aeroallergens, their cross-allergenicity, and the relevance of their effect on human health in specific locales. Novel routes for more effective, convenient, and safer allergen immunotherapy are being investigated throughout the world.

For example, the sublingual route of administering allergen immunotherapy has been studied extensively in Europe. A meta-analysis confirmed its clinical effectiveness in allergic rhinitis,[302] and it has been reported to be effective in asthma as well.[337] Sublingual immunotherapy appears to have a very low risk of serious life-threatening systemic side effects, which might allow for home administration.[324,338] In some studies the clinical benefits of sublingual immunotherapy were not significant until the second year of treatment,[306,339] and comparisons suggest that the magnitude of the clinical benefit of sublingual immunotherapy might not be as great as that of subcutaneous immunotherapy.[311]

Trials with non–IgE-binding peptides containing T-cell stimulating peptides have been reported.[340] Site-directed mutagenesis has produced allergens with decreased IgE-binding capacity without decreased T-cell responses.[341,342]

Immunostimulatory sequences mimicking bacterial and viral DNA have been prepared that stimulate the innate immune system to direct T-cell responses toward

T_H1 rather than T_H2 phenotypes.[343] The results of clinical trials with a conjugate of the immunostimulatory sequence to the major allergen of ragweed, Amb a 1 (AIC), have been reported.[34,343] In a double-blind, placebo-controlled study of 25 adults who received 6 weekly injections of the AIC or placebo vaccine before ragweed season, the AIC group had better peak-season rhinitis scores on the visual analog scale ($P = .006$), peak-season daily nasal symptom diary scores ($P = .02$), and midseason overall quality-of-life scores ($P = .05$) than the placebo group during the first ragweed season, and this effect was observed in the subsequent ragweed season.[344]

Humanized anti-IgE mAb has been shown to have clinical effects in both allergic rhinitis and asthma.[345-348] Theoretically, this new therapeutic modality could be used as protective cover for clinical applications of rapid forms of immunotherapy. It is possible that preadministration of anti-IgE could provide a more effective protective effect than premedication with antihistamines and therefore permit a rush allergen immunotherapeutic regimen with reduced risk of serious systemic reactions.[282]

AUTHOR'S 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 2 systemic reaction grading systems (the European Academy of Allergy and Clinical Immunology's grading of severity for systemic side effects and the Portnoy method for numeric grading of reactions to allergen immunotherapy) can be found in the Appendix section. These forms can also be found along with examples of immunotherapy instruction and consent forms, preinjection health questionnaires, and indications for beginning and continuing immunotherapy forms at www.aaaai.org.

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APPENDIX 1. American College of Medical Quality's policy on the development and use of practice parameters for medical quality decision-making[1]

Practice parameters are strategies for patient management developed to assist health care professionals in clinical decision making. Practice parameters include standards, guidelines, and other patient management strategies. Standards are accepted principles for patient management. Guidelines are recommendations for patient management that identify a particular management strategy or a range of management strategies. Other strategies for patient management include practice policies and practice options. Practice parameters are to be used as screening tools to identify possible deviations from the applicable standards of care. Such parameters are not to be used as absolute standards or to profile or report on health care personnel. Parameters are designed to trigger a process in which possible deviations from the standard of care are identified as outlier practice patterns. Once a deviation from the parameter is identified, such a deviation should be referred to the appropriate qualified physician advisor or reviewer for a determination of medical necessity that conforms to the applicable standard of care. Parameters used in the day-to-day practice of clinical medicine should be clinically relevant. They should not be considered as substitutes for the standard of care but might contribute to its formulation.

Practice parameters must be developed, designed, and implemented only by board-certified, clinically practicing, specialty-matched physician advisors/reviewers with unrestricted medical licenses. Qualified nonphysicians might participate in the development of these parameters only in the areas in which their clinical expertise based on the standard of care is applicable. The health care personnel who develop these parameters should sign their names and date the final version as evidence of their participation and support. Practice parameters must be based on sound scientific research findings, professional literature, clinical experience and appropriate well-recognized methodologies and reflect professionally recognized national standards of care practiced in the clinical community of medicine. The development procedures followed, the participants involved, the evidence used, the assumptions and rationales accepted, and the analytic methods used should be meticulously documented, described, and made publicly available for national peer review. Parameters should be updated as needed.

Practice parameters are used as tools to enhance medical decision making but not as replacements for physicians' clinical judgment. They can be considered as means to enhance the performance of clinical and review personnel but not to replace them. It is below the standard of care of the medical review process to substitute qualified physician reviewer experts with unqualified reviewers who are using parameters.

APPENDIX 2. Examples of possible abbreviations for allergen immunotherapy extract 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

APPENDIX 3. 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

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

APPENDIX 4. Example of immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals (modification of the AAAAI skin testing and immunotherapy consent and instruction forms: immunotherapy administration instruction form, which can be found at http://www.aaaai.org)

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

- Up to 7 days, continue as scheduled (ie, if on weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection).
- Eight to 13 days after missed scheduled injection; repeat previous dose.
- Fourteen to 21 days after missed scheduled injection; reduce dose 25%.
- Twenty-one to 28 days after missed scheduled injection; reduce previous dose 50%.

Then increase dose each injection visit as directed on the immunotherapy schedule until therapeutic maintenance dose is reached.

This suggested approach to modification of doses of allergen immunotherapy because of gaps between treatment during the build-up phase is not based on retrospective or prospective published evidence, but it is presented as a sample for your consideration. The individual physician should use this or a similar protocol as a standard operating procedure for the specific clinical setting. A similar dose-reduction protocol should be developed for gaps in maintenance immunotherapy.

APPENDIX 5. Example of a cluster immunotherapy schedule[22,26]

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

APPENDIX 6. Recommended documentation for allergen immunotherapy prescription forms

The purpose of the allergen immunotherapy prescription form is to define the contents of the allergen immunotherapy extract in enough detail that it could be precisely duplicated. The following information should be on an immunotherapy prescription form:

Patient information:

- Patient name, patient number (if applicable), birth date, telephone number, and picture (if available) should be included.

Preparation information:

- Name of person and signature preparing the allergen immunotherapy extract should be included.
- Date of preparation should be recorded.
- Bottle name should be included (eg, trees and grass). If abbreviations are used, a 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 should be included.
- Volume of manufacturer's extract to add to achieve the projected effective concentration should be included. 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) should be included.
- Extract manufacturer should be included.
- Lot number should be included.
- Expiration date should be recorded and should not exceed the expiration date of any of the individual components.

APPENDIX 7. Allergen immunotherapy extract prescription 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:

_____
_____
_____
_____

_____ ____/____/____
Prescribing Physician Signature Date

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

APPENDIX 8. Maintenance concentrate prescription form

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: 6/10/06

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial **4** from Vial **1** on **8/30/06** Expiration date: **10/15/06**
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	Short ragweed	1:20 w/v G (150 Amb a1)	0.5ml	Greer	12345	1/01/08
2	Amaranthus Retroflexus	1:10 w/v G	0.5ml	H-S	6789	2/07/08
3	Ash	1:10 w/v G	0.5ml	Center	3333	3/17/08
4	Cat	10,000 BAU/ml G	2.00ml	ALO	9898	2/27/08
5	Timothy Grass	100,000 BAU/ml G	0.4ml	ALK	56789	7/09/08
6	Johnson Grass	1:10 w/v G	0.5ml	Greer	2434	7/20/08
7						
8						
9						
10						
Diluent	HSA		0.6ml	ALK	68597	12/08
Total Volume			5.00 ml			6/10/07

*** Components of mixes listed on a separate sheet**
**** Assumes 0.5 ml injection as target maintenance dose**

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

Specific Instructions:

_____

_____

Prescribing Physician Signature

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

APPENDIX 9. Labels for allergen immunotherapy extracts

Each vial of allergen immunotherapy extract should be labeled in a way that permits easy identification. Each label should include the following information (example in Figs 3 and 4):

- Appropriate patient identifiers might include the patient's name, patient's number, patient's picture, and birth date.
- The contents of the allergen immunotherapy extract in a general way should be included. The detail with which this can be identified depends on the size of the label and the number of allergens in the vial. Ideally, allergens should be identified as trees, grasses, weeds, mold, dust mite, cockroach, cat, and dog. Because of space limitations, it might be necessary to abbreviate the antigens (eg, T, G, W, M, DM, Cr, C, and D respectively [see Appendix 2]). A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate (vol/vol) should be recorded. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- The expiration date should be included.

APPENDIX 10. Allergen immunotherapy administration form recommended documentation

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

Patient information:

- Patient's name, date of birth, telephone number, and patient's picture (optional but helpful).

Allergen immunotherapy extract information:

- Allergen immunotherapy extract name and dilution from maintenance in vol/vol bottle letter (eg, A and B), bottle color, or number, if used.
- Expiration date of all dilutions.

Administration information in separate columns:

- Date of injection.
- Arm administered injection, which might facilitate determination of exact cause of local reaction.
- Projected build-up schedule.
- Delivered volume reported in milliliters.
- Description of any reactions. The details of any treatment given in response to a reaction would be documented elsewhere in the medical record and referenced on the administration form.
- *Patient's health before injection*. This can be performed through a verbal or written interview of the patient before administering the immunotherapy injection. The patient should be questioned about increased asthma or allergy symptoms, β-blocker use, change in health status (including pregnancy and recent infections), or an adverse reaction to a previous injection (including delayed large local reactions persisting through the next day). Patients with significant systemic illness generally should not receive an injection.
- *Antihistamine use*. Antihistamines are frequently a component of an allergy medication regimen, and it would be important to note whether a patient is taking an antihistamine on the day he or she receives his or her immunotherapy injection. For consistency in interpretation of reactions, it might be desirable for a patient to either take or avoid antihistamines on a regular basis on the days he or she receives immunotherapy. The physician should note on the form whether he or she recommends the patient consistently take an antihistamine on immunotherapy treatment days.
- *Peak flow reading*. Consider obtaining a peak expiratory flow rate measurement before administering an immunotherapy injection to asthmatic patients. Poorly controlled asthma is considered a risk factor for immunotherapy. Obtaining a peak expiratory flow rate measurement before the immunotherapy injection might help identify patients with symptomatic asthma. The patient's baseline peak expiratory flow rate should be provided on the form as a reference. Health care professionals administering immunotherapy injections should be provided with specific guidelines about the peak expiratory flow rate measurement for when an immunotherapy injection should be withheld and the patient referred for clinical evaluation.
- **Baseline blood pressure**. It might be useful to record the patient's blood pressure as a baseline for future reference.

APPENDIX 11. Allergen immunotherapy administration form

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 allergy or 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

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

Date to reorder: __/__/__

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 allergy or 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**	

APPENDIX 12. 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: _____
_____
Staff action taken (if any): _____

APPENDIX 13. 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.

APPENDIX 14. Allergen immunotherapy systemic reaction/anaphylaxis 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
__Epinephrine IM into 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	

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:
_____
_____
_____
_____

Clinical impression: True SR Questionable SR No SR

Systemic reaction severity classification: EAACI_____ **Portnoy** _____

Dosage adjustment? _____

Signatures_____ **RN** _____**MD/DO**

APPENDIX 15. Grading severity of allergen immunotherapy reactions: Two methods

1. **The European Academy of Allergy and Clinical Immunology grading of severity for systemic side effects***

Classification of systemic reactions

0 = No symptoms or nonspecific symptoms

I = Mild systemic reactions: symptoms—localized urticaria, rhinitis, or mild asthma (PF <20% decrease from baseline).

II = Moderate systemic reaction: symptoms—slow onset (>15 minutes) of generalized urticaria, moderate asthma, or both (PF < 40% decrease from baseline).

III = Severe (non–life-threatening) systemic reactions: symptoms—rapid onset (<15 minutes) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).

IV = Anaphylactic shock: symptoms—immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, and hypotension, for example.

2. **Portnoy method for numeric grading of reactions to allergen immunotherapy†**

Local

0+ = No significant reaction or small area of erythema less than the size of a half dollar without swelling or wheal formation

1+ = Erythema greater than the size of a half dollar, swelling or wheal formation, or both

Systemic

2+ = Systemic reactions: cutaneous only—might consist of a cutaneous eruption, such as urticaria

3+ = Systemic reaction: generalized pruritus, sneezing, or both—might consist of increased allergy symptoms, such as nasal congestion, sneezing, or pruritus, especially in the mouth or throat

4+ = Systemic reaction: pulmonary—consists of wheezing, shortness of breath, and tightness. Might be associated with decreased pulmonary function tests

5+ = Systemic reaction: anaphylaxis—a sensation of not feeling right is a frequent prelude; might consist of hypotension, laryngeal edema, severe wheezing, and cramping

6+ = Cardiopulmonary arrest

PF, Peak expiratory flow.

*Subcutaneous immunotherapy. Allergy 2006;61(suppl 82):5-13.

†Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80.

Allergen immunotherapy: A practice parameter second update

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

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the "Allergen immunotherapy: a practice parameter second 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 and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
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11. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999;83(suppl): S665–S700.
12. Diagnosis and management of urticaria: a practice parameter. Ann Allergy 2000;85(suppl):S521-S544.
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14. Symptom severity assessment of allergic rhinitis: part I. Ann Allergy 2003;91:105-14.
15. Disease management of atopic dermatitis: an updated practice parameter. Ann Allergy 2004;93(suppl): S1-S21.
16. Stinging insect hypersensitivity: a practice parameter update. J Allergy Clin Immunol 2004;114:869-86.
17. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol 2005;115(suppl):S483-S523.

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22. Contact dermatitis: a practice parameter. Ann Allergy Asthma Immunol 2006;97(suppl 2):S1-S38.

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

CONTRIBUTORS

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Allergen immunotherapy: A practice parameter second update

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PREFACE

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

The objective of ''Allergen immunotherapy: A practice parameter second update'' is to optimize the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. 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's ''Policy on development and use of practice parameters for medical quality decision-making'' (Appendix 1).[1]

This document builds on the previous Joint Task Force document, ''Allergen immunotherapy: a practice parameter'' published in the *Annals of Allergy, Asthma and Immunology* in 2003.[2] The updated practice parameters draft was prepared by Drs Linda Cox, James Li, Hal Nelson, and Richard Lockey. The Joint Task Force reworked the initial draft into a working draft of the document. The project was exclusively funded by the 3 allergy and immunology societies noted above.

In preparation for the 2003 ''Allergen immunotherapy: a practice parameter'' and the second update, a comprehensive search of the medical literature was conducted with various search engines, including PubMed; *immunotherapy*, *allergic rhinitis*, *asthma*, *stinging insect allergy*, and related search terms were used. 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 second update'' was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the ACAAI, AAAAI, and JCAAI. In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for review and comments from members of the sponsoring organizations. 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 allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. This document also contains recommendations for the safe practice of allergen immunotherapy, including specific recommendations on the prevention and management of 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 or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. Symptoms of allergic conjunctivitis (eg, itchy watery eyes) are often considered part of allergic rhinitis or are included in the diagnosis of rhinoconjunctivitis. Particularly good candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures, those in whom it is important to avoid the potential adverse effects of medications, and those who wish to reduce the long-term use of medications. Immunotherapy is recommended for patients with a history of systemic reaction to Hymenoptera stings and specific IgE antibodies to Hymenoptera venom.

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.[3]

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. 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 *maintenance concentrate* should be used to identify the allergen immunotherapy extract that contains a therapeutic effective dose for each of its individual constituents (see the Immunotherapy schedules and doses section).

The term *manufacturer's extract* refers to the allergy extract purchased from the manufacturer. The terms *stock*, *full-strength*, and *concentrate* are ambiguous and should not be used. 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).

Allergen immunotherapy is effective when appropriate doses of the allergens are administered. ''Allergen immunotherapy: A practice parameter'' recommends that vials of allergen immunotherapy extracts should be prepared individually for each patient to enhance the individualization of therapy, reduce the risk of allergen cross-contamination, and reduce the risk of error in administration.[4,5] This parameter recommends the use of standardized allergen immunotherapy prescription and administration forms to improve the safety, uniformity, and standardization of allergen immunotherapy practice.[4,5] The suggested forms are found in the Appendix (Appendices 7, 8, 11, 12, and 14) and in the members' section of the www.aaaai.org Web site. The routine use of these standardized forms should improve the quality of immunotherapy practice.

Members' feedback comments on the recommended allergen extract dilution dating in the 2003 ''Allergen immunotherapy: A practice parameter'' led to an allergen immunotherapy extract dilution stability study designed by the AAAAI Immunotherapy and Allergy Diagnostics Committee and funded by the AAAAI Board of Directors. The study was designed to investigate the effect of time, temperature, and dilution of standardized allergen extract potency, and the results of this study were considered in this update.

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 3 years after publication. Requests for information about or an interpretation of these practice parameters should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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. Allergen immunotherapy

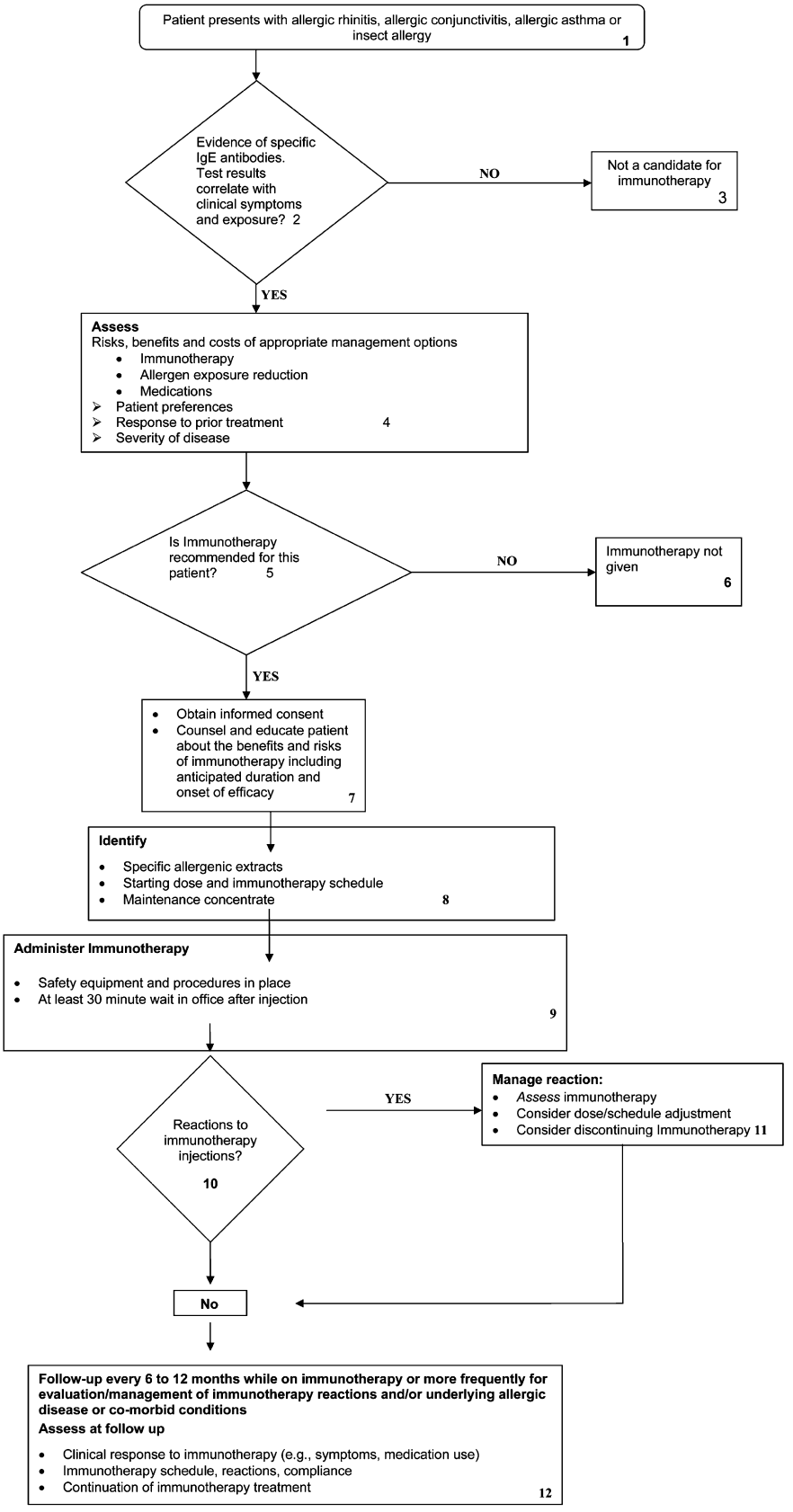


FIG 1. Algorithm for allergen immunotherapy.

might prevent the development of asthma in individuals with allergic rhinitis.[6-9] Evaluation of a patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic conjunctivitis, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for specific IgE antibody).[10]

Box 2

Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although *in vitro* testing for 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

Management of complex medical conditions, such as allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity, should include the careful evaluation of management 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 patient 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. On the basis of clinical considerations and patient 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 good candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy (VIT).

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 on the basis of 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 (see the Immunotherapy schedules and doses section). In general, the starting immunotherapy dose is 1000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 1000 to 4000 arbitrary units (AU; eg, for dust mite) or bioequivalent allergy units (BAU; eg, for grass) 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 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 referred to as *up-dosing*, *induction*, or the *dose-increase phase*) entails administration of gradually increasing doses during a period of approximately 14 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 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, in particular anaphylaxis. Patients should wait at the physician's office for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly, if they occur.

In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring 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. Some physicians recommend providing certain patients with epinephrine for self-administration in case of severe late reactions to immunotherapy injections.

Box 10

Injections of allergen immunotherapy extract can cause local or systemic reactions. Most severe reactions develop within 30 minutes after the immunotherapy injection, but reactions can occur after this time.

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 (anaphylaxis). Epinephrine is the treatment of choice in anaphylaxis, preferably when administered intramuscularly,[11] although subcutaneous administration is acceptable.[12]

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, see the practice parameters for anaphylaxis.[12]

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. After a severe systemic reaction, careful evaluation by the prescribing physician is recommended. For some patients, the immunotherapy maintenance dose might need to be reduced because of repeated systemic reactions to immunotherapy injections. The decision to continue immunotherapy should be re-evaluated after severe or repeated systemic reactions to allergen immunotherapy extracts.

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 doses, 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,[13] but others might experience a recurrence of their symptoms after discontinuation of allergen immunotherapy.[14] 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, and 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 on the basis of the patient's clinical response, disease severity, immunotherapy reaction history, and patient preference.

IMMUNOTHERAPY GLOSSARY

For more information on immunotherapy definitions, see the article by Kao.[15]

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 (pigments and salts; see the Allergen selection and handling section). Other terms used to describe the allergen immunotherapy extract include *allergen product*,[16] *allergy serum*, *allergen vaccine*,[17] 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.[18] Other terms that have been used for allergen immunotherapy include *hyposensitization*, *allergen-specific desensitization*, and the lay terms *allergy shots* or *allergy injections*.[15]

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

TABLE II. Allergen immunotherapy dose-calculation table

- Express weight per volume as a fraction: $\frac{1}{N}$ or 1:*N*.
- Calculate concentration of individual allergens in mixtures. If a mixture is made of equal amounts of N individual allergens to make a total concentration (C), the final concentration of an individual allergen (Ca) can be calculated by using the following equation:

$Ca = C \times \frac{1}{N} = \frac{C}{N}$ or *C*:*N*.

For example, if a mixture of equal amounts of 5 (N) allergens has a total concentration (C) of 100,000 BAU/mL, then the final concentration of each individual allergen (Ca) is: $Ca = \frac{C}{N} = \frac{100{,}000}{5} = 20{,}000\ BAU/mL$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{C}{N} = \frac{1/10}{5} = \frac{0.1}{5} = 0.02$ or $\frac{1}{50}$ or 1:50.

- Dilution of individual allergen: If an initial volume, Vi (in milliliters), of an individual antigen with concentration, Ci, is added to an allergen extract to make a final volume of Vf (in milliliters), the final allergen concentration (Ca) in the allergen extract mixture will be: $Ca = Ci \times \frac{Vi}{Vf}$.
- Final concentration of an allergen in a mixture of mixtures is determined by multiplying the initial concentration by the dilution factors from each mixing step.

For example, consider a mixture containing equal amounts of 5 (N) allergens with a total concentration (C) of 100,000 BAU/mL (first dilution). If an initial volume (Vi) of 0.5 mL of this mixture is further mixed with other components and diluent to make a final allergen extract mixture volume (Vf) of 5.0 mL (second dilution), the final concentration of an individual allergen (Ca) will be:

$$Ca = C \times \underbrace{\frac{1}{N}}_{\text{Mixture dilution}} \times \underbrace{\frac{Vi}{Vf}}_{\text{Allergen extract dilution}} = 100{,}000 \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{100{,}000}{50} = 2000\ BAU/mL$$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{1}{10} \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{1}{500}$ or 1:500.

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).

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 to 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-medicated 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 multiplied by volume of administered dose (see Table II for a dose-calculation table).

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, cat, 1000 BAU, [highest tolerated dose] vs 2000 BAU [projected effective dose]).

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 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 by a variety of immunologic transformations. Early definitions of the term immunotherapy included active and passive immunization for the purpose of improving 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 by means of induction of clonal deletion, anergy, immune tolerance, or immune deviation.

The *maintenance concentrate* is a preparation that contains individual 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 may not be the initially calculated projected effective dose.

The *maintenance goal* (or projected effective dose) is the allergen dose projected to provide therapeutic efficacy. The maintenance goal is based on published studies, but a projected effective dose has not been established for allergens. 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 the 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 large local reaction causing discomfort). The intervals between maintenance immunotherapy injections generally ranges 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 by means of immunoblotting or crossed allergoimmunoelectrophoresis.

For a definition of *projected effective dose*, see 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 test responses), and premedication with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similar high incidence of systemic reactions.

Off the board into one syringe is a phrase that describes a method of allergen immunotherapy preparation and administration that involves specifically mixing the patient's allergen immunotherapy injection in a single syringe, which is not recommended. This syringe might be inserted into more than one allergen extract vial, and this poses a risk of cross-contamination of the allergen extracts and might dull the needle with repeated penetration of the rubber stopper.

Shared specific patient vials is a method of allergen immunotherapy preparation and administration in which the allergy immunotherapy extract is withdrawn from a shared vial (eg, mixed vespids or dust mite mix). This is sometimes referred to as off the board, but it is distinct from the method of off the board into one syringe in that the syringe enters only one allergen extract vial.

INTRODUCTION

Immunity has been defined as protection against certain diseases. The initial immunotherapeutic interventions, which included the use of preventive vaccines and xenogenic 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 the field of allergen immunotherapy. From its humble empiric emergence in 1900, when ragweed injections were proposed as therapy for autumnal hay fever, allergen immunotherapy has progressed in both theory and practice from the passive immunologic approach to the active immunologic procedures pioneered by Noon[19] and Freeman.[20,21] 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 10 years. Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Some studies have suggested that allergen immunotherapy might prevent the development of asthma in individuals with allergic rhinitis.[6-9]

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,[22-26] and it should be differentiated from unproved methods, such as neutralization-provocation therapy and low-dose subcutaneous regimens based on the Rinkel technique, which have been found to ineffective in a double-blind placebo-controlled study.[27,28]

SUMMARY STATEMENTS

Mechanisms of immunotherapy

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, defined as a relative decrease in allergen-specific responsiveness and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

Allergen extracts

Summary Statement 6: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. **A**

Summary Statement 7: Nonstandardized extracts might vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Summary Statement 8: 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**

Cross-reactivity of allergen extract. Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

Efficacy of immunotherapy

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Summary Statement 10: Immunotherapy is effective for 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**

Food allergy, urticaria, and atopic dermatitis. Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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**

Measures of efficacy. Summary Statement 12: 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**

Safety of immunotherapy

Reaction rates. Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

Timing of anaphylactic reactions to immunotherapy injections. Summary Statement 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

β-*Adrenergic blocking agents.* Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

Contraindications. Summary Statement 18: 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**

Reducing the risk of anaphylaxis to immunotherapy injections. Summary Statement 19: 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**

Patient selection

Clinical indications. Summary Statement 20: 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 depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Special precautions in patients with asthma. Summary Statement 21: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. **C**

Clinical indications for VIT. Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Summary Statement 23: Patients selected for immunotherapy should be cooperative and compliant. **D**

Allergen selection and handling

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted in vitro tests for specific IgE antibodies can also be used. **A**

Specific allergens. Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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, supported by the presence of specific IgE antibodies. **A**

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Dose selection. Summary Statement 30: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. **A**

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens, is recommended. **B**

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extract handling

STORAGE

Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

STORING DILUTE EXTRACTS

Summary Statement 34a: More dilute concentrations of allergen immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: 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 a number of 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. **B**

Immunotherapy schedules and doses

Summary Statement 35: A customized individual 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 be based on single or multiple allergens. **D**

Maintenance concentrate. Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

Recommended doses. Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

Effect of dilution on dose. Summary Statement 38: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. **A**

Dilutions of the maintenance concentrate. Summary Statement 39: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. **D**

Labeling dilutions. Summary Statement 40: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. **D**

Individualized treatment vials. Summary Statement 41: 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. The mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. **C**

Starting doses. Summary Statement 42: The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. **D**

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

Dose adjustments for systemic reactions. Summary Statement 44: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. **D**

Reductions during periods of exacerbation of symptoms. Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Dose adjustments for late injections. Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

Cluster schedules. Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. **C**

Rush schedules. Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. **A**

Systemic reactions and rush schedules. Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

Premedication and weekly immunotherapy. Summary Statement 50: Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

Premedication with cluster and rush immunotherapy. Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

Maintenance schedules. Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. **A**

Continuing care

TIME COURSE OF IMPROVEMENT

Summary Statement 53: Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **A**

FOLLOW-UP VISITS

Summary Statement 54: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. **D**

DURATION OF TREATMENT

Summary Statement 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

DOCUMENTATION AND RECORD KEEPING

Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. **D**

INJECTION TECHNIQUES

Summary Statement 57: Allergen immunotherapy extract injections should be administered with a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **D**

Summary Statement 58: The injection should be administered subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Location of allergen immunotherapy administration

Physician's office. Summary Statement 59: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Summary Statement 60: 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**

Other locations. Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **D**

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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**

Summary Statement 63: 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for his or her immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extract might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Special considerations in immunotherapy

Allergen immunotherapy in children. Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Pregnancy. Summary Statement 71: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. **C**

Immunotherapy in the elderly patient. Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy in patients with immunodeficiency and autoimmune disorders. Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

Alternative routes of immunotherapy

Sublingual and oral immunotherapy. Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no US Food and Drug Administration (FDA)–approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **A**

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Immunotherapy techniques that are not recommended. Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

MECHANISMS OF IMMUNOTHERAPY

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, which is defined as a relative decrease in allergen-specific responsiveness, and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

The immunologic changes associated with immunotherapy are complex, and the exact mechanism or mechanisms responsible for its' clinical efficacy are continually being elucidated. Data support the concept that successful immunotherapy is associated with a change to a T_H1 $CD4^+$ cytokine profile.[29-34] Data indicate that increased production of IL-12, a strong inducer of T_H1 responses, contributes to this shift.[33] Clinically successful immunotherapy has been reported to be associated with immunologic tolerance, which is defined as a relative decrease in antigen-specific responsiveness, immune deviation, or anergy. For example, lymphoproliferative responses to allergen are reduced with immunotherapy.[32] Successful immunotherapy results in generation of a population of T regulatory cells, which are $CD4^+CD25^+$ T lymphocytes producing IL-10, TGF-β, or both.[35-39] Regulatory T-cell release has been described in allergen immunotherapy with Hymenoptera venom,[35] grass pollen extract,[37] and house dust mites.[38] IL-10 reduces B-cell antigen-specific IgE and increases IgG4 levels; reduces proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicits tolerance in T cells by means of selective inhibition of the CD28 costimulatory pathway.[36,37]

Allergen immunotherapy has been shown to block both the immediate and late-phase allergic response.[40] Allergen immunotherapy has been shown to decrease the recruitment of mast cells, basophils, and eosinophils in the skin, nose, eye, and bronchial mucosa after provocation or natural exposure to allergens.[41]

In patients receiving immunotherapy, initially there is an increase in specific IgE antibody levels, followed by a gradual decrease to a level that is still higher than that present before treatment. Clinical improvement in many patients develops before decreases in their IgE antibody levels occur or in other patients whose IgE antibody levels never decrease, thereby demonstrating that efficacy is not dependent on reductions in specific IgE levels.[42,43] Immunotherapy does diminish the seasonal increase in specific IgE levels.[44] Despite the persistence of significant levels of specific IgE antibody levels, immunotherapy usually causes a reduction in 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.[45-48]

An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, has also been associated with immunotherapy. The properties of allergen-specific IgA have yet to be determined, and there is a weak correlation between the increase in allergen-specific IgG levels and immunotherapy's clinical efficacy.[30,49,50]

Immunotherapy might alter the affinity and specificity of allergen-specific IgG.[51,52] During the initial phase of ultrarush VIT, a change in IgG specificity (ie, a change in the set of epitopes dominantly recognized by IgG on wasp venom antigens) occurred concomitantly with early clinical tolerance and was seen within 12 hours of ultrarush VIT ($P < .001$).[51] 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 individuals.[52] This change in IgG specificity preceded the increase in IgG titers and was sustained for up to 6 months.[52]

Allergen-specific IgG induced from immunotherapy can block IgE-dependent histamine release and subsequent IgE-mediated antigen presentation to T cells.[53] This effect might be dependent on IgE, allergen concentration, and CD23, the low-affinity receptor for IgE.

Whereas 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.[37,53]

The relationship between these immunologic changes and immunotherapy efficacy is not completely understood.

ALLERGEN EXTRACTS

Summary Statement 6: 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 has 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.[2,18,54-56] 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.

United States–licensed extracts can be obtained in aqueous, glycerinated, lyophilized, and acetone-precipitated and alum-precipitated formulations. Some commonly used allergens are standardized. These include extracts for cat hair, cat pelt, *Dermatophagoides pteronyssinus*, *Dermatophagoides 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.[57] 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.

Most standardized extracts are labeled in BAU. Short ragweed potency units were originally based on the content of the major allergen Amb a 1. Ragweed potency is reported in FDA units and BAU. One FDA unit of Amb a 1 equals 1 μg of Amb a 1, and 350 units of Amb a 1/mL is equivalent to 100,000 BAU/mL. Cat extracts were also originally standardized based on the content of major allergen (Fel d 1), with 100,000 arbitrary units (AU) per milliliter containing between 10 to 19.9 FDA units of Fel d 1 per milliliter (1 FDA unit of Fel d 1 equals 2 to 4 μg of Fel d 1).[55,58,59] Subsequently, $ID_{50}EAL$ testing suggested that 100,000 AU/mL was equal to 10,000 BAU/mL.[60] Approximately 22% of individuals with cat allergy have specific IgE antibodies to cat albumin.[61] Cat pelt extracts have a greater amount of albumin than cat hair extracts.[60]

Dust mites were originally standardized in AU by means of inhibition radioimmunoassay (RIA), and subsequent $ID_{50}EAL$ testing indicated that the AU was bioequivalent to the BAU, and the original AU nomenclature was kept. Dust mite extracts are still labeled in AU.

Summary Statement 7: Nonstandardized extracts can vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Nonstandardized extracts are labeled as wt/vol, which expresses weight in grams per volume in milliliters; that is, a potency of 1:100 indicates that 1 g 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 with a particular wt/vol or PNU potency can have widely varying biologic activities.[62-64] Therefore they should not be considered equipotent.

Summary Statement 8: 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**

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. The major clinically relevant aeroallergens of North America are listed in Table III. Furthermore, nonrelevant allergens in such mixtures could act as sensitizers rather than as tolerogens.[65,66] The physician must therefore select only those aeroallergens for testing and treatment that are clinically relevant in a particular geographic area.

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, dog), insect (cockroach), and Hymenoptera venom source materials.

Cross-reactivity of allergen extract

Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

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. A summary of cross-reactivity patterns of the clinically relevant North American aeroallergens can be found in Fig 2. 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,[67] inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[68-75] Grasses in other subfamilies (eg, Bermuda, Bahia, and Johnson) show greater diversity and should be evaluated separately.[76-78] Bermuda and Johnson grasses are increasingly important in the South,

TABLE III. The major clinically relevant aeroallergens of North America*

- Tree pollen
  - Chinese elm *(Ulmus parvifolia)*†‡; Siberian elm *(Ulmus pumila)*†‡; American elm *(Ulmus Americana)*†‡
  - Red oak *(Quercus rubra)*†; White oak *(Quercus alba)*†
  - Paper birch *(Betula papyrifera)*
  - Alder *(Alnus rubra)*
  - Box elder *(Acer negundo)*†; Red maple *(Acer rubra)*†
  - Eastern cottonwood *(Populus deltoides)*
  - Sycamore *(Platanus occidentalis)*
  - White ash *(Fraxinus americana)*†; Olive *(Olea europaea)*†‡
  - Black walnut *(Juglans nigra)*
  - Mulberry *(Morus rubra)*
  - Mountain cedar *(Juniperus ashei)*
  - Pecan *(Carya illinoensis)*
- Grass pollen
  - Rye *(Lolium perenne)*§‖
  - Timothy *(Phleum pratense)*§‖
  - Meadow fescue *(Festuca elatior)*§‖
  - Bermuda *(Cynodon dactylon)*‖
  - Johnson *(Holcus halepensis)*
  - Bahia *(Paspalum notatum)*
- Weed pollen
  - Short ragweed *(Ambrosia artemisiifolia)*‖
  - English (narrow leaf) plantain *(Plantago lanceolata)*
  - Mugwort *(Artemisia vulgaris)*
  - Russian thistle *(Salsola kali)*
  - Burning bush *(Kochia scoparia)*
  - Sheet (red) sorrel *(Rumex asetosella)*
  - Red root pigweed *(Amaranthus retroflexus)*
- Indoor aeroallergens
  - Cat epithelium *(Felis domesticus)*‖
  - Dog epithelium *(Canis familiaris)*
  - Arthropods (domestic mites: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*)‖
  - Insects (German cockroach: *Blattella germanica*)
- Fungi
  - *Alternaria alternata*¶
  - *Cladosporium* (*C cladosporioides*, *C herbarum*)¶
  - *Penicillium* (*P chrysogenum*, *P expansum*)¶
  - *Aspergillus fumigatus*¶
  - *Epicoccum nigrum*, *Drechslera* or *Bipolaris* type (eg, *Helminthosporium solani*)¶

*Compiled and selected in collaboration with the AAAAI Immunotherapy Committee Allergen Subcommittee for the identification of 35 key allergens of North America.
†Extensive cross-reaction of species within the genus.
‡Apart from regional prevalence, they are limited to local sites with substantial stands of these trees.
§Extensively cross-react with one another and bluegrass, orchard, red top, and sweet vernal.
‖Allergens for which standardized extracts are commercially available.
¶Species that are widely distributed and clinically important.

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.[79-82] 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.[83-85] Significant cross-reactivity between Betulaceae pollens and oak of the Fagaceae family has been demonstrated with percutaneous skin testing.[75] RAST inhibition studies have shown cross-inhibition between oaks and other *Fagales* species.[86] IgE immunoblot inhibition experiments have demonstrated that the *Fagales* species might be strongly inhibited by birch species.[87] The use of one of the locally prevalent members (eg, birch and alder) should be adequate.[88]

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.[89,90] Maple and box elder trees are found throughout the United States, except for the arid southwest. Although in the same genus as maple, *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,[91,92] and there are allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.[93]

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.[94] Similarly, Chenopod-Amaranth families have wide ranges in the western regions but are present throughout North America.[95] Current information on cross-reactivity of these families is limited.[96-98] 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.[99] The use of a single Amaranth extract should be sufficient to cover this family.[100,101] Similarly, *Atriplex* species (eg, saltbushes and scales) show near identity, and use of a single member is adequate. 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,

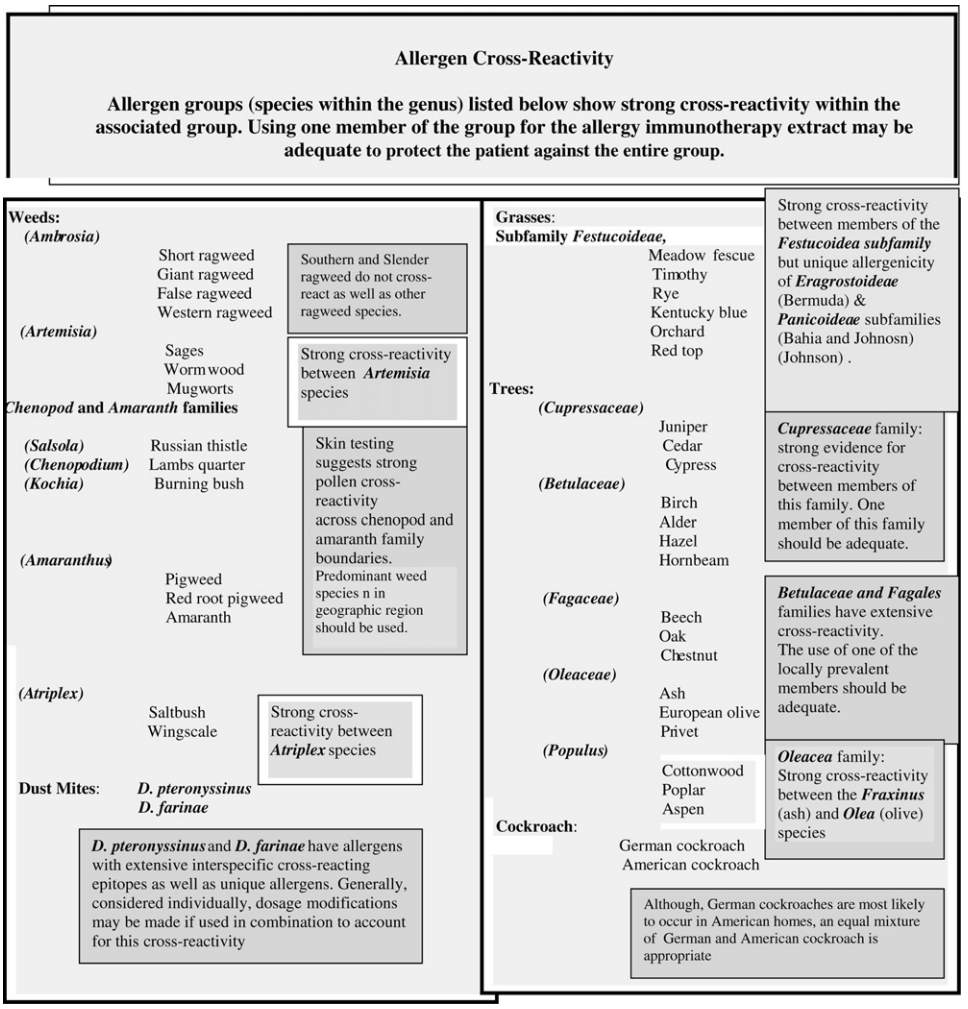


FIG 2. Patterns of allergen cross-reactivity.

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*).

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.[102,103] Stinging Hymenoptera insects occur throughout the United States; the fire ant is found only in Gulf Coast states, Texas, and some other southern and western states. Commercial venom extracts are available for some Hymenoptera species, except the fire ant, for which only whole-body extract is available.

EFFICACY OF IMMUNOTHERAPY

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity

Summary Statement 10: Immunotherapy is effective for 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.[104-111] Immunotherapy is effective for the treatment of allergic rhinitis[107] (including ocular symptoms[112,113]), allergic asthma,[104,109,111,114,115] and stinging insect hypersensitivity[108,116] and is effective in both adults and children.[117-124] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollens,[13,125-132] fungi,[133-138] animal allergens,[22,25,26,139-143] dust mite,[114,115,144-153] and cockroach.[154] There have been no controlled trials of fire ant whole-body extract, but it does appear to be effective in

TABLE IV. Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy

Outcome measure	House dust mite	Other allergens*†
Symptomatic improvement	2.7 (1.7-4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2-7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50)	5.5 (2.8-10.7)

Data are used with permission from Abramson et al.[104]
ND, Not done.
*Odds ratio (95% CI).
†Pollen, mold, or animal dander.

uncontrolled trials.[155-157] 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. A number of studies have also demonstrated a significant improvement in quality of life, as measured by using standardized questionnaires.[24,158-161] The magnitude of the effect depends on the outcome that is used (Table IV). For dust mite, the effect size ranges from a 2.7-fold improvement in symptoms to a 13.7-fold reduction in bronchial hyperresponsiveness. 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.[110] 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[107] and asthma[104,109,111] have been performed to deal with the issue of power. One review of 75 trials involving 3188 asthmatic patients found that, overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyperreactivity after immunotherapy, and it would have been necessary to treat 4 patients (95% CI, 3-5) with immunotherapy to avoid 1 deterioration in asthma symptoms and 5 (95% CI, 4-6) patients to avoid 1 requiring increased medication.[111] These meta-analyses strongly support the efficacy of allergen immunotherapy. Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued[13,162,163] and might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6,9,122,162-165] Allergen immunotherapy might also prevent the development of new allergen sensitivities in monosensitized patients.[120,166,167]

Food allergy, urticaria, and atopic dermatitis

Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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 use of allergen immunotherapy for individuals with the potential for IgE-mediated (anaphylaxis) reactions to foods should be regarded as investigational at this time.[168-171] There have been 2 investigational studies demonstrating efficacy in food hypersensitivity, the first using aqueous subcutaneous injections to peanut and the second using sublingual immunotherapy to hazelnut.[171-173]

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 a modified peanut extract is needed for clinical application of this method of treatment.[171] There is currently no FDA-approved formulation for sublingual immunotherapy, and this route of allergen immunotherapy is currently considered investigational at this time (see Summary Statement 73).

At the present time, there is not enough evidence to support food immunotherapy.

There is no evidence supporting the efficacy of immunotherapy for individuals with chronic urticaria, angioedema, or both.

There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[174-176] 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 ($P = .0379$) and topical corticosteroid use ($P = .0007$).[174]

The potential for benefit in symptoms related to oral allergy syndrome with the cross-reacting inhalant immunotherapy, which includes cross-reacting 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 subcutaneous immunotherapy directed against birch tree,[177] whereas another double-blind, double-dummy, placebo-controlled study comparing the effect of subcutaneous immunotherapy with sublingual immunotherapy 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, medication use, and decrease in IgE reactivity.[178] More investigation is required to substantiate the contention that benefits in oral symptoms will occur with immunotherapy.

Measures of efficacy

Summary Statement 12: 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. Objective measures, such as increase in allergen-specific IgG levels and decreased skin test reactivity, as measured by skin test titration, are changes generally associated with effective immunotherapy but, at present, are not practical for routine clinical use.[147] Nonquantitative skin testing or *in vitro* 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 are not very reliable given the strong placebo-like effect (Hawthorne effect) associated with any treatment. A more objective means for determining efficacy as validated in controlled clinical studies is the use of clinical symptom scores and the amount of medication required to control symptoms and maintain peak flow rates or pulmonary function tests within acceptable limits. Successful immunotherapy often results in a reduction in medication. Sequential measurement of disease-specific quality of life also might be helpful.

SAFETY OF IMMUNOTHERAPY

Reaction rates

Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Large local reactions associated with allergen immunotherapy are fairly common, with a frequency ranging from 26% to 86% of injections.[179] Two retrospective studies compared the effect of not adjusting immunotherapy dose based on large local reactions on the immunotherapy systemic reaction rate with dose-adjustment protocols.[179,180] There was a total of 12,464 injections administered with a dose-adjustment protocol in the 2 studies compared with 9542 injections administered with a no-dose-adjustment protocol. 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 for subsequent systemic reactions, 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 large local reactions, defined as 25 mm or larger, in patients who had experienced systemic reactions with age-, sex-, and allergen sensitivity–matched control subjects who had not had allergen immunotherapy systemic reactions found the rate of large local reactions was 4 times higher among the 258 patients who had subsequently experienced a systemic reaction compared with those who had never experienced a systemic reaction.[181] Patients who had experienced systemic reactions had 1573 large local reactions in 4460 visits (ie, 35.2% of visits) and 8081 injections (ie, 19.5% of injections) compared with the matched control group without systemic reactions who had 1388 large local reactions in 15,540 visits (8.9% per visit) and 26,259 injections (5.3% per injection; difference between groups, $P < .001$). Individual large local reactions were not predictive of future systemic reactions, but large local reactions preceded systemic reactions in approximately one third of the systemic reactions. These findings suggest that individuals with a greater frequency of large local reactions might be at greater risk for systemic reaction. Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy protocol modifications based on them are needed.

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

The prevalence of severe systemic reactions after allergen immunotherapy ranges from less than 1% of patients receiving conventional immunotherapy to greater than 36% of patients in some studies of patients receiving rush immunotherapy.[182,183]

In a recent survey of fatal and near-fatal reactions (NFRs) sent to physician members of the AAAAI, 273 of 646 respondents reported NFRs during the period of 1990-2001.[184]

The incidence of unconfirmed NFRs was 23 per year (5.4 events per million injections). Administration during the height of 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 angiotensin-converting enzyme 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 systemic reactions to subcutaneous immunotherapy over a 20-year period (1981-2000) during which 435,854 injections were administered to 4000 patients, 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.[185,186] In a prospective multicenter study there were 53 systemic reactions (0.3% of the doses) out of 17,526 administered doses in 18 (3.7%) of 423 patients.[187] 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 (21 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, there were 41 fatalities identified in the initial brief survey (20 directly reported and 17 with completed detailed questionnaire) from immunotherapy injections.[188] 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.[189,190] Therefore although severe systemic reactions to allergen immunotherapy are not common, serious systemic reactions (some fatal) can occur.

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

In the AAAAI survey of physician members on immunotherapy and skin testing, fatal reactions, and NFRs during the period of 1990-2001, 15 of the 17 fatalities had asthma, and in 9 patients asthma was considered the susceptibility factor that contributed to the fatal outcome.[188]

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.[184]

Administration during the peak pollen season (3 patients) and previous systemic reactions (4 patients) were cited as other contributing factors. Five fatalities occurred in outside medical facilities, and 2 fatalities occurred at home. No patients were receiving β-blockers; 1 patient was taking an angiotensin-converting enzyme inhibitor. In the most comprehensive evaluation of fatalities associated with allergen immunotherapy, from 1945-1987, there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[189] 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, with 73.3% of patients with an FEV_1 of less than 80% of predicted value experiencing 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 ($P < .0001$).[191] 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% of patients. These studies suggest that symptomatic asthma, severe asthma, or both might be a risk factor for immunotherapy.

In addition to symptomatic asthma and injections giving 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.[17] With the exception of dosing errors and 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 recent 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 or allergy symptom exacerbation, β-blocker use, change in health status (including pregnancy), or adverse reaction to previous allergen immunotherapy injection. The preinjection evaluation might also include a peak flow measurement to assess the airway function of asthmatic patients.

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 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

In a retrospective study the time to onset of a systemic reaction after an immunotherapy injection was less than 30 minutes in most cases.[189] A review of the literature indicates that 70% of systemic reactions occur within 30 minutes after an injection.[183] In the AAAAI 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.[184,188] 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.[190] 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 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.[192] In another prospective study 8% of systemic reactions occurred more than 2 hours after injection.[193]

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.[194]

Because most reactions that resulted from allergen immunotherapy occurred within 30 minutes after an injection, patients should remain in the physician's office for at least 30 minutes after receiving an injection, but longer waits are reasonable, as directed by the physician. In addition, patients who are at increased risk of a systemic reaction might need to carry injectable epinephrine. Such patients might also need to remain in the physician's office more than 30 minutes after an injection. 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.

β-Adrenergic blocking agents

Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

β-Blockade enhances pulmonary, cardiovascular, and dermatologic end-organ effects of mediators and increases mortality associated with experimental anaphylaxis induced by either immunologic or nonimmunologic mechanisms. Patients who are receiving β-adrenergic blocking medications might be at increased risk if they experience a systemic reaction to an allergen immunotherapy injection because the β-receptor blockade might attenuate the response to epinephrine.[195-202] Patients who are receiving β-blocking drugs were almost 9 times more likely to be hospitalized after an anaphylactoid reaction from radiocontrast media.[198] Although topical β-blockers have markedly less systemic β-antagonist effects than oral β-blockers, they still might exhibit some systemic β-antagonist effects. Whether topical β-blockers pose the same or a smaller risk than oral β-blockers in regard to the treatment of allergen immunotherapy–related systemic reactions is not known.

There have been very few studies that have examined the effect of β-blocker medications on allergen immunotherapy. A prospective 1-year study designed to determine whether patients taking β-blocker drugs were at increased risk of immunotherapy-induced systemic reactions found that there were 166 systemic reactions out of 56,105 injection visits in 3178 patients (68 were receiving a β-blocker).[203] The systemic reactions occurred in 144 (4.5%) patients, and only 1 of these patients was receiving a β-blocker medication. The authors calculated that by chance, 3.08 patients receiving the β-blocker medications drugs were expected to have had an systemic reaction and concluded that β-blocker medications did not increase the frequency of allergen immunotherapy systemic reactions ($P > .95$).

In another study of 1389 patients prescribed immunotherapy for Hymenoptera venom hypersensitivity who were followed for 34 months, there were 25 patients who received concomitant β-blocker medications.[204] Three (12%) of the 25 patients receiving β-blocker medications experienced systemic reactions during immunotherapy compared with 23 (16.7%) of 117 patients with cardiovascular disease not receiving β-blockers. Systemic reactions after a field sting or challenge occurred in 1 (14.3%) of 7 cardiovascular patients receiving β-blocker medications compared with 4 (13.8%) of 29 cardiovascular patients not receiving β-blocker medications. No severe reactions to immunotherapy or sting re-exposure were observed in patients receiving β-blockers medications.

Immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. In such cases, intravenous glucagon, which might reverse the refractory bronchospasm and hypotension by activating the adenyl cyclase directing and bypassing the β-adrenergic receptor, might be used if epinephrine has not been effective.[205,206] Prospective studies are necessary to clarify the magnitude of the risk of systemic reactions to allergens in patients who are receiving concomitant therapy with β-blockers, and a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy.

Contraindications

Summary Statement 18: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications

TABLE V. Actions to reduce the risk of anaphylaxis

- Assess the patient's general medical condition at the time of injection (eg, asthma exacerbation).
- Consider obtaining a PEFR before administration of the injection. If the PEFR is significantly less than the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.
- 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 with increased allergen sensitivity or those who have previously had a systemic reaction) might need to wait longer.
- Carefully evaluate any patient with a late reaction (eg, persistent large local reaction lasting >24 hours, systemic reaction occurring more than 30 minutes after the immunotherapy injection).
- 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.

PEFR, Peak expiratory flow rate measurement.

TABLE VI. Recommended equipment and medications to treat anaphylaxis

Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur. This should include at least the following equipment and medications:

- stethoscope and sphygmomanometer;
- tourniquet, syringes, hypodermic needles, and large-bore needles (14-gauge);
- aqueous epinephrine HCL 1:1000 wt/vol;
- equipment to administer oxygen by mask.
- intravenous fluid set-up;
- antihistamine for injection (second-line agents for anaphylaxis, but H_1 and H_2 antihistamines work better together than either one alone);
- corticosteroids for intravenous injection;
- vasopressor;
- equipment to maintain an airway appropriate for the supervising physician's expertise and skill.

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 venom hypersensitivity and cardiac disease being treated with β-blocker medications.

Reducing the risk of anaphylaxis to immunotherapy injections

Summary Statement 19: 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 extremely 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 or other health care professional appropriately trained in emergency treatment.

The 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. Epinephrine is the first-line treatment for anaphylaxis. 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.[12,207-213] It is important to administer epinephrine early in the management of anaphylaxis. 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 V and VI, respectively. Before allergen immunotherapy is chosen as a treatment, the physician should educate the patient about the benefits and risks of immunotherapy, as well as methods for minimizing risks. The patient also should be told that despite appropriate precautions, reactions might occur without warning signs or symptoms. Informed consent should include a discussion of the potential immunotherapy adverse reactions, and this discussion should be documented in the patient's medical record.

PATIENT SELECTION

Clinical indications

Summary Statement 20: Allergen immunotherapy should be considered for patients who have demonstrable

TABLE VII. Clinical indications for allergen immunotherapy

Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or both:
- symptoms of allergic rhinitis after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medications;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medication;
- coexisting allergic rhinitis and asthma;
- possible prevention of asthma in patients with allergic rhinitis

Symptoms of asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medication;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medications;
- coexisting allergic rhinitis and allergic asthma.

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);
- adults and children with a history of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.

evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic rhinitis.[107] Prospective, randomized, double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic asthma.[104,109,111]

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 proper identification and selection of component allergens on the basis of 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 (Table VII). The severity and duration of symptoms should also be considered in assessing the need for specific allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. In addition, specific allergen immunotherapy should be considered if the patient wishes to avoid long-term pharmacotherapy. Time lost from work, emergency department or physician's office visits, and responses to pharmacotherapy are important objective indicators of allergic disease severity.

Patients with allergic rhinitis who are unable to sleep because of symptoms or whose symptoms interfere with their work or school performance should be considered strong candidates for specific allergen immunotherapy. 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 considered. Unacceptable adverse effects of medications should also favor one's decision to initiate allergen immunotherapy. Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.[214]

Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued, and it might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6-9,122,162-165] These benefits of immunotherapy should be discussed with patients and might provide a clinical indication for immunotherapy for individual patients with allergic rhinitis.

Coexisting medical conditions should also be considered in the evaluation of a patient who might be a candidate for allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed with a combined aggressive regimen of allergen avoidance and pharmacotherapy and might also benefit from allergen immunotherapy.[215,216]

However, the patient's asthma must be stable before allergen immunotherapy is administered.[188,191]

Special precautions in patients with asthma

Summary Statement 21: 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 might be at increased risk for systemic reactions to immunotherapy injections.[182,188,191] Two surveys found that deaths from

immunotherapy were more common in symptomatic subjects with asthma.[188,189] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2,217]

Clinical indications for VIT

Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Systemic reactions to Hymenoptera stings, especially when associated with respiratory symptoms, cardiovascular symptoms, or both and positive skin test or *in vitro* test results for specific IgE antibodies, are a strong indication for allergen immunotherapy.[218] In the United States patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Several studies of patients with imported fire ant allergy have demonstrated the effectiveness of immunotherapy with whole-body extracts of fire ants.[155,156,219] 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. Patients younger than 16 years of age who present only with a cutaneous reaction to imported fire ant or Hymenoptera stings might not require immunotherapy.[218,220-222] In addition to allergen immunotherapy, patients with imported fire ant and Hymenoptera venom sensitivity should be instructed in how to best avoid insect stings, be prescribed epinephrine, and be taught how 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 the population that has not had a systemic reaction.[223] In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific IgE is recommended.[218] If the venom-specific IgE test result is also negative, it is recommended that the skin tests, venom-specific 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 IgE test result.[224] 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 re-stung. 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%).[225] 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 IgE test results who have had severe anaphylaxis to an insect sting.

Some patients who have negative venom skin test results and negative venom-specific IgE test results are reported to have had subsequent systemic reactions to stinging insects.[225-227] Controlled studies designed to evaluate the efficacy of immunotherapy in these patients have not been performed. There are very 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.[226] 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.

Summary Statement 23: 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.

ALLERGEN SELECTION AND HANDLING

Allergen selection

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

A careful history, noting environmental exposures and an understanding of the local and regional aerobiology of suspected allergens, such as pollen, fungi (mold), 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 skin or *in vitro* test results for specific IgE antibodies, provide good evidence that such exposures are relevant. Information concerning regional and local aerobiology is available on various Web sites or through the National Allergy Bureau at http://www.aaaai.org/nab. There are

no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma. 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 clinical history of an allergic disease.

There is no evidence to support the administration of immunotherapy based solely on results of specific *in vitro* 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.

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

The omission of clinically relevant allergens from an allergic patient's allergen immunotherapy extract contributes to decreased effectiveness of allergen immunotherapy. The 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 can make allergen immunotherapy less effective.

Knowledge of the total allergenic burden facing a patient and the realistic possibility of avoidance is important in determining whether allergen immunotherapy should be initiated. 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. Many individuals travel extensively for business or pleasure into different regions, and symptoms might worsen at these times. However, inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective. Determination of the significance of indoor allergens for a particular patient is harder because it is difficult to determine exposure in the home, school, and/or workplace. Historical factors, such as the presence of a furry animal in the home, a history of water damage and subsequent fungal exposure, or a history of insect infestation, might be helpful. However, such information is subjective and is often of uncertain reliability. In addition, some studies have demonstrated significant indoor levels of cat and dog allergen in households without pets[228] and significant levels of mouse allergen in suburban[229] and inner-city[230] homes 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 with increased asthma morbidity in inner-city children was found.[231] 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. Nevertheless, for most patients, determination of the clinical relevance of an allergen requires a strong correlation between the patient's history and evidence of allergen-specific IgE antibodies.

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted *in vitro* tests for specific IgE antibodies can also be used. **A**

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 the skin test results have demonstrated the efficacy of immunotherapy for relevant allergens.[25,26,112,130,134,135,140,141,149,154] 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 from skin testing in a highly sensitive individual.[232,233] In addition, skin tests might be difficult to perform in patients with dermatographism or atopic dermatitis. *In vitro* tests are particularly useful in such patients.

Studies indicate that skin testing is generally more sensitive than *in vitro* tests in detecting allergen-specific IgE.[234,235] Based on inhalation challenge test results, skin tests have shown specificity and sensitivity generally superior to those of *in vitro* tests. The comparability of skin tests and *in vitro* tests for specific IgE antibodies depends on the allergen being tested. For all of 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, prick testing is sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass[236] and cat,[237] are used. Intradermal/intracutaneous skin testing might be required for some allergen extracts. It is appropriate in some patients to use *in vitro* tests for specific IgE antibody as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. *In vitro* tests can also be used to define the allergens that should be used in allergen immunotherapy. If the allergy skin test result is negative and the *in vitro* test result is positive, a controlled challenge can be performed, and if the latter is positive, immunotherapy can be considered. 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 *in vitro* test results.

Specific allergens

Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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.[17,104,106,107,109] 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.[112,122] Because a particular pollen extract is a mixture of multiple glycoproteins, this suggests that mixing pollen allergens does not alter biologic activity.

Fungi (molds). Several studies with *Alternaria* and *Cladosporium* species suggest that allergen immunotherapy with fungi might be effective.[133-138] The allergen content of most mold extracts is highly variable.[238,239] However, there is evidence that proteolytic enzymes present in some mold extracts could digest other antigens, such as pollens, when combined in a mixture.[240] For this reason, it might be desirable to separate all pollen extracts from mold extracts when using mixtures.

Unfortunately, extracts for some potentially clinically important fungi are not available.[241] 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 distinguish 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.

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.

Because immunotherapy has been shown to be effective for cat[22,26,139-143,242] and dog,[25,141] the decision to include dog or cat allergen in an allergen immunotherapy extract should be considered in those circumstances in which there is exposure.

Dust mites and cockroach allergens. Crude house dust extract is generally an inappropriate substitute for house dust mite extract because the protein content measured is not restricted to dust mite allergens, nor does it necessarily guarantee inclusion of dust mite protein. Immunotherapy with standardized dust mite is generally more effective than that with crude house dust allergens. The house dust mites *D farinae* and *D 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, such as *Blomia tropicalis* and *Euroglyphus maynei*, partially cross-react with allergens from *Dermatophagoides* species. Only 50% of the projected amounts of each of the 2 house dust mites (*D pteronyssinus* and *D farinae*) need 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[144,147-149,151] 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. Dust mite hypersensitivity should particularly be considered in patients who have perennial symptoms exacerbated by a dusty environment at home, work, or both and periods of high humidity.

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. The major allergen of *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.[243] Immunotherapy with cockroach allergens is effective[154] and should 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.

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.[108,116,244] Efficacy has also been demonstrated with immunotherapy by using whole-body extracts of imported fire ants.[155,156]

Foods. Only a single clinical study accessing the efficacy and safety of subcutaneous immunotherapy with foods has been performed.[171,173] This study, which evaluated immunotherapy with peanut, found the incidence of systemic reactions, even during maintenance, was unacceptable. Thus there is no evidence to support the use of immunotherapy with food extracts. Currently, strict avoidance of the offending food is advisable, and subcutaneous immunotherapy for food allergy is not recommended.

Mixing of extracts

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Once the relevant allergens for each patient are identified, it is necessary to prepare a mixture that contains each of these allergens. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts. A number of 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 interactions between different types of allergens, when mixed, that could lead to degradation or unmasking of epitopes on exposure to proteolytic enzymes.

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Immunologic and 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.[71] 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 genera 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 the Allergen extract section, Fig 2, and the allergens and allergy diagnostic tests practice parameters).

Dose selection. Summary Statement 30: 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.[22-26,128,149,245] Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000 vol/vol).[28] A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy vaccine. Failure to do so might reduce the efficacy of immunotherapy. This occurs because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased (see the Immunotherapy schedules and doses section for further discussion and for recommended maintenance doses).

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as fungi (mold) and cockroach, from other extracts, such as pollens, is recommended. **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.[240,246,247] 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, and some weeds.[240,246,247] Cockroach had a similar deleterious effect on pollen extract potency.[246,248] Short ragweed appeared resistant to the effects of the proteolytic enzymes in one study,[240] 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.[247]

Dust mite extracts do not appear to have a deleterious effect on pollen extracts.[240,246,248] These studies suggest that pollen, dust mite, and cat extracts can be mixed together. 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. The evidence on mixing cockroach extract with other extracts is conflicting, and the clinical relevance of the changes is also unclear; therefore the clinician has the option of separating cockroach or not.

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 with lesser activities, such as pollen extracts.

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.

In this regard the number of separate injections that need to be given at each patient visit depends on whether all of the relevant extracts mixed into a single vial still deliver an optimal dose of each allergen. If mixing causes excessive dilution or if there are advantages to separating allergens into separate vials, then more than one vial might be necessary for successful immunotherapy.

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extracts are high-alert products that carry the risk for anaphylaxis. Policies, procedures, and processes intended for conventional drugs and medications might be highly 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 fatal anaphylactic reactions with allergenic products. 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. There are no reports of infection associated with allergen immunotherapy injections. Allergen vaccines are prepared by using sterile manufacturer's extracts and sterile diluents containing antibacterial constituents (usually phenol). A summary of the AAAAI/ACAAI/JCAAI proposed USP allergen immunotherapy extract preparation guidelines can be found in Table VIII.

TABLE VIII. AAAAI/ACAAI/JCAAI-proposed USP 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 below.*
   - 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.
2. **Physician responsibility**: A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in the preparation of immunotherapy using an aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files.
3. **Bacteriostasis**: Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if 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 the FDA-approved package insert 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 treatment with sanitizing agents containing alcohol and/or 70% isopropanol 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 the physical integrity of the vial.
10. **Labeling**: Immunotherapy vials are to be clearly labeled with the patient's name and 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.

*__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 media, such as from Valiteq (http://www.valiteq.com), 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.

Allergen immunotherapy extract handling

Storage. Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

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 a number of 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 extract, including reconstituted lyophilized extracts, should be stored at 4°C to minimize the rate of potency loss because storage at higher temperatures (eg, room temperature) can result in rapid deterioration.[249]

Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions (personal communication). These studies include actual shipments made by their carriers to places like

Phoenix in the summer and Alaska in the winter. 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.

Storing dilute extracts. Summary Statement 34a: More dilute concentrations of allergy immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than do more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: In determining the allergy vaccine expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of 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 allergen immunotherapy 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.[249,250]

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.[250] Phenol is a preservative added to extracts to prevent growth of microorganisms.

Phenol can denature proteins in allergen extracts.[251,252] Human serum albumin might protect against the deleterious effect of phenol on allergen extracts.[251] 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,[250,253] possibly through inhibition of the activity of proteolytic and glycosidic enzymes that are present in certain extracts. However, it is irritating when injected and should be diluted before beginning immunotherapy. Recommendations for extract stability are found in the manufacturers' product insert sheets. 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. The pain associated with glycerin increases in proportion to the glycerin concentration and injection volume, and the pain is proportional to the total injected dose of glycerin.[254] However, individual pain perception can vary substantially. Total glycerin doses of less than 0.05 mL rarely produce clinically important pain.

TABLE IX. Potency of selected manufacturer's extracts currently available

Extract	Potency
Cat hair and pelt	5000 and 10,000 BAU/mL
Dust mite	3000, 5000, 10,000, and 30,000 AU/mL
Bermuda grass	10,000 AU/mL
Short ragweed	1:10-1:20 wt/vol or 100,000 AU/mL
Other grasses*	10,000 and 100,000 BAU/mL
Other pollen	1:10 to 1:40 (wt/vol) or 10,000 PNU/mL
Molds	1:10 to 1:40 (wt/vol) or 20,000 to 100,000 PNU/mL

AU, Allergy unit; *BAU*, bioequivalent allergy unit; *PNU*, protein nitrogen unit.
*Perennial rye, Kentucky blue/June, timothy, sweet vernal, redtop, orchard, and meadow.

There have been few studies that have investigated the potency of dilutions of allergen extract mixture over time. Expiration dates for allergen extract dilutions are somewhat empiric and not strongly evidence based. A study undertaken by the AAAAI 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. Dust mite and cat at 1:10 and 1:100 vol/vol dilution were also stable in all conditions of storage over 12 months, as measured by an ELISA assay using 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.

IMMUNOTHERAPY SCHEDULES AND DOSES

Summary Statement 35: A customized individual 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 can be based on single or multiple allergens. **D**

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. Animal dander contains between 10 and 20 antigens,[255] house dust mites between 20 and 40 antigens,[256] and pollens between 30 and 50 antigens,[257,258] and fungal extract can contain as many as 80 antigens.[259]

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. This is designated as the patient's maintenance concentrate.

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. Standardized extracts are available with biologic potencies of 10,000 and 100,000 BAU for grasses; 5000 and 10,000 BAU for cat allergen; 5000, 10,000, or 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 wt/vol extracts (Table IX). 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.

Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

The highest concentration of an allergen extract mixture that is projected to be used as the therapeutically effective dose is called the maintenance concentrate. This should be prescribed individually for each patient by an allergist/immunologist. 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 individual manufacturer's extracts. Some patients might be unable to attain the projected therapeutically effective dose of the maintenance concentrate because of local reactions, systemic reactions, or both (eg, cat, 1000 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose]; see Table X for probable effective therapeutic dose range). Such patients might need weaker dilutions of their maintenance concentrate. Even so, 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 referred to as the maintenance dose. The consistent use of this nomenclature system is essential because errors in choosing the correct vial are a common cause of systemic reactions, especially when the patient transfers from one physician to another. Therefore it is important that standard terminology be adopted by all physicians who prescribe allergen immunotherapy.

Recommended doses

Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

The effective maintenance dose of immunotherapy for a particular patient must be individualized. To do this, the allergist/immunologist who prepares the allergen immunotherapy extract must balance the dose necessary to produce efficacy and the risk of reactions if such a dose is reached. The allergist/immunologist might need to prepare more than one maintenance concentrate to provide a therapeutic dose of each of the allergens for the polysensitized patient. Therapeutically effective doses for immunotherapy have been reported for some allergen extracts.[22,24,25,128,134,135,149,246,260,261] Effective doses have been determined for Hymenoptera venom, dust mite, cat allergen, dog, grass, and short ragweed (Table X).

Controlled studies demonstrate that the content of particular allergens in allergen immunotherapy extracts can be used to predict a therapeutic dose for those allergens, particularly when the extracts are standardized. For antigens 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. The therapeutically effective doses used in the most recent controlled clinical studies are the basis of the recommended dosage range of standardized extracts presented in Table X. 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 time that it is administered.[14]

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.[27] 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 risk of systemic reactions to immunotherapy injections with higher maintenance doses. The maintenance concentrate should be formulated to deliver a full therapeutic dose of each of its constituent components. However, some sensitive patients might not tolerate the targeted therapeutic dose, and their maintenance dose would be lower. Individuals 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 referred to as the maintenance dose.

Regardless of dose schedule, some patients are unable to progress to the predetermined maintenance dose because of large local or systemic reactions to the allergen

TABLE X. Probable effective dose range for allergen extracts US standardized units[a]

Antigen	Labeled potency or concentration[a,b]	Probable effective dose range
Dust mites: *D farinae* and *D pteronyssinus*[c]	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat[d]	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized[e]	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed[f]	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 μg of Amb a 1 1000-4000 AU Concentration of Amb a 1 is on the label of wt/vol extracts in FDA units[358]
Nonstandardized extract, dog[g]	1:10 to 1:100 wt/vol	15 μg of Can f 1
Nonstandardized extracts	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose

[a]Multiple studies have demonstrated that the efficacious dose for allergen immunotherapy is between 5 and 20 μg of the major allergen per injection. Only 2 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).

[b]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).

[c]There have been no dose-response studies with United States–licensed dust mite extracts, and dosing recommendations in AU value are extrapolated from published European studies that used aqueous[349] and alum-precipitated[149,151] extracts. 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.[149] The authors suggested the optimal maintenance dose was 7 μg of Der p 1. Corresponding doses were based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Extrapolating effective and safe doses in this manner might not be scientifically valid. *D farinae* and *D pteronyssinus* are similar in group 1 allergen content according to the FDA's current reference standards. 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*.

[d]The major cat allergen Fed d 1 is reported in FDA units, with 1 Fel d 1 unit equaling approximately 2 to 4 μg of Fel d 1.[55,58,59] The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 to 19.9 U/mL. One study demonstrated clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 dose in terms of decreased cat extract PD_{20}, titrated skin test results, and allergen-specific IgE and IgG levels.[350,351] In a recent study that investigated the efficacy in terms of immunologic changes of 3 doses of a United States–licensed cat extract (0.6, 3, and 15 μg) demonstrated that a significant effect on titrated skin prick test results, allergen-specific IgG4 levels, and $CD4^+$/IL-4 levels was only seen in the group treated with 15 μg of Fel d 1, although the 3-μg dose group did demonstrate a significant change in titrated skin test response and increase in cat-specific IgG4 levels.[22]

[e]There have been no dose-response studies with United States–licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,[130] alum-precipitated,[24,161] and calcium phosphate–precipitated grass pollen extracts.[352] One of these studies compared a dose of 2 μg with 20 μg of major timothy allergen (Phl p 5) and found clinical efficacy at both doses.[24] The efficacy was greater in the 20 μg of Phl p 5 dose, but the systemic reaction rate was also higher in the high-dose group. The package inserts for United States–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 BAU. Extrapolating effective and safe doses in this manner might not be scientifically valid. 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).

[f]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 suggested that 1 unit of Amb a 1 is equivalent to 1 μg of Amb a 1, and 350 Amb a 1 units/mL is equivalent to 100,000 BAU/mL.[60] The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2000 AU, with a range of 1000-4000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrated 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.[45] A ragweed dose-response study (0.6, 12.4, and 24.8 μg of Amb a 1) demonstrated efficacy, as measured by nasal challenge, at 12 and 24 μg of Amb a 1.[128] The efficacy of the 24-μg dose was not significantly better than the 12-μg dose, and the authors concluded that the optimal dose for ragweed extract was greater than 0.6 μg but not more than 12.4 μg of Amb a 1.

[g]Dog extracts are not standardized. However, one dose-response study with a United States–licensed acetone-precipitated dog extract investigated the efficacy of 3 doses (AP dog; Hollister-Stier, Spokane, Wash; 0.6, 3, and 15 μg) in terms of immunologic changes and found the dose of 15 μg of Can f 1 to be most efficacious.[25] 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 have assayed between 128 and 208 μg/mL (average Can f 1, 162 μg/mL [SD ± 26 μg/mL]; information provided by the extract manufacturer, Hollister-Stier).

immunotherapy extract. The evidence is not clear whether large local reactions are a potential risk for subsequent allergen immunotherapy systemic reactions.

Published studies do not indicate that an individual large local reaction is predictive of a subsequent systemic reaction.[179,180] However, one retrospective study found that individuals who have a history of repeated large local reactions (defined as >25 mm) might be at greater risk for a subsequent systemic reaction.[181]

The concept of highest tolerated dose does not apply for VIT, and all patients are expected to achieve the full recommended dose to achieve the necessary degree of protection. There are conflicting data over whether lower doses (50 μg) are less effective, but there are also data showing that 200 μg is more reliably effective.[245] In the case of VIT, patients are asked to tolerate more large local reactions to achieve the full dose, even though with inhalant immunotherapy the dose can be reduced for such large local reactions to minimize patient discomfort.

Effect of dilution on dose

Summary Statement 38: 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 vaccine, thereby limiting the ability to deliver a therapeutic effective dose for any given allergen.

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

Dilution from maintenance concentrate vaccine	Volume	Volume (mL)	Diluent volume (mL)	Final volume
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.

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 2000 BAU/mL, 2 mL of the manufacturer's extract (cat, 10,000 BAU/mL) can be added to 8 mL of diluent or 8 mL of other allergens, and the final concentration of cat will be 2000 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.

Dilutions of the maintenance concentrate

Summary Statement 39: 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 vol/vol 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, 1000 BAU or 100 BAU), but this system can be complicated if allergens with different potency units are used (eg, wt/vol, BAU, AU, or PNU) and make it difficult to easily interpret the vial label.

Instructions on how to prepare various allergen extracts 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.

Labeling dilutions

Summary Statement 40: 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, a number of 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 (vol/vol), a numbering system, a color-coding system, or an alphabetical system should be used. If this uniform labels 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.

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
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

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 3 and 4).

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 Appendix 2]).

Individualized treatment vials

Summary Statement 41: 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 (wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for 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). Labels on patient-specific vials can provide at least 2 patient identifiers (birth date and patient name), which would be consistent with the recommendations of the Joint Commission on Accreditation of Health Care Organizations National Patient Safety Goals: ''Goal 1: Improve the accuracy of patient identification by using at least two patient identifiers when providing care, treatment or services.''[5] 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 administration of the injection.[4,5]

In a survey of 1717 allergists endorsed by the AAAAI and JCAAI, 57% of the 476 respondents reported at least one wrong-patient injection, and 74% of the 473 respondents reported at least one wrong-dose injection.[4] 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 reasons why this might reduce incorrect injection errors. One reason was that patient-specific vials can be prepared in a quiet laboratory setting, which might provide substantially less distraction than the nurse in a room with a patient who is trying to concentrate only on drawing up the injection correctly. In addition, the specific components are mixed once with the preparation of individually prepared patient-labeled vials, whereas the mixing would be repeated on every injection visit if the allergen extract is withdrawn from different stock solutions, as it is in the off-the-board method. For safety reasons and to avoid cross-mixing of allergens removed from the manufacturer's extract, the mixing of antigens in the syringe (off the board) is not recommended.

Some allergists/immunologists prefer to administer immunotherapy doses drawn directly from a single stock dilution of individual allergens or common mixes (shared specific patient vials). In this way the immunotherapy dose is transferred to the patient without cross-contamination. If shared-patient (eg, mixed vespids and dust mite mix) vials are used, it is essential that policies and procedures are developed to verify that the correct dose from the correct vial is administered to the correct patient.

Starting doses

Summary Statement 42: The starting dose for build-up is usually a 1000- 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 slowly 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 1:1000 (vol/vol), although more diluted concentrations frequently are used for patients who are highly sensitive, as indicated by history or skin test reaction (see Appendix 3 for an example of a conventional immunotherapy schedule).

Frequency of build-up injections

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 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 2 times per week. 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 4 to 6 months, depending on the starting dilution and the occurrence of reactions. It is acceptable for patients to receive injections more frequently, provided there is adequate spacing between injections. The interval between injections is empiric but might be as short as 1 day without any increase in the occurrence of systemic reactions[262] if there is some urgency to achieve a maintenance dose (eg, allergy season is approaching) or for practical reasons (eg, patient's schedule). Alternatively, treatment schedules can be used that more rapidly achieve maintenance dosing. These cluster and rush dosing schedules are discussed in Summary Statements 47 through 49.

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 a number of 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).

Dose adjustments for systemic reactions

Summary Statement 44: 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 benefit/risk ratio justifies continuation of immunotherapy.

Reductions during periods of exacerbation of symptoms

Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Immunotherapy administered during periods of exacerbation of symptoms is considered a risk factor for immunotherapy.[17,184] Injections administered during periods when a patient is exposed to increased levels of allergen to which they are 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.[184] 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 sensitive, especially if their symptoms are poorly controlled.

Dose adjustments for late injections

Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

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 depends 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 Appendix 4 for an example of a dose-modification regimen for gaps in treatment).

Cluster schedules

Summary Statement 47: 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 (see Appendix 5).[22,26] 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. The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules.[145,263-266] The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.[267]

Rush schedules

Summary Statement 48: 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.[268] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.[191,269-272]

The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections over the course of 4 hours.[273] Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours.[274-276] 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 cluster[145,266] and rush[134,277] schedules.

Systemic reactions and rush schedules

Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

The advantages of rush immunotherapy come at a cost because there is an increased risk of local and systemic reactions. Systemic reaction rates have been reported to be

as high as 73% of patients, with the risk of such reactions reduced to 27% by premedication in one study.[272] Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing.[273]

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

Rush protocols for administration of Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions.[274-276,278,279]

Premedication and weekly immunotherapy

Summary Statement 50: Premedication can reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

There is concern that antihistamines taken before each injection with conventional immunotherapy might mask a minor reaction that would otherwise alert a physician to an impending systemic reaction. 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.[280] One study that compared terfenadine premedication with placebo premedication during rush VIT demonstrated greater clinical efficacy in the terfenadine-premedicated group in terms of subsequent responses to field stings or sting challenge.[281] There was also a significant difference in the systemic reaction rate between the 2 groups: 6 patients in the placebo-premedicated group had systemic reactions, whereas none of the patients in the terfenadine-premedicated group had systemic reactions ($P = .012$).

Unfortunately, patients might still have life-threatening anaphylaxis despite 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.

Premedication with cluster and rush immunotherapy

Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

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.[267] Premedication with a 3-day course of prednisone, an H_1 histamine receptor antagonist, and an H_2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.[272] In one study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on the safety and efficacy of rush immunotherapy, there was a 5-fold decrease in the risk of anaphylaxis in the group premedicated with omalizumab compared with the placebo premedication group.[282]

There are anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist, but there have been no published studies. Because the risk of a systemic reaction from rush VIT is relatively low, routine premedication before rush VIT is usually unnecessary.[274,276,278,279] In a study evaluating premedication with antihistamines and steroids for rush immunotherapy with imported fire ant venom, there was no statistically significant differences in the systemic reaction rates between the premedication and placebo premedication group (3.6% of the premedication group vs 6.7% of the placebo group, $P = .87$).[157]

Maintenance schedules

Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals 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 individuals might tolerate longer intervals between maintenance dose injections.

The interval between venom injections can be safely increased up to 8 weeks in some patients without loss of efficacy. 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.

Continuing care

Time course of improvement. Summary Statement 53: Clinical 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.[24,134,143,277] Improvement might not be observed for a number of reasons, including (1) failure to remove significant allergenic exposures (eg, a cat), (2) exposure to high levels of

allergen (eg, pollen or molds), (3) continued exposure to nonallergen triggers (eg, tobacco smoke), or (4) incomplete identification and treatment of clinically relevant allergens. 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 54: 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 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 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

The patient's response to immunotherapy should be evaluated on a regular basis. 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. 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.

There have been very 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 individuals.[283-285] However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported.[283,285] Nevertheless, systemic reactions to stings after discontinuing VIT were generally much milder than the pretreatment reactions and were rarely severe. Two studies did not find a difference in relapse rates between the patients treated for 3 years compared with those treated for 5 years,[283,286] but one of the studies noted that the small number of patients in the 3-year treatment group prevented them from making any conclusions about the risk of discontinuing treatment after 3 years.[283] However, one study found that patients who had experienced re-sting reactions after discontinuing VIT had received VIT for a significantly shorter duration (mean, 43.35 months) than those with continued protection (mean, 54.65 months; $P < .01$).[285] Another study reported that 5 years of VIT provided better immunologic and clinical outcomes than 2 to 4 years of treatment.[287]

Change in skin test reactivity did not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who experienced a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE.[286,288] Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment.[288] The relapse rate and the frequency of severe reactions were greater in patients who had a history of very severe reactions to stings before treatment, in patients who had systemic reactions during VIT (to a sting or a venom injection), in patients with honeybee allergy, and in those who had less than 5 years of treatment.

The duration of inhalant allergen immunotherapy efficacy has not been as extensively studied. Some studies have suggested 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 *(D pteronyssinus)* extract for 12 to 96 months.[14] 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.[13] There was a switch to placebo in half of 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. These studies demonstrate the uncertainty of the long-term benefit of inhalant immunotherapy after discontinuation.

Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained clinical remission after discontinuing inhalant immunotherapy, and 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 indication for continuation of immunotherapy can be found at http://www.aaaai.org or http://www.jcaai.org.

Documentation and record keeping. Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully 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 allergy immunotherapy and prescription forms can be found in the Appendix (Appendices 6-15), and these include examples of immunotherapy prescription and administration forms. These forms, along with examples of immunotherapy consent and instruction forms, can also be found at http://www.aaaai.org.

Injection techniques. Summary Statement 57: Allergen immunotherapy extract injections should be given using a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **C**

Immunotherapy should be given with a 26- to 27-gauge syringe with a half-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.[289-291]

If using shared specific patient vials (stock vials, such as mixed vespid or dust mite mix), a single dose should be drawn from each vial. Antigens from different vials should not be combined in a single syringe. Furthermore, extra care is needed to prevent using the wrong stock antigen.

Summary Statement 58: The injection should be given subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Each immunotherapy injection should be given in the posterior portion of the middle third of the upper 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.

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.

The syringe should be aspirated to check for blood return in the syringe before injecting. If blood is present, 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 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 syringe should be appropriately discarded. A fresh syringe and needle are necessary to determine whether a blood vessel has been entered.

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 could result in a local reaction.

LOCATION OF ALLERGEN IMMUNOTHERAPY ADMINISTRATION

Physician's office

Summary Statement 59: 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 to treat anaphylaxis should be in the immediate vicinity when immunotherapy injections are administered.

Summary Statement 60: 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.[292] 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.[184] 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 might be frequently necessary in the patient's immunotherapy schedule, as well as the patients total treatment program.

Other locations

Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **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.[292] The health care professional and staff 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, or allergy/asthma exacerbations at the time of allergen immunotherapy extract injection or poorly controlled asthma).

Appropriate adjustment of dose should be made as clinically indicated. The physician who prepared the patient's allergen immunotherapy extract should provide adequately labeled allergen immunotherapy extract vials, detailed directions regarding dosage schedule for build-up and maintenance, and instructions on adjustments that might be necessary under the following circumstances:

1. when providing patients with new vials;
2. during seasonal exposure to allergens that are in the patient's allergen vaccine, to which the patient is very sensitive, or both;
3. if the patient has missed injections; and
4. when reactions occur to the allergen immunotherapy extract.

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

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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 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 very 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 fully trained to administer the injection and to treat anaphylaxis if this should 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 supports (personnel, medications, supplies, and equipment) are more optimal for encouraging prompt recognition and treatment of anaphylaxis (Table V). 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.

Summary Statement 63: If a patient on 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for their immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extracts might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Patients often 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 brought from the previous physician (ie, an unchanged immunotherapy program) or one to be prepared by the current physician (ie, a new immunotherapy program).

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 full, clear, and detailed documentation of the patient's previous schedule and the contents of the allergen immunotherapy extract (see Appendices 7, 8, 11, 12, and 14 for examples of allergen immunotherapy prescription and administration forms and documentation guidelines for allergen immunotherapy forms). In addition, the patient's previous response to and compliance with this program 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 a schedule and the allergen immunotherapy extract, (2) the patient has shown significant improvement on this immunotherapy program, and (3) the contents of the allergen immunotherapy extract are appropriate for the area in which the patient is now living.

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, vaccine type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient's dose is not modified. This increased risk is due to the significant variability in content and potency of extracts and the variability in methods used by physicians to prepare the patient's maintenance concentrate and its dilutions. For example, the strength of a given concentration of nonstandardized extracts might vary significantly from vial to vial. The risk of systemic reactions in such a situation might be greater with nonstandardized extracts and allergen immunotherapy extracts that contain mixtures of allergens.

Therefore if the allergen immunotherapy extract is to be changed, the patient might need to be retested for specific IgE to the appropriate allergens 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 provided the interval of time since the last injection has not been too long. For lot changes from the same manufacturer, the physician can consider decreasing the dose by 50% to 90%. For changes in manufacturer and nonstandardized extracts, a greater decrease in dose might be necessary.

SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

Allergen immunotherapy in children

Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children

with allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Immunotherapy for children has been shown to be effective and often well tolerated,[137,242] although at least one study did not show efficacy.[293] 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.[294] In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (see the Patient selection section and Table VII). In recent studies children receiving allergen immunotherapy have demonstrated:

1. improvement in symptom control for asthma[117,119,121,122] and allergic rhinitis[118];
2. increased PC_{20} to histamine[121];
3. increased PC_{20} to cat and house dust mite allergens[121,149];
4. decreased risk of development of asthma[6,9,163-165];
5. decreased development of new sensitivities[120,166]; and
6. modification in release of mediators in children receiving immunotherapy that correlates with decreased clinical symptoms.[123]

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Although there is some disagreement about the role of allergen immunotherapy in children under the age of 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.[117,122] In children with allergic rhinitis, allergen immunotherapy might prevent the development of asthma.[6,9,163-165] However, allergen immunotherapy for inhalant allergens is usually not considered necessary in infants and toddlers because (1) there is 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 in pregnancy

Summary Statement 71: Allergen immunotherapy might be continued but is usually not initiated in the pregnant patient. **C**

The physician must be aware of the benefits and risks of immunotherapy in pregnant patients. The recommended precautions for prevention of adverse reactions are especially important in the pregnant patient. Allergen immunotherapy is effective in the pregnant patient. Thus allergen immunotherapy maintenance doses can be continued during pregnancy. Allergen immunotherapy is usually not initiated during pregnancy because of risks associated with systemic reactions and their treatment (ie, spontaneous abortion, premature labor, or fetal hypoxia). 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, and the patient is maintained on the dose that she is receiving at that time.

Immunotherapy in the elderly patient

Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy might be considered in the treatment of the elderly patient, but the benefit/risk assessment must be evaluated carefully in this population. Older 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. However, elderly patients may also benefit from allergen immunotherapy and age alone should not preclude the consideration of allergen immunotherapy.[295]

Immunotherapy in patients with immunodeficiency and autoimmune disorders

Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with immunodeficiency or autoimmune disorders. Therefore the decision to begin immunotherapy in patients with major humoral or cellular immune defects must be individualized. Concern about the increased risk of immunotherapy in such patients is largely hypothetical.

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

ALTERNATIVE ROUTES OF IMMUNOTHERAPY

Sublingual and oral immunotherapy

Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be

effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no FDA-approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **B**

Alternative routes of administration of allergen immunotherapy are ''a viable alternative to parenteral injection therapy'' in some cases.[106,296] Studies of oral immunotherapy have provided conflicting results for ragweed,[297] birch,[298] and cat[299] immunotherapy. The present dosage of oral immunotherapy extract is 20 to 200 times the parenteral injected dosage, which requires a cost assessment for this type of therapy. Furthermore, adverse effects have included gastrointestinal and oral reactions (50% in 1 study) that might preclude home therapy. Oral immunotherapy should be considered investigational at this time.

Optimal-dose (high-dose) sublingual swallow immunotherapy is effective in adults and children.[300-304] In a study of 855 patients with grass pollen allergy and allergic rhinitis randomized to placebo or one of 3 grass tablet doses, there was a significant reduction in symptom and medication scores in the highest-dose subgroup, who were treated for at least 8 weeks before the grass pollen season, compared with the placebo group (symptoms, 21%, $P = .0020$; medication use, 29%, $P = .0120$).[303]

Sublingual allergen studies have evaluated house dust, olive pollen, grass pollen, ragweed, birch, cat, latex, *Alternaria* species, and *Parietaria judaica*.[305-313] Sublingual immunotherapy has been shown to be effective in patients sensitized to 2 non–cross-reacting allergens, grass and birch.[314] It has been noted that the allergen is not degraded by saliva and that there is no direct sublingual absorption of allergen. Radiolabeled allergen has been detected after 48 hours in the sublingual region.[315,316] Alternative protocols, such as rush and ultra-rush (20 minutes) sublingual swallow[307,316,318] and no induction (build-up) phase,[301,303,317,319,320] have been studied. Several studies have suggested a relationship between dose and efficacy with sublingual immunotherapy,[303,310,321] but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. The majority of sublingual studies have demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both, but approximately 35% of the randomized, double-blind, placebo-controlled studies did not demonstrate efficacy in either parameter during the first year of treatment.[322] Further studies are needed to confirm the optimal dose for sublingual immunotherapy.

One of the potential advantages of sublingual immunotherapy is that it appears to be safe, even at very high doses (up to 500 times the usual monthly subcutaneous dose), and to be associated with a lower incidence of serious side effects.[310,320,323] This appears to apply to young children (<5 years), for whom there are prospective safety data[324,325] and a postmarketing survey.[326]



FIG 3. Sample of labels for allergen immunotherapy extract vials.

There have been no SLIT-related fatalities, but there have been 3 case reports of anaphylaxis caused by sublingual immunotherapy. One patient with latex hypersensitivity had anaphylactic shock 20 minutes after reaching the maximal dose on the fourth day of latex rush sublingual rush immunotherapy.[327]

The other 2 reported cases of SLIT anaphylaxis involved patients treated with multiple inhalant allergens. In one case a patient with allergic rhinitis and asthma who was prescribed a sublingual immunotherapy extract composed of multiple non–cross-reacting allergens (*Alternaria* species, dog, cat, ragweed mix, weed mix, and grass mix)[328] had generalized pruritis, followed by angioedema, shortness of breath, and dizziness, within a few minutes of administering 6 drops of the 1:100 vol/vol dilution on the third day of treatment. This episode was preceded by a milder systemic reaction the previous day (generalized pruritis). In the other case, a 13-year-old girl with allergic rhinitis and asthma had swelling of her lower lip 3 minutes after pollen drops, high fever, chest pain, nausea, and abdominal pain.[329] She was treated in the emergency department for anaphylaxis and hospitalized for observation. The reaction occurred 1 month after she had reached the maintenance dose during the peak of the spring season.

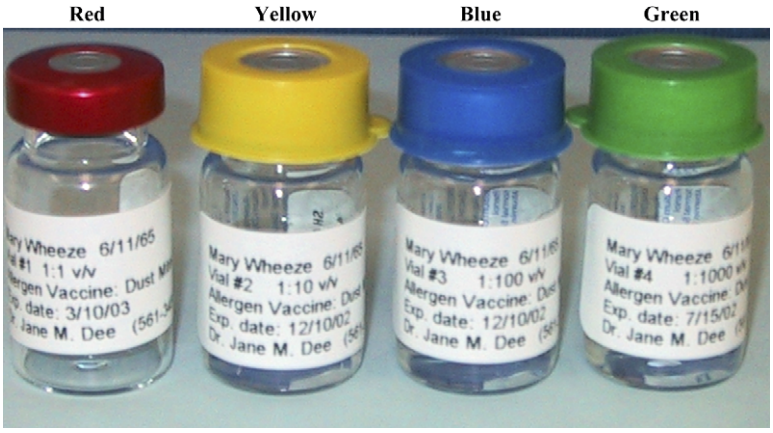


FIG 4. Sample set of color-coded vials of allergen vaccine.

There is currently no FDA-approved formulation for sublingual immunotherapy in the United States at this time, and this modality should be considered investigational. Current investigation of sublingual immunotherapy should not be confused with low-dose sublingual immunotherapy based on provocation neutralization testing or Rinkel-type skin testing.

Intranasal immunotherapy

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Based on controlled, well-designed studies, intranasal immunotherapy has been shown to improve the nasal symptoms of rhinitis.[330] Intranasal dry powder extract immunotherapy has been studied in grass,[330] birch,[331] *P judaica*,[332-334] and house dust mite[335] allergy. Clinical efficacy was noted in all of these studies. Nasal reactivity to allergen challenge was reduced, and only minor side effects were noted in 2 of the above studies. A 3-year study with *P judaica* reported to provide persistent benefits for up to 12 months after conclusion of allergen immunotherapy.[333] Local administration of nasal allergen in an aqueous solution for immunotherapy might be limited by the local side effects. Further studies in both pediatric and adult groups are needed. In human studies the antigen has been noted to appear in the serum within 15 to 30 minutes of administration, with a peak level occurring within 2 to 3 hours.[315] Some allergens have been reported to be retained in the nasal mucosa for up to 48 hours after administration. Intranasal immunotherapy is not currently available in the United States but has gained some acceptance in other parts of the world.

Immunotherapy techniques that are not recommended

Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

Low-dose regimens, including coseasonal low-dose immunotherapy for aeroallergens and the Rinkel low-dose titration techniques, are not effective.[27,28] Immunotherapy based on provocation–neutralization testing with food and aeroallergens and enzyme-potentiated desensitization is not effective.[336]

FUTURE TRENDS IN IMMUNOTHERAPY

Therapy with aeroallergen extracts will become more uniform (as is the current practice for insect venoms) as greater numbers of biologically standardized allergen extracts become available. The actual number of commercially available allergen extracts will be reduced based on consensus agreements about the regional prevalence of aeroallergens, their cross-allergenicity, and the relevance of their effect on human health in specific locales. Novel routes for more effective, convenient, and safer allergen immunotherapy are being investigated throughout the world.

For example, the sublingual route of administering allergen immunotherapy has been studied extensively in Europe. A meta-analysis confirmed its clinical effectiveness in allergic rhinitis,[302] and it has been reported to be effective in asthma as well.[337] Sublingual immunotherapy appears to have a very low risk of serious life-threatening systemic side effects, which might allow for home administration.[324,338] In some studies the clinical benefits of sublingual immunotherapy were not significant until the second year of treatment,[306,339] and comparisons suggest that the magnitude of the clinical benefit of sublingual immunotherapy might not be as great as that of subcutaneous immunotherapy.[311]

Trials with non–IgE-binding peptides containing T-cell stimulating peptides have been reported.[340] Site-directed mutagenesis has produced allergens with decreased IgE-binding capacity without decreased T-cell responses.[341,342]

Immunostimulatory sequences mimicking bacterial and viral DNA have been prepared that stimulate the innate immune system to direct T-cell responses toward

T_H1 rather than T_H2 phenotypes.[343] The results of clinical trials with a conjugate of the immunostimulatory sequence to the major allergen of ragweed, Amb a 1 (AIC), have been reported.[34,343] In a double-blind, placebo-controlled study of 25 adults who received 6 weekly injections of the AIC or placebo vaccine before ragweed season, the AIC group had better peak-season rhinitis scores on the visual analog scale ($P = .006$), peak-season daily nasal symptom diary scores ($P = .02$), and midseason overall quality-of-life scores ($P = .05$) than the placebo group during the first ragweed season, and this effect was observed in the subsequent ragweed season.[344]

Humanized anti-IgE mAb has been shown to have clinical effects in both allergic rhinitis and asthma.[345-348] Theoretically, this new therapeutic modality could be used as protective cover for clinical applications of rapid forms of immunotherapy. It is possible that preadministration of anti-IgE could provide a more effective protective effect than premedication with antihistamines and therefore permit a rush allergen immunotherapeutic regimen with reduced risk of serious systemic reactions.[282]

AUTHOR'S 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 2 systemic reaction grading systems (the European Academy of Allergy and Clinical Immunology's grading of severity for systemic side effects and the Portnoy method for numeric grading of reactions to allergen immunotherapy) can be found in the Appendix section. These forms can also be found along with examples of immunotherapy instruction and consent forms, preinjection health questionnaires, and indications for beginning and continuing immunotherapy forms at www.aaaai.org.

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352. Leynadier F, Banoun L, Dollois B, Terrier P, Epstein M, Guinnepain MT, 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.

APPENDIX 1. American College of Medical Quality's policy on the development and use of practice parameters for medical quality decision-making[1]

Practice parameters are strategies for patient management developed to assist health care professionals in clinical decision making. Practice parameters include standards, guidelines, and other patient management strategies. Standards are accepted principles for patient management. Guidelines are recommendations for patient management that identify a particular management strategy or a range of management strategies. Other strategies for patient management include practice policies and practice options. Practice parameters are to be used as screening tools to identify possible deviations from the applicable standards of care. Such parameters are not to be used as absolute standards or to profile or report on health care personnel. Parameters are designed to trigger a process in which possible deviations from the standard of care are identified as outlier practice patterns. Once a deviation from the parameter is identified, such a deviation should be referred to the appropriate qualified physician advisor or reviewer for a determination of medical necessity that conforms to the applicable standard of care. Parameters used in the day-to-day practice of clinical medicine should be clinically relevant. They should not be considered as substitutes for the standard of care but might contribute to its formulation.

Practice parameters must be developed, designed, and implemented only by board-certified, clinically practicing, specialty-matched physician advisors/reviewers with unrestricted medical licenses. Qualified nonphysicians might participate in the development of these parameters only in the areas in which their clinical expertise based on the standard of care is applicable. The health care personnel who develop these parameters should sign their names and date the final version as evidence of their participation and support. Practice parameters must be based on sound scientific research findings, professional literature, clinical experience and appropriate well-recognized methodologies and reflect professionally recognized national standards of care practiced in the clinical community of medicine. The development procedures followed, the participants involved, the evidence used, the assumptions and rationales accepted, and the analytic methods used should be meticulously documented, described, and made publicly available for national peer review. Parameters should be updated as needed.

Practice parameters are used as tools to enhance medical decision making but not as replacements for physicians' clinical judgment. They can be considered as means to enhance the performance of clinical and review personnel but not to replace them. It is below the standard of care of the medical review process to substitute qualified physician reviewer experts with unqualified reviewers who are using parameters.

APPENDIX 2. Examples of possible abbreviations for allergen immunotherapy extract 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

APPENDIX 3. 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

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

APPENDIX 4. Example of immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals (modification of the AAAAI skin testing and immunotherapy consent and instruction forms: immunotherapy administration instruction form, which can be found at http://www.aaaai.org)

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

- Up to 7 days, continue as scheduled (ie, if on weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection).
- Eight to 13 days after missed scheduled injection; repeat previous dose.
- Fourteen to 21 days after missed scheduled injection; reduce dose 25%.
- Twenty-one to 28 days after missed scheduled injection; reduce previous dose 50%.

Then increase dose each injection visit as directed on the immunotherapy schedule until therapeutic maintenance dose is reached.

This suggested approach to modification of doses of allergen immunotherapy because of gaps between treatment during the build-up phase is not based on retrospective or prospective published evidence, but it is presented as a sample for your consideration. The individual physician should use this or a similar protocol as a standard operating procedure for the specific clinical setting. A similar dose-reduction protocol should be developed for gaps in maintenance immunotherapy.

APPENDIX 5. Example of a cluster immunotherapy schedule[22,26]

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

APPENDIX 6. Recommended documentation for allergen immunotherapy prescription forms

The purpose of the allergen immunotherapy prescription form is to define the contents of the allergen immunotherapy extract in enough detail that it could be precisely duplicated. The following information should be on an immunotherapy prescription form:

Patient information:

- Patient name, patient number (if applicable), birth date, telephone number, and picture (if available) should be included.

Preparation information:

- Name of person and signature preparing the allergen immunotherapy extract should be included.
- Date of preparation should be recorded.
- Bottle name should be included (eg, trees and grass). If abbreviations are used, a 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 should be included.
- Volume of manufacturer's extract to add to achieve the projected effective concentration should be included. 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) should be included.
- Extract manufacturer should be included.
- Lot number should be included.
- Expiration date should be recorded and should not exceed the expiration date of any of the individual components.

APPENDIX 7. Allergen immunotherapy extract prescription 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:

_____
_____
_____
_____

_____ ____/____/____
Prescribing Physician Signature Date

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

APPENDIX 8. Maintenance concentrate prescription form

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: 6/10/06

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial **4** from Vial **1** on **8/30/06** Expiration date: **10/15/06**
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	Short ragweed	1:20 w/v G (150 Amb a1)	0.5ml	Greer	12345	1/01/08
2	Amaranthus Retroflexus	1:10 w/v G	0.5ml	H-S	6789	2/07/08
3	Ash	1:10 w/v G	0.5ml	Center	3333	3/17/08
4	Cat	10,000 BAU/ml G	2.00ml	ALO	9898	2/27/08
5	Timothy Grass	100,000 BAU/ml G	0.4ml	ALK	56789	7/09/08
6	Johnson Grass	1:10 w/v G	0.5ml	Greer	2434	7/20/08
7						
8						
9						
10						
Diluent	HSA		0.6ml	ALK	68597	12/08
Total Volume			5.00 ml			6/10/07

*** Components of mixes listed on a separate sheet**
**** Assumes 0.5 ml injection as target maintenance dose**

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

Specific Instructions:

_____

_____

Prescribing Physician Signature

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

APPENDIX 9. Labels for allergen immunotherapy extracts

Each vial of allergen immunotherapy extract should be labeled in a way that permits easy identification. Each label should include the following information (example in Figs 3 and 4):

- Appropriate patient identifiers might include the patient's name, patient's number, patient's picture, and birth date.
- The contents of the allergen immunotherapy extract in a general way should be included. The detail with which this can be identified depends on the size of the label and the number of allergens in the vial. Ideally, allergens should be identified as trees, grasses, weeds, mold, dust mite, cockroach, cat, and dog. Because of space limitations, it might be necessary to abbreviate the antigens (eg, T, G, W, M, DM, Cr, C, and D respectively [see Appendix 2]). A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate (vol/vol) should be recorded. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- The expiration date should be included.

APPENDIX 10. Allergen immunotherapy administration form recommended documentation

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

Patient information:

- Patient's name, date of birth, telephone number, and patient's picture (optional but helpful).

Allergen immunotherapy extract information:

- Allergen immunotherapy extract name and dilution from maintenance in vol/vol bottle letter (eg, A and B), bottle color, or number, if used.
- Expiration date of all dilutions.

Administration information in separate columns:

- Date of injection.
- Arm administered injection, which might facilitate determination of exact cause of local reaction.
- Projected build-up schedule.
- Delivered volume reported in milliliters.
- Description of any reactions. The details of any treatment given in response to a reaction would be documented elsewhere in the medical record and referenced on the administration form.
- *Patient's health before injection*. This can be performed through a verbal or written interview of the patient before administering the immunotherapy injection. The patient should be questioned about increased asthma or allergy symptoms, β-blocker use, change in health status (including pregnancy and recent infections), or an adverse reaction to a previous injection (including delayed large local reactions persisting through the next day). Patients with significant systemic illness generally should not receive an injection.
- *Antihistamine use*. Antihistamines are frequently a component of an allergy medication regimen, and it would be important to note whether a patient is taking an antihistamine on the day he or she receives his or her immunotherapy injection. For consistency in interpretation of reactions, it might be desirable for a patient to either take or avoid antihistamines on a regular basis on the days he or she receives immunotherapy. The physician should note on the form whether he or she recommends the patient consistently take an antihistamine on immunotherapy treatment days.
- *Peak flow reading*. Consider obtaining a peak expiratory flow rate measurement before administering an immunotherapy injection to asthmatic patients. Poorly controlled asthma is considered a risk factor for immunotherapy. Obtaining a peak expiratory flow rate measurement before the immunotherapy injection might help identify patients with symptomatic asthma. The patient's baseline peak expiratory flow rate should be provided on the form as a reference. Health care professionals administering immunotherapy injections should be provided with specific guidelines about the peak expiratory flow rate measurement for when an immunotherapy injection should be withheld and the patient referred for clinical evaluation.
- **Baseline blood pressure**. It might be useful to record the patient's blood pressure as a baseline for future reference.

APPENDIX 11. Allergen immunotherapy administration form

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 allergy or 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

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

Date to reorder: __/__/__

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 allergy or 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**	

APPENDIX 12. 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: _____
_____
Staff action taken (if any): _____

APPENDIX 13. 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.

APPENDIX 14. Allergen immunotherapy systemic reaction/anaphylaxis 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
__Epinephrine IM into 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	

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:
_____
_____
_____
_____

Clinical impression: True SR Questionable SR No SR

Systemic reaction severity classification: EAACI_____ **Portnoy** _____

Dosage adjustment? _____

Signatures_____ **RN** _____**MD/DO**

APPENDIX 15. Grading severity of allergen immunotherapy reactions: Two methods

1. **The European Academy of Allergy and Clinical Immunology grading of severity for systemic side effects***

Classification of systemic reactions

0 = No symptoms or nonspecific symptoms

I = Mild systemic reactions: symptoms—localized urticaria, rhinitis, or mild asthma (PF <20% decrease from baseline).

II = Moderate systemic reaction: symptoms—slow onset (>15 minutes) of generalized urticaria, moderate asthma, or both (PF < 40% decrease from baseline).

III = Severe (non–life-threatening) systemic reactions: symptoms—rapid onset (<15 minutes) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).

IV = Anaphylactic shock: symptoms—immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, and hypotension, for example.

2. **Portnoy method for numeric grading of reactions to allergen immunotherapy†**

Local

0+ = No significant reaction or small area of erythema less than the size of a half dollar without swelling or wheal formation

1+ = Erythema greater than the size of a half dollar, swelling or wheal formation, or both

Systemic

2+ = Systemic reactions: cutaneous only—might consist of a cutaneous eruption, such as urticaria

3+ = Systemic reaction: generalized pruritus, sneezing, or both—might consist of increased allergy symptoms, such as nasal congestion, sneezing, or pruritus, especially in the mouth or throat

4+ = Systemic reaction: pulmonary—consists of wheezing, shortness of breath, and tightness. Might be associated with decreased pulmonary function tests

5+ = Systemic reaction: anaphylaxis—a sensation of not feeling right is a frequent prelude; might consist of hypotension, laryngeal edema, severe wheezing, and cramping

6+ = Cardiopulmonary arrest

PF, Peak expiratory flow.

*Subcutaneous immunotherapy. Allergy 2006;61(suppl 82):5-13.

†Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80.

Allergen immunotherapy: A practice parameter second update

Supplement Editor: **Linda Cox, MD**
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These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology.

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the "Allergen immunotherapy: a practice parameter second 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 and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
5. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
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11. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999;83(suppl): S665–S700.
12. Diagnosis and management of urticaria: a practice parameter. Ann Allergy 2000;85(suppl):S521-S544.
13. Allergen immunotherapy: a practice parameter. Ann Allergy 2003;90(suppl):SI-S540.
14. Symptom severity assessment of allergic rhinitis: part I. Ann Allergy 2003;91:105-14.
15. Disease management of atopic dermatitis: an updated practice parameter. Ann Allergy 2004;93(suppl): S1-S21.
16. Stinging insect hypersensitivity: a practice parameter update. J Allergy Clin Immunol 2004;114:869-86.
17. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol 2005;115(suppl):S483-S523.

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22. Contact dermatitis: a practice parameter. Ann Allergy Asthma Immunol 2006;97(suppl 2):S1-S38.

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

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Allergen immunotherapy: A practice parameter second update

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PREFACE

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

The objective of ''Allergen immunotherapy: A practice parameter second update'' is to optimize the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. 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's ''Policy on development and use of practice parameters for medical quality decision-making'' (Appendix 1).[1]

This document builds on the previous Joint Task Force document, ''Allergen immunotherapy: a practice parameter'' published in the *Annals of Allergy, Asthma and Immunology* in 2003.[2] The updated practice parameters draft was prepared by Drs Linda Cox, James Li, Hal Nelson, and Richard Lockey. The Joint Task Force reworked the initial draft into a working draft of the document. The project was exclusively funded by the 3 allergy and immunology societies noted above.

In preparation for the 2003 ''Allergen immunotherapy: a practice parameter'' and the second update, a comprehensive search of the medical literature was conducted with various search engines, including PubMed; *immunotherapy*, *allergic rhinitis*, *asthma*, *stinging insect allergy*, and related search terms were used. 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 second update'' was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the ACAAI, AAAAI, and JCAAI. In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for review and comments from members of the sponsoring organizations. 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 allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. This document also contains recommendations for the safe practice of allergen immunotherapy, including specific recommendations on the prevention and management of 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 or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. Symptoms of allergic conjunctivitis (eg, itchy watery eyes) are often considered part of allergic rhinitis or are included in the diagnosis of rhinoconjunctivitis. Particularly good candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures, those in whom it is important to avoid the potential adverse effects of medications, and those who wish to reduce the long-term use of medications. Immunotherapy is recommended for patients with a history of systemic reaction to Hymenoptera stings and specific IgE antibodies to Hymenoptera venom.

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.[3]

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. 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 *maintenance concentrate* should be used to identify the allergen immunotherapy extract that contains a therapeutic effective dose for each of its individual constituents (see the Immunotherapy schedules and doses section).

The term *manufacturer's extract* refers to the allergy extract purchased from the manufacturer. The terms *stock*, *full-strength*, and *concentrate* are ambiguous and should not be used. 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).

Allergen immunotherapy is effective when appropriate doses of the allergens are administered. ''Allergen immunotherapy: A practice parameter'' recommends that vials of allergen immunotherapy extracts should be prepared individually for each patient to enhance the individualization of therapy, reduce the risk of allergen cross-contamination, and reduce the risk of error in administration.[4,5] This parameter recommends the use of standardized allergen immunotherapy prescription and administration forms to improve the safety, uniformity, and standardization of allergen immunotherapy practice.[4,5] The suggested forms are found in the Appendix (Appendices 7, 8, 11, 12, and 14) and in the members' section of the www.aaaai.org Web site. The routine use of these standardized forms should improve the quality of immunotherapy practice.

Members' feedback comments on the recommended allergen extract dilution dating in the 2003 ''Allergen immunotherapy: A practice parameter'' led to an allergen immunotherapy extract dilution stability study designed by the AAAAI Immunotherapy and Allergy Diagnostics Committee and funded by the AAAAI Board of Directors. The study was designed to investigate the effect of time, temperature, and dilution of standardized allergen extract potency, and the results of this study were considered in this update.

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 3 years after publication. Requests for information about or an interpretation of these practice parameters should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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. Allergen immunotherapy

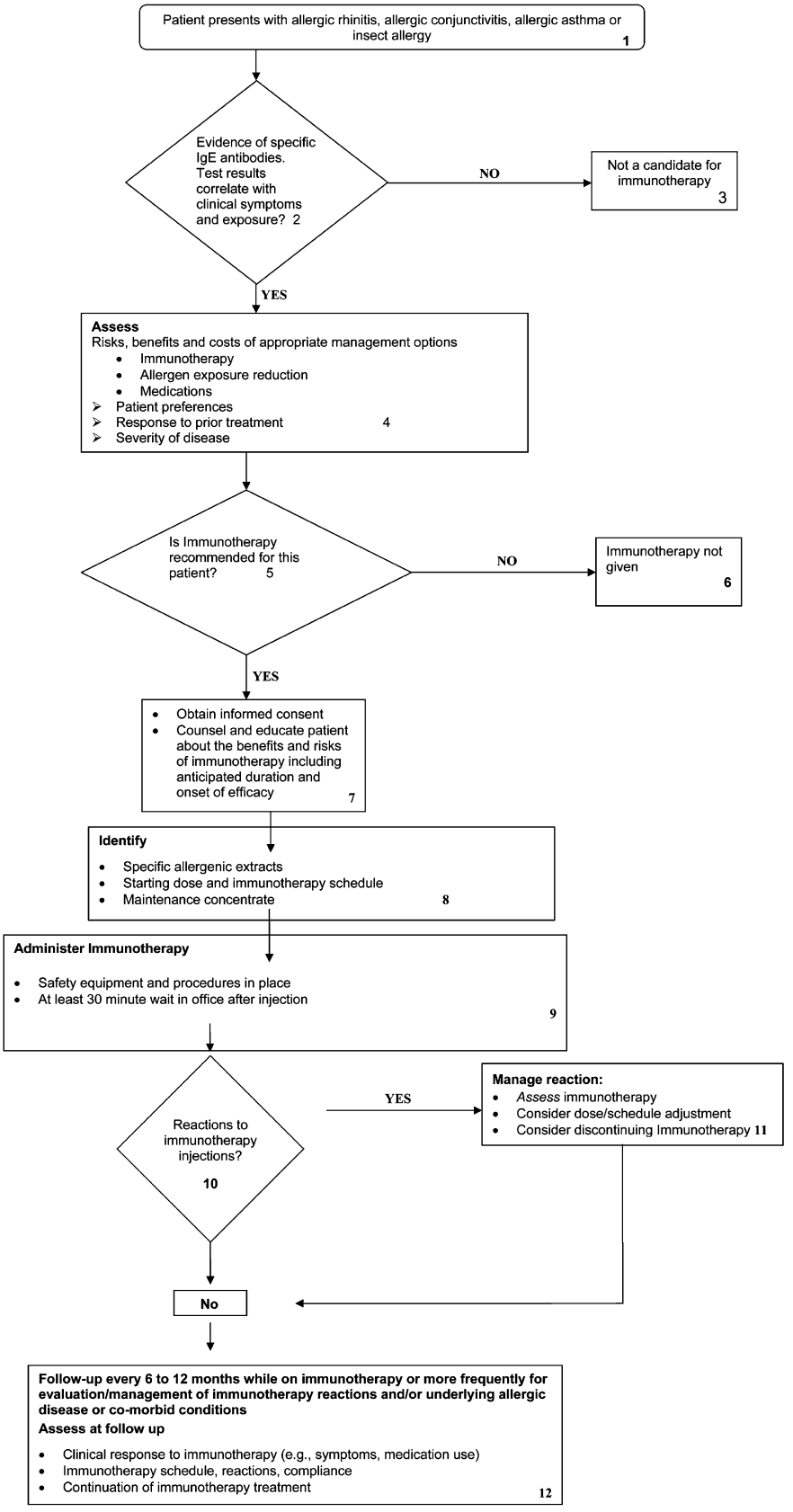


FIG 1. Algorithm for allergen immunotherapy.

might prevent the development of asthma in individuals with allergic rhinitis.[6-9] Evaluation of a patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic conjunctivitis, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for specific IgE antibody).[10]

Box 2

Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although *in vitro* testing for 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

Management of complex medical conditions, such as allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity, should include the careful evaluation of management 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 patient 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. On the basis of clinical considerations and patient 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 good candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy (VIT).

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 on the basis of 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 (see the Immunotherapy schedules and doses section). In general, the starting immunotherapy dose is 1000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 1000 to 4000 arbitrary units (AU; eg, for dust mite) or bioequivalent allergy units (BAU; eg, for grass) 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 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 referred to as *up-dosing*, *induction*, or the *dose-increase phase*) entails administration of gradually increasing doses during a period of approximately 14 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 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, in particular anaphylaxis. Patients should wait at the physician's office for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly, if they occur.

In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring 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. Some physicians recommend providing certain patients with epinephrine for self-administration in case of severe late reactions to immunotherapy injections.

Box 10

Injections of allergen immunotherapy extract can cause local or systemic reactions. Most severe reactions develop within 30 minutes after the immunotherapy injection, but reactions can occur after this time.

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 (anaphylaxis). Epinephrine is the treatment of choice in anaphylaxis, preferably when administered intramuscularly,[11] although subcutaneous administration is acceptable.[12]

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, see the practice parameters for anaphylaxis.[12]

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. After a severe systemic reaction, careful evaluation by the prescribing physician is recommended. For some patients, the immunotherapy maintenance dose might need to be reduced because of repeated systemic reactions to immunotherapy injections. The decision to continue immunotherapy should be re-evaluated after severe or repeated systemic reactions to allergen immunotherapy extracts.

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 doses, 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,[13] but others might experience a recurrence of their symptoms after discontinuation of allergen immunotherapy.[14] 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, and 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 on the basis of the patient's clinical response, disease severity, immunotherapy reaction history, and patient preference.

IMMUNOTHERAPY GLOSSARY

For more information on immunotherapy definitions, see the article by Kao.[15]

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 (pigments and salts; see the Allergen selection and handling section). Other terms used to describe the allergen immunotherapy extract include *allergen product*,[16] *allergy serum*, *allergen vaccine*,[17] 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.[18] Other terms that have been used for allergen immunotherapy include *hyposensitization*, *allergen-specific desensitization*, and the lay terms *allergy shots* or *allergy injections*.[15]

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

TABLE II. Allergen immunotherapy dose-calculation table

- Express weight per volume as a fraction: $\frac{1}{N}$ or 1:*N*.
- Calculate concentration of individual allergens in mixtures. If a mixture is made of equal amounts of N individual allergens to make a total concentration (C), the final concentration of an individual allergen (Ca) can be calculated by using the following equation:

$Ca = C \times \frac{1}{N} = \frac{C}{N}$ or *C*:*N*.

For example, if a mixture of equal amounts of 5 (N) allergens has a total concentration (C) of 100,000 BAU/mL, then the final concentration of each individual allergen (Ca) is: $Ca = \frac{C}{N} = \frac{100{,}000}{5} = 20{,}000\ BAU/mL$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{C}{N} = \frac{1/10}{5} = \frac{0.1}{5} = 0.02$ or $\frac{1}{50}$ or 1:50.

- Dilution of individual allergen: If an initial volume, Vi (in milliliters), of an individual antigen with concentration, Ci, is added to an allergen extract to make a final volume of Vf (in milliliters), the final allergen concentration (Ca) in the allergen extract mixture will be: $Ca = Ci \times \frac{Vi}{Vf}$.
- Final concentration of an allergen in a mixture of mixtures is determined by multiplying the initial concentration by the dilution factors from each mixing step.

For example, consider a mixture containing equal amounts of 5 (N) allergens with a total concentration (C) of 100,000 BAU/mL (first dilution). If an initial volume (Vi) of 0.5 mL of this mixture is further mixed with other components and diluent to make a final allergen extract mixture volume (Vf) of 5.0 mL (second dilution), the final concentration of an individual allergen (Ca) will be:

$$Ca = C \times \underbrace{\frac{1}{N}}_{\text{Mixture dilution}} \times \underbrace{\frac{Vi}{Vf}}_{\text{Allergen extract dilution}} = 100{,}000 \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{100{,}000}{50} = 2000\ BAU/mL$$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{1}{10} \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{1}{500}$ or 1:500.

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).

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 to 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-medicated 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 multiplied by volume of administered dose (see Table II for a dose-calculation table).

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, cat, 1000 BAU, [highest tolerated dose] vs 2000 BAU [projected effective dose]).

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 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 by a variety of immunologic transformations. Early definitions of the term immunotherapy included active and passive immunization for the purpose of improving 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 by means of induction of clonal deletion, anergy, immune tolerance, or immune deviation.

The *maintenance concentrate* is a preparation that contains individual 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 may not be the initially calculated projected effective dose.

The *maintenance goal* (or projected effective dose) is the allergen dose projected to provide therapeutic efficacy. The maintenance goal is based on published studies, but a projected effective dose has not been established for allergens. 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 the 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 large local reaction causing discomfort). The intervals between maintenance immunotherapy injections generally ranges 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 by means of immunoblotting or crossed allergoimmunoelectrophoresis.

For a definition of *projected effective dose*, see 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 test responses), and premedication with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similar high incidence of systemic reactions.

Off the board into one syringe is a phrase that describes a method of allergen immunotherapy preparation and administration that involves specifically mixing the patient's allergen immunotherapy injection in a single syringe, which is not recommended. This syringe might be inserted into more than one allergen extract vial, and this poses a risk of cross-contamination of the allergen extracts and might dull the needle with repeated penetration of the rubber stopper.

Shared specific patient vials is a method of allergen immunotherapy preparation and administration in which the allergy immunotherapy extract is withdrawn from a shared vial (eg, mixed vespids or dust mite mix). This is sometimes referred to as off the board, but it is distinct from the method of off the board into one syringe in that the syringe enters only one allergen extract vial.

INTRODUCTION

Immunity has been defined as protection against certain diseases. The initial immunotherapeutic interventions, which included the use of preventive vaccines and xenogenic 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 the field of allergen immunotherapy. From its humble empiric emergence in 1900, when ragweed injections were proposed as therapy for autumnal hay fever, allergen immunotherapy has progressed in both theory and practice from the passive immunologic approach to the active immunologic procedures pioneered by Noon[19] and Freeman.[20,21] 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 10 years. Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Some studies have suggested that allergen immunotherapy might prevent the development of asthma in individuals with allergic rhinitis.[6-9]

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,[22-26] and it should be differentiated from unproved methods, such as neutralization-provocation therapy and low-dose subcutaneous regimens based on the Rinkel technique, which have been found to ineffective in a double-blind placebo-controlled study.[27,28]

SUMMARY STATEMENTS

Mechanisms of immunotherapy

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, defined as a relative decrease in allergen-specific responsiveness and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

Allergen extracts

Summary Statement 6: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. **A**

Summary Statement 7: Nonstandardized extracts might vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Summary Statement 8: 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**

Cross-reactivity of allergen extract. Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

Efficacy of immunotherapy

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Summary Statement 10: Immunotherapy is effective for 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**

Food allergy, urticaria, and atopic dermatitis. Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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**

Measures of efficacy. Summary Statement 12: 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**

Safety of immunotherapy

Reaction rates. Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

Timing of anaphylactic reactions to immunotherapy injections. Summary Statement 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

β-*Adrenergic blocking agents.* Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

Contraindications. Summary Statement 18: 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**

Reducing the risk of anaphylaxis to immunotherapy injections. Summary Statement 19: 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**

Patient selection

Clinical indications. Summary Statement 20: 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 depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Special precautions in patients with asthma. Summary Statement 21: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. **C**

Clinical indications for VIT. Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Summary Statement 23: Patients selected for immunotherapy should be cooperative and compliant. **D**

Allergen selection and handling

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted in vitro tests for specific IgE antibodies can also be used. **A**

Specific allergens. Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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, supported by the presence of specific IgE antibodies. **A**

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Dose selection. Summary Statement 30: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. **A**

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens, is recommended. **B**

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extract handling

STORAGE

Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

STORING DILUTE EXTRACTS

Summary Statement 34a: More dilute concentrations of allergen immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: 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 a number of 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. **B**

Immunotherapy schedules and doses

Summary Statement 35: A customized individual 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 be based on single or multiple allergens. **D**

Maintenance concentrate. Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

Recommended doses. Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

Effect of dilution on dose. Summary Statement 38: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. **A**

Dilutions of the maintenance concentrate. Summary Statement 39: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. **D**

Labeling dilutions. Summary Statement 40: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. **D**

Individualized treatment vials. Summary Statement 41: 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. The mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. **C**

Starting doses. Summary Statement 42: The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. **D**

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

Dose adjustments for systemic reactions. Summary Statement 44: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. **D**

Reductions during periods of exacerbation of symptoms. Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Dose adjustments for late injections. Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

Cluster schedules. Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. **C**

Rush schedules. Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. **A**

Systemic reactions and rush schedules. Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

Premedication and weekly immunotherapy. Summary Statement 50: Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

Premedication with cluster and rush immunotherapy. Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

Maintenance schedules. Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. **A**

Continuing care

TIME COURSE OF IMPROVEMENT

Summary Statement 53: Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **A**

FOLLOW-UP VISITS

Summary Statement 54: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. **D**

DURATION OF TREATMENT

Summary Statement 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

DOCUMENTATION AND RECORD KEEPING

Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. **D**

INJECTION TECHNIQUES

Summary Statement 57: Allergen immunotherapy extract injections should be administered with a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **D**

Summary Statement 58: The injection should be administered subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Location of allergen immunotherapy administration

Physician's office. Summary Statement 59: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Summary Statement 60: 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**

Other locations. Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **D**

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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**

Summary Statement 63: 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for his or her immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extract might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Special considerations in immunotherapy

Allergen immunotherapy in children. Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Pregnancy. Summary Statement 71: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. **C**

Immunotherapy in the elderly patient. Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy in patients with immunodeficiency and autoimmune disorders. Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

Alternative routes of immunotherapy

Sublingual and oral immunotherapy. Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no US Food and Drug Administration (FDA)–approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **A**

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Immunotherapy techniques that are not recommended. Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

MECHANISMS OF IMMUNOTHERAPY

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, which is defined as a relative decrease in allergen-specific responsiveness, and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

The immunologic changes associated with immunotherapy are complex, and the exact mechanism or mechanisms responsible for its' clinical efficacy are continually being elucidated. Data support the concept that successful immunotherapy is associated with a change to a T_H1 $CD4^+$ cytokine profile.[29-34] Data indicate that increased production of IL-12, a strong inducer of T_H1 responses, contributes to this shift.[33] Clinically successful immunotherapy has been reported to be associated with immunologic tolerance, which is defined as a relative decrease in antigen-specific responsiveness, immune deviation, or anergy. For example, lymphoproliferative responses to allergen are reduced with immunotherapy.[32] Successful immunotherapy results in generation of a population of T regulatory cells, which are $CD4^+CD25^+$ T lymphocytes producing IL-10, TGF-β, or both.[35-39] Regulatory T-cell release has been described in allergen immunotherapy with Hymenoptera venom,[35] grass pollen extract,[37] and house dust mites.[38] IL-10 reduces B-cell antigen-specific IgE and increases IgG4 levels; reduces proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicits tolerance in T cells by means of selective inhibition of the CD28 costimulatory pathway.[36,37]

Allergen immunotherapy has been shown to block both the immediate and late-phase allergic response.[40] Allergen immunotherapy has been shown to decrease the recruitment of mast cells, basophils, and eosinophils in the skin, nose, eye, and bronchial mucosa after provocation or natural exposure to allergens.[41]

In patients receiving immunotherapy, initially there is an increase in specific IgE antibody levels, followed by a gradual decrease to a level that is still higher than that present before treatment. Clinical improvement in many patients develops before decreases in their IgE antibody levels occur or in other patients whose IgE antibody levels never decrease, thereby demonstrating that efficacy is not dependent on reductions in specific IgE levels.[42,43] Immunotherapy does diminish the seasonal increase in specific IgE levels.[44] Despite the persistence of significant levels of specific IgE antibody levels, immunotherapy usually causes a reduction in 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.[45-48]

An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, has also been associated with immunotherapy. The properties of allergen-specific IgA have yet to be determined, and there is a weak correlation between the increase in allergen-specific IgG levels and immunotherapy's clinical efficacy.[30,49,50]

Immunotherapy might alter the affinity and specificity of allergen-specific IgG.[51,52] During the initial phase of ultrarush VIT, a change in IgG specificity (ie, a change in the set of epitopes dominantly recognized by IgG on wasp venom antigens) occurred concomitantly with early clinical tolerance and was seen within 12 hours of ultrarush VIT ($P < .001$).[51] 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 individuals.[52] This change in IgG specificity preceded the increase in IgG titers and was sustained for up to 6 months.[52]

Allergen-specific IgG induced from immunotherapy can block IgE-dependent histamine release and subsequent IgE-mediated antigen presentation to T cells.[53] This effect might be dependent on IgE, allergen concentration, and CD23, the low-affinity receptor for IgE.

Whereas 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.[37,53]

The relationship between these immunologic changes and immunotherapy efficacy is not completely understood.

ALLERGEN EXTRACTS

Summary Statement 6: 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 has 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.[2,18,54-56] 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.

United States–licensed extracts can be obtained in aqueous, glycerinated, lyophilized, and acetone-precipitated and alum-precipitated formulations. Some commonly used allergens are standardized. These include extracts for cat hair, cat pelt, *Dermatophagoides pteronyssinus*, *Dermatophagoides 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.[57] 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.

Most standardized extracts are labeled in BAU. Short ragweed potency units were originally based on the content of the major allergen Amb a 1. Ragweed potency is reported in FDA units and BAU. One FDA unit of Amb a 1 equals 1 μg of Amb a 1, and 350 units of Amb a 1/mL is equivalent to 100,000 BAU/mL. Cat extracts were also originally standardized based on the content of major allergen (Fel d 1), with 100,000 arbitrary units (AU) per milliliter containing between 10 to 19.9 FDA units of Fel d 1 per milliliter (1 FDA unit of Fel d 1 equals 2 to 4 μg of Fel d 1).[55,58,59] Subsequently, $ID_{50}EAL$ testing suggested that 100,000 AU/mL was equal to 10,000 BAU/mL.[60] Approximately 22% of individuals with cat allergy have specific IgE antibodies to cat albumin.[61] Cat pelt extracts have a greater amount of albumin than cat hair extracts.[60]

Dust mites were originally standardized in AU by means of inhibition radioimmunoassay (RIA), and subsequent $ID_{50}EAL$ testing indicated that the AU was bioequivalent to the BAU, and the original AU nomenclature was kept. Dust mite extracts are still labeled in AU.

Summary Statement 7: Nonstandardized extracts can vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Nonstandardized extracts are labeled as wt/vol, which expresses weight in grams per volume in milliliters; that is, a potency of 1:100 indicates that 1 g 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 with a particular wt/vol or PNU potency can have widely varying biologic activities.[62-64] Therefore they should not be considered equipotent.

Summary Statement 8: 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**

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. The major clinically relevant aeroallergens of North America are listed in Table III. Furthermore, nonrelevant allergens in such mixtures could act as sensitizers rather than as tolerogens.[65,66] The physician must therefore select only those aeroallergens for testing and treatment that are clinically relevant in a particular geographic area.

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, dog), insect (cockroach), and Hymenoptera venom source materials.

Cross-reactivity of allergen extract

Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

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. A summary of cross-reactivity patterns of the clinically relevant North American aeroallergens can be found in Fig 2. 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,[67] inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[68-75] Grasses in other subfamilies (eg, Bermuda, Bahia, and Johnson) show greater diversity and should be evaluated separately.[76-78] Bermuda and Johnson grasses are increasingly important in the South,

TABLE III. The major clinically relevant aeroallergens of North America*

- Tree pollen
  - Chinese elm *(Ulmus parvifolia)*†‡; Siberian elm *(Ulmus pumila)*†‡; American elm *(Ulmus Americana)*†‡
  - Red oak *(Quercus rubra)*†; White oak *(Quercus alba)*†
  - Paper birch *(Betula papyrifera)*
  - Alder *(Alnus rubra)*
  - Box elder *(Acer negundo)*†; Red maple *(Acer rubra)*†
  - Eastern cottonwood *(Populus deltoides)*
  - Sycamore *(Platanus occidentalis)*
  - White ash *(Fraxinus americana)*†; Olive *(Olea europaea)*†‡
  - Black walnut *(Juglans nigra)*
  - Mulberry *(Morus rubra)*
  - Mountain cedar *(Juniperus ashei)*
  - Pecan *(Carya illinoensis)*
- Grass pollen
  - Rye *(Lolium perenne)*§‖
  - Timothy *(Phleum pratense)*§‖
  - Meadow fescue *(Festuca elatior)*§‖
  - Bermuda *(Cynodon dactylon)*‖
  - Johnson *(Holcus halepensis)*
  - Bahia *(Paspalum notatum)*
- Weed pollen
  - Short ragweed *(Ambrosia artemisiifolia)*‖
  - English (narrow leaf) plantain *(Plantago lanceolata)*
  - Mugwort *(Artemisia vulgaris)*
  - Russian thistle *(Salsola kali)*
  - Burning bush *(Kochia scoparia)*
  - Sheet (red) sorrel *(Rumex asetosella)*
  - Red root pigweed *(Amaranthus retroflexus)*
- Indoor aeroallergens
  - Cat epithelium *(Felis domesticus)*‖
  - Dog epithelium *(Canis familiaris)*
  - Arthropods (domestic mites: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*)‖
  - Insects (German cockroach: *Blattella germanica*)
- Fungi
  - *Alternaria alternata*¶
  - *Cladosporium* (*C cladosporioides*, *C herbarum*)¶
  - *Penicillium* (*P chrysogenum*, *P expansum*)¶
  - *Aspergillus fumigatus*¶
  - *Epicoccum nigrum*, *Drechslera* or *Bipolaris* type (eg, *Helminthosporium solani*)¶

*Compiled and selected in collaboration with the AAAAI Immunotherapy Committee Allergen Subcommittee for the identification of 35 key allergens of North America.
†Extensive cross-reaction of species within the genus.
‡Apart from regional prevalence, they are limited to local sites with substantial stands of these trees.
§Extensively cross-react with one another and bluegrass, orchard, red top, and sweet vernal.
‖Allergens for which standardized extracts are commercially available.
¶Species that are widely distributed and clinically important.

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.[79-82] 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.[83-85] Significant cross-reactivity between Betulaceae pollens and oak of the Fagaceae family has been demonstrated with percutaneous skin testing.[75] RAST inhibition studies have shown cross-inhibition between oaks and other *Fagales* species.[86] IgE immunoblot inhibition experiments have demonstrated that the *Fagales* species might be strongly inhibited by birch species.[87] The use of one of the locally prevalent members (eg, birch and alder) should be adequate.[88]

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.[89,90] Maple and box elder trees are found throughout the United States, except for the arid southwest. Although in the same genus as maple, *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,[91,92] and there are allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.[93]

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.[94] Similarly, Chenopod-Amaranth families have wide ranges in the western regions but are present throughout North America.[95] Current information on cross-reactivity of these families is limited.[96-98] 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.[99] The use of a single Amaranth extract should be sufficient to cover this family.[100,101] Similarly, *Atriplex* species (eg, saltbushes and scales) show near identity, and use of a single member is adequate. 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,

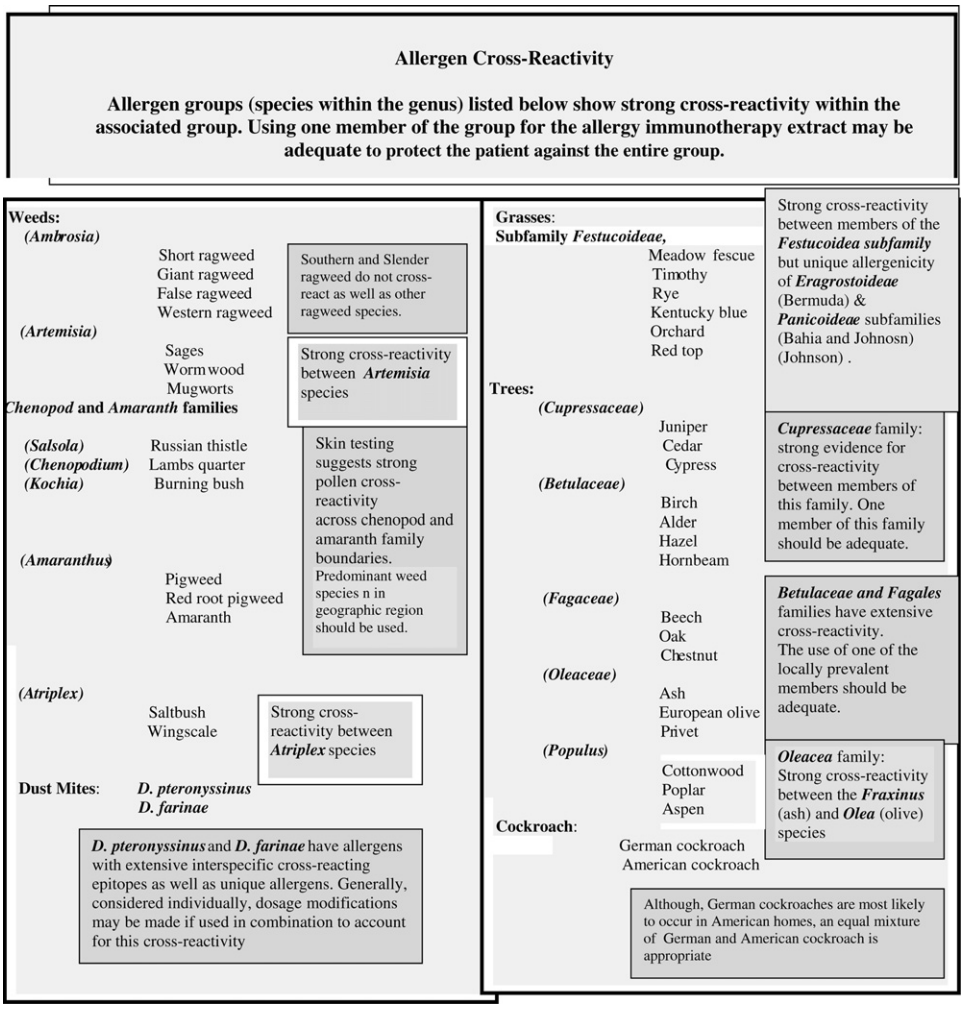


FIG 2. Patterns of allergen cross-reactivity.

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*).

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.[102,103] Stinging Hymenoptera insects occur throughout the United States; the fire ant is found only in Gulf Coast states, Texas, and some other southern and western states. Commercial venom extracts are available for some Hymenoptera species, except the fire ant, for which only whole-body extract is available.

EFFICACY OF IMMUNOTHERAPY

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity

Summary Statement 10: Immunotherapy is effective for 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.[104-111] Immunotherapy is effective for the treatment of allergic rhinitis[107] (including ocular symptoms[112,113]), allergic asthma,[104,109,111,114,115] and stinging insect hypersensitivity[108,116] and is effective in both adults and children.[117-124] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollens,[13,125-132] fungi,[133-138] animal allergens,[22,25,26,139-143] dust mite,[114,115,144-153] and cockroach.[154] There have been no controlled trials of fire ant whole-body extract, but it does appear to be effective in

TABLE IV. Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy

Outcome measure	House dust mite	Other allergens*†
Symptomatic improvement	2.7 (1.7-4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2-7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50)	5.5 (2.8-10.7)

Data are used with permission from Abramson et al.[104]
ND, Not done.
*Odds ratio (95% CI).
†Pollen, mold, or animal dander.

uncontrolled trials.[155-157] 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. A number of studies have also demonstrated a significant improvement in quality of life, as measured by using standardized questionnaires.[24,158-161] The magnitude of the effect depends on the outcome that is used (Table IV). For dust mite, the effect size ranges from a 2.7-fold improvement in symptoms to a 13.7-fold reduction in bronchial hyperresponsiveness. 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.[110] 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[107] and asthma[104,109,111] have been performed to deal with the issue of power. One review of 75 trials involving 3188 asthmatic patients found that, overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyperreactivity after immunotherapy, and it would have been necessary to treat 4 patients (95% CI, 3-5) with immunotherapy to avoid 1 deterioration in asthma symptoms and 5 (95% CI, 4-6) patients to avoid 1 requiring increased medication.[111] These meta-analyses strongly support the efficacy of allergen immunotherapy. Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued[13,162,163] and might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6,9,122,162-165] Allergen immunotherapy might also prevent the development of new allergen sensitivities in monosensitized patients.[120,166,167]

Food allergy, urticaria, and atopic dermatitis

Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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 use of allergen immunotherapy for individuals with the potential for IgE-mediated (anaphylaxis) reactions to foods should be regarded as investigational at this time.[168-171] There have been 2 investigational studies demonstrating efficacy in food hypersensitivity, the first using aqueous subcutaneous injections to peanut and the second using sublingual immunotherapy to hazelnut.[171-173]

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 a modified peanut extract is needed for clinical application of this method of treatment.[171] There is currently no FDA-approved formulation for sublingual immunotherapy, and this route of allergen immunotherapy is currently considered investigational at this time (see Summary Statement 73).

At the present time, there is not enough evidence to support food immunotherapy.

There is no evidence supporting the efficacy of immunotherapy for individuals with chronic urticaria, angioedema, or both.

There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[174-176] 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 ($P = .0379$) and topical corticosteroid use ($P = .0007$).[174]

The potential for benefit in symptoms related to oral allergy syndrome with the cross-reacting inhalant immunotherapy, which includes cross-reacting 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 subcutaneous immunotherapy directed against birch tree,[177] whereas another double-blind, double-dummy, placebo-controlled study comparing the effect of subcutaneous immunotherapy with sublingual immunotherapy 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, medication use, and decrease in IgE reactivity.[178] More investigation is required to substantiate the contention that benefits in oral symptoms will occur with immunotherapy.

Measures of efficacy

Summary Statement 12: 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. Objective measures, such as increase in allergen-specific IgG levels and decreased skin test reactivity, as measured by skin test titration, are changes generally associated with effective immunotherapy but, at present, are not practical for routine clinical use.[147] Nonquantitative skin testing or *in vitro* 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 are not very reliable given the strong placebo-like effect (Hawthorne effect) associated with any treatment. A more objective means for determining efficacy as validated in controlled clinical studies is the use of clinical symptom scores and the amount of medication required to control symptoms and maintain peak flow rates or pulmonary function tests within acceptable limits. Successful immunotherapy often results in a reduction in medication. Sequential measurement of disease-specific quality of life also might be helpful.

SAFETY OF IMMUNOTHERAPY

Reaction rates

Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Large local reactions associated with allergen immunotherapy are fairly common, with a frequency ranging from 26% to 86% of injections.[179] Two retrospective studies compared the effect of not adjusting immunotherapy dose based on large local reactions on the immunotherapy systemic reaction rate with dose-adjustment protocols.[179,180] There was a total of 12,464 injections administered with a dose-adjustment protocol in the 2 studies compared with 9542 injections administered with a no-dose-adjustment protocol. 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 for subsequent systemic reactions, 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 large local reactions, defined as 25 mm or larger, in patients who had experienced systemic reactions with age-, sex-, and allergen sensitivity–matched control subjects who had not had allergen immunotherapy systemic reactions found the rate of large local reactions was 4 times higher among the 258 patients who had subsequently experienced a systemic reaction compared with those who had never experienced a systemic reaction.[181] Patients who had experienced systemic reactions had 1573 large local reactions in 4460 visits (ie, 35.2% of visits) and 8081 injections (ie, 19.5% of injections) compared with the matched control group without systemic reactions who had 1388 large local reactions in 15,540 visits (8.9% per visit) and 26,259 injections (5.3% per injection; difference between groups, $P < .001$). Individual large local reactions were not predictive of future systemic reactions, but large local reactions preceded systemic reactions in approximately one third of the systemic reactions. These findings suggest that individuals with a greater frequency of large local reactions might be at greater risk for systemic reaction. Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy protocol modifications based on them are needed.

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

The prevalence of severe systemic reactions after allergen immunotherapy ranges from less than 1% of patients receiving conventional immunotherapy to greater than 36% of patients in some studies of patients receiving rush immunotherapy.[182,183]

In a recent survey of fatal and near-fatal reactions (NFRs) sent to physician members of the AAAAI, 273 of 646 respondents reported NFRs during the period of 1990-2001.[184]

The incidence of unconfirmed NFRs was 23 per year (5.4 events per million injections). Administration during the height of 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 angiotensin-converting enzyme 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 systemic reactions to subcutaneous immunotherapy over a 20-year period (1981-2000) during which 435,854 injections were administered to 4000 patients, 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.[185,186] In a prospective multicenter study there were 53 systemic reactions (0.3% of the doses) out of 17,526 administered doses in 18 (3.7%) of 423 patients.[187] 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 (21 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, there were 41 fatalities identified in the initial brief survey (20 directly reported and 17 with completed detailed questionnaire) from immunotherapy injections.[188] 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.[189,190] Therefore although severe systemic reactions to allergen immunotherapy are not common, serious systemic reactions (some fatal) can occur.

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

In the AAAAI survey of physician members on immunotherapy and skin testing, fatal reactions, and NFRs during the period of 1990-2001, 15 of the 17 fatalities had asthma, and in 9 patients asthma was considered the susceptibility factor that contributed to the fatal outcome.[188]

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.[184]

Administration during the peak pollen season (3 patients) and previous systemic reactions (4 patients) were cited as other contributing factors. Five fatalities occurred in outside medical facilities, and 2 fatalities occurred at home. No patients were receiving β-blockers; 1 patient was taking an angiotensin-converting enzyme inhibitor. In the most comprehensive evaluation of fatalities associated with allergen immunotherapy, from 1945-1987, there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[189] 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, with 73.3% of patients with an FEV_1 of less than 80% of predicted value experiencing 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 ($P < .0001$).[191] 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% of patients. These studies suggest that symptomatic asthma, severe asthma, or both might be a risk factor for immunotherapy.

In addition to symptomatic asthma and injections giving 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.[17] With the exception of dosing errors and 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 recent 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 or allergy symptom exacerbation, β-blocker use, change in health status (including pregnancy), or adverse reaction to previous allergen immunotherapy injection. The preinjection evaluation might also include a peak flow measurement to assess the airway function of asthmatic patients.

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 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

In a retrospective study the time to onset of a systemic reaction after an immunotherapy injection was less than 30 minutes in most cases.[189] A review of the literature indicates that 70% of systemic reactions occur within 30 minutes after an injection.[183] In the AAAAI 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.[184,188] 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.[190] 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 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.[192] In another prospective study 8% of systemic reactions occurred more than 2 hours after injection.[193]

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.[194]

Because most reactions that resulted from allergen immunotherapy occurred within 30 minutes after an injection, patients should remain in the physician's office for at least 30 minutes after receiving an injection, but longer waits are reasonable, as directed by the physician. In addition, patients who are at increased risk of a systemic reaction might need to carry injectable epinephrine. Such patients might also need to remain in the physician's office more than 30 minutes after an injection. 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.

β-Adrenergic blocking agents

Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

β-Blockade enhances pulmonary, cardiovascular, and dermatologic end-organ effects of mediators and increases mortality associated with experimental anaphylaxis induced by either immunologic or nonimmunologic mechanisms. Patients who are receiving β-adrenergic blocking medications might be at increased risk if they experience a systemic reaction to an allergen immunotherapy injection because the β-receptor blockade might attenuate the response to epinephrine.[195-202] Patients who are receiving β-blocking drugs were almost 9 times more likely to be hospitalized after an anaphylactoid reaction from radiocontrast media.[198] Although topical β-blockers have markedly less systemic β-antagonist effects than oral β-blockers, they still might exhibit some systemic β-antagonist effects. Whether topical β-blockers pose the same or a smaller risk than oral β-blockers in regard to the treatment of allergen immunotherapy–related systemic reactions is not known.

There have been very few studies that have examined the effect of β-blocker medications on allergen immunotherapy. A prospective 1-year study designed to determine whether patients taking β-blocker drugs were at increased risk of immunotherapy-induced systemic reactions found that there were 166 systemic reactions out of 56,105 injection visits in 3178 patients (68 were receiving a β-blocker).[203] The systemic reactions occurred in 144 (4.5%) patients, and only 1 of these patients was receiving a β-blocker medication. The authors calculated that by chance, 3.08 patients receiving the β-blocker medications drugs were expected to have had an systemic reaction and concluded that β-blocker medications did not increase the frequency of allergen immunotherapy systemic reactions ($P > .95$).

In another study of 1389 patients prescribed immunotherapy for Hymenoptera venom hypersensitivity who were followed for 34 months, there were 25 patients who received concomitant β-blocker medications.[204] Three (12%) of the 25 patients receiving β-blocker medications experienced systemic reactions during immunotherapy compared with 23 (16.7%) of 117 patients with cardiovascular disease not receiving β-blockers. Systemic reactions after a field sting or challenge occurred in 1 (14.3%) of 7 cardiovascular patients receiving β-blocker medications compared with 4 (13.8%) of 29 cardiovascular patients not receiving β-blocker medications. No severe reactions to immunotherapy or sting re-exposure were observed in patients receiving β-blockers medications.

Immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. In such cases, intravenous glucagon, which might reverse the refractory bronchospasm and hypotension by activating the adenyl cyclase directing and bypassing the β-adrenergic receptor, might be used if epinephrine has not been effective.[205,206] Prospective studies are necessary to clarify the magnitude of the risk of systemic reactions to allergens in patients who are receiving concomitant therapy with β-blockers, and a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy.

Contraindications

Summary Statement 18: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications

TABLE V. Actions to reduce the risk of anaphylaxis

- Assess the patient's general medical condition at the time of injection (eg, asthma exacerbation).
- Consider obtaining a PEFR before administration of the injection. If the PEFR is significantly less than the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.
- 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 with increased allergen sensitivity or those who have previously had a systemic reaction) might need to wait longer.
- Carefully evaluate any patient with a late reaction (eg, persistent large local reaction lasting >24 hours, systemic reaction occurring more than 30 minutes after the immunotherapy injection).
- 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.

PEFR, Peak expiratory flow rate measurement.

TABLE VI. Recommended equipment and medications to treat anaphylaxis

Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur. This should include at least the following equipment and medications:

- stethoscope and sphygmomanometer;
- tourniquet, syringes, hypodermic needles, and large-bore needles (14-gauge);
- aqueous epinephrine HCL 1:1000 wt/vol;
- equipment to administer oxygen by mask.
- intravenous fluid set-up;
- antihistamine for injection (second-line agents for anaphylaxis, but H_1 and H_2 antihistamines work better together than either one alone);
- corticosteroids for intravenous injection;
- vasopressor;
- equipment to maintain an airway appropriate for the supervising physician's expertise and skill.

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 venom hypersensitivity and cardiac disease being treated with β-blocker medications.

Reducing the risk of anaphylaxis to immunotherapy injections

Summary Statement 19: 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 extremely 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 or other health care professional appropriately trained in emergency treatment.

The 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. Epinephrine is the first-line treatment for anaphylaxis. 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.[12,207-213] It is important to administer epinephrine early in the management of anaphylaxis. 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 V and VI, respectively. Before allergen immunotherapy is chosen as a treatment, the physician should educate the patient about the benefits and risks of immunotherapy, as well as methods for minimizing risks. The patient also should be told that despite appropriate precautions, reactions might occur without warning signs or symptoms. Informed consent should include a discussion of the potential immunotherapy adverse reactions, and this discussion should be documented in the patient's medical record.

PATIENT SELECTION

Clinical indications

Summary Statement 20: Allergen immunotherapy should be considered for patients who have demonstrable

TABLE VII. Clinical indications for allergen immunotherapy

Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or both:
- symptoms of allergic rhinitis after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medications;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medication;
- coexisting allergic rhinitis and asthma;
- possible prevention of asthma in patients with allergic rhinitis

Symptoms of asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medication;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medications;
- coexisting allergic rhinitis and allergic asthma.

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);
- adults and children with a history of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.

evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic rhinitis.[107] Prospective, randomized, double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic asthma.[104,109,111]

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 proper identification and selection of component allergens on the basis of 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 (Table VII). The severity and duration of symptoms should also be considered in assessing the need for specific allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. In addition, specific allergen immunotherapy should be considered if the patient wishes to avoid long-term pharmacotherapy. Time lost from work, emergency department or physician's office visits, and responses to pharmacotherapy are important objective indicators of allergic disease severity.

Patients with allergic rhinitis who are unable to sleep because of symptoms or whose symptoms interfere with their work or school performance should be considered strong candidates for specific allergen immunotherapy. 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 considered. Unacceptable adverse effects of medications should also favor one's decision to initiate allergen immunotherapy. Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.[214]

Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued, and it might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6-9,122,162-165] These benefits of immunotherapy should be discussed with patients and might provide a clinical indication for immunotherapy for individual patients with allergic rhinitis.

Coexisting medical conditions should also be considered in the evaluation of a patient who might be a candidate for allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed with a combined aggressive regimen of allergen avoidance and pharmacotherapy and might also benefit from allergen immunotherapy.[215,216]

However, the patient's asthma must be stable before allergen immunotherapy is administered.[188,191]

Special precautions in patients with asthma

Summary Statement 21: 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 might be at increased risk for systemic reactions to immunotherapy injections.[182,188,191] Two surveys found that deaths from

immunotherapy were more common in symptomatic subjects with asthma.[188,189] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2,217]

Clinical indications for VIT

Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Systemic reactions to Hymenoptera stings, especially when associated with respiratory symptoms, cardiovascular symptoms, or both and positive skin test or *in vitro* test results for specific IgE antibodies, are a strong indication for allergen immunotherapy.[218] In the United States patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Several studies of patients with imported fire ant allergy have demonstrated the effectiveness of immunotherapy with whole-body extracts of fire ants.[155,156,219] 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. Patients younger than 16 years of age who present only with a cutaneous reaction to imported fire ant or Hymenoptera stings might not require immunotherapy.[218,220-222] In addition to allergen immunotherapy, patients with imported fire ant and Hymenoptera venom sensitivity should be instructed in how to best avoid insect stings, be prescribed epinephrine, and be taught how 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 the population that has not had a systemic reaction.[223] In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific IgE is recommended.[218] If the venom-specific IgE test result is also negative, it is recommended that the skin tests, venom-specific 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 IgE test result.[224] 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 re-stung. 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%).[225] 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 IgE test results who have had severe anaphylaxis to an insect sting.

Some patients who have negative venom skin test results and negative venom-specific IgE test results are reported to have had subsequent systemic reactions to stinging insects.[225-227] Controlled studies designed to evaluate the efficacy of immunotherapy in these patients have not been performed. There are very 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.[226] 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.

Summary Statement 23: 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.

ALLERGEN SELECTION AND HANDLING

Allergen selection

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

A careful history, noting environmental exposures and an understanding of the local and regional aerobiology of suspected allergens, such as pollen, fungi (mold), 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 skin or *in vitro* test results for specific IgE antibodies, provide good evidence that such exposures are relevant. Information concerning regional and local aerobiology is available on various Web sites or through the National Allergy Bureau at http://www.aaaai.org/nab. There are

no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma. 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 clinical history of an allergic disease.

There is no evidence to support the administration of immunotherapy based solely on results of specific *in vitro* 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.

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

The omission of clinically relevant allergens from an allergic patient's allergen immunotherapy extract contributes to decreased effectiveness of allergen immunotherapy. The 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 can make allergen immunotherapy less effective.

Knowledge of the total allergenic burden facing a patient and the realistic possibility of avoidance is important in determining whether allergen immunotherapy should be initiated. 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. Many individuals travel extensively for business or pleasure into different regions, and symptoms might worsen at these times. However, inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective. Determination of the significance of indoor allergens for a particular patient is harder because it is difficult to determine exposure in the home, school, and/or workplace. Historical factors, such as the presence of a furry animal in the home, a history of water damage and subsequent fungal exposure, or a history of insect infestation, might be helpful. However, such information is subjective and is often of uncertain reliability. In addition, some studies have demonstrated significant indoor levels of cat and dog allergen in households without pets[228] and significant levels of mouse allergen in suburban[229] and inner-city[230] homes 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 with increased asthma morbidity in inner-city children was found.[231] 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. Nevertheless, for most patients, determination of the clinical relevance of an allergen requires a strong correlation between the patient's history and evidence of allergen-specific IgE antibodies.

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted *in vitro* tests for specific IgE antibodies can also be used. **A**

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 the skin test results have demonstrated the efficacy of immunotherapy for relevant allergens.[25,26,112,130,134,135,140,141,149,154] 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 from skin testing in a highly sensitive individual.[232,233] In addition, skin tests might be difficult to perform in patients with dermatographism or atopic dermatitis. *In vitro* tests are particularly useful in such patients.

Studies indicate that skin testing is generally more sensitive than *in vitro* tests in detecting allergen-specific IgE.[234,235] Based on inhalation challenge test results, skin tests have shown specificity and sensitivity generally superior to those of *in vitro* tests. The comparability of skin tests and *in vitro* tests for specific IgE antibodies depends on the allergen being tested. For all of 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, prick testing is sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass[236] and cat,[237] are used. Intradermal/intracutaneous skin testing might be required for some allergen extracts. It is appropriate in some patients to use *in vitro* tests for specific IgE antibody as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. *In vitro* tests can also be used to define the allergens that should be used in allergen immunotherapy. If the allergy skin test result is negative and the *in vitro* test result is positive, a controlled challenge can be performed, and if the latter is positive, immunotherapy can be considered. 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 *in vitro* test results.

Specific allergens

Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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.[17,104,106,107,109] 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.[112,122] Because a particular pollen extract is a mixture of multiple glycoproteins, this suggests that mixing pollen allergens does not alter biologic activity.

Fungi (molds). Several studies with *Alternaria* and *Cladosporium* species suggest that allergen immunotherapy with fungi might be effective.[133-138] The allergen content of most mold extracts is highly variable.[238,239] However, there is evidence that proteolytic enzymes present in some mold extracts could digest other antigens, such as pollens, when combined in a mixture.[240] For this reason, it might be desirable to separate all pollen extracts from mold extracts when using mixtures.

Unfortunately, extracts for some potentially clinically important fungi are not available.[241] 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 distinguish 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.

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.

Because immunotherapy has been shown to be effective for cat[22,26,139-143,242] and dog,[25,141] the decision to include dog or cat allergen in an allergen immunotherapy extract should be considered in those circumstances in which there is exposure.

Dust mites and cockroach allergens. Crude house dust extract is generally an inappropriate substitute for house dust mite extract because the protein content measured is not restricted to dust mite allergens, nor does it necessarily guarantee inclusion of dust mite protein. Immunotherapy with standardized dust mite is generally more effective than that with crude house dust allergens. The house dust mites *D farinae* and *D 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, such as *Blomia tropicalis* and *Euroglyphus maynei*, partially cross-react with allergens from *Dermatophagoides* species. Only 50% of the projected amounts of each of the 2 house dust mites (*D pteronyssinus* and *D farinae*) need 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[144,147-149,151] 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. Dust mite hypersensitivity should particularly be considered in patients who have perennial symptoms exacerbated by a dusty environment at home, work, or both and periods of high humidity.

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. The major allergen of *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.[243] Immunotherapy with cockroach allergens is effective[154] and should 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.

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.[108,116,244] Efficacy has also been demonstrated with immunotherapy by using whole-body extracts of imported fire ants.[155,156]

Foods. Only a single clinical study accessing the efficacy and safety of subcutaneous immunotherapy with foods has been performed.[171,173] This study, which evaluated immunotherapy with peanut, found the incidence of systemic reactions, even during maintenance, was unacceptable. Thus there is no evidence to support the use of immunotherapy with food extracts. Currently, strict avoidance of the offending food is advisable, and subcutaneous immunotherapy for food allergy is not recommended.

Mixing of extracts

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Once the relevant allergens for each patient are identified, it is necessary to prepare a mixture that contains each of these allergens. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts. A number of 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 interactions between different types of allergens, when mixed, that could lead to degradation or unmasking of epitopes on exposure to proteolytic enzymes.

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Immunologic and 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.[71] 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 genera 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 the Allergen extract section, Fig 2, and the allergens and allergy diagnostic tests practice parameters).

Dose selection. Summary Statement 30: 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.[22-26,128,149,245] Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000 vol/vol).[28] A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy vaccine. Failure to do so might reduce the efficacy of immunotherapy. This occurs because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased (see the Immunotherapy schedules and doses section for further discussion and for recommended maintenance doses).

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as fungi (mold) and cockroach, from other extracts, such as pollens, is recommended. **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.[240,246,247] 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, and some weeds.[240,246,247] Cockroach had a similar deleterious effect on pollen extract potency.[246,248] Short ragweed appeared resistant to the effects of the proteolytic enzymes in one study,[240] 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.[247]

Dust mite extracts do not appear to have a deleterious effect on pollen extracts.[240,246,248] These studies suggest that pollen, dust mite, and cat extracts can be mixed together. 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. The evidence on mixing cockroach extract with other extracts is conflicting, and the clinical relevance of the changes is also unclear; therefore the clinician has the option of separating cockroach or not.

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 with lesser activities, such as pollen extracts.

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.

In this regard the number of separate injections that need to be given at each patient visit depends on whether all of the relevant extracts mixed into a single vial still deliver an optimal dose of each allergen. If mixing causes excessive dilution or if there are advantages to separating allergens into separate vials, then more than one vial might be necessary for successful immunotherapy.

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extracts are high-alert products that carry the risk for anaphylaxis. Policies, procedures, and processes intended for conventional drugs and medications might be highly 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 fatal anaphylactic reactions with allergenic products. 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. There are no reports of infection associated with allergen immunotherapy injections. Allergen vaccines are prepared by using sterile manufacturer's extracts and sterile diluents containing antibacterial constituents (usually phenol). A summary of the AAAAI/ACAAI/JCAAI proposed USP allergen immunotherapy extract preparation guidelines can be found in Table VIII.

TABLE VIII. AAAAI/ACAAI/JCAAI-proposed USP 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 below.*
   - 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.
2. **Physician responsibility**: A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in the preparation of immunotherapy using an aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files.
3. **Bacteriostasis**: Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if 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 the FDA-approved package insert 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 treatment with sanitizing agents containing alcohol and/or 70% isopropanol 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 the physical integrity of the vial.
10. **Labeling**: Immunotherapy vials are to be clearly labeled with the patient's name and 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.

*__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 media, such as from Valiteq (http://www.valiteq.com), 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.

Allergen immunotherapy extract handling

Storage. Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

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 a number of 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 extract, including reconstituted lyophilized extracts, should be stored at 4°C to minimize the rate of potency loss because storage at higher temperatures (eg, room temperature) can result in rapid deterioration.[249]

Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions (personal communication). These studies include actual shipments made by their carriers to places like

Phoenix in the summer and Alaska in the winter. 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.

Storing dilute extracts. Summary Statement 34a: More dilute concentrations of allergy immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than do more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: In determining the allergy vaccine expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of 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 allergen immunotherapy 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.[249,250]

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.[250] Phenol is a preservative added to extracts to prevent growth of microorganisms.

Phenol can denature proteins in allergen extracts.[251,252] Human serum albumin might protect against the deleterious effect of phenol on allergen extracts.[251] 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,[250,253] possibly through inhibition of the activity of proteolytic and glycosidic enzymes that are present in certain extracts. However, it is irritating when injected and should be diluted before beginning immunotherapy. Recommendations for extract stability are found in the manufacturers' product insert sheets. 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. The pain associated with glycerin increases in proportion to the glycerin concentration and injection volume, and the pain is proportional to the total injected dose of glycerin.[254] However, individual pain perception can vary substantially. Total glycerin doses of less than 0.05 mL rarely produce clinically important pain.

TABLE IX. Potency of selected manufacturer's extracts currently available

Extract	Potency
Cat hair and pelt	5000 and 10,000 BAU/mL
Dust mite	3000, 5000, 10,000, and 30,000 AU/mL
Bermuda grass	10,000 AU/mL
Short ragweed	1:10-1:20 wt/vol or 100,000 AU/mL
Other grasses*	10,000 and 100,000 BAU/mL
Other pollen	1:10 to 1:40 (wt/vol) or 10,000 PNU/mL
Molds	1:10 to 1:40 (wt/vol) or 20,000 to 100,000 PNU/mL

AU, Allergy unit; *BAU*, bioequivalent allergy unit; *PNU*, protein nitrogen unit.
*Perennial rye, Kentucky blue/June, timothy, sweet vernal, redtop, orchard, and meadow.

There have been few studies that have investigated the potency of dilutions of allergen extract mixture over time. Expiration dates for allergen extract dilutions are somewhat empiric and not strongly evidence based. A study undertaken by the AAAAI 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. Dust mite and cat at 1:10 and 1:100 vol/vol dilution were also stable in all conditions of storage over 12 months, as measured by an ELISA assay using 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.

IMMUNOTHERAPY SCHEDULES AND DOSES

Summary Statement 35: A customized individual 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 can be based on single or multiple allergens. **D**

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. Animal dander contains between 10 and 20 antigens,[255] house dust mites between 20 and 40 antigens,[256] and pollens between 30 and 50 antigens,[257,258] and fungal extract can contain as many as 80 antigens.[259]

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. This is designated as the patient's maintenance concentrate.

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. Standardized extracts are available with biologic potencies of 10,000 and 100,000 BAU for grasses; 5000 and 10,000 BAU for cat allergen; 5000, 10,000, or 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 wt/vol extracts (Table IX). 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.

Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

The highest concentration of an allergen extract mixture that is projected to be used as the therapeutically effective dose is called the maintenance concentrate. This should be prescribed individually for each patient by an allergist/immunologist. 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 individual manufacturer's extracts. Some patients might be unable to attain the projected therapeutically effective dose of the maintenance concentrate because of local reactions, systemic reactions, or both (eg, cat, 1000 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose]; see Table X for probable effective therapeutic dose range). Such patients might need weaker dilutions of their maintenance concentrate. Even so, 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 referred to as the maintenance dose. The consistent use of this nomenclature system is essential because errors in choosing the correct vial are a common cause of systemic reactions, especially when the patient transfers from one physician to another. Therefore it is important that standard terminology be adopted by all physicians who prescribe allergen immunotherapy.

Recommended doses

Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

The effective maintenance dose of immunotherapy for a particular patient must be individualized. To do this, the allergist/immunologist who prepares the allergen immunotherapy extract must balance the dose necessary to produce efficacy and the risk of reactions if such a dose is reached. The allergist/immunologist might need to prepare more than one maintenance concentrate to provide a therapeutic dose of each of the allergens for the polysensitized patient. Therapeutically effective doses for immunotherapy have been reported for some allergen extracts.[22,24,25,128,134,135,149,246,260,261] Effective doses have been determined for Hymenoptera venom, dust mite, cat allergen, dog, grass, and short ragweed (Table X).

Controlled studies demonstrate that the content of particular allergens in allergen immunotherapy extracts can be used to predict a therapeutic dose for those allergens, particularly when the extracts are standardized. For antigens 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. The therapeutically effective doses used in the most recent controlled clinical studies are the basis of the recommended dosage range of standardized extracts presented in Table X. 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 time that it is administered.[14]

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.[27] 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 risk of systemic reactions to immunotherapy injections with higher maintenance doses. The maintenance concentrate should be formulated to deliver a full therapeutic dose of each of its constituent components. However, some sensitive patients might not tolerate the targeted therapeutic dose, and their maintenance dose would be lower. Individuals 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 referred to as the maintenance dose.

Regardless of dose schedule, some patients are unable to progress to the predetermined maintenance dose because of large local or systemic reactions to the allergen

TABLE X. Probable effective dose range for allergen extracts US standardized units[a]

Antigen	Labeled potency or concentration[a,b]	Probable effective dose range
Dust mites: *D farinae* and *D pteronyssinus*[c]	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat[d]	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized[e]	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed[f]	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 μg of Amb a 1 1000-4000 AU Concentration of Amb a 1 is on the label of wt/vol extracts in FDA units[358]
Nonstandardized extract, dog[g]	1:10 to 1:100 wt/vol	15 μg of Can f 1
Nonstandardized extracts	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose

[a]Multiple studies have demonstrated that the efficacious dose for allergen immunotherapy is between 5 and 20 μg of the major allergen per injection. Only 2 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).

[b]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).

[c]There have been no dose-response studies with United States–licensed dust mite extracts, and dosing recommendations in AU value are extrapolated from published European studies that used aqueous[349] and alum-precipitated[149,151] extracts. 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.[149] The authors suggested the optimal maintenance dose was 7 μg of Der p 1. Corresponding doses were based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Extrapolating effective and safe doses in this manner might not be scientifically valid. *D farinae* and *D pteronyssinus* are similar in group 1 allergen content according to the FDA's current reference standards. 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*.

[d]The major cat allergen Fed d 1 is reported in FDA units, with 1 Fel d 1 unit equaling approximately 2 to 4 μg of Fel d 1.[55,58,59] The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 to 19.9 U/mL. One study demonstrated clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 dose in terms of decreased cat extract PD_{20}, titrated skin test results, and allergen-specific IgE and IgG levels.[350,351] In a recent study that investigated the efficacy in terms of immunologic changes of 3 doses of a United States–licensed cat extract (0.6, 3, and 15 μg) demonstrated that a significant effect on titrated skin prick test results, allergen-specific IgG4 levels, and $CD4^+$/IL-4 levels was only seen in the group treated with 15 μg of Fel d 1, although the 3-μg dose group did demonstrate a significant change in titrated skin test response and increase in cat-specific IgG4 levels.[22]

[e]There have been no dose-response studies with United States–licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,[130] alum-precipitated,[24,161] and calcium phosphate–precipitated grass pollen extracts.[352] One of these studies compared a dose of 2 μg with 20 μg of major timothy allergen (Phl p 5) and found clinical efficacy at both doses.[24] The efficacy was greater in the 20 μg of Phl p 5 dose, but the systemic reaction rate was also higher in the high-dose group. The package inserts for United States–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 BAU. Extrapolating effective and safe doses in this manner might not be scientifically valid. 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).

[f]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 suggested that 1 unit of Amb a 1 is equivalent to 1 μg of Amb a 1, and 350 Amb a 1 units/mL is equivalent to 100,000 BAU/mL.[60] The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2000 AU, with a range of 1000-4000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrated 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.[45] A ragweed dose-response study (0.6, 12.4, and 24.8 μg of Amb a 1) demonstrated efficacy, as measured by nasal challenge, at 12 and 24 μg of Amb a 1.[128] The efficacy of the 24-μg dose was not significantly better than the 12-μg dose, and the authors concluded that the optimal dose for ragweed extract was greater than 0.6 μg but not more than 12.4 μg of Amb a 1.

[g]Dog extracts are not standardized. However, one dose-response study with a United States–licensed acetone-precipitated dog extract investigated the efficacy of 3 doses (AP dog; Hollister-Stier, Spokane, Wash; 0.6, 3, and 15 μg) in terms of immunologic changes and found the dose of 15 μg of Can f 1 to be most efficacious.[25] 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 have assayed between 128 and 208 μg/mL (average Can f 1, 162 μg/mL [SD ± 26 μg/mL]; information provided by the extract manufacturer, Hollister-Stier).

immunotherapy extract. The evidence is not clear whether large local reactions are a potential risk for subsequent allergen immunotherapy systemic reactions.

Published studies do not indicate that an individual large local reaction is predictive of a subsequent systemic reaction.[179,180] However, one retrospective study found that individuals who have a history of repeated large local reactions (defined as >25 mm) might be at greater risk for a subsequent systemic reaction.[181]

The concept of highest tolerated dose does not apply for VIT, and all patients are expected to achieve the full recommended dose to achieve the necessary degree of protection. There are conflicting data over whether lower doses (50 μg) are less effective, but there are also data showing that 200 μg is more reliably effective.[245] In the case of VIT, patients are asked to tolerate more large local reactions to achieve the full dose, even though with inhalant immunotherapy the dose can be reduced for such large local reactions to minimize patient discomfort.

Effect of dilution on dose

Summary Statement 38: 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 vaccine, thereby limiting the ability to deliver a therapeutic effective dose for any given allergen.

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

Dilution from maintenance concentrate vaccine	Volume	Volume (mL)	Diluent volume (mL)	Final volume
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.

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 2000 BAU/mL, 2 mL of the manufacturer's extract (cat, 10,000 BAU/mL) can be added to 8 mL of diluent or 8 mL of other allergens, and the final concentration of cat will be 2000 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.

Dilutions of the maintenance concentrate

Summary Statement 39: 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 vol/vol 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, 1000 BAU or 100 BAU), but this system can be complicated if allergens with different potency units are used (eg, wt/vol, BAU, AU, or PNU) and make it difficult to easily interpret the vial label.

Instructions on how to prepare various allergen extracts 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.

Labeling dilutions

Summary Statement 40: 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, a number of 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 (vol/vol), a numbering system, a color-coding system, or an alphabetical system should be used. If this uniform labels 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.

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
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

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 3 and 4).

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 Appendix 2]).

Individualized treatment vials

Summary Statement 41: 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 (wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for 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). Labels on patient-specific vials can provide at least 2 patient identifiers (birth date and patient name), which would be consistent with the recommendations of the Joint Commission on Accreditation of Health Care Organizations National Patient Safety Goals: ''Goal 1: Improve the accuracy of patient identification by using at least two patient identifiers when providing care, treatment or services.''[5] 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 administration of the injection.[4,5]

In a survey of 1717 allergists endorsed by the AAAAI and JCAAI, 57% of the 476 respondents reported at least one wrong-patient injection, and 74% of the 473 respondents reported at least one wrong-dose injection.[4] 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 reasons why this might reduce incorrect injection errors. One reason was that patient-specific vials can be prepared in a quiet laboratory setting, which might provide substantially less distraction than the nurse in a room with a patient who is trying to concentrate only on drawing up the injection correctly. In addition, the specific components are mixed once with the preparation of individually prepared patient-labeled vials, whereas the mixing would be repeated on every injection visit if the allergen extract is withdrawn from different stock solutions, as it is in the off-the-board method. For safety reasons and to avoid cross-mixing of allergens removed from the manufacturer's extract, the mixing of antigens in the syringe (off the board) is not recommended.

Some allergists/immunologists prefer to administer immunotherapy doses drawn directly from a single stock dilution of individual allergens or common mixes (shared specific patient vials). In this way the immunotherapy dose is transferred to the patient without cross-contamination. If shared-patient (eg, mixed vespids and dust mite mix) vials are used, it is essential that policies and procedures are developed to verify that the correct dose from the correct vial is administered to the correct patient.

Starting doses

Summary Statement 42: The starting dose for build-up is usually a 1000- 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 slowly 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 1:1000 (vol/vol), although more diluted concentrations frequently are used for patients who are highly sensitive, as indicated by history or skin test reaction (see Appendix 3 for an example of a conventional immunotherapy schedule).

Frequency of build-up injections

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 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 2 times per week. 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 4 to 6 months, depending on the starting dilution and the occurrence of reactions. It is acceptable for patients to receive injections more frequently, provided there is adequate spacing between injections. The interval between injections is empiric but might be as short as 1 day without any increase in the occurrence of systemic reactions[262] if there is some urgency to achieve a maintenance dose (eg, allergy season is approaching) or for practical reasons (eg, patient's schedule). Alternatively, treatment schedules can be used that more rapidly achieve maintenance dosing. These cluster and rush dosing schedules are discussed in Summary Statements 47 through 49.

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 a number of 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).

Dose adjustments for systemic reactions

Summary Statement 44: 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 benefit/risk ratio justifies continuation of immunotherapy.

Reductions during periods of exacerbation of symptoms

Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Immunotherapy administered during periods of exacerbation of symptoms is considered a risk factor for immunotherapy.[17,184] Injections administered during periods when a patient is exposed to increased levels of allergen to which they are 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.[184] 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 sensitive, especially if their symptoms are poorly controlled.

Dose adjustments for late injections

Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

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 depends 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 Appendix 4 for an example of a dose-modification regimen for gaps in treatment).

Cluster schedules

Summary Statement 47: 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 (see Appendix 5).[22,26] 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. The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules.[145,263-266] The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.[267]

Rush schedules

Summary Statement 48: 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.[268] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.[191,269-272]

The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections over the course of 4 hours.[273] Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours.[274-276] 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 cluster[145,266] and rush[134,277] schedules.

Systemic reactions and rush schedules

Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

The advantages of rush immunotherapy come at a cost because there is an increased risk of local and systemic reactions. Systemic reaction rates have been reported to be

as high as 73% of patients, with the risk of such reactions reduced to 27% by premedication in one study.[272] Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing.[273]

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

Rush protocols for administration of Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions.[274-276,278,279]

Premedication and weekly immunotherapy

Summary Statement 50: Premedication can reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

There is concern that antihistamines taken before each injection with conventional immunotherapy might mask a minor reaction that would otherwise alert a physician to an impending systemic reaction. 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.[280] One study that compared terfenadine premedication with placebo premedication during rush VIT demonstrated greater clinical efficacy in the terfenadine-premedicated group in terms of subsequent responses to field stings or sting challenge.[281] There was also a significant difference in the systemic reaction rate between the 2 groups: 6 patients in the placebo-premedicated group had systemic reactions, whereas none of the patients in the terfenadine-premedicated group had systemic reactions ($P = .012$).

Unfortunately, patients might still have life-threatening anaphylaxis despite 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.

Premedication with cluster and rush immunotherapy

Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

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.[267] Premedication with a 3-day course of prednisone, an H_1 histamine receptor antagonist, and an H_2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.[272] In one study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on the safety and efficacy of rush immunotherapy, there was a 5-fold decrease in the risk of anaphylaxis in the group premedicated with omalizumab compared with the placebo premedication group.[282]

There are anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist, but there have been no published studies. Because the risk of a systemic reaction from rush VIT is relatively low, routine premedication before rush VIT is usually unnecessary.[274,276,278,279] In a study evaluating premedication with antihistamines and steroids for rush immunotherapy with imported fire ant venom, there was no statistically significant differences in the systemic reaction rates between the premedication and placebo premedication group (3.6% of the premedication group vs 6.7% of the placebo group, $P = .87$).[157]

Maintenance schedules

Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals 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 individuals might tolerate longer intervals between maintenance dose injections.

The interval between venom injections can be safely increased up to 8 weeks in some patients without loss of efficacy. 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.

Continuing care

Time course of improvement. Summary Statement 53: Clinical 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.[24,134,143,277] Improvement might not be observed for a number of reasons, including (1) failure to remove significant allergenic exposures (eg, a cat), (2) exposure to high levels of

allergen (eg, pollen or molds), (3) continued exposure to nonallergen triggers (eg, tobacco smoke), or (4) incomplete identification and treatment of clinically relevant allergens. 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 54: 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 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 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

The patient's response to immunotherapy should be evaluated on a regular basis. 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. 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.

There have been very 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 individuals.[283-285] However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported.[283,285] Nevertheless, systemic reactions to stings after discontinuing VIT were generally much milder than the pretreatment reactions and were rarely severe. Two studies did not find a difference in relapse rates between the patients treated for 3 years compared with those treated for 5 years,[283,286] but one of the studies noted that the small number of patients in the 3-year treatment group prevented them from making any conclusions about the risk of discontinuing treatment after 3 years.[283] However, one study found that patients who had experienced re-sting reactions after discontinuing VIT had received VIT for a significantly shorter duration (mean, 43.35 months) than those with continued protection (mean, 54.65 months; $P < .01$).[285] Another study reported that 5 years of VIT provided better immunologic and clinical outcomes than 2 to 4 years of treatment.[287]

Change in skin test reactivity did not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who experienced a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE.[286,288] Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment.[288] The relapse rate and the frequency of severe reactions were greater in patients who had a history of very severe reactions to stings before treatment, in patients who had systemic reactions during VIT (to a sting or a venom injection), in patients with honeybee allergy, and in those who had less than 5 years of treatment.

The duration of inhalant allergen immunotherapy efficacy has not been as extensively studied. Some studies have suggested 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 *(D pteronyssinus)* extract for 12 to 96 months.[14] 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.[13] There was a switch to placebo in half of 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. These studies demonstrate the uncertainty of the long-term benefit of inhalant immunotherapy after discontinuation.

Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained clinical remission after discontinuing inhalant immunotherapy, and 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 indication for continuation of immunotherapy can be found at http://www.aaaai.org or http://www.jcaai.org.

Documentation and record keeping. Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully 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 allergy immunotherapy and prescription forms can be found in the Appendix (Appendices 6-15), and these include examples of immunotherapy prescription and administration forms. These forms, along with examples of immunotherapy consent and instruction forms, can also be found at http://www.aaaai.org.

Injection techniques. Summary Statement 57: Allergen immunotherapy extract injections should be given using a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **C**

Immunotherapy should be given with a 26- to 27-gauge syringe with a half-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.[289-291]

If using shared specific patient vials (stock vials, such as mixed vespid or dust mite mix), a single dose should be drawn from each vial. Antigens from different vials should not be combined in a single syringe. Furthermore, extra care is needed to prevent using the wrong stock antigen.

Summary Statement 58: The injection should be given subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Each immunotherapy injection should be given in the posterior portion of the middle third of the upper 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.

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.

The syringe should be aspirated to check for blood return in the syringe before injecting. If blood is present, 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 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 syringe should be appropriately discarded. A fresh syringe and needle are necessary to determine whether a blood vessel has been entered.

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 could result in a local reaction.

LOCATION OF ALLERGEN IMMUNOTHERAPY ADMINISTRATION

Physician's office

Summary Statement 59: 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 to treat anaphylaxis should be in the immediate vicinity when immunotherapy injections are administered.

Summary Statement 60: 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.[292] 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.[184] 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 might be frequently necessary in the patient's immunotherapy schedule, as well as the patients total treatment program.

Other locations

Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **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.[292] The health care professional and staff 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, or allergy/asthma exacerbations at the time of allergen immunotherapy extract injection or poorly controlled asthma).

Appropriate adjustment of dose should be made as clinically indicated. The physician who prepared the patient's allergen immunotherapy extract should provide adequately labeled allergen immunotherapy extract vials, detailed directions regarding dosage schedule for build-up and maintenance, and instructions on adjustments that might be necessary under the following circumstances:

1. when providing patients with new vials;
2. during seasonal exposure to allergens that are in the patient's allergen vaccine, to which the patient is very sensitive, or both;
3. if the patient has missed injections; and
4. when reactions occur to the allergen immunotherapy extract.

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

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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 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 very 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 fully trained to administer the injection and to treat anaphylaxis if this should 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 supports (personnel, medications, supplies, and equipment) are more optimal for encouraging prompt recognition and treatment of anaphylaxis (Table V). 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.

Summary Statement 63: If a patient on 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for their immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extracts might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Patients often 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 brought from the previous physician (ie, an unchanged immunotherapy program) or one to be prepared by the current physician (ie, a new immunotherapy program).

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 full, clear, and detailed documentation of the patient's previous schedule and the contents of the allergen immunotherapy extract (see Appendices 7, 8, 11, 12, and 14 for examples of allergen immunotherapy prescription and administration forms and documentation guidelines for allergen immunotherapy forms). In addition, the patient's previous response to and compliance with this program 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 a schedule and the allergen immunotherapy extract, (2) the patient has shown significant improvement on this immunotherapy program, and (3) the contents of the allergen immunotherapy extract are appropriate for the area in which the patient is now living.

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, vaccine type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient's dose is not modified. This increased risk is due to the significant variability in content and potency of extracts and the variability in methods used by physicians to prepare the patient's maintenance concentrate and its dilutions. For example, the strength of a given concentration of nonstandardized extracts might vary significantly from vial to vial. The risk of systemic reactions in such a situation might be greater with nonstandardized extracts and allergen immunotherapy extracts that contain mixtures of allergens.

Therefore if the allergen immunotherapy extract is to be changed, the patient might need to be retested for specific IgE to the appropriate allergens 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 provided the interval of time since the last injection has not been too long. For lot changes from the same manufacturer, the physician can consider decreasing the dose by 50% to 90%. For changes in manufacturer and nonstandardized extracts, a greater decrease in dose might be necessary.

SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

Allergen immunotherapy in children

Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children

with allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Immunotherapy for children has been shown to be effective and often well tolerated,[137,242] although at least one study did not show efficacy.[293] 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.[294] In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (see the Patient selection section and Table VII). In recent studies children receiving allergen immunotherapy have demonstrated:

1. improvement in symptom control for asthma[117,119,121,122] and allergic rhinitis[118];
2. increased PC_{20} to histamine[121];
3. increased PC_{20} to cat and house dust mite allergens[121,149];
4. decreased risk of development of asthma[6,9,163-165];
5. decreased development of new sensitivities[120,166]; and
6. modification in release of mediators in children receiving immunotherapy that correlates with decreased clinical symptoms.[123]

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Although there is some disagreement about the role of allergen immunotherapy in children under the age of 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.[117,122] In children with allergic rhinitis, allergen immunotherapy might prevent the development of asthma.[6,9,163-165] However, allergen immunotherapy for inhalant allergens is usually not considered necessary in infants and toddlers because (1) there is 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 in pregnancy

Summary Statement 71: Allergen immunotherapy might be continued but is usually not initiated in the pregnant patient. **C**

The physician must be aware of the benefits and risks of immunotherapy in pregnant patients. The recommended precautions for prevention of adverse reactions are especially important in the pregnant patient. Allergen immunotherapy is effective in the pregnant patient. Thus allergen immunotherapy maintenance doses can be continued during pregnancy. Allergen immunotherapy is usually not initiated during pregnancy because of risks associated with systemic reactions and their treatment (ie, spontaneous abortion, premature labor, or fetal hypoxia). 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, and the patient is maintained on the dose that she is receiving at that time.

Immunotherapy in the elderly patient

Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy might be considered in the treatment of the elderly patient, but the benefit/risk assessment must be evaluated carefully in this population. Older 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. However, elderly patients may also benefit from allergen immunotherapy and age alone should not preclude the consideration of allergen immunotherapy.[295]

Immunotherapy in patients with immunodeficiency and autoimmune disorders

Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with immunodeficiency or autoimmune disorders. Therefore the decision to begin immunotherapy in patients with major humoral or cellular immune defects must be individualized. Concern about the increased risk of immunotherapy in such patients is largely hypothetical.

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

ALTERNATIVE ROUTES OF IMMUNOTHERAPY

Sublingual and oral immunotherapy

Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be

effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no FDA-approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **B**

Alternative routes of administration of allergen immunotherapy are ''a viable alternative to parenteral injection therapy'' in some cases.[106,296] Studies of oral immunotherapy have provided conflicting results for ragweed,[297] birch,[298] and cat[299] immunotherapy. The present dosage of oral immunotherapy extract is 20 to 200 times the parenteral injected dosage, which requires a cost assessment for this type of therapy. Furthermore, adverse effects have included gastrointestinal and oral reactions (50% in 1 study) that might preclude home therapy. Oral immunotherapy should be considered investigational at this time.

Optimal-dose (high-dose) sublingual swallow immunotherapy is effective in adults and children.[300-304] In a study of 855 patients with grass pollen allergy and allergic rhinitis randomized to placebo or one of 3 grass tablet doses, there was a significant reduction in symptom and medication scores in the highest-dose subgroup, who were treated for at least 8 weeks before the grass pollen season, compared with the placebo group (symptoms, 21%, $P = .0020$; medication use, 29%, $P = .0120$).[303]

Sublingual allergen studies have evaluated house dust, olive pollen, grass pollen, ragweed, birch, cat, latex, *Alternaria* species, and *Parietaria judaica*.[305-313] Sublingual immunotherapy has been shown to be effective in patients sensitized to 2 non–cross-reacting allergens, grass and birch.[314] It has been noted that the allergen is not degraded by saliva and that there is no direct sublingual absorption of allergen. Radiolabeled allergen has been detected after 48 hours in the sublingual region.[315,316] Alternative protocols, such as rush and ultra-rush (20 minutes) sublingual swallow[307,316,318] and no induction (build-up) phase,[301,303,317,319,320] have been studied. Several studies have suggested a relationship between dose and efficacy with sublingual immunotherapy,[303,310,321] but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. The majority of sublingual studies have demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both, but approximately 35% of the randomized, double-blind, placebo-controlled studies did not demonstrate efficacy in either parameter during the first year of treatment.[322] Further studies are needed to confirm the optimal dose for sublingual immunotherapy.

One of the potential advantages of sublingual immunotherapy is that it appears to be safe, even at very high doses (up to 500 times the usual monthly subcutaneous dose), and to be associated with a lower incidence of serious side effects.[310,320,323] This appears to apply to young children (<5 years), for whom there are prospective safety data[324,325] and a postmarketing survey.[326]



FIG 3. Sample of labels for allergen immunotherapy extract vials.

There have been no SLIT-related fatalities, but there have been 3 case reports of anaphylaxis caused by sublingual immunotherapy. One patient with latex hypersensitivity had anaphylactic shock 20 minutes after reaching the maximal dose on the fourth day of latex rush sublingual rush immunotherapy.[327]

The other 2 reported cases of SLIT anaphylaxis involved patients treated with multiple inhalant allergens. In one case a patient with allergic rhinitis and asthma who was prescribed a sublingual immunotherapy extract composed of multiple non–cross-reacting allergens (*Alternaria* species, dog, cat, ragweed mix, weed mix, and grass mix)[328] had generalized pruritis, followed by angioedema, shortness of breath, and dizziness, within a few minutes of administering 6 drops of the 1:100 vol/vol dilution on the third day of treatment. This episode was preceded by a milder systemic reaction the previous day (generalized pruritis). In the other case, a 13-year-old girl with allergic rhinitis and asthma had swelling of her lower lip 3 minutes after pollen drops, high fever, chest pain, nausea, and abdominal pain.[329] She was treated in the emergency department for anaphylaxis and hospitalized for observation. The reaction occurred 1 month after she had reached the maintenance dose during the peak of the spring season.

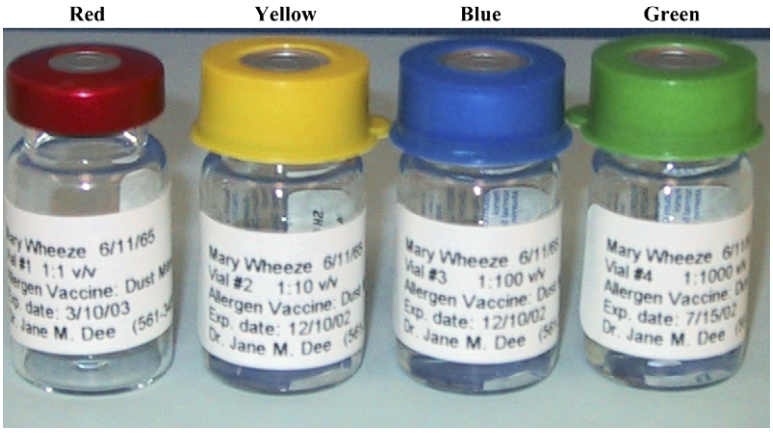


FIG 4. Sample set of color-coded vials of allergen vaccine.

There is currently no FDA-approved formulation for sublingual immunotherapy in the United States at this time, and this modality should be considered investigational. Current investigation of sublingual immunotherapy should not be confused with low-dose sublingual immunotherapy based on provocation neutralization testing or Rinkel-type skin testing.

Intranasal immunotherapy

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Based on controlled, well-designed studies, intranasal immunotherapy has been shown to improve the nasal symptoms of rhinitis.[330] Intranasal dry powder extract immunotherapy has been studied in grass,[330] birch,[331] *P judaica*,[332-334] and house dust mite[335] allergy. Clinical efficacy was noted in all of these studies. Nasal reactivity to allergen challenge was reduced, and only minor side effects were noted in 2 of the above studies. A 3-year study with *P judaica* reported to provide persistent benefits for up to 12 months after conclusion of allergen immunotherapy.[333] Local administration of nasal allergen in an aqueous solution for immunotherapy might be limited by the local side effects. Further studies in both pediatric and adult groups are needed. In human studies the antigen has been noted to appear in the serum within 15 to 30 minutes of administration, with a peak level occurring within 2 to 3 hours.[315] Some allergens have been reported to be retained in the nasal mucosa for up to 48 hours after administration. Intranasal immunotherapy is not currently available in the United States but has gained some acceptance in other parts of the world.

Immunotherapy techniques that are not recommended

Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

Low-dose regimens, including coseasonal low-dose immunotherapy for aeroallergens and the Rinkel low-dose titration techniques, are not effective.[27,28] Immunotherapy based on provocation–neutralization testing with food and aeroallergens and enzyme-potentiated desensitization is not effective.[336]

FUTURE TRENDS IN IMMUNOTHERAPY

Therapy with aeroallergen extracts will become more uniform (as is the current practice for insect venoms) as greater numbers of biologically standardized allergen extracts become available. The actual number of commercially available allergen extracts will be reduced based on consensus agreements about the regional prevalence of aeroallergens, their cross-allergenicity, and the relevance of their effect on human health in specific locales. Novel routes for more effective, convenient, and safer allergen immunotherapy are being investigated throughout the world.

For example, the sublingual route of administering allergen immunotherapy has been studied extensively in Europe. A meta-analysis confirmed its clinical effectiveness in allergic rhinitis,[302] and it has been reported to be effective in asthma as well.[337] Sublingual immunotherapy appears to have a very low risk of serious life-threatening systemic side effects, which might allow for home administration.[324,338] In some studies the clinical benefits of sublingual immunotherapy were not significant until the second year of treatment,[306,339] and comparisons suggest that the magnitude of the clinical benefit of sublingual immunotherapy might not be as great as that of subcutaneous immunotherapy.[311]

Trials with non–IgE-binding peptides containing T-cell stimulating peptides have been reported.[340] Site-directed mutagenesis has produced allergens with decreased IgE-binding capacity without decreased T-cell responses.[341,342]

Immunostimulatory sequences mimicking bacterial and viral DNA have been prepared that stimulate the innate immune system to direct T-cell responses toward

T_H1 rather than T_H2 phenotypes.[343] The results of clinical trials with a conjugate of the immunostimulatory sequence to the major allergen of ragweed, Amb a 1 (AIC), have been reported.[34,343] In a double-blind, placebo-controlled study of 25 adults who received 6 weekly injections of the AIC or placebo vaccine before ragweed season, the AIC group had better peak-season rhinitis scores on the visual analog scale ($P = .006$), peak-season daily nasal symptom diary scores ($P = .02$), and midseason overall quality-of-life scores ($P = .05$) than the placebo group during the first ragweed season, and this effect was observed in the subsequent ragweed season.[344]

Humanized anti-IgE mAb has been shown to have clinical effects in both allergic rhinitis and asthma.[345-348] Theoretically, this new therapeutic modality could be used as protective cover for clinical applications of rapid forms of immunotherapy. It is possible that preadministration of anti-IgE could provide a more effective protective effect than premedication with antihistamines and therefore permit a rush allergen immunotherapeutic regimen with reduced risk of serious systemic reactions.[282]

AUTHOR'S 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 2 systemic reaction grading systems (the European Academy of Allergy and Clinical Immunology's grading of severity for systemic side effects and the Portnoy method for numeric grading of reactions to allergen immunotherapy) can be found in the Appendix section. These forms can also be found along with examples of immunotherapy instruction and consent forms, preinjection health questionnaires, and indications for beginning and continuing immunotherapy forms at www.aaaai.org.

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APPENDIX 1. American College of Medical Quality's policy on the development and use of practice parameters for medical quality decision-making[1]

Practice parameters are strategies for patient management developed to assist health care professionals in clinical decision making. Practice parameters include standards, guidelines, and other patient management strategies. Standards are accepted principles for patient management. Guidelines are recommendations for patient management that identify a particular management strategy or a range of management strategies. Other strategies for patient management include practice policies and practice options. Practice parameters are to be used as screening tools to identify possible deviations from the applicable standards of care. Such parameters are not to be used as absolute standards or to profile or report on health care personnel. Parameters are designed to trigger a process in which possible deviations from the standard of care are identified as outlier practice patterns. Once a deviation from the parameter is identified, such a deviation should be referred to the appropriate qualified physician advisor or reviewer for a determination of medical necessity that conforms to the applicable standard of care. Parameters used in the day-to-day practice of clinical medicine should be clinically relevant. They should not be considered as substitutes for the standard of care but might contribute to its formulation.

Practice parameters must be developed, designed, and implemented only by board-certified, clinically practicing, specialty-matched physician advisors/reviewers with unrestricted medical licenses. Qualified nonphysicians might participate in the development of these parameters only in the areas in which their clinical expertise based on the standard of care is applicable. The health care personnel who develop these parameters should sign their names and date the final version as evidence of their participation and support. Practice parameters must be based on sound scientific research findings, professional literature, clinical experience and appropriate well-recognized methodologies and reflect professionally recognized national standards of care practiced in the clinical community of medicine. The development procedures followed, the participants involved, the evidence used, the assumptions and rationales accepted, and the analytic methods used should be meticulously documented, described, and made publicly available for national peer review. Parameters should be updated as needed.

Practice parameters are used as tools to enhance medical decision making but not as replacements for physicians' clinical judgment. They can be considered as means to enhance the performance of clinical and review personnel but not to replace them. It is below the standard of care of the medical review process to substitute qualified physician reviewer experts with unqualified reviewers who are using parameters.

APPENDIX 2. Examples of possible abbreviations for allergen immunotherapy extract 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

APPENDIX 3. 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

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

APPENDIX 4. Example of immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals (modification of the AAAAI skin testing and immunotherapy consent and instruction forms: immunotherapy administration instruction form, which can be found at http://www.aaaai.org)

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

- Up to 7 days, continue as scheduled (ie, if on weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection).
- Eight to 13 days after missed scheduled injection; repeat previous dose.
- Fourteen to 21 days after missed scheduled injection; reduce dose 25%.
- Twenty-one to 28 days after missed scheduled injection; reduce previous dose 50%.

Then increase dose each injection visit as directed on the immunotherapy schedule until therapeutic maintenance dose is reached.

This suggested approach to modification of doses of allergen immunotherapy because of gaps between treatment during the build-up phase is not based on retrospective or prospective published evidence, but it is presented as a sample for your consideration. The individual physician should use this or a similar protocol as a standard operating procedure for the specific clinical setting. A similar dose-reduction protocol should be developed for gaps in maintenance immunotherapy.

APPENDIX 5. Example of a cluster immunotherapy schedule[22,26]

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

APPENDIX 6. Recommended documentation for allergen immunotherapy prescription forms

The purpose of the allergen immunotherapy prescription form is to define the contents of the allergen immunotherapy extract in enough detail that it could be precisely duplicated. The following information should be on an immunotherapy prescription form:

Patient information:

- Patient name, patient number (if applicable), birth date, telephone number, and picture (if available) should be included.

Preparation information:

- Name of person and signature preparing the allergen immunotherapy extract should be included.
- Date of preparation should be recorded.
- Bottle name should be included (eg, trees and grass). If abbreviations are used, a 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 should be included.
- Volume of manufacturer's extract to add to achieve the projected effective concentration should be included. 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) should be included.
- Extract manufacturer should be included.
- Lot number should be included.
- Expiration date should be recorded and should not exceed the expiration date of any of the individual components.

APPENDIX 7. Allergen immunotherapy extract prescription 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:

_____
_____
_____
_____

_____ ____/____/____
Prescribing Physician Signature Date

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

APPENDIX 8. Maintenance concentrate prescription form

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: 6/10/06

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial **4** from Vial **1** on **8/30/06** Expiration date: **10/15/06**
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	Short ragweed	1:20 w/v G (150 Amb a1)	0.5ml	Greer	12345	1/01/08
2	Amaranthus Retroflexus	1:10 w/v G	0.5ml	H-S	6789	2/07/08
3	Ash	1:10 w/v G	0.5ml	Center	3333	3/17/08
4	Cat	10,000 BAU/ml G	2.00ml	ALO	9898	2/27/08
5	Timothy Grass	100,000 BAU/ml G	0.4ml	ALK	56789	7/09/08
6	Johnson Grass	1:10 w/v G	0.5ml	Greer	2434	7/20/08
7						
8						
9						
10						
Diluent	HSA		0.6ml	ALK	68597	12/08
Total Volume			5.00 ml			6/10/07

*** Components of mixes listed on a separate sheet**
**** Assumes 0.5 ml injection as target maintenance dose**

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

Specific Instructions:

_____

_____

Prescribing Physician Signature

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

APPENDIX 9. Labels for allergen immunotherapy extracts

Each vial of allergen immunotherapy extract should be labeled in a way that permits easy identification. Each label should include the following information (example in Figs 3 and 4):

- Appropriate patient identifiers might include the patient's name, patient's number, patient's picture, and birth date.
- The contents of the allergen immunotherapy extract in a general way should be included. The detail with which this can be identified depends on the size of the label and the number of allergens in the vial. Ideally, allergens should be identified as trees, grasses, weeds, mold, dust mite, cockroach, cat, and dog. Because of space limitations, it might be necessary to abbreviate the antigens (eg, T, G, W, M, DM, Cr, C, and D respectively [see Appendix 2]). A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate (vol/vol) should be recorded. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- The expiration date should be included.

APPENDIX 10. Allergen immunotherapy administration form recommended documentation

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

Patient information:

- Patient's name, date of birth, telephone number, and patient's picture (optional but helpful).

Allergen immunotherapy extract information:

- Allergen immunotherapy extract name and dilution from maintenance in vol/vol bottle letter (eg, A and B), bottle color, or number, if used.
- Expiration date of all dilutions.

Administration information in separate columns:

- Date of injection.
- Arm administered injection, which might facilitate determination of exact cause of local reaction.
- Projected build-up schedule.
- Delivered volume reported in milliliters.
- Description of any reactions. The details of any treatment given in response to a reaction would be documented elsewhere in the medical record and referenced on the administration form.
- *Patient's health before injection*. This can be performed through a verbal or written interview of the patient before administering the immunotherapy injection. The patient should be questioned about increased asthma or allergy symptoms, β-blocker use, change in health status (including pregnancy and recent infections), or an adverse reaction to a previous injection (including delayed large local reactions persisting through the next day). Patients with significant systemic illness generally should not receive an injection.
- *Antihistamine use*. Antihistamines are frequently a component of an allergy medication regimen, and it would be important to note whether a patient is taking an antihistamine on the day he or she receives his or her immunotherapy injection. For consistency in interpretation of reactions, it might be desirable for a patient to either take or avoid antihistamines on a regular basis on the days he or she receives immunotherapy. The physician should note on the form whether he or she recommends the patient consistently take an antihistamine on immunotherapy treatment days.
- *Peak flow reading*. Consider obtaining a peak expiratory flow rate measurement before administering an immunotherapy injection to asthmatic patients. Poorly controlled asthma is considered a risk factor for immunotherapy. Obtaining a peak expiratory flow rate measurement before the immunotherapy injection might help identify patients with symptomatic asthma. The patient's baseline peak expiratory flow rate should be provided on the form as a reference. Health care professionals administering immunotherapy injections should be provided with specific guidelines about the peak expiratory flow rate measurement for when an immunotherapy injection should be withheld and the patient referred for clinical evaluation.
- **Baseline blood pressure**. It might be useful to record the patient's blood pressure as a baseline for future reference.

APPENDIX 11. Allergen immunotherapy administration form

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 allergy or 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

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

Date to reorder: __/__/__

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 allergy or 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**	

APPENDIX 12. 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: _____
_____
Staff action taken (if any): _____

APPENDIX 13. 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.

APPENDIX 14. Allergen immunotherapy systemic reaction/anaphylaxis 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
__Epinephrine IM into 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	

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:
_____
_____
_____
_____

Clinical impression: True SR Questionable SR No SR

Systemic reaction severity classification: EAACI_____ **Portnoy** _____

Dosage adjustment? _____

Signatures_____ **RN** _____**MD/DO**

APPENDIX 15. Grading severity of allergen immunotherapy reactions: Two methods

1. **The European Academy of Allergy and Clinical Immunology grading of severity for systemic side effects***

Classification of systemic reactions

0 = No symptoms or nonspecific symptoms

I = Mild systemic reactions: symptoms—localized urticaria, rhinitis, or mild asthma (PF <20% decrease from baseline).

II = Moderate systemic reaction: symptoms—slow onset (>15 minutes) of generalized urticaria, moderate asthma, or both (PF < 40% decrease from baseline).

III = Severe (non–life-threatening) systemic reactions: symptoms—rapid onset (<15 minutes) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).

IV = Anaphylactic shock: symptoms—immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, and hypotension, for example.

2. **Portnoy method for numeric grading of reactions to allergen immunotherapy†**

Local

0+ = No significant reaction or small area of erythema less than the size of a half dollar without swelling or wheal formation

1+ = Erythema greater than the size of a half dollar, swelling or wheal formation, or both

Systemic

2+ = Systemic reactions: cutaneous only—might consist of a cutaneous eruption, such as urticaria

3+ = Systemic reaction: generalized pruritus, sneezing, or both—might consist of increased allergy symptoms, such as nasal congestion, sneezing, or pruritus, especially in the mouth or throat

4+ = Systemic reaction: pulmonary—consists of wheezing, shortness of breath, and tightness. Might be associated with decreased pulmonary function tests

5+ = Systemic reaction: anaphylaxis—a sensation of not feeling right is a frequent prelude; might consist of hypotension, laryngeal edema, severe wheezing, and cramping

6+ = Cardiopulmonary arrest

PF, Peak expiratory flow.

*Subcutaneous immunotherapy. Allergy 2006;61(suppl 82):5-13.

†Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80.

Allergen immunotherapy: A practice parameter second update

Supplement Editor: **Linda Cox, MD**
Co-editors: **James T. Li, MD, Harold Nelson, MD, and Richard Lockey, MD**

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

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the "Allergen immunotherapy: a practice parameter second 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 and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
5. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
6. The diagnosis and management of anaphylaxis. J Allergy Clin Immunol 1998;101(suppl):S465-S528.
7. Algorithm for the diagnosis and management of asthma: a practice parameter update. Ann Allergy 1998;81:415-20.
8. Diagnosis and management of rhinitis: parameter documents of the Joint Task Force on Practice parameters in Allergy, Asthma and Immunology. Ann Allergy 1998;81(suppl):S463-S518.
9. Parameters for the diagnosis and management of sinusitis. J Allergy Clin Immunol 1998;102(suppl): S107-S144.
10. Stinging insect hypersensitivity: a practice parameter. J Allergy Clin Immunol 1999;103:963-80.
11. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999;83(suppl): S665–S700.
12. Diagnosis and management of urticaria: a practice parameter. Ann Allergy 2000;85(suppl):S521-S544.
13. Allergen immunotherapy: a practice parameter. Ann Allergy 2003;90(suppl):SI-S540.
14. Symptom severity assessment of allergic rhinitis: part I. Ann Allergy 2003;91:105-14.
15. Disease management of atopic dermatitis: an updated practice parameter. Ann Allergy 2004;93(suppl): S1-S21.
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These parameters are also available on the internet at http://www.jcaai.org.

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PREFACE

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

The objective of ''Allergen immunotherapy: A practice parameter second update'' is to optimize the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. 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's ''Policy on development and use of practice parameters for medical quality decision-making'' (Appendix 1).[1]

This document builds on the previous Joint Task Force document, ''Allergen immunotherapy: a practice parameter'' published in the *Annals of Allergy, Asthma and Immunology* in 2003.[2] The updated practice parameters draft was prepared by Drs Linda Cox, James Li, Hal Nelson, and Richard Lockey. The Joint Task Force reworked the initial draft into a working draft of the document. The project was exclusively funded by the 3 allergy and immunology societies noted above.

In preparation for the 2003 ''Allergen immunotherapy: a practice parameter'' and the second update, a comprehensive search of the medical literature was conducted with various search engines, including PubMed; *immunotherapy*, *allergic rhinitis*, *asthma*, *stinging insect allergy*, and related search terms were used. 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 second update'' was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the ACAAI, AAAAI, and JCAAI. In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for review and comments from members of the sponsoring organizations. 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 allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. This document also contains recommendations for the safe practice of allergen immunotherapy, including specific recommendations on the prevention and management of 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 or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. Symptoms of allergic conjunctivitis (eg, itchy watery eyes) are often considered part of allergic rhinitis or are included in the diagnosis of rhinoconjunctivitis. Particularly good candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures, those in whom it is important to avoid the potential adverse effects of medications, and those who wish to reduce the long-term use of medications. Immunotherapy is recommended for patients with a history of systemic reaction to Hymenoptera stings and specific IgE antibodies to Hymenoptera venom.

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.[3]

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. 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 *maintenance concentrate* should be used to identify the allergen immunotherapy extract that contains a therapeutic effective dose for each of its individual constituents (see the Immunotherapy schedules and doses section).

The term *manufacturer's extract* refers to the allergy extract purchased from the manufacturer. The terms *stock*, *full-strength*, and *concentrate* are ambiguous and should not be used. 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).

Allergen immunotherapy is effective when appropriate doses of the allergens are administered. ''Allergen immunotherapy: A practice parameter'' recommends that vials of allergen immunotherapy extracts should be prepared individually for each patient to enhance the individualization of therapy, reduce the risk of allergen cross-contamination, and reduce the risk of error in administration.[4,5] This parameter recommends the use of standardized allergen immunotherapy prescription and administration forms to improve the safety, uniformity, and standardization of allergen immunotherapy practice.[4,5] The suggested forms are found in the Appendix (Appendices 7, 8, 11, 12, and 14) and in the members' section of the www.aaaai.org Web site. The routine use of these standardized forms should improve the quality of immunotherapy practice.

Members' feedback comments on the recommended allergen extract dilution dating in the 2003 ''Allergen immunotherapy: A practice parameter'' led to an allergen immunotherapy extract dilution stability study designed by the AAAAI Immunotherapy and Allergy Diagnostics Committee and funded by the AAAAI Board of Directors. The study was designed to investigate the effect of time, temperature, and dilution of standardized allergen extract potency, and the results of this study were considered in this update.

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 3 years after publication. Requests for information about or an interpretation of these practice parameters should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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. Allergen immunotherapy

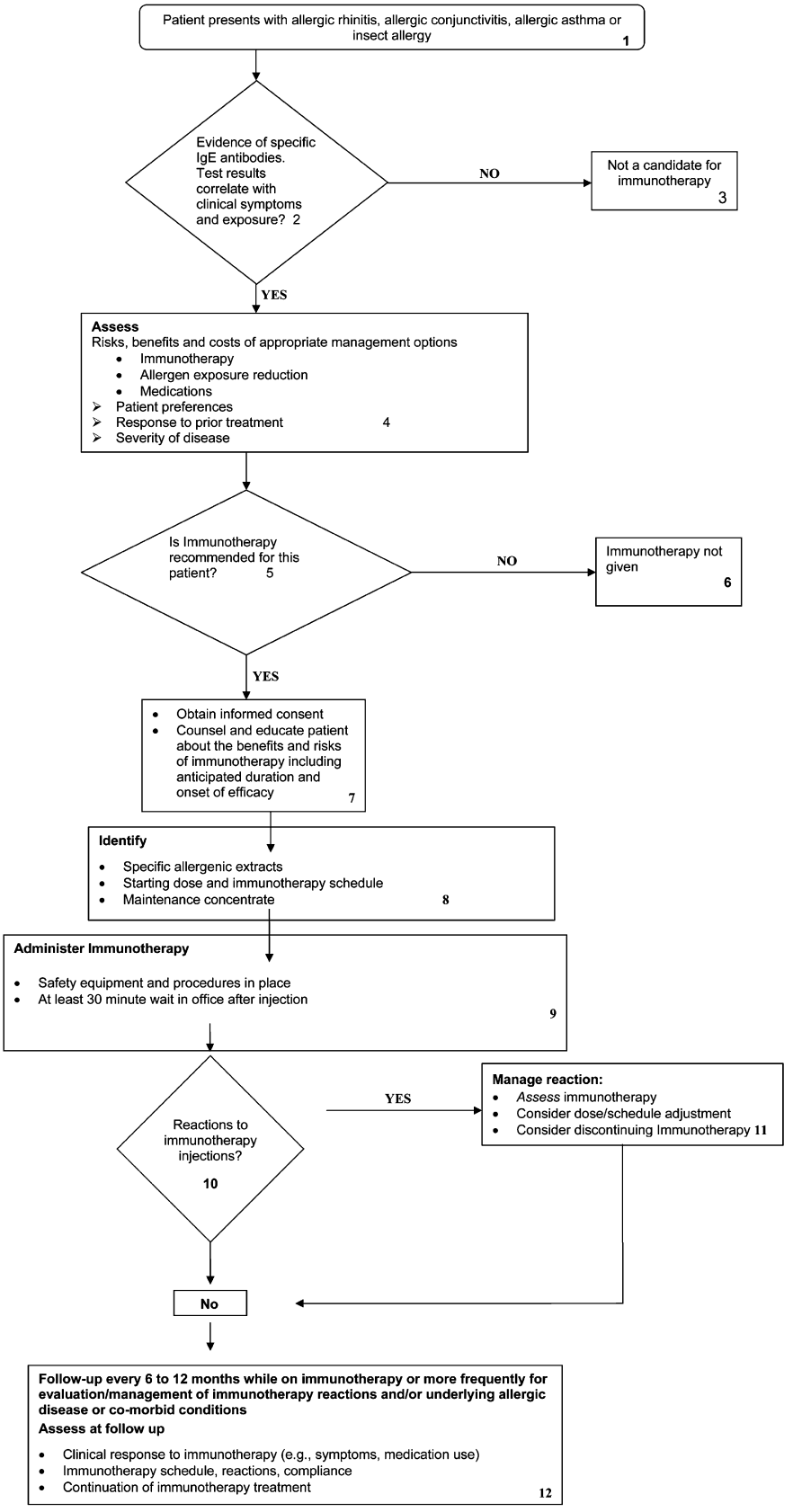


FIG 1. Algorithm for allergen immunotherapy.

might prevent the development of asthma in individuals with allergic rhinitis.[6-9] Evaluation of a patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic conjunctivitis, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for specific IgE antibody).[10]

Box 2

Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although *in vitro* testing for 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

Management of complex medical conditions, such as allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity, should include the careful evaluation of management 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 patient 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. On the basis of clinical considerations and patient 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 good candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy (VIT).

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 on the basis of 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 (see the Immunotherapy schedules and doses section). In general, the starting immunotherapy dose is 1000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 1000 to 4000 arbitrary units (AU; eg, for dust mite) or bioequivalent allergy units (BAU; eg, for grass) 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 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 referred to as *up-dosing*, *induction*, or the *dose-increase phase*) entails administration of gradually increasing doses during a period of approximately 14 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 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, in particular anaphylaxis. Patients should wait at the physician's office for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly, if they occur.

In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring 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. Some physicians recommend providing certain patients with epinephrine for self-administration in case of severe late reactions to immunotherapy injections.

Box 10

Injections of allergen immunotherapy extract can cause local or systemic reactions. Most severe reactions develop within 30 minutes after the immunotherapy injection, but reactions can occur after this time.

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 (anaphylaxis). Epinephrine is the treatment of choice in anaphylaxis, preferably when administered intramuscularly,[11] although subcutaneous administration is acceptable.[12]

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, see the practice parameters for anaphylaxis.[12]

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. After a severe systemic reaction, careful evaluation by the prescribing physician is recommended. For some patients, the immunotherapy maintenance dose might need to be reduced because of repeated systemic reactions to immunotherapy injections. The decision to continue immunotherapy should be re-evaluated after severe or repeated systemic reactions to allergen immunotherapy extracts.

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 doses, 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,[13] but others might experience a recurrence of their symptoms after discontinuation of allergen immunotherapy.[14] 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, and 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 on the basis of the patient's clinical response, disease severity, immunotherapy reaction history, and patient preference.

IMMUNOTHERAPY GLOSSARY

For more information on immunotherapy definitions, see the article by Kao.[15]

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 (pigments and salts; see the Allergen selection and handling section). Other terms used to describe the allergen immunotherapy extract include *allergen product*,[16] *allergy serum*, *allergen vaccine*,[17] 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.[18] Other terms that have been used for allergen immunotherapy include *hyposensitization*, *allergen-specific desensitization*, and the lay terms *allergy shots* or *allergy injections*.[15]

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

TABLE II. Allergen immunotherapy dose-calculation table

- Express weight per volume as a fraction: $\frac{1}{N}$ or 1:*N*.
- Calculate concentration of individual allergens in mixtures. If a mixture is made of equal amounts of N individual allergens to make a total concentration (C), the final concentration of an individual allergen (Ca) can be calculated by using the following equation:

$Ca = C \times \frac{1}{N} = \frac{C}{N}$ or *C*:*N*.

For example, if a mixture of equal amounts of 5 (N) allergens has a total concentration (C) of 100,000 BAU/mL, then the final concentration of each individual allergen (Ca) is: $Ca = \frac{C}{N} = \frac{100{,}000}{5} = 20{,}000\ BAU/mL$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{C}{N} = \frac{1/10}{5} = \frac{0.1}{5} = 0.02$ or $\frac{1}{50}$ or 1:50.

- Dilution of individual allergen: If an initial volume, Vi (in milliliters), of an individual antigen with concentration, Ci, is added to an allergen extract to make a final volume of Vf (in milliliters), the final allergen concentration (Ca) in the allergen extract mixture will be: $Ca = Ci \times \frac{Vi}{Vf}$.
- Final concentration of an allergen in a mixture of mixtures is determined by multiplying the initial concentration by the dilution factors from each mixing step.

For example, consider a mixture containing equal amounts of 5 (N) allergens with a total concentration (C) of 100,000 BAU/mL (first dilution). If an initial volume (Vi) of 0.5 mL of this mixture is further mixed with other components and diluent to make a final allergen extract mixture volume (Vf) of 5.0 mL (second dilution), the final concentration of an individual allergen (Ca) will be:

$$Ca = C \times \underbrace{\frac{1}{N}}_{\text{Mixture dilution}} \times \underbrace{\frac{Vi}{Vf}}_{\text{Allergen extract dilution}} = 100{,}000 \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{100{,}000}{50} = 2000\ BAU/mL$$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{1}{10} \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{1}{500}$ or 1:500.

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).

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 to 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-medicated 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 multiplied by volume of administered dose (see Table II for a dose-calculation table).

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, cat, 1000 BAU, [highest tolerated dose] vs 2000 BAU [projected effective dose]).

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 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 by a variety of immunologic transformations. Early definitions of the term immunotherapy included active and passive immunization for the purpose of improving 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 by means of induction of clonal deletion, anergy, immune tolerance, or immune deviation.

The *maintenance concentrate* is a preparation that contains individual 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 may not be the initially calculated projected effective dose.

The *maintenance goal* (or projected effective dose) is the allergen dose projected to provide therapeutic efficacy. The maintenance goal is based on published studies, but a projected effective dose has not been established for allergens. 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 the 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 large local reaction causing discomfort). The intervals between maintenance immunotherapy injections generally ranges 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 by means of immunoblotting or crossed allergoimmunoelectrophoresis.

For a definition of *projected effective dose*, see 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 test responses), and premedication with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similar high incidence of systemic reactions.

Off the board into one syringe is a phrase that describes a method of allergen immunotherapy preparation and administration that involves specifically mixing the patient's allergen immunotherapy injection in a single syringe, which is not recommended. This syringe might be inserted into more than one allergen extract vial, and this poses a risk of cross-contamination of the allergen extracts and might dull the needle with repeated penetration of the rubber stopper.

Shared specific patient vials is a method of allergen immunotherapy preparation and administration in which the allergy immunotherapy extract is withdrawn from a shared vial (eg, mixed vespids or dust mite mix). This is sometimes referred to as off the board, but it is distinct from the method of off the board into one syringe in that the syringe enters only one allergen extract vial.

INTRODUCTION

Immunity has been defined as protection against certain diseases. The initial immunotherapeutic interventions, which included the use of preventive vaccines and xenogenic 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 the field of allergen immunotherapy. From its humble empiric emergence in 1900, when ragweed injections were proposed as therapy for autumnal hay fever, allergen immunotherapy has progressed in both theory and practice from the passive immunologic approach to the active immunologic procedures pioneered by Noon[19] and Freeman.[20,21] 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 10 years. Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Some studies have suggested that allergen immunotherapy might prevent the development of asthma in individuals with allergic rhinitis.[6-9]

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,[22-26] and it should be differentiated from unproved methods, such as neutralization-provocation therapy and low-dose subcutaneous regimens based on the Rinkel technique, which have been found to ineffective in a double-blind placebo-controlled study.[27,28]

SUMMARY STATEMENTS

Mechanisms of immunotherapy

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, defined as a relative decrease in allergen-specific responsiveness and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

Allergen extracts

Summary Statement 6: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. **A**

Summary Statement 7: Nonstandardized extracts might vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Summary Statement 8: 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**

Cross-reactivity of allergen extract. Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

Efficacy of immunotherapy

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Summary Statement 10: Immunotherapy is effective for 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**

Food allergy, urticaria, and atopic dermatitis. Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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**

Measures of efficacy. Summary Statement 12: 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**

Safety of immunotherapy

Reaction rates. Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

Timing of anaphylactic reactions to immunotherapy injections. Summary Statement 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

β-*Adrenergic blocking agents.* Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

Contraindications. Summary Statement 18: 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**

Reducing the risk of anaphylaxis to immunotherapy injections. Summary Statement 19: 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**

Patient selection

Clinical indications. Summary Statement 20: 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 depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Special precautions in patients with asthma. Summary Statement 21: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. **C**

Clinical indications for VIT. Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Summary Statement 23: Patients selected for immunotherapy should be cooperative and compliant. **D**

Allergen selection and handling

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted in vitro tests for specific IgE antibodies can also be used. **A**

Specific allergens. Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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, supported by the presence of specific IgE antibodies. **A**

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Dose selection. Summary Statement 30: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. **A**

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens, is recommended. **B**

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extract handling

STORAGE

Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

STORING DILUTE EXTRACTS

Summary Statement 34a: More dilute concentrations of allergen immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: 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 a number of 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. **B**

Immunotherapy schedules and doses

Summary Statement 35: A customized individual 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 be based on single or multiple allergens. **D**

Maintenance concentrate. Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

Recommended doses. Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

Effect of dilution on dose. Summary Statement 38: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. **A**

Dilutions of the maintenance concentrate. Summary Statement 39: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. **D**

Labeling dilutions. Summary Statement 40: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. **D**

Individualized treatment vials. Summary Statement 41: 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. The mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. **C**

Starting doses. Summary Statement 42: The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. **D**

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

Dose adjustments for systemic reactions. Summary Statement 44: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. **D**

Reductions during periods of exacerbation of symptoms. Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Dose adjustments for late injections. Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

Cluster schedules. Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. **C**

Rush schedules. Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. **A**

Systemic reactions and rush schedules. Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

Premedication and weekly immunotherapy. Summary Statement 50: Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

Premedication with cluster and rush immunotherapy. Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

Maintenance schedules. Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. **A**

Continuing care

TIME COURSE OF IMPROVEMENT

Summary Statement 53: Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **A**

FOLLOW-UP VISITS

Summary Statement 54: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. **D**

DURATION OF TREATMENT

Summary Statement 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

DOCUMENTATION AND RECORD KEEPING

Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. **D**

INJECTION TECHNIQUES

Summary Statement 57: Allergen immunotherapy extract injections should be administered with a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **D**

Summary Statement 58: The injection should be administered subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Location of allergen immunotherapy administration

Physician's office. Summary Statement 59: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Summary Statement 60: 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**

Other locations. Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **D**

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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**

Summary Statement 63: 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for his or her immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extract might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Special considerations in immunotherapy

Allergen immunotherapy in children. Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Pregnancy. Summary Statement 71: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. **C**

Immunotherapy in the elderly patient. Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy in patients with immunodeficiency and autoimmune disorders. Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

Alternative routes of immunotherapy

Sublingual and oral immunotherapy. Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no US Food and Drug Administration (FDA)–approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **A**

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Immunotherapy techniques that are not recommended. Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

MECHANISMS OF IMMUNOTHERAPY

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, which is defined as a relative decrease in allergen-specific responsiveness, and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

The immunologic changes associated with immunotherapy are complex, and the exact mechanism or mechanisms responsible for its' clinical efficacy are continually being elucidated. Data support the concept that successful immunotherapy is associated with a change to a T_H1 $CD4^+$ cytokine profile.[29-34] Data indicate that increased production of IL-12, a strong inducer of T_H1 responses, contributes to this shift.[33] Clinically successful immunotherapy has been reported to be associated with immunologic tolerance, which is defined as a relative decrease in antigen-specific responsiveness, immune deviation, or anergy. For example, lymphoproliferative responses to allergen are reduced with immunotherapy.[32] Successful immunotherapy results in generation of a population of T regulatory cells, which are $CD4^+CD25^+$ T lymphocytes producing IL-10, TGF-β, or both.[35-39] Regulatory T-cell release has been described in allergen immunotherapy with Hymenoptera venom,[35] grass pollen extract,[37] and house dust mites.[38] IL-10 reduces B-cell antigen-specific IgE and increases IgG4 levels; reduces proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicits tolerance in T cells by means of selective inhibition of the CD28 costimulatory pathway.[36,37]

Allergen immunotherapy has been shown to block both the immediate and late-phase allergic response.[40] Allergen immunotherapy has been shown to decrease the recruitment of mast cells, basophils, and eosinophils in the skin, nose, eye, and bronchial mucosa after provocation or natural exposure to allergens.[41]

In patients receiving immunotherapy, initially there is an increase in specific IgE antibody levels, followed by a gradual decrease to a level that is still higher than that present before treatment. Clinical improvement in many patients develops before decreases in their IgE antibody levels occur or in other patients whose IgE antibody levels never decrease, thereby demonstrating that efficacy is not dependent on reductions in specific IgE levels.[42,43] Immunotherapy does diminish the seasonal increase in specific IgE levels.[44] Despite the persistence of significant levels of specific IgE antibody levels, immunotherapy usually causes a reduction in 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.[45-48]

An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, has also been associated with immunotherapy. The properties of allergen-specific IgA have yet to be determined, and there is a weak correlation between the increase in allergen-specific IgG levels and immunotherapy's clinical efficacy.[30,49,50]

Immunotherapy might alter the affinity and specificity of allergen-specific IgG.[51,52] During the initial phase of ultrarush VIT, a change in IgG specificity (ie, a change in the set of epitopes dominantly recognized by IgG on wasp venom antigens) occurred concomitantly with early clinical tolerance and was seen within 12 hours of ultrarush VIT ($P < .001$).[51] 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 individuals.[52] This change in IgG specificity preceded the increase in IgG titers and was sustained for up to 6 months.[52]

Allergen-specific IgG induced from immunotherapy can block IgE-dependent histamine release and subsequent IgE-mediated antigen presentation to T cells.[53] This effect might be dependent on IgE, allergen concentration, and CD23, the low-affinity receptor for IgE.

Whereas 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.[37,53]

The relationship between these immunologic changes and immunotherapy efficacy is not completely understood.

ALLERGEN EXTRACTS

Summary Statement 6: 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 has 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.[2,18,54-56] 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.

United States–licensed extracts can be obtained in aqueous, glycerinated, lyophilized, and acetone-precipitated and alum-precipitated formulations. Some commonly used allergens are standardized. These include extracts for cat hair, cat pelt, *Dermatophagoides pteronyssinus*, *Dermatophagoides 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.[57] 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.

Most standardized extracts are labeled in BAU. Short ragweed potency units were originally based on the content of the major allergen Amb a 1. Ragweed potency is reported in FDA units and BAU. One FDA unit of Amb a 1 equals 1 μg of Amb a 1, and 350 units of Amb a 1/mL is equivalent to 100,000 BAU/mL. Cat extracts were also originally standardized based on the content of major allergen (Fel d 1), with 100,000 arbitrary units (AU) per milliliter containing between 10 to 19.9 FDA units of Fel d 1 per milliliter (1 FDA unit of Fel d 1 equals 2 to 4 μg of Fel d 1).[55,58,59] Subsequently, $ID_{50}EAL$ testing suggested that 100,000 AU/mL was equal to 10,000 BAU/mL.[60] Approximately 22% of individuals with cat allergy have specific IgE antibodies to cat albumin.[61] Cat pelt extracts have a greater amount of albumin than cat hair extracts.[60]

Dust mites were originally standardized in AU by means of inhibition radioimmunoassay (RIA), and subsequent $ID_{50}EAL$ testing indicated that the AU was bioequivalent to the BAU, and the original AU nomenclature was kept. Dust mite extracts are still labeled in AU.

Summary Statement 7: Nonstandardized extracts can vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Nonstandardized extracts are labeled as wt/vol, which expresses weight in grams per volume in milliliters; that is, a potency of 1:100 indicates that 1 g 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 with a particular wt/vol or PNU potency can have widely varying biologic activities.[62-64] Therefore they should not be considered equipotent.

Summary Statement 8: 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**

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. The major clinically relevant aeroallergens of North America are listed in Table III. Furthermore, nonrelevant allergens in such mixtures could act as sensitizers rather than as tolerogens.[65,66] The physician must therefore select only those aeroallergens for testing and treatment that are clinically relevant in a particular geographic area.

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, dog), insect (cockroach), and Hymenoptera venom source materials.

Cross-reactivity of allergen extract

Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

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. A summary of cross-reactivity patterns of the clinically relevant North American aeroallergens can be found in Fig 2. 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,[67] inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[68-75] Grasses in other subfamilies (eg, Bermuda, Bahia, and Johnson) show greater diversity and should be evaluated separately.[76-78] Bermuda and Johnson grasses are increasingly important in the South,

TABLE III. The major clinically relevant aeroallergens of North America*

- Tree pollen
  - Chinese elm *(Ulmus parvifolia)*†‡; Siberian elm *(Ulmus pumila)*†‡; American elm *(Ulmus Americana)*†‡
  - Red oak *(Quercus rubra)*†; White oak *(Quercus alba)*†
  - Paper birch *(Betula papyrifera)*
  - Alder *(Alnus rubra)*
  - Box elder *(Acer negundo)*†; Red maple *(Acer rubra)*†
  - Eastern cottonwood *(Populus deltoides)*
  - Sycamore *(Platanus occidentalis)*
  - White ash *(Fraxinus americana)*†; Olive *(Olea europaea)*†‡
  - Black walnut *(Juglans nigra)*
  - Mulberry *(Morus rubra)*
  - Mountain cedar *(Juniperus ashei)*
  - Pecan *(Carya illinoensis)*
- Grass pollen
  - Rye *(Lolium perenne)*§‖
  - Timothy *(Phleum pratense)*§‖
  - Meadow fescue *(Festuca elatior)*§‖
  - Bermuda *(Cynodon dactylon)*‖
  - Johnson *(Holcus halepensis)*
  - Bahia *(Paspalum notatum)*
- Weed pollen
  - Short ragweed *(Ambrosia artemisiifolia)*‖
  - English (narrow leaf) plantain *(Plantago lanceolata)*
  - Mugwort *(Artemisia vulgaris)*
  - Russian thistle *(Salsola kali)*
  - Burning bush *(Kochia scoparia)*
  - Sheet (red) sorrel *(Rumex asetosella)*
  - Red root pigweed *(Amaranthus retroflexus)*
- Indoor aeroallergens
  - Cat epithelium *(Felis domesticus)*‖
  - Dog epithelium *(Canis familiaris)*
  - Arthropods (domestic mites: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*)‖
  - Insects (German cockroach: *Blattella germanica*)
- Fungi
  - *Alternaria alternata*¶
  - *Cladosporium* (*C cladosporioides*, *C herbarum*)¶
  - *Penicillium* (*P chrysogenum*, *P expansum*)¶
  - *Aspergillus fumigatus*¶
  - *Epicoccum nigrum*, *Drechslera* or *Bipolaris* type (eg, *Helminthosporium solani*)¶

*Compiled and selected in collaboration with the AAAAI Immunotherapy Committee Allergen Subcommittee for the identification of 35 key allergens of North America.
†Extensive cross-reaction of species within the genus.
‡Apart from regional prevalence, they are limited to local sites with substantial stands of these trees.
§Extensively cross-react with one another and bluegrass, orchard, red top, and sweet vernal.
‖Allergens for which standardized extracts are commercially available.
¶Species that are widely distributed and clinically important.

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.[79-82] 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.[83-85] Significant cross-reactivity between Betulaceae pollens and oak of the Fagaceae family has been demonstrated with percutaneous skin testing.[75] RAST inhibition studies have shown cross-inhibition between oaks and other *Fagales* species.[86] IgE immunoblot inhibition experiments have demonstrated that the *Fagales* species might be strongly inhibited by birch species.[87] The use of one of the locally prevalent members (eg, birch and alder) should be adequate.[88]

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.[89,90] Maple and box elder trees are found throughout the United States, except for the arid southwest. Although in the same genus as maple, *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,[91,92] and there are allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.[93]

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.[94] Similarly, Chenopod-Amaranth families have wide ranges in the western regions but are present throughout North America.[95] Current information on cross-reactivity of these families is limited.[96-98] 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.[99] The use of a single Amaranth extract should be sufficient to cover this family.[100,101] Similarly, *Atriplex* species (eg, saltbushes and scales) show near identity, and use of a single member is adequate. 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,

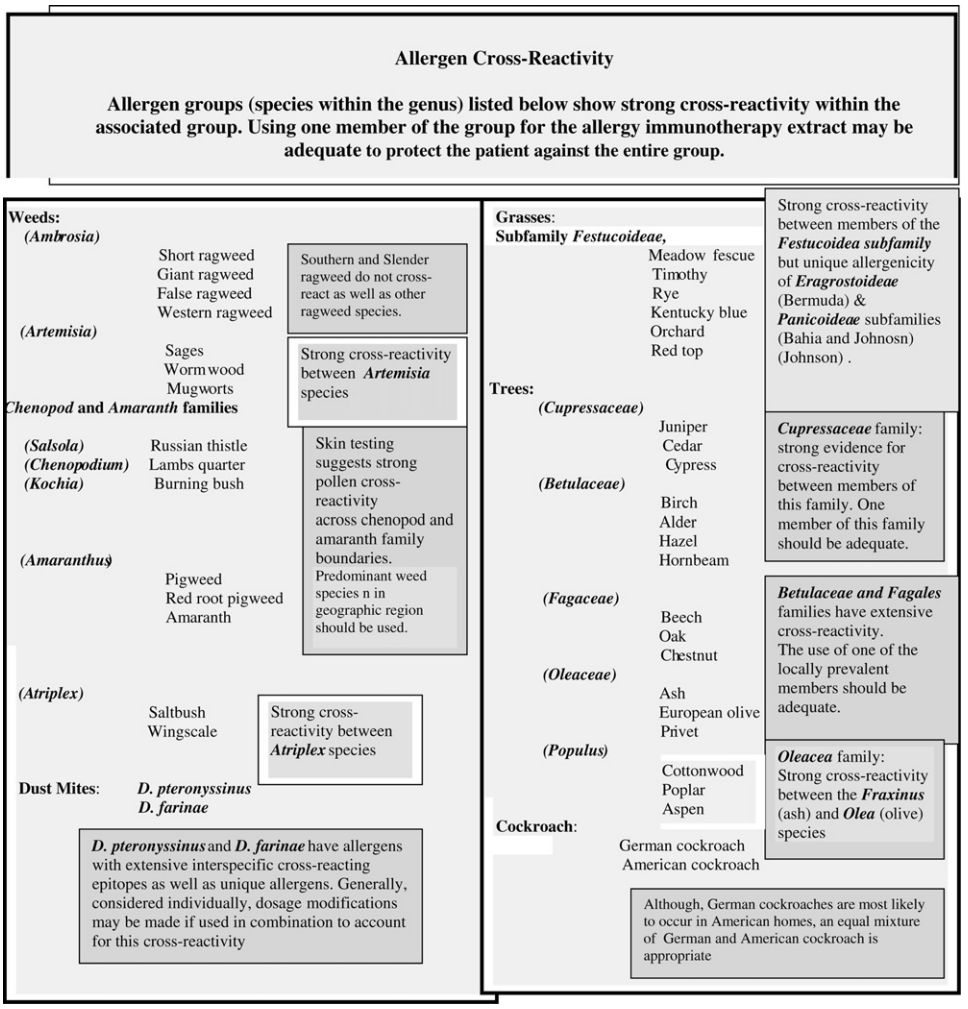


FIG 2. Patterns of allergen cross-reactivity.

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*).

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.[102,103] Stinging Hymenoptera insects occur throughout the United States; the fire ant is found only in Gulf Coast states, Texas, and some other southern and western states. Commercial venom extracts are available for some Hymenoptera species, except the fire ant, for which only whole-body extract is available.

EFFICACY OF IMMUNOTHERAPY

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity

Summary Statement 10: Immunotherapy is effective for 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.[104-111] Immunotherapy is effective for the treatment of allergic rhinitis[107] (including ocular symptoms[112,113]), allergic asthma,[104,109,111,114,115] and stinging insect hypersensitivity[108,116] and is effective in both adults and children.[117-124] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollens,[13,125-132] fungi,[133-138] animal allergens,[22,25,26,139-143] dust mite,[114,115,144-153] and cockroach.[154] There have been no controlled trials of fire ant whole-body extract, but it does appear to be effective in

TABLE IV. Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy

Outcome measure	House dust mite	Other allergens*†
Symptomatic improvement	2.7 (1.7-4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2-7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50)	5.5 (2.8-10.7)

Data are used with permission from Abramson et al.[104]
ND, Not done.
*Odds ratio (95% CI).
†Pollen, mold, or animal dander.

uncontrolled trials.[155-157] 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. A number of studies have also demonstrated a significant improvement in quality of life, as measured by using standardized questionnaires.[24,158-161] The magnitude of the effect depends on the outcome that is used (Table IV). For dust mite, the effect size ranges from a 2.7-fold improvement in symptoms to a 13.7-fold reduction in bronchial hyperresponsiveness. 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.[110] 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[107] and asthma[104,109,111] have been performed to deal with the issue of power. One review of 75 trials involving 3188 asthmatic patients found that, overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyperreactivity after immunotherapy, and it would have been necessary to treat 4 patients (95% CI, 3-5) with immunotherapy to avoid 1 deterioration in asthma symptoms and 5 (95% CI, 4-6) patients to avoid 1 requiring increased medication.[111] These meta-analyses strongly support the efficacy of allergen immunotherapy. Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued[13,162,163] and might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6,9,122,162-165] Allergen immunotherapy might also prevent the development of new allergen sensitivities in monosensitized patients.[120,166,167]

Food allergy, urticaria, and atopic dermatitis

Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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 use of allergen immunotherapy for individuals with the potential for IgE-mediated (anaphylaxis) reactions to foods should be regarded as investigational at this time.[168-171] There have been 2 investigational studies demonstrating efficacy in food hypersensitivity, the first using aqueous subcutaneous injections to peanut and the second using sublingual immunotherapy to hazelnut.[171-173]

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 a modified peanut extract is needed for clinical application of this method of treatment.[171] There is currently no FDA-approved formulation for sublingual immunotherapy, and this route of allergen immunotherapy is currently considered investigational at this time (see Summary Statement 73).

At the present time, there is not enough evidence to support food immunotherapy.

There is no evidence supporting the efficacy of immunotherapy for individuals with chronic urticaria, angioedema, or both.

There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[174-176] 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 ($P = .0379$) and topical corticosteroid use ($P = .0007$).[174]

The potential for benefit in symptoms related to oral allergy syndrome with the cross-reacting inhalant immunotherapy, which includes cross-reacting 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 subcutaneous immunotherapy directed against birch tree,[177] whereas another double-blind, double-dummy, placebo-controlled study comparing the effect of subcutaneous immunotherapy with sublingual immunotherapy 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, medication use, and decrease in IgE reactivity.[178] More investigation is required to substantiate the contention that benefits in oral symptoms will occur with immunotherapy.

Measures of efficacy

Summary Statement 12: 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. Objective measures, such as increase in allergen-specific IgG levels and decreased skin test reactivity, as measured by skin test titration, are changes generally associated with effective immunotherapy but, at present, are not practical for routine clinical use.[147] Nonquantitative skin testing or *in vitro* 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 are not very reliable given the strong placebo-like effect (Hawthorne effect) associated with any treatment. A more objective means for determining efficacy as validated in controlled clinical studies is the use of clinical symptom scores and the amount of medication required to control symptoms and maintain peak flow rates or pulmonary function tests within acceptable limits. Successful immunotherapy often results in a reduction in medication. Sequential measurement of disease-specific quality of life also might be helpful.

SAFETY OF IMMUNOTHERAPY

Reaction rates

Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Large local reactions associated with allergen immunotherapy are fairly common, with a frequency ranging from 26% to 86% of injections.[179] Two retrospective studies compared the effect of not adjusting immunotherapy dose based on large local reactions on the immunotherapy systemic reaction rate with dose-adjustment protocols.[179,180] There was a total of 12,464 injections administered with a dose-adjustment protocol in the 2 studies compared with 9542 injections administered with a no-dose-adjustment protocol. 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 for subsequent systemic reactions, 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 large local reactions, defined as 25 mm or larger, in patients who had experienced systemic reactions with age-, sex-, and allergen sensitivity–matched control subjects who had not had allergen immunotherapy systemic reactions found the rate of large local reactions was 4 times higher among the 258 patients who had subsequently experienced a systemic reaction compared with those who had never experienced a systemic reaction.[181] Patients who had experienced systemic reactions had 1573 large local reactions in 4460 visits (ie, 35.2% of visits) and 8081 injections (ie, 19.5% of injections) compared with the matched control group without systemic reactions who had 1388 large local reactions in 15,540 visits (8.9% per visit) and 26,259 injections (5.3% per injection; difference between groups, $P < .001$). Individual large local reactions were not predictive of future systemic reactions, but large local reactions preceded systemic reactions in approximately one third of the systemic reactions. These findings suggest that individuals with a greater frequency of large local reactions might be at greater risk for systemic reaction. Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy protocol modifications based on them are needed.

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

The prevalence of severe systemic reactions after allergen immunotherapy ranges from less than 1% of patients receiving conventional immunotherapy to greater than 36% of patients in some studies of patients receiving rush immunotherapy.[182,183]

In a recent survey of fatal and near-fatal reactions (NFRs) sent to physician members of the AAAAI, 273 of 646 respondents reported NFRs during the period of 1990-2001.[184]

The incidence of unconfirmed NFRs was 23 per year (5.4 events per million injections). Administration during the height of 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 angiotensin-converting enzyme 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 systemic reactions to subcutaneous immunotherapy over a 20-year period (1981-2000) during which 435,854 injections were administered to 4000 patients, 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.[185,186] In a prospective multicenter study there were 53 systemic reactions (0.3% of the doses) out of 17,526 administered doses in 18 (3.7%) of 423 patients.[187] 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 (21 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, there were 41 fatalities identified in the initial brief survey (20 directly reported and 17 with completed detailed questionnaire) from immunotherapy injections.[188] 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.[189,190] Therefore although severe systemic reactions to allergen immunotherapy are not common, serious systemic reactions (some fatal) can occur.

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

In the AAAAI survey of physician members on immunotherapy and skin testing, fatal reactions, and NFRs during the period of 1990-2001, 15 of the 17 fatalities had asthma, and in 9 patients asthma was considered the susceptibility factor that contributed to the fatal outcome.[188]

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.[184]

Administration during the peak pollen season (3 patients) and previous systemic reactions (4 patients) were cited as other contributing factors. Five fatalities occurred in outside medical facilities, and 2 fatalities occurred at home. No patients were receiving β-blockers; 1 patient was taking an angiotensin-converting enzyme inhibitor. In the most comprehensive evaluation of fatalities associated with allergen immunotherapy, from 1945-1987, there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[189] 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, with 73.3% of patients with an FEV_1 of less than 80% of predicted value experiencing 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 ($P < .0001$).[191] 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% of patients. These studies suggest that symptomatic asthma, severe asthma, or both might be a risk factor for immunotherapy.

In addition to symptomatic asthma and injections giving 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.[17] With the exception of dosing errors and 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 recent 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 or allergy symptom exacerbation, β-blocker use, change in health status (including pregnancy), or adverse reaction to previous allergen immunotherapy injection. The preinjection evaluation might also include a peak flow measurement to assess the airway function of asthmatic patients.

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 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

In a retrospective study the time to onset of a systemic reaction after an immunotherapy injection was less than 30 minutes in most cases.[189] A review of the literature indicates that 70% of systemic reactions occur within 30 minutes after an injection.[183] In the AAAAI 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.[184,188] 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.[190] 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 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.[192] In another prospective study 8% of systemic reactions occurred more than 2 hours after injection.[193]

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.[194]

Because most reactions that resulted from allergen immunotherapy occurred within 30 minutes after an injection, patients should remain in the physician's office for at least 30 minutes after receiving an injection, but longer waits are reasonable, as directed by the physician. In addition, patients who are at increased risk of a systemic reaction might need to carry injectable epinephrine. Such patients might also need to remain in the physician's office more than 30 minutes after an injection. 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.

β-Adrenergic blocking agents

Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

β-Blockade enhances pulmonary, cardiovascular, and dermatologic end-organ effects of mediators and increases mortality associated with experimental anaphylaxis induced by either immunologic or nonimmunologic mechanisms. Patients who are receiving β-adrenergic blocking medications might be at increased risk if they experience a systemic reaction to an allergen immunotherapy injection because the β-receptor blockade might attenuate the response to epinephrine.[195-202] Patients who are receiving β-blocking drugs were almost 9 times more likely to be hospitalized after an anaphylactoid reaction from radiocontrast media.[198] Although topical β-blockers have markedly less systemic β-antagonist effects than oral β-blockers, they still might exhibit some systemic β-antagonist effects. Whether topical β-blockers pose the same or a smaller risk than oral β-blockers in regard to the treatment of allergen immunotherapy–related systemic reactions is not known.

There have been very few studies that have examined the effect of β-blocker medications on allergen immunotherapy. A prospective 1-year study designed to determine whether patients taking β-blocker drugs were at increased risk of immunotherapy-induced systemic reactions found that there were 166 systemic reactions out of 56,105 injection visits in 3178 patients (68 were receiving a β-blocker).[203] The systemic reactions occurred in 144 (4.5%) patients, and only 1 of these patients was receiving a β-blocker medication. The authors calculated that by chance, 3.08 patients receiving the β-blocker medications drugs were expected to have had an systemic reaction and concluded that β-blocker medications did not increase the frequency of allergen immunotherapy systemic reactions ($P > .95$).

In another study of 1389 patients prescribed immunotherapy for Hymenoptera venom hypersensitivity who were followed for 34 months, there were 25 patients who received concomitant β-blocker medications.[204] Three (12%) of the 25 patients receiving β-blocker medications experienced systemic reactions during immunotherapy compared with 23 (16.7%) of 117 patients with cardiovascular disease not receiving β-blockers. Systemic reactions after a field sting or challenge occurred in 1 (14.3%) of 7 cardiovascular patients receiving β-blocker medications compared with 4 (13.8%) of 29 cardiovascular patients not receiving β-blocker medications. No severe reactions to immunotherapy or sting re-exposure were observed in patients receiving β-blockers medications.

Immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. In such cases, intravenous glucagon, which might reverse the refractory bronchospasm and hypotension by activating the adenyl cyclase directing and bypassing the β-adrenergic receptor, might be used if epinephrine has not been effective.[205,206] Prospective studies are necessary to clarify the magnitude of the risk of systemic reactions to allergens in patients who are receiving concomitant therapy with β-blockers, and a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy.

Contraindications

Summary Statement 18: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications

TABLE V. Actions to reduce the risk of anaphylaxis

- Assess the patient's general medical condition at the time of injection (eg, asthma exacerbation).
- Consider obtaining a PEFR before administration of the injection. If the PEFR is significantly less than the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.
- 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 with increased allergen sensitivity or those who have previously had a systemic reaction) might need to wait longer.
- Carefully evaluate any patient with a late reaction (eg, persistent large local reaction lasting >24 hours, systemic reaction occurring more than 30 minutes after the immunotherapy injection).
- 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.

PEFR, Peak expiratory flow rate measurement.

TABLE VI. Recommended equipment and medications to treat anaphylaxis

Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur. This should include at least the following equipment and medications:

- stethoscope and sphygmomanometer;
- tourniquet, syringes, hypodermic needles, and large-bore needles (14-gauge);
- aqueous epinephrine HCL 1:1000 wt/vol;
- equipment to administer oxygen by mask.
- intravenous fluid set-up;
- antihistamine for injection (second-line agents for anaphylaxis, but H_1 and H_2 antihistamines work better together than either one alone);
- corticosteroids for intravenous injection;
- vasopressor;
- equipment to maintain an airway appropriate for the supervising physician's expertise and skill.

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 venom hypersensitivity and cardiac disease being treated with β-blocker medications.

Reducing the risk of anaphylaxis to immunotherapy injections

Summary Statement 19: 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 extremely 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 or other health care professional appropriately trained in emergency treatment.

The 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. Epinephrine is the first-line treatment for anaphylaxis. 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.[12,207-213] It is important to administer epinephrine early in the management of anaphylaxis. 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 V and VI, respectively. Before allergen immunotherapy is chosen as a treatment, the physician should educate the patient about the benefits and risks of immunotherapy, as well as methods for minimizing risks. The patient also should be told that despite appropriate precautions, reactions might occur without warning signs or symptoms. Informed consent should include a discussion of the potential immunotherapy adverse reactions, and this discussion should be documented in the patient's medical record.

PATIENT SELECTION

Clinical indications

Summary Statement 20: Allergen immunotherapy should be considered for patients who have demonstrable

TABLE VII. Clinical indications for allergen immunotherapy

Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or both:
- symptoms of allergic rhinitis after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medications;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medication;
- coexisting allergic rhinitis and asthma;
- possible prevention of asthma in patients with allergic rhinitis

Symptoms of asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medication;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medications;
- coexisting allergic rhinitis and allergic asthma.

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);
- adults and children with a history of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.

evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic rhinitis.[107] Prospective, randomized, double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic asthma.[104,109,111]

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 proper identification and selection of component allergens on the basis of 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 (Table VII). The severity and duration of symptoms should also be considered in assessing the need for specific allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. In addition, specific allergen immunotherapy should be considered if the patient wishes to avoid long-term pharmacotherapy. Time lost from work, emergency department or physician's office visits, and responses to pharmacotherapy are important objective indicators of allergic disease severity.

Patients with allergic rhinitis who are unable to sleep because of symptoms or whose symptoms interfere with their work or school performance should be considered strong candidates for specific allergen immunotherapy. 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 considered. Unacceptable adverse effects of medications should also favor one's decision to initiate allergen immunotherapy. Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.[214]

Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued, and it might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6-9,122,162-165] These benefits of immunotherapy should be discussed with patients and might provide a clinical indication for immunotherapy for individual patients with allergic rhinitis.

Coexisting medical conditions should also be considered in the evaluation of a patient who might be a candidate for allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed with a combined aggressive regimen of allergen avoidance and pharmacotherapy and might also benefit from allergen immunotherapy.[215,216]

However, the patient's asthma must be stable before allergen immunotherapy is administered.[188,191]

Special precautions in patients with asthma

Summary Statement 21: 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 might be at increased risk for systemic reactions to immunotherapy injections.[182,188,191] Two surveys found that deaths from

immunotherapy were more common in symptomatic subjects with asthma.[188,189] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2,217]

Clinical indications for VIT

Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Systemic reactions to Hymenoptera stings, especially when associated with respiratory symptoms, cardiovascular symptoms, or both and positive skin test or *in vitro* test results for specific IgE antibodies, are a strong indication for allergen immunotherapy.[218] In the United States patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Several studies of patients with imported fire ant allergy have demonstrated the effectiveness of immunotherapy with whole-body extracts of fire ants.[155,156,219] 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. Patients younger than 16 years of age who present only with a cutaneous reaction to imported fire ant or Hymenoptera stings might not require immunotherapy.[218,220-222] In addition to allergen immunotherapy, patients with imported fire ant and Hymenoptera venom sensitivity should be instructed in how to best avoid insect stings, be prescribed epinephrine, and be taught how 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 the population that has not had a systemic reaction.[223] In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific IgE is recommended.[218] If the venom-specific IgE test result is also negative, it is recommended that the skin tests, venom-specific 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 IgE test result.[224] 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 re-stung. 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%).[225] 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 IgE test results who have had severe anaphylaxis to an insect sting.

Some patients who have negative venom skin test results and negative venom-specific IgE test results are reported to have had subsequent systemic reactions to stinging insects.[225-227] Controlled studies designed to evaluate the efficacy of immunotherapy in these patients have not been performed. There are very 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.[226] 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.

Summary Statement 23: 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.

ALLERGEN SELECTION AND HANDLING

Allergen selection

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

A careful history, noting environmental exposures and an understanding of the local and regional aerobiology of suspected allergens, such as pollen, fungi (mold), 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 skin or *in vitro* test results for specific IgE antibodies, provide good evidence that such exposures are relevant. Information concerning regional and local aerobiology is available on various Web sites or through the National Allergy Bureau at http://www.aaaai.org/nab. There are

no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma. 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 clinical history of an allergic disease.

There is no evidence to support the administration of immunotherapy based solely on results of specific *in vitro* 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.

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

The omission of clinically relevant allergens from an allergic patient's allergen immunotherapy extract contributes to decreased effectiveness of allergen immunotherapy. The 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 can make allergen immunotherapy less effective.

Knowledge of the total allergenic burden facing a patient and the realistic possibility of avoidance is important in determining whether allergen immunotherapy should be initiated. 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. Many individuals travel extensively for business or pleasure into different regions, and symptoms might worsen at these times. However, inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective. Determination of the significance of indoor allergens for a particular patient is harder because it is difficult to determine exposure in the home, school, and/or workplace. Historical factors, such as the presence of a furry animal in the home, a history of water damage and subsequent fungal exposure, or a history of insect infestation, might be helpful. However, such information is subjective and is often of uncertain reliability. In addition, some studies have demonstrated significant indoor levels of cat and dog allergen in households without pets[228] and significant levels of mouse allergen in suburban[229] and inner-city[230] homes 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 with increased asthma morbidity in inner-city children was found.[231] 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. Nevertheless, for most patients, determination of the clinical relevance of an allergen requires a strong correlation between the patient's history and evidence of allergen-specific IgE antibodies.

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted *in vitro* tests for specific IgE antibodies can also be used. **A**

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 the skin test results have demonstrated the efficacy of immunotherapy for relevant allergens.[25,26,112,130,134,135,140,141,149,154] 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 from skin testing in a highly sensitive individual.[232,233] In addition, skin tests might be difficult to perform in patients with dermatographism or atopic dermatitis. *In vitro* tests are particularly useful in such patients.

Studies indicate that skin testing is generally more sensitive than *in vitro* tests in detecting allergen-specific IgE.[234,235] Based on inhalation challenge test results, skin tests have shown specificity and sensitivity generally superior to those of *in vitro* tests. The comparability of skin tests and *in vitro* tests for specific IgE antibodies depends on the allergen being tested. For all of 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, prick testing is sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass[236] and cat,[237] are used. Intradermal/intracutaneous skin testing might be required for some allergen extracts. It is appropriate in some patients to use *in vitro* tests for specific IgE antibody as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. *In vitro* tests can also be used to define the allergens that should be used in allergen immunotherapy. If the allergy skin test result is negative and the *in vitro* test result is positive, a controlled challenge can be performed, and if the latter is positive, immunotherapy can be considered. 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 *in vitro* test results.

Specific allergens

Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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.[17,104,106,107,109] 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.[112,122] Because a particular pollen extract is a mixture of multiple glycoproteins, this suggests that mixing pollen allergens does not alter biologic activity.

Fungi (molds). Several studies with *Alternaria* and *Cladosporium* species suggest that allergen immunotherapy with fungi might be effective.[133-138] The allergen content of most mold extracts is highly variable.[238,239] However, there is evidence that proteolytic enzymes present in some mold extracts could digest other antigens, such as pollens, when combined in a mixture.[240] For this reason, it might be desirable to separate all pollen extracts from mold extracts when using mixtures.

Unfortunately, extracts for some potentially clinically important fungi are not available.[241] 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 distinguish 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.

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.

Because immunotherapy has been shown to be effective for cat[22,26,139-143,242] and dog,[25,141] the decision to include dog or cat allergen in an allergen immunotherapy extract should be considered in those circumstances in which there is exposure.

Dust mites and cockroach allergens. Crude house dust extract is generally an inappropriate substitute for house dust mite extract because the protein content measured is not restricted to dust mite allergens, nor does it necessarily guarantee inclusion of dust mite protein. Immunotherapy with standardized dust mite is generally more effective than that with crude house dust allergens. The house dust mites *D farinae* and *D 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, such as *Blomia tropicalis* and *Euroglyphus maynei*, partially cross-react with allergens from *Dermatophagoides* species. Only 50% of the projected amounts of each of the 2 house dust mites (*D pteronyssinus* and *D farinae*) need 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[144,147-149,151] 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. Dust mite hypersensitivity should particularly be considered in patients who have perennial symptoms exacerbated by a dusty environment at home, work, or both and periods of high humidity.

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. The major allergen of *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.[243] Immunotherapy with cockroach allergens is effective[154] and should 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.

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.[108,116,244] Efficacy has also been demonstrated with immunotherapy by using whole-body extracts of imported fire ants.[155,156]

Foods. Only a single clinical study accessing the efficacy and safety of subcutaneous immunotherapy with foods has been performed.[171,173] This study, which evaluated immunotherapy with peanut, found the incidence of systemic reactions, even during maintenance, was unacceptable. Thus there is no evidence to support the use of immunotherapy with food extracts. Currently, strict avoidance of the offending food is advisable, and subcutaneous immunotherapy for food allergy is not recommended.

Mixing of extracts

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Once the relevant allergens for each patient are identified, it is necessary to prepare a mixture that contains each of these allergens. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts. A number of 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 interactions between different types of allergens, when mixed, that could lead to degradation or unmasking of epitopes on exposure to proteolytic enzymes.

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Immunologic and 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.[71] 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 genera 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 the Allergen extract section, Fig 2, and the allergens and allergy diagnostic tests practice parameters).

Dose selection. Summary Statement 30: 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.[22-26,128,149,245] Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000 vol/vol).[28] A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy vaccine. Failure to do so might reduce the efficacy of immunotherapy. This occurs because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased (see the Immunotherapy schedules and doses section for further discussion and for recommended maintenance doses).

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as fungi (mold) and cockroach, from other extracts, such as pollens, is recommended. **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.[240,246,247] 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, and some weeds.[240,246,247] Cockroach had a similar deleterious effect on pollen extract potency.[246,248] Short ragweed appeared resistant to the effects of the proteolytic enzymes in one study,[240] 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.[247]

Dust mite extracts do not appear to have a deleterious effect on pollen extracts.[240,246,248] These studies suggest that pollen, dust mite, and cat extracts can be mixed together. 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. The evidence on mixing cockroach extract with other extracts is conflicting, and the clinical relevance of the changes is also unclear; therefore the clinician has the option of separating cockroach or not.

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 with lesser activities, such as pollen extracts.

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.

In this regard the number of separate injections that need to be given at each patient visit depends on whether all of the relevant extracts mixed into a single vial still deliver an optimal dose of each allergen. If mixing causes excessive dilution or if there are advantages to separating allergens into separate vials, then more than one vial might be necessary for successful immunotherapy.

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extracts are high-alert products that carry the risk for anaphylaxis. Policies, procedures, and processes intended for conventional drugs and medications might be highly 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 fatal anaphylactic reactions with allergenic products. 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. There are no reports of infection associated with allergen immunotherapy injections. Allergen vaccines are prepared by using sterile manufacturer's extracts and sterile diluents containing antibacterial constituents (usually phenol). A summary of the AAAAI/ACAAI/JCAAI proposed USP allergen immunotherapy extract preparation guidelines can be found in Table VIII.

TABLE VIII. AAAAI/ACAAI/JCAAI-proposed USP 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 below.*
   - 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.
2. **Physician responsibility**: A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in the preparation of immunotherapy using an aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files.
3. **Bacteriostasis**: Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if 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 the FDA-approved package insert 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 treatment with sanitizing agents containing alcohol and/or 70% isopropanol 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 the physical integrity of the vial.
10. **Labeling**: Immunotherapy vials are to be clearly labeled with the patient's name and 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.

*__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 media, such as from Valiteq (http://www.valiteq.com), 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.

Allergen immunotherapy extract handling

Storage. Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

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 a number of 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 extract, including reconstituted lyophilized extracts, should be stored at 4°C to minimize the rate of potency loss because storage at higher temperatures (eg, room temperature) can result in rapid deterioration.[249]

Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions (personal communication). These studies include actual shipments made by their carriers to places like

Phoenix in the summer and Alaska in the winter. 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.

Storing dilute extracts. Summary Statement 34a: More dilute concentrations of allergy immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than do more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: In determining the allergy vaccine expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of 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 allergen immunotherapy 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.[249,250]

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.[250] Phenol is a preservative added to extracts to prevent growth of microorganisms.

Phenol can denature proteins in allergen extracts.[251,252] Human serum albumin might protect against the deleterious effect of phenol on allergen extracts.[251] 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,[250,253] possibly through inhibition of the activity of proteolytic and glycosidic enzymes that are present in certain extracts. However, it is irritating when injected and should be diluted before beginning immunotherapy. Recommendations for extract stability are found in the manufacturers' product insert sheets. 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. The pain associated with glycerin increases in proportion to the glycerin concentration and injection volume, and the pain is proportional to the total injected dose of glycerin.[254] However, individual pain perception can vary substantially. Total glycerin doses of less than 0.05 mL rarely produce clinically important pain.

TABLE IX. Potency of selected manufacturer's extracts currently available

Extract	Potency
Cat hair and pelt	5000 and 10,000 BAU/mL
Dust mite	3000, 5000, 10,000, and 30,000 AU/mL
Bermuda grass	10,000 AU/mL
Short ragweed	1:10-1:20 wt/vol or 100,000 AU/mL
Other grasses*	10,000 and 100,000 BAU/mL
Other pollen	1:10 to 1:40 (wt/vol) or 10,000 PNU/mL
Molds	1:10 to 1:40 (wt/vol) or 20,000 to 100,000 PNU/mL

AU, Allergy unit; *BAU*, bioequivalent allergy unit; *PNU*, protein nitrogen unit.
*Perennial rye, Kentucky blue/June, timothy, sweet vernal, redtop, orchard, and meadow.

There have been few studies that have investigated the potency of dilutions of allergen extract mixture over time. Expiration dates for allergen extract dilutions are somewhat empiric and not strongly evidence based. A study undertaken by the AAAAI 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. Dust mite and cat at 1:10 and 1:100 vol/vol dilution were also stable in all conditions of storage over 12 months, as measured by an ELISA assay using 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.

IMMUNOTHERAPY SCHEDULES AND DOSES

Summary Statement 35: A customized individual 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 can be based on single or multiple allergens. **D**

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. Animal dander contains between 10 and 20 antigens,[255] house dust mites between 20 and 40 antigens,[256] and pollens between 30 and 50 antigens,[257,258] and fungal extract can contain as many as 80 antigens.[259]

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. This is designated as the patient's maintenance concentrate.

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. Standardized extracts are available with biologic potencies of 10,000 and 100,000 BAU for grasses; 5000 and 10,000 BAU for cat allergen; 5000, 10,000, or 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 wt/vol extracts (Table IX). 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.

Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

The highest concentration of an allergen extract mixture that is projected to be used as the therapeutically effective dose is called the maintenance concentrate. This should be prescribed individually for each patient by an allergist/immunologist. 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 individual manufacturer's extracts. Some patients might be unable to attain the projected therapeutically effective dose of the maintenance concentrate because of local reactions, systemic reactions, or both (eg, cat, 1000 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose]; see Table X for probable effective therapeutic dose range). Such patients might need weaker dilutions of their maintenance concentrate. Even so, 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 referred to as the maintenance dose. The consistent use of this nomenclature system is essential because errors in choosing the correct vial are a common cause of systemic reactions, especially when the patient transfers from one physician to another. Therefore it is important that standard terminology be adopted by all physicians who prescribe allergen immunotherapy.

Recommended doses

Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

The effective maintenance dose of immunotherapy for a particular patient must be individualized. To do this, the allergist/immunologist who prepares the allergen immunotherapy extract must balance the dose necessary to produce efficacy and the risk of reactions if such a dose is reached. The allergist/immunologist might need to prepare more than one maintenance concentrate to provide a therapeutic dose of each of the allergens for the polysensitized patient. Therapeutically effective doses for immunotherapy have been reported for some allergen extracts.[22,24,25,128,134,135,149,246,260,261] Effective doses have been determined for Hymenoptera venom, dust mite, cat allergen, dog, grass, and short ragweed (Table X).

Controlled studies demonstrate that the content of particular allergens in allergen immunotherapy extracts can be used to predict a therapeutic dose for those allergens, particularly when the extracts are standardized. For antigens 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. The therapeutically effective doses used in the most recent controlled clinical studies are the basis of the recommended dosage range of standardized extracts presented in Table X. 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 time that it is administered.[14]

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.[27] 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 risk of systemic reactions to immunotherapy injections with higher maintenance doses. The maintenance concentrate should be formulated to deliver a full therapeutic dose of each of its constituent components. However, some sensitive patients might not tolerate the targeted therapeutic dose, and their maintenance dose would be lower. Individuals 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 referred to as the maintenance dose.

Regardless of dose schedule, some patients are unable to progress to the predetermined maintenance dose because of large local or systemic reactions to the allergen

TABLE X. Probable effective dose range for allergen extracts US standardized units[a]

Antigen	Labeled potency or concentration[a,b]	Probable effective dose range
Dust mites: *D farinae* and *D pteronyssinus*[c]	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat[d]	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized[e]	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed[f]	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 μg of Amb a 1 1000-4000 AU Concentration of Amb a 1 is on the label of wt/vol extracts in FDA units[358]
Nonstandardized extract, dog[g]	1:10 to 1:100 wt/vol	15 μg of Can f 1
Nonstandardized extracts	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose

[a]Multiple studies have demonstrated that the efficacious dose for allergen immunotherapy is between 5 and 20 μg of the major allergen per injection. Only 2 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).

[b]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).

[c]There have been no dose-response studies with United States–licensed dust mite extracts, and dosing recommendations in AU value are extrapolated from published European studies that used aqueous[349] and alum-precipitated[149,151] extracts. 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.[149] The authors suggested the optimal maintenance dose was 7 μg of Der p 1. Corresponding doses were based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Extrapolating effective and safe doses in this manner might not be scientifically valid. *D farinae* and *D pteronyssinus* are similar in group 1 allergen content according to the FDA's current reference standards. 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*.

[d]The major cat allergen Fed d 1 is reported in FDA units, with 1 Fel d 1 unit equaling approximately 2 to 4 μg of Fel d 1.[55,58,59] The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 to 19.9 U/mL. One study demonstrated clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 dose in terms of decreased cat extract PD_{20}, titrated skin test results, and allergen-specific IgE and IgG levels.[350,351] In a recent study that investigated the efficacy in terms of immunologic changes of 3 doses of a United States–licensed cat extract (0.6, 3, and 15 μg) demonstrated that a significant effect on titrated skin prick test results, allergen-specific IgG4 levels, and $CD4^+$/IL-4 levels was only seen in the group treated with 15 μg of Fel d 1, although the 3-μg dose group did demonstrate a significant change in titrated skin test response and increase in cat-specific IgG4 levels.[22]

[e]There have been no dose-response studies with United States–licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,[130] alum-precipitated,[24,161] and calcium phosphate–precipitated grass pollen extracts.[352] One of these studies compared a dose of 2 μg with 20 μg of major timothy allergen (Phl p 5) and found clinical efficacy at both doses.[24] The efficacy was greater in the 20 μg of Phl p 5 dose, but the systemic reaction rate was also higher in the high-dose group. The package inserts for United States–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 BAU. Extrapolating effective and safe doses in this manner might not be scientifically valid. 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).

[f]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 suggested that 1 unit of Amb a 1 is equivalent to 1 μg of Amb a 1, and 350 Amb a 1 units/mL is equivalent to 100,000 BAU/mL.[60] The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2000 AU, with a range of 1000-4000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrated 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.[45] A ragweed dose-response study (0.6, 12.4, and 24.8 μg of Amb a 1) demonstrated efficacy, as measured by nasal challenge, at 12 and 24 μg of Amb a 1.[128] The efficacy of the 24-μg dose was not significantly better than the 12-μg dose, and the authors concluded that the optimal dose for ragweed extract was greater than 0.6 μg but not more than 12.4 μg of Amb a 1.

[g]Dog extracts are not standardized. However, one dose-response study with a United States–licensed acetone-precipitated dog extract investigated the efficacy of 3 doses (AP dog; Hollister-Stier, Spokane, Wash; 0.6, 3, and 15 μg) in terms of immunologic changes and found the dose of 15 μg of Can f 1 to be most efficacious.[25] 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 have assayed between 128 and 208 μg/mL (average Can f 1, 162 μg/mL [SD ± 26 μg/mL]; information provided by the extract manufacturer, Hollister-Stier).

immunotherapy extract. The evidence is not clear whether large local reactions are a potential risk for subsequent allergen immunotherapy systemic reactions.

Published studies do not indicate that an individual large local reaction is predictive of a subsequent systemic reaction.[179,180] However, one retrospective study found that individuals who have a history of repeated large local reactions (defined as >25 mm) might be at greater risk for a subsequent systemic reaction.[181]

The concept of highest tolerated dose does not apply for VIT, and all patients are expected to achieve the full recommended dose to achieve the necessary degree of protection. There are conflicting data over whether lower doses (50 μg) are less effective, but there are also data showing that 200 μg is more reliably effective.[245] In the case of VIT, patients are asked to tolerate more large local reactions to achieve the full dose, even though with inhalant immunotherapy the dose can be reduced for such large local reactions to minimize patient discomfort.

Effect of dilution on dose

Summary Statement 38: 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 vaccine, thereby limiting the ability to deliver a therapeutic effective dose for any given allergen.

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

Dilution from maintenance concentrate vaccine	Volume	Volume (mL)	Diluent volume (mL)	Final volume
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.

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 2000 BAU/mL, 2 mL of the manufacturer's extract (cat, 10,000 BAU/mL) can be added to 8 mL of diluent or 8 mL of other allergens, and the final concentration of cat will be 2000 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.

Dilutions of the maintenance concentrate

Summary Statement 39: 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 vol/vol 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, 1000 BAU or 100 BAU), but this system can be complicated if allergens with different potency units are used (eg, wt/vol, BAU, AU, or PNU) and make it difficult to easily interpret the vial label.

Instructions on how to prepare various allergen extracts 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.

Labeling dilutions

Summary Statement 40: 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, a number of 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 (vol/vol), a numbering system, a color-coding system, or an alphabetical system should be used. If this uniform labels 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.

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
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

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 3 and 4).

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 Appendix 2]).

Individualized treatment vials

Summary Statement 41: 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 (wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for 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). Labels on patient-specific vials can provide at least 2 patient identifiers (birth date and patient name), which would be consistent with the recommendations of the Joint Commission on Accreditation of Health Care Organizations National Patient Safety Goals: ''Goal 1: Improve the accuracy of patient identification by using at least two patient identifiers when providing care, treatment or services.''[5] 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 administration of the injection.[4,5]

In a survey of 1717 allergists endorsed by the AAAAI and JCAAI, 57% of the 476 respondents reported at least one wrong-patient injection, and 74% of the 473 respondents reported at least one wrong-dose injection.[4] 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 reasons why this might reduce incorrect injection errors. One reason was that patient-specific vials can be prepared in a quiet laboratory setting, which might provide substantially less distraction than the nurse in a room with a patient who is trying to concentrate only on drawing up the injection correctly. In addition, the specific components are mixed once with the preparation of individually prepared patient-labeled vials, whereas the mixing would be repeated on every injection visit if the allergen extract is withdrawn from different stock solutions, as it is in the off-the-board method. For safety reasons and to avoid cross-mixing of allergens removed from the manufacturer's extract, the mixing of antigens in the syringe (off the board) is not recommended.

Some allergists/immunologists prefer to administer immunotherapy doses drawn directly from a single stock dilution of individual allergens or common mixes (shared specific patient vials). In this way the immunotherapy dose is transferred to the patient without cross-contamination. If shared-patient (eg, mixed vespids and dust mite mix) vials are used, it is essential that policies and procedures are developed to verify that the correct dose from the correct vial is administered to the correct patient.

Starting doses

Summary Statement 42: The starting dose for build-up is usually a 1000- 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 slowly 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 1:1000 (vol/vol), although more diluted concentrations frequently are used for patients who are highly sensitive, as indicated by history or skin test reaction (see Appendix 3 for an example of a conventional immunotherapy schedule).

Frequency of build-up injections

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 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 2 times per week. 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 4 to 6 months, depending on the starting dilution and the occurrence of reactions. It is acceptable for patients to receive injections more frequently, provided there is adequate spacing between injections. The interval between injections is empiric but might be as short as 1 day without any increase in the occurrence of systemic reactions[262] if there is some urgency to achieve a maintenance dose (eg, allergy season is approaching) or for practical reasons (eg, patient's schedule). Alternatively, treatment schedules can be used that more rapidly achieve maintenance dosing. These cluster and rush dosing schedules are discussed in Summary Statements 47 through 49.

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 a number of 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).

Dose adjustments for systemic reactions

Summary Statement 44: 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 benefit/risk ratio justifies continuation of immunotherapy.

Reductions during periods of exacerbation of symptoms

Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Immunotherapy administered during periods of exacerbation of symptoms is considered a risk factor for immunotherapy.[17,184] Injections administered during periods when a patient is exposed to increased levels of allergen to which they are 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.[184] 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 sensitive, especially if their symptoms are poorly controlled.

Dose adjustments for late injections

Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

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 depends 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 Appendix 4 for an example of a dose-modification regimen for gaps in treatment).

Cluster schedules

Summary Statement 47: 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 (see Appendix 5).[22,26] 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. The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules.[145,263-266] The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.[267]

Rush schedules

Summary Statement 48: 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.[268] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.[191,269-272]

The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections over the course of 4 hours.[273] Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours.[274-276] 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 cluster[145,266] and rush[134,277] schedules.

Systemic reactions and rush schedules

Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

The advantages of rush immunotherapy come at a cost because there is an increased risk of local and systemic reactions. Systemic reaction rates have been reported to be

as high as 73% of patients, with the risk of such reactions reduced to 27% by premedication in one study.[272] Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing.[273]

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

Rush protocols for administration of Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions.[274-276,278,279]

Premedication and weekly immunotherapy

Summary Statement 50: Premedication can reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

There is concern that antihistamines taken before each injection with conventional immunotherapy might mask a minor reaction that would otherwise alert a physician to an impending systemic reaction. 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.[280] One study that compared terfenadine premedication with placebo premedication during rush VIT demonstrated greater clinical efficacy in the terfenadine-premedicated group in terms of subsequent responses to field stings or sting challenge.[281] There was also a significant difference in the systemic reaction rate between the 2 groups: 6 patients in the placebo-premedicated group had systemic reactions, whereas none of the patients in the terfenadine-premedicated group had systemic reactions ($P = .012$).

Unfortunately, patients might still have life-threatening anaphylaxis despite 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.

Premedication with cluster and rush immunotherapy

Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

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.[267] Premedication with a 3-day course of prednisone, an H_1 histamine receptor antagonist, and an H_2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.[272] In one study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on the safety and efficacy of rush immunotherapy, there was a 5-fold decrease in the risk of anaphylaxis in the group premedicated with omalizumab compared with the placebo premedication group.[282]

There are anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist, but there have been no published studies. Because the risk of a systemic reaction from rush VIT is relatively low, routine premedication before rush VIT is usually unnecessary.[274,276,278,279] In a study evaluating premedication with antihistamines and steroids for rush immunotherapy with imported fire ant venom, there was no statistically significant differences in the systemic reaction rates between the premedication and placebo premedication group (3.6% of the premedication group vs 6.7% of the placebo group, $P = .87$).[157]

Maintenance schedules

Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals 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 individuals might tolerate longer intervals between maintenance dose injections.

The interval between venom injections can be safely increased up to 8 weeks in some patients without loss of efficacy. 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.

Continuing care

Time course of improvement. Summary Statement 53: Clinical 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.[24,134,143,277] Improvement might not be observed for a number of reasons, including (1) failure to remove significant allergenic exposures (eg, a cat), (2) exposure to high levels of

allergen (eg, pollen or molds), (3) continued exposure to nonallergen triggers (eg, tobacco smoke), or (4) incomplete identification and treatment of clinically relevant allergens. 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 54: 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 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 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

The patient's response to immunotherapy should be evaluated on a regular basis. 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. 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.

There have been very 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 individuals.[283-285] However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported.[283,285] Nevertheless, systemic reactions to stings after discontinuing VIT were generally much milder than the pretreatment reactions and were rarely severe. Two studies did not find a difference in relapse rates between the patients treated for 3 years compared with those treated for 5 years,[283,286] but one of the studies noted that the small number of patients in the 3-year treatment group prevented them from making any conclusions about the risk of discontinuing treatment after 3 years.[283] However, one study found that patients who had experienced re-sting reactions after discontinuing VIT had received VIT for a significantly shorter duration (mean, 43.35 months) than those with continued protection (mean, 54.65 months; $P < .01$).[285] Another study reported that 5 years of VIT provided better immunologic and clinical outcomes than 2 to 4 years of treatment.[287]

Change in skin test reactivity did not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who experienced a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE.[286,288] Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment.[288] The relapse rate and the frequency of severe reactions were greater in patients who had a history of very severe reactions to stings before treatment, in patients who had systemic reactions during VIT (to a sting or a venom injection), in patients with honeybee allergy, and in those who had less than 5 years of treatment.

The duration of inhalant allergen immunotherapy efficacy has not been as extensively studied. Some studies have suggested 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 *(D pteronyssinus)* extract for 12 to 96 months.[14] 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.[13] There was a switch to placebo in half of 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. These studies demonstrate the uncertainty of the long-term benefit of inhalant immunotherapy after discontinuation.

Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained clinical remission after discontinuing inhalant immunotherapy, and 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 indication for continuation of immunotherapy can be found at http://www.aaaai.org or http://www.jcaai.org.

Documentation and record keeping. Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully 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 allergy immunotherapy and prescription forms can be found in the Appendix (Appendices 6-15), and these include examples of immunotherapy prescription and administration forms. These forms, along with examples of immunotherapy consent and instruction forms, can also be found at http://www.aaaai.org.

Injection techniques. Summary Statement 57: Allergen immunotherapy extract injections should be given using a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **C**

Immunotherapy should be given with a 26- to 27-gauge syringe with a half-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.[289-291]

If using shared specific patient vials (stock vials, such as mixed vespid or dust mite mix), a single dose should be drawn from each vial. Antigens from different vials should not be combined in a single syringe. Furthermore, extra care is needed to prevent using the wrong stock antigen.

Summary Statement 58: The injection should be given subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Each immunotherapy injection should be given in the posterior portion of the middle third of the upper 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.

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.

The syringe should be aspirated to check for blood return in the syringe before injecting. If blood is present, 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 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 syringe should be appropriately discarded. A fresh syringe and needle are necessary to determine whether a blood vessel has been entered.

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 could result in a local reaction.

LOCATION OF ALLERGEN IMMUNOTHERAPY ADMINISTRATION

Physician's office

Summary Statement 59: 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 to treat anaphylaxis should be in the immediate vicinity when immunotherapy injections are administered.

Summary Statement 60: 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.[292] 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.[184] 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 might be frequently necessary in the patient's immunotherapy schedule, as well as the patients total treatment program.

Other locations

Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **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.[292] The health care professional and staff 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, or allergy/asthma exacerbations at the time of allergen immunotherapy extract injection or poorly controlled asthma).

Appropriate adjustment of dose should be made as clinically indicated. The physician who prepared the patient's allergen immunotherapy extract should provide adequately labeled allergen immunotherapy extract vials, detailed directions regarding dosage schedule for build-up and maintenance, and instructions on adjustments that might be necessary under the following circumstances:

1. when providing patients with new vials;
2. during seasonal exposure to allergens that are in the patient's allergen vaccine, to which the patient is very sensitive, or both;
3. if the patient has missed injections; and
4. when reactions occur to the allergen immunotherapy extract.

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

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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 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 very 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 fully trained to administer the injection and to treat anaphylaxis if this should 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 supports (personnel, medications, supplies, and equipment) are more optimal for encouraging prompt recognition and treatment of anaphylaxis (Table V). 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.

Summary Statement 63: If a patient on 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for their immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extracts might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Patients often 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 brought from the previous physician (ie, an unchanged immunotherapy program) or one to be prepared by the current physician (ie, a new immunotherapy program).

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 full, clear, and detailed documentation of the patient's previous schedule and the contents of the allergen immunotherapy extract (see Appendices 7, 8, 11, 12, and 14 for examples of allergen immunotherapy prescription and administration forms and documentation guidelines for allergen immunotherapy forms). In addition, the patient's previous response to and compliance with this program 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 a schedule and the allergen immunotherapy extract, (2) the patient has shown significant improvement on this immunotherapy program, and (3) the contents of the allergen immunotherapy extract are appropriate for the area in which the patient is now living.

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, vaccine type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient's dose is not modified. This increased risk is due to the significant variability in content and potency of extracts and the variability in methods used by physicians to prepare the patient's maintenance concentrate and its dilutions. For example, the strength of a given concentration of nonstandardized extracts might vary significantly from vial to vial. The risk of systemic reactions in such a situation might be greater with nonstandardized extracts and allergen immunotherapy extracts that contain mixtures of allergens.

Therefore if the allergen immunotherapy extract is to be changed, the patient might need to be retested for specific IgE to the appropriate allergens 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 provided the interval of time since the last injection has not been too long. For lot changes from the same manufacturer, the physician can consider decreasing the dose by 50% to 90%. For changes in manufacturer and nonstandardized extracts, a greater decrease in dose might be necessary.

SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

Allergen immunotherapy in children

Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children

with allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Immunotherapy for children has been shown to be effective and often well tolerated,[137,242] although at least one study did not show efficacy.[293] 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.[294] In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (see the Patient selection section and Table VII). In recent studies children receiving allergen immunotherapy have demonstrated:

1. improvement in symptom control for asthma[117,119,121,122] and allergic rhinitis[118];
2. increased PC_{20} to histamine[121];
3. increased PC_{20} to cat and house dust mite allergens[121,149];
4. decreased risk of development of asthma[6,9,163-165];
5. decreased development of new sensitivities[120,166]; and
6. modification in release of mediators in children receiving immunotherapy that correlates with decreased clinical symptoms.[123]

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Although there is some disagreement about the role of allergen immunotherapy in children under the age of 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.[117,122] In children with allergic rhinitis, allergen immunotherapy might prevent the development of asthma.[6,9,163-165] However, allergen immunotherapy for inhalant allergens is usually not considered necessary in infants and toddlers because (1) there is 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 in pregnancy

Summary Statement 71: Allergen immunotherapy might be continued but is usually not initiated in the pregnant patient. **C**

The physician must be aware of the benefits and risks of immunotherapy in pregnant patients. The recommended precautions for prevention of adverse reactions are especially important in the pregnant patient. Allergen immunotherapy is effective in the pregnant patient. Thus allergen immunotherapy maintenance doses can be continued during pregnancy. Allergen immunotherapy is usually not initiated during pregnancy because of risks associated with systemic reactions and their treatment (ie, spontaneous abortion, premature labor, or fetal hypoxia). 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, and the patient is maintained on the dose that she is receiving at that time.

Immunotherapy in the elderly patient

Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy might be considered in the treatment of the elderly patient, but the benefit/risk assessment must be evaluated carefully in this population. Older 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. However, elderly patients may also benefit from allergen immunotherapy and age alone should not preclude the consideration of allergen immunotherapy.[295]

Immunotherapy in patients with immunodeficiency and autoimmune disorders

Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with immunodeficiency or autoimmune disorders. Therefore the decision to begin immunotherapy in patients with major humoral or cellular immune defects must be individualized. Concern about the increased risk of immunotherapy in such patients is largely hypothetical.

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

ALTERNATIVE ROUTES OF IMMUNOTHERAPY

Sublingual and oral immunotherapy

Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be

effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no FDA-approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **B**

Alternative routes of administration of allergen immunotherapy are ''a viable alternative to parenteral injection therapy'' in some cases.[106,296] Studies of oral immunotherapy have provided conflicting results for ragweed,[297] birch,[298] and cat[299] immunotherapy. The present dosage of oral immunotherapy extract is 20 to 200 times the parenteral injected dosage, which requires a cost assessment for this type of therapy. Furthermore, adverse effects have included gastrointestinal and oral reactions (50% in 1 study) that might preclude home therapy. Oral immunotherapy should be considered investigational at this time.

Optimal-dose (high-dose) sublingual swallow immunotherapy is effective in adults and children.[300-304] In a study of 855 patients with grass pollen allergy and allergic rhinitis randomized to placebo or one of 3 grass tablet doses, there was a significant reduction in symptom and medication scores in the highest-dose subgroup, who were treated for at least 8 weeks before the grass pollen season, compared with the placebo group (symptoms, 21%, $P = .0020$; medication use, 29%, $P = .0120$).[303]

Sublingual allergen studies have evaluated house dust, olive pollen, grass pollen, ragweed, birch, cat, latex, *Alternaria* species, and *Parietaria judaica*.[305-313] Sublingual immunotherapy has been shown to be effective in patients sensitized to 2 non–cross-reacting allergens, grass and birch.[314] It has been noted that the allergen is not degraded by saliva and that there is no direct sublingual absorption of allergen. Radiolabeled allergen has been detected after 48 hours in the sublingual region.[315,316] Alternative protocols, such as rush and ultra-rush (20 minutes) sublingual swallow[307,316,318] and no induction (build-up) phase,[301,303,317,319,320] have been studied. Several studies have suggested a relationship between dose and efficacy with sublingual immunotherapy,[303,310,321] but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. The majority of sublingual studies have demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both, but approximately 35% of the randomized, double-blind, placebo-controlled studies did not demonstrate efficacy in either parameter during the first year of treatment.[322] Further studies are needed to confirm the optimal dose for sublingual immunotherapy.

One of the potential advantages of sublingual immunotherapy is that it appears to be safe, even at very high doses (up to 500 times the usual monthly subcutaneous dose), and to be associated with a lower incidence of serious side effects.[310,320,323] This appears to apply to young children (<5 years), for whom there are prospective safety data[324,325] and a postmarketing survey.[326]



FIG 3. Sample of labels for allergen immunotherapy extract vials.

There have been no SLIT-related fatalities, but there have been 3 case reports of anaphylaxis caused by sublingual immunotherapy. One patient with latex hypersensitivity had anaphylactic shock 20 minutes after reaching the maximal dose on the fourth day of latex rush sublingual rush immunotherapy.[327]

The other 2 reported cases of SLIT anaphylaxis involved patients treated with multiple inhalant allergens. In one case a patient with allergic rhinitis and asthma who was prescribed a sublingual immunotherapy extract composed of multiple non–cross-reacting allergens (*Alternaria* species, dog, cat, ragweed mix, weed mix, and grass mix)[328] had generalized pruritis, followed by angioedema, shortness of breath, and dizziness, within a few minutes of administering 6 drops of the 1:100 vol/vol dilution on the third day of treatment. This episode was preceded by a milder systemic reaction the previous day (generalized pruritis). In the other case, a 13-year-old girl with allergic rhinitis and asthma had swelling of her lower lip 3 minutes after pollen drops, high fever, chest pain, nausea, and abdominal pain.[329] She was treated in the emergency department for anaphylaxis and hospitalized for observation. The reaction occurred 1 month after she had reached the maintenance dose during the peak of the spring season.

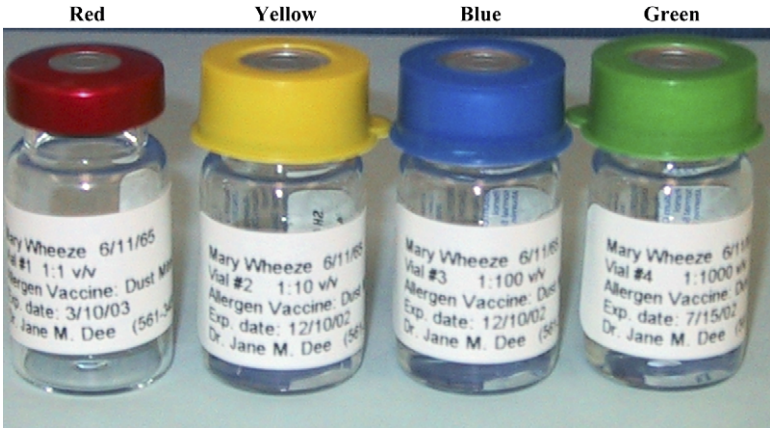


FIG 4. Sample set of color-coded vials of allergen vaccine.

There is currently no FDA-approved formulation for sublingual immunotherapy in the United States at this time, and this modality should be considered investigational. Current investigation of sublingual immunotherapy should not be confused with low-dose sublingual immunotherapy based on provocation neutralization testing or Rinkel-type skin testing.

Intranasal immunotherapy

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Based on controlled, well-designed studies, intranasal immunotherapy has been shown to improve the nasal symptoms of rhinitis.[330] Intranasal dry powder extract immunotherapy has been studied in grass,[330] birch,[331] *P judaica*,[332-334] and house dust mite[335] allergy. Clinical efficacy was noted in all of these studies. Nasal reactivity to allergen challenge was reduced, and only minor side effects were noted in 2 of the above studies. A 3-year study with *P judaica* reported to provide persistent benefits for up to 12 months after conclusion of allergen immunotherapy.[333] Local administration of nasal allergen in an aqueous solution for immunotherapy might be limited by the local side effects. Further studies in both pediatric and adult groups are needed. In human studies the antigen has been noted to appear in the serum within 15 to 30 minutes of administration, with a peak level occurring within 2 to 3 hours.[315] Some allergens have been reported to be retained in the nasal mucosa for up to 48 hours after administration. Intranasal immunotherapy is not currently available in the United States but has gained some acceptance in other parts of the world.

Immunotherapy techniques that are not recommended

Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

Low-dose regimens, including coseasonal low-dose immunotherapy for aeroallergens and the Rinkel low-dose titration techniques, are not effective.[27,28] Immunotherapy based on provocation–neutralization testing with food and aeroallergens and enzyme-potentiated desensitization is not effective.[336]

FUTURE TRENDS IN IMMUNOTHERAPY

Therapy with aeroallergen extracts will become more uniform (as is the current practice for insect venoms) as greater numbers of biologically standardized allergen extracts become available. The actual number of commercially available allergen extracts will be reduced based on consensus agreements about the regional prevalence of aeroallergens, their cross-allergenicity, and the relevance of their effect on human health in specific locales. Novel routes for more effective, convenient, and safer allergen immunotherapy are being investigated throughout the world.

For example, the sublingual route of administering allergen immunotherapy has been studied extensively in Europe. A meta-analysis confirmed its clinical effectiveness in allergic rhinitis,[302] and it has been reported to be effective in asthma as well.[337] Sublingual immunotherapy appears to have a very low risk of serious life-threatening systemic side effects, which might allow for home administration.[324,338] In some studies the clinical benefits of sublingual immunotherapy were not significant until the second year of treatment,[306,339] and comparisons suggest that the magnitude of the clinical benefit of sublingual immunotherapy might not be as great as that of subcutaneous immunotherapy.[311]

Trials with non–IgE-binding peptides containing T-cell stimulating peptides have been reported.[340] Site-directed mutagenesis has produced allergens with decreased IgE-binding capacity without decreased T-cell responses.[341,342]

Immunostimulatory sequences mimicking bacterial and viral DNA have been prepared that stimulate the innate immune system to direct T-cell responses toward

T_H1 rather than T_H2 phenotypes.[343] The results of clinical trials with a conjugate of the immunostimulatory sequence to the major allergen of ragweed, Amb a 1 (AIC), have been reported.[34,343] In a double-blind, placebo-controlled study of 25 adults who received 6 weekly injections of the AIC or placebo vaccine before ragweed season, the AIC group had better peak-season rhinitis scores on the visual analog scale ($P = .006$), peak-season daily nasal symptom diary scores ($P = .02$), and midseason overall quality-of-life scores ($P = .05$) than the placebo group during the first ragweed season, and this effect was observed in the subsequent ragweed season.[344]

Humanized anti-IgE mAb has been shown to have clinical effects in both allergic rhinitis and asthma.[345-348] Theoretically, this new therapeutic modality could be used as protective cover for clinical applications of rapid forms of immunotherapy. It is possible that preadministration of anti-IgE could provide a more effective protective effect than premedication with antihistamines and therefore permit a rush allergen immunotherapeutic regimen with reduced risk of serious systemic reactions.[282]

AUTHOR'S 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 2 systemic reaction grading systems (the European Academy of Allergy and Clinical Immunology's grading of severity for systemic side effects and the Portnoy method for numeric grading of reactions to allergen immunotherapy) can be found in the Appendix section. These forms can also be found along with examples of immunotherapy instruction and consent forms, preinjection health questionnaires, and indications for beginning and continuing immunotherapy forms at www.aaaai.org.

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APPENDIX 1. American College of Medical Quality's policy on the development and use of practice parameters for medical quality decision-making[1]

Practice parameters are strategies for patient management developed to assist health care professionals in clinical decision making. Practice parameters include standards, guidelines, and other patient management strategies. Standards are accepted principles for patient management. Guidelines are recommendations for patient management that identify a particular management strategy or a range of management strategies. Other strategies for patient management include practice policies and practice options. Practice parameters are to be used as screening tools to identify possible deviations from the applicable standards of care. Such parameters are not to be used as absolute standards or to profile or report on health care personnel. Parameters are designed to trigger a process in which possible deviations from the standard of care are identified as outlier practice patterns. Once a deviation from the parameter is identified, such a deviation should be referred to the appropriate qualified physician advisor or reviewer for a determination of medical necessity that conforms to the applicable standard of care. Parameters used in the day-to-day practice of clinical medicine should be clinically relevant. They should not be considered as substitutes for the standard of care but might contribute to its formulation.

Practice parameters must be developed, designed, and implemented only by board-certified, clinically practicing, specialty-matched physician advisors/reviewers with unrestricted medical licenses. Qualified nonphysicians might participate in the development of these parameters only in the areas in which their clinical expertise based on the standard of care is applicable. The health care personnel who develop these parameters should sign their names and date the final version as evidence of their participation and support. Practice parameters must be based on sound scientific research findings, professional literature, clinical experience and appropriate well-recognized methodologies and reflect professionally recognized national standards of care practiced in the clinical community of medicine. The development procedures followed, the participants involved, the evidence used, the assumptions and rationales accepted, and the analytic methods used should be meticulously documented, described, and made publicly available for national peer review. Parameters should be updated as needed.

Practice parameters are used as tools to enhance medical decision making but not as replacements for physicians' clinical judgment. They can be considered as means to enhance the performance of clinical and review personnel but not to replace them. It is below the standard of care of the medical review process to substitute qualified physician reviewer experts with unqualified reviewers who are using parameters.

APPENDIX 2. Examples of possible abbreviations for allergen immunotherapy extract 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

APPENDIX 3. 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

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

APPENDIX 4. Example of immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals (modification of the AAAAI skin testing and immunotherapy consent and instruction forms: immunotherapy administration instruction form, which can be found at http://www.aaaai.org)

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

- Up to 7 days, continue as scheduled (ie, if on weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection).
- Eight to 13 days after missed scheduled injection; repeat previous dose.
- Fourteen to 21 days after missed scheduled injection; reduce dose 25%.
- Twenty-one to 28 days after missed scheduled injection; reduce previous dose 50%.

Then increase dose each injection visit as directed on the immunotherapy schedule until therapeutic maintenance dose is reached.

This suggested approach to modification of doses of allergen immunotherapy because of gaps between treatment during the build-up phase is not based on retrospective or prospective published evidence, but it is presented as a sample for your consideration. The individual physician should use this or a similar protocol as a standard operating procedure for the specific clinical setting. A similar dose-reduction protocol should be developed for gaps in maintenance immunotherapy.

APPENDIX 5. Example of a cluster immunotherapy schedule[22,26]

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

APPENDIX 6. Recommended documentation for allergen immunotherapy prescription forms

The purpose of the allergen immunotherapy prescription form is to define the contents of the allergen immunotherapy extract in enough detail that it could be precisely duplicated. The following information should be on an immunotherapy prescription form:

Patient information:

- Patient name, patient number (if applicable), birth date, telephone number, and picture (if available) should be included.

Preparation information:

- Name of person and signature preparing the allergen immunotherapy extract should be included.
- Date of preparation should be recorded.
- Bottle name should be included (eg, trees and grass). If abbreviations are used, a 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 should be included.
- Volume of manufacturer's extract to add to achieve the projected effective concentration should be included. 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) should be included.
- Extract manufacturer should be included.
- Lot number should be included.
- Expiration date should be recorded and should not exceed the expiration date of any of the individual components.

APPENDIX 7. Allergen immunotherapy extract prescription 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:

_____
_____
_____
_____

_____ ____/____/____
Prescribing Physician Signature Date

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

APPENDIX 8. Maintenance concentrate prescription form

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: 6/10/06

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial **4** from Vial **1** on **8/30/06** Expiration date: **10/15/06**
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	Short ragweed	1:20 w/v G (150 Amb a1)	0.5ml	Greer	12345	1/01/08
2	Amaranthus Retroflexus	1:10 w/v G	0.5ml	H-S	6789	2/07/08
3	Ash	1:10 w/v G	0.5ml	Center	3333	3/17/08
4	Cat	10,000 BAU/ml G	2.00ml	ALO	9898	2/27/08
5	Timothy Grass	100,000 BAU/ml G	0.4ml	ALK	56789	7/09/08
6	Johnson Grass	1:10 w/v G	0.5ml	Greer	2434	7/20/08
7						
8						
9						
10						
Diluent	HSA		0.6ml	ALK	68597	12/08
Total Volume			5.00 ml			6/10/07

*** Components of mixes listed on a separate sheet**
**** Assumes 0.5 ml injection as target maintenance dose**

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

Specific Instructions:

_____

_____

Prescribing Physician Signature

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

APPENDIX 9. Labels for allergen immunotherapy extracts

Each vial of allergen immunotherapy extract should be labeled in a way that permits easy identification. Each label should include the following information (example in Figs 3 and 4):

- Appropriate patient identifiers might include the patient's name, patient's number, patient's picture, and birth date.
- The contents of the allergen immunotherapy extract in a general way should be included. The detail with which this can be identified depends on the size of the label and the number of allergens in the vial. Ideally, allergens should be identified as trees, grasses, weeds, mold, dust mite, cockroach, cat, and dog. Because of space limitations, it might be necessary to abbreviate the antigens (eg, T, G, W, M, DM, Cr, C, and D respectively [see Appendix 2]). A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate (vol/vol) should be recorded. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- The expiration date should be included.

APPENDIX 10. Allergen immunotherapy administration form recommended documentation

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

Patient information:

- Patient's name, date of birth, telephone number, and patient's picture (optional but helpful).

Allergen immunotherapy extract information:

- Allergen immunotherapy extract name and dilution from maintenance in vol/vol bottle letter (eg, A and B), bottle color, or number, if used.
- Expiration date of all dilutions.

Administration information in separate columns:

- Date of injection.
- Arm administered injection, which might facilitate determination of exact cause of local reaction.
- Projected build-up schedule.
- Delivered volume reported in milliliters.
- Description of any reactions. The details of any treatment given in response to a reaction would be documented elsewhere in the medical record and referenced on the administration form.
- *Patient's health before injection*. This can be performed through a verbal or written interview of the patient before administering the immunotherapy injection. The patient should be questioned about increased asthma or allergy symptoms, β-blocker use, change in health status (including pregnancy and recent infections), or an adverse reaction to a previous injection (including delayed large local reactions persisting through the next day). Patients with significant systemic illness generally should not receive an injection.
- *Antihistamine use*. Antihistamines are frequently a component of an allergy medication regimen, and it would be important to note whether a patient is taking an antihistamine on the day he or she receives his or her immunotherapy injection. For consistency in interpretation of reactions, it might be desirable for a patient to either take or avoid antihistamines on a regular basis on the days he or she receives immunotherapy. The physician should note on the form whether he or she recommends the patient consistently take an antihistamine on immunotherapy treatment days.
- *Peak flow reading*. Consider obtaining a peak expiratory flow rate measurement before administering an immunotherapy injection to asthmatic patients. Poorly controlled asthma is considered a risk factor for immunotherapy. Obtaining a peak expiratory flow rate measurement before the immunotherapy injection might help identify patients with symptomatic asthma. The patient's baseline peak expiratory flow rate should be provided on the form as a reference. Health care professionals administering immunotherapy injections should be provided with specific guidelines about the peak expiratory flow rate measurement for when an immunotherapy injection should be withheld and the patient referred for clinical evaluation.
- **Baseline blood pressure**. It might be useful to record the patient's blood pressure as a baseline for future reference.

APPENDIX 11. Allergen immunotherapy administration form

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 allergy or 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

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

Date to reorder: __/__/__

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 allergy or 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**	

APPENDIX 12. 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: _____
_____
Staff action taken (if any): _____

APPENDIX 13. 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.

APPENDIX 14. Allergen immunotherapy systemic reaction/anaphylaxis 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
__Epinephrine IM into 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	

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:
_____
_____
_____
_____

Clinical impression: True SR Questionable SR No SR

Systemic reaction severity classification: EAACI_____ **Portnoy** _____

Dosage adjustment? _____

Signatures_____ **RN** _____**MD/DO**

APPENDIX 15. Grading severity of allergen immunotherapy reactions: Two methods

1. **The European Academy of Allergy and Clinical Immunology grading of severity for systemic side effects***

Classification of systemic reactions

0 = No symptoms or nonspecific symptoms

I = Mild systemic reactions: symptoms—localized urticaria, rhinitis, or mild asthma (PF <20% decrease from baseline).

II = Moderate systemic reaction: symptoms—slow onset (>15 minutes) of generalized urticaria, moderate asthma, or both (PF < 40% decrease from baseline).

III = Severe (non–life-threatening) systemic reactions: symptoms—rapid onset (<15 minutes) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).

IV = Anaphylactic shock: symptoms—immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, and hypotension, for example.

2. **Portnoy method for numeric grading of reactions to allergen immunotherapy†**

Local

0+ = No significant reaction or small area of erythema less than the size of a half dollar without swelling or wheal formation

1+ = Erythema greater than the size of a half dollar, swelling or wheal formation, or both

Systemic

2+ = Systemic reactions: cutaneous only—might consist of a cutaneous eruption, such as urticaria

3+ = Systemic reaction: generalized pruritus, sneezing, or both—might consist of increased allergy symptoms, such as nasal congestion, sneezing, or pruritus, especially in the mouth or throat

4+ = Systemic reaction: pulmonary—consists of wheezing, shortness of breath, and tightness. Might be associated with decreased pulmonary function tests

5+ = Systemic reaction: anaphylaxis—a sensation of not feeling right is a frequent prelude; might consist of hypotension, laryngeal edema, severe wheezing, and cramping

6+ = Cardiopulmonary arrest

PF, Peak expiratory flow.

*Subcutaneous immunotherapy. Allergy 2006;61(suppl 82):5-13.

†Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80.

Allergen immunotherapy: A practice parameter second update

Supplement Editor: **Linda Cox, MD**
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These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology.

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the "Allergen immunotherapy: a practice parameter second 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 and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
5. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
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These parameters are also available on the internet at http://www.jcaai.org.

CONTRIBUTORS

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Allergen immunotherapy: A practice parameter second update

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PREFACE

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

The objective of ''Allergen immunotherapy: A practice parameter second update'' is to optimize the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. 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's ''Policy on development and use of practice parameters for medical quality decision-making'' (Appendix 1).[1]

This document builds on the previous Joint Task Force document, ''Allergen immunotherapy: a practice parameter'' published in the *Annals of Allergy, Asthma and Immunology* in 2003.[2] The updated practice parameters draft was prepared by Drs Linda Cox, James Li, Hal Nelson, and Richard Lockey. The Joint Task Force reworked the initial draft into a working draft of the document. The project was exclusively funded by the 3 allergy and immunology societies noted above.

In preparation for the 2003 ''Allergen immunotherapy: a practice parameter'' and the second update, a comprehensive search of the medical literature was conducted with various search engines, including PubMed; *immunotherapy*, *allergic rhinitis*, *asthma*, *stinging insect allergy*, and related search terms were used. 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 second update'' was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the ACAAI, AAAAI, and JCAAI. In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for review and comments from members of the sponsoring organizations. 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 allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. This document also contains recommendations for the safe practice of allergen immunotherapy, including specific recommendations on the prevention and management of 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 or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. Symptoms of allergic conjunctivitis (eg, itchy watery eyes) are often considered part of allergic rhinitis or are included in the diagnosis of rhinoconjunctivitis. Particularly good candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures, those in whom it is important to avoid the potential adverse effects of medications, and those who wish to reduce the long-term use of medications. Immunotherapy is recommended for patients with a history of systemic reaction to Hymenoptera stings and specific IgE antibodies to Hymenoptera venom.

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.[3]

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. 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 *maintenance concentrate* should be used to identify the allergen immunotherapy extract that contains a therapeutic effective dose for each of its individual constituents (see the Immunotherapy schedules and doses section).

The term *manufacturer's extract* refers to the allergy extract purchased from the manufacturer. The terms *stock*, *full-strength*, and *concentrate* are ambiguous and should not be used. 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).

Allergen immunotherapy is effective when appropriate doses of the allergens are administered. ''Allergen immunotherapy: A practice parameter'' recommends that vials of allergen immunotherapy extracts should be prepared individually for each patient to enhance the individualization of therapy, reduce the risk of allergen cross-contamination, and reduce the risk of error in administration.[4,5] This parameter recommends the use of standardized allergen immunotherapy prescription and administration forms to improve the safety, uniformity, and standardization of allergen immunotherapy practice.[4,5] The suggested forms are found in the Appendix (Appendices 7, 8, 11, 12, and 14) and in the members' section of the www.aaaai.org Web site. The routine use of these standardized forms should improve the quality of immunotherapy practice.

Members' feedback comments on the recommended allergen extract dilution dating in the 2003 ''Allergen immunotherapy: A practice parameter'' led to an allergen immunotherapy extract dilution stability study designed by the AAAAI Immunotherapy and Allergy Diagnostics Committee and funded by the AAAAI Board of Directors. The study was designed to investigate the effect of time, temperature, and dilution of standardized allergen extract potency, and the results of this study were considered in this update.

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 3 years after publication. Requests for information about or an interpretation of these practice parameters should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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. Allergen immunotherapy

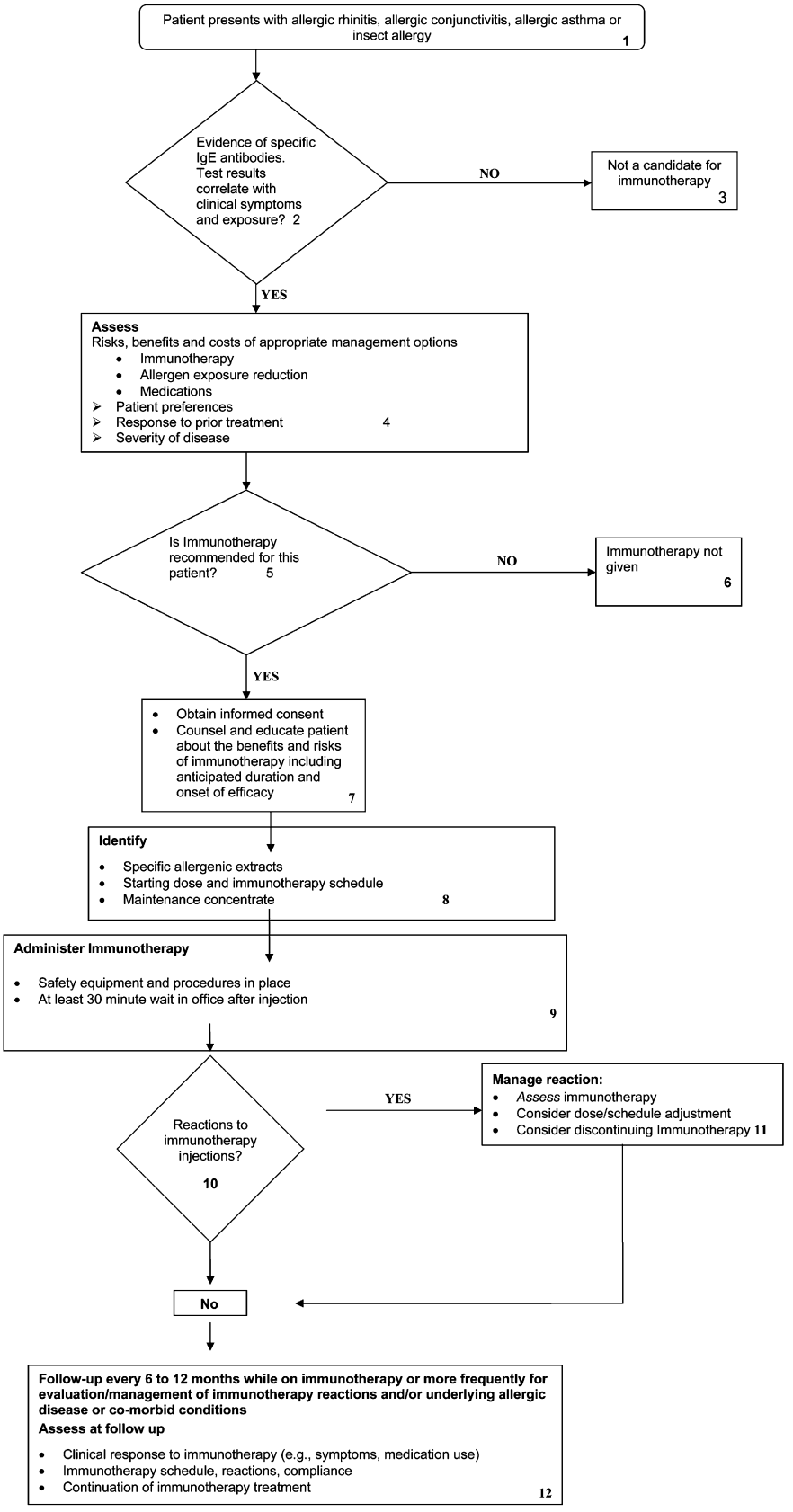


FIG 1. Algorithm for allergen immunotherapy.

might prevent the development of asthma in individuals with allergic rhinitis.[6-9] Evaluation of a patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic conjunctivitis, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for specific IgE antibody).[10]

Box 2

Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although *in vitro* testing for 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

Management of complex medical conditions, such as allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity, should include the careful evaluation of management 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 patient 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. On the basis of clinical considerations and patient 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 good candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy (VIT).

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 on the basis of 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 (see the Immunotherapy schedules and doses section). In general, the starting immunotherapy dose is 1000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 1000 to 4000 arbitrary units (AU; eg, for dust mite) or bioequivalent allergy units (BAU; eg, for grass) 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 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 referred to as *up-dosing*, *induction*, or the *dose-increase phase*) entails administration of gradually increasing doses during a period of approximately 14 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 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, in particular anaphylaxis. Patients should wait at the physician's office for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly, if they occur.

In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring 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. Some physicians recommend providing certain patients with epinephrine for self-administration in case of severe late reactions to immunotherapy injections.

Box 10

Injections of allergen immunotherapy extract can cause local or systemic reactions. Most severe reactions develop within 30 minutes after the immunotherapy injection, but reactions can occur after this time.

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 (anaphylaxis). Epinephrine is the treatment of choice in anaphylaxis, preferably when administered intramuscularly,[11] although subcutaneous administration is acceptable.[12]

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, see the practice parameters for anaphylaxis.[12]

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. After a severe systemic reaction, careful evaluation by the prescribing physician is recommended. For some patients, the immunotherapy maintenance dose might need to be reduced because of repeated systemic reactions to immunotherapy injections. The decision to continue immunotherapy should be re-evaluated after severe or repeated systemic reactions to allergen immunotherapy extracts.

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 doses, 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,[13] but others might experience a recurrence of their symptoms after discontinuation of allergen immunotherapy.[14] 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, and 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 on the basis of the patient's clinical response, disease severity, immunotherapy reaction history, and patient preference.

IMMUNOTHERAPY GLOSSARY

For more information on immunotherapy definitions, see the article by Kao.[15]

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 (pigments and salts; see the Allergen selection and handling section). Other terms used to describe the allergen immunotherapy extract include *allergen product*,[16] *allergy serum*, *allergen vaccine*,[17] 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.[18] Other terms that have been used for allergen immunotherapy include *hyposensitization*, *allergen-specific desensitization*, and the lay terms *allergy shots* or *allergy injections*.[15]

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

TABLE II. Allergen immunotherapy dose-calculation table

- Express weight per volume as a fraction: $\frac{1}{N}$ or 1:*N*.
- Calculate concentration of individual allergens in mixtures. If a mixture is made of equal amounts of N individual allergens to make a total concentration (C), the final concentration of an individual allergen (Ca) can be calculated by using the following equation:

$Ca = C \times \frac{1}{N} = \frac{C}{N}$ or *C*:*N*.

For example, if a mixture of equal amounts of 5 (N) allergens has a total concentration (C) of 100,000 BAU/mL, then the final concentration of each individual allergen (Ca) is: $Ca = \frac{C}{N} = \frac{100{,}000}{5} = 20{,}000\ BAU/mL$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{C}{N} = \frac{1/10}{5} = \frac{0.1}{5} = 0.02$ or $\frac{1}{50}$ or 1:50.

- Dilution of individual allergen: If an initial volume, Vi (in milliliters), of an individual antigen with concentration, Ci, is added to an allergen extract to make a final volume of Vf (in milliliters), the final allergen concentration (Ca) in the allergen extract mixture will be: $Ca = Ci \times \frac{Vi}{Vf}$.
- Final concentration of an allergen in a mixture of mixtures is determined by multiplying the initial concentration by the dilution factors from each mixing step.

For example, consider a mixture containing equal amounts of 5 (N) allergens with a total concentration (C) of 100,000 BAU/mL (first dilution). If an initial volume (Vi) of 0.5 mL of this mixture is further mixed with other components and diluent to make a final allergen extract mixture volume (Vf) of 5.0 mL (second dilution), the final concentration of an individual allergen (Ca) will be:

$$Ca = C \times \underbrace{\frac{1}{N}}_{\text{Mixture dilution}} \times \underbrace{\frac{Vi}{Vf}}_{\text{Allergen extract dilution}} = 100{,}000 \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{100{,}000}{50} = 2000\ BAU/mL$$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{1}{10} \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{1}{500}$ or 1:500.

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).

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 to 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-medicated 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 multiplied by volume of administered dose (see Table II for a dose-calculation table).

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, cat, 1000 BAU, [highest tolerated dose] vs 2000 BAU [projected effective dose]).

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 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 by a variety of immunologic transformations. Early definitions of the term immunotherapy included active and passive immunization for the purpose of improving 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 by means of induction of clonal deletion, anergy, immune tolerance, or immune deviation.

The *maintenance concentrate* is a preparation that contains individual 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 may not be the initially calculated projected effective dose.

The *maintenance goal* (or projected effective dose) is the allergen dose projected to provide therapeutic efficacy. The maintenance goal is based on published studies, but a projected effective dose has not been established for allergens. 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 the 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 large local reaction causing discomfort). The intervals between maintenance immunotherapy injections generally ranges 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 by means of immunoblotting or crossed allergoimmunoelectrophoresis.

For a definition of *projected effective dose*, see 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 test responses), and premedication with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similar high incidence of systemic reactions.

Off the board into one syringe is a phrase that describes a method of allergen immunotherapy preparation and administration that involves specifically mixing the patient's allergen immunotherapy injection in a single syringe, which is not recommended. This syringe might be inserted into more than one allergen extract vial, and this poses a risk of cross-contamination of the allergen extracts and might dull the needle with repeated penetration of the rubber stopper.

Shared specific patient vials is a method of allergen immunotherapy preparation and administration in which the allergy immunotherapy extract is withdrawn from a shared vial (eg, mixed vespids or dust mite mix). This is sometimes referred to as off the board, but it is distinct from the method of off the board into one syringe in that the syringe enters only one allergen extract vial.

INTRODUCTION

Immunity has been defined as protection against certain diseases. The initial immunotherapeutic interventions, which included the use of preventive vaccines and xenogenic 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 the field of allergen immunotherapy. From its humble empiric emergence in 1900, when ragweed injections were proposed as therapy for autumnal hay fever, allergen immunotherapy has progressed in both theory and practice from the passive immunologic approach to the active immunologic procedures pioneered by Noon[19] and Freeman.[20,21] 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 10 years. Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Some studies have suggested that allergen immunotherapy might prevent the development of asthma in individuals with allergic rhinitis.[6-9]

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,[22-26] and it should be differentiated from unproved methods, such as neutralization-provocation therapy and low-dose subcutaneous regimens based on the Rinkel technique, which have been found to ineffective in a double-blind placebo-controlled study.[27,28]

SUMMARY STATEMENTS

Mechanisms of immunotherapy

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, defined as a relative decrease in allergen-specific responsiveness and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

Allergen extracts

Summary Statement 6: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. **A**

Summary Statement 7: Nonstandardized extracts might vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Summary Statement 8: 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**

Cross-reactivity of allergen extract. Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

Efficacy of immunotherapy

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Summary Statement 10: Immunotherapy is effective for 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**

Food allergy, urticaria, and atopic dermatitis. Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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**

Measures of efficacy. Summary Statement 12: 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**

Safety of immunotherapy

Reaction rates. Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

Timing of anaphylactic reactions to immunotherapy injections. Summary Statement 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

β-*Adrenergic blocking agents.* Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

Contraindications. Summary Statement 18: 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**

Reducing the risk of anaphylaxis to immunotherapy injections. Summary Statement 19: 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**

Patient selection

Clinical indications. Summary Statement 20: 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 depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Special precautions in patients with asthma. Summary Statement 21: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. **C**

Clinical indications for VIT. Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Summary Statement 23: Patients selected for immunotherapy should be cooperative and compliant. **D**

Allergen selection and handling

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted in vitro tests for specific IgE antibodies can also be used. **A**

Specific allergens. Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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, supported by the presence of specific IgE antibodies. **A**

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Dose selection. Summary Statement 30: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. **A**

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens, is recommended. **B**

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extract handling

STORAGE

Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

STORING DILUTE EXTRACTS

Summary Statement 34a: More dilute concentrations of allergen immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: 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 a number of 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. **B**

Immunotherapy schedules and doses

Summary Statement 35: A customized individual 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 be based on single or multiple allergens. **D**

Maintenance concentrate. Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

Recommended doses. Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

Effect of dilution on dose. Summary Statement 38: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. **A**

Dilutions of the maintenance concentrate. Summary Statement 39: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. **D**

Labeling dilutions. Summary Statement 40: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. **D**

Individualized treatment vials. Summary Statement 41: 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. The mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. **C**

Starting doses. Summary Statement 42: The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. **D**

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

Dose adjustments for systemic reactions. Summary Statement 44: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. **D**

Reductions during periods of exacerbation of symptoms. Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Dose adjustments for late injections. Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

Cluster schedules. Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. **C**

Rush schedules. Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. **A**

Systemic reactions and rush schedules. Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

Premedication and weekly immunotherapy. Summary Statement 50: Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

Premedication with cluster and rush immunotherapy. Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

Maintenance schedules. Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. **A**

Continuing care

TIME COURSE OF IMPROVEMENT

Summary Statement 53: Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **A**

FOLLOW-UP VISITS

Summary Statement 54: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. **D**

DURATION OF TREATMENT

Summary Statement 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

DOCUMENTATION AND RECORD KEEPING

Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. **D**

INJECTION TECHNIQUES

Summary Statement 57: Allergen immunotherapy extract injections should be administered with a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **D**

Summary Statement 58: The injection should be administered subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Location of allergen immunotherapy administration

Physician's office. Summary Statement 59: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Summary Statement 60: 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**

Other locations. Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **D**

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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**

Summary Statement 63: 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for his or her immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extract might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Special considerations in immunotherapy

Allergen immunotherapy in children. Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Pregnancy. Summary Statement 71: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. **C**

Immunotherapy in the elderly patient. Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy in patients with immunodeficiency and autoimmune disorders. Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

Alternative routes of immunotherapy

Sublingual and oral immunotherapy. Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no US Food and Drug Administration (FDA)–approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **A**

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Immunotherapy techniques that are not recommended. Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

MECHANISMS OF IMMUNOTHERAPY

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, which is defined as a relative decrease in allergen-specific responsiveness, and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

The immunologic changes associated with immunotherapy are complex, and the exact mechanism or mechanisms responsible for its' clinical efficacy are continually being elucidated. Data support the concept that successful immunotherapy is associated with a change to a T_H1 $CD4^+$ cytokine profile.[29-34] Data indicate that increased production of IL-12, a strong inducer of T_H1 responses, contributes to this shift.[33] Clinically successful immunotherapy has been reported to be associated with immunologic tolerance, which is defined as a relative decrease in antigen-specific responsiveness, immune deviation, or anergy. For example, lymphoproliferative responses to allergen are reduced with immunotherapy.[32] Successful immunotherapy results in generation of a population of T regulatory cells, which are $CD4^+CD25^+$ T lymphocytes producing IL-10, TGF-β, or both.[35-39] Regulatory T-cell release has been described in allergen immunotherapy with Hymenoptera venom,[35] grass pollen extract,[37] and house dust mites.[38] IL-10 reduces B-cell antigen-specific IgE and increases IgG4 levels; reduces proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicits tolerance in T cells by means of selective inhibition of the CD28 costimulatory pathway.[36,37]

Allergen immunotherapy has been shown to block both the immediate and late-phase allergic response.[40] Allergen immunotherapy has been shown to decrease the recruitment of mast cells, basophils, and eosinophils in the skin, nose, eye, and bronchial mucosa after provocation or natural exposure to allergens.[41]

In patients receiving immunotherapy, initially there is an increase in specific IgE antibody levels, followed by a gradual decrease to a level that is still higher than that present before treatment. Clinical improvement in many patients develops before decreases in their IgE antibody levels occur or in other patients whose IgE antibody levels never decrease, thereby demonstrating that efficacy is not dependent on reductions in specific IgE levels.[42,43] Immunotherapy does diminish the seasonal increase in specific IgE levels.[44] Despite the persistence of significant levels of specific IgE antibody levels, immunotherapy usually causes a reduction in 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.[45-48]

An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, has also been associated with immunotherapy. The properties of allergen-specific IgA have yet to be determined, and there is a weak correlation between the increase in allergen-specific IgG levels and immunotherapy's clinical efficacy.[30,49,50]

Immunotherapy might alter the affinity and specificity of allergen-specific IgG.[51,52] During the initial phase of ultrarush VIT, a change in IgG specificity (ie, a change in the set of epitopes dominantly recognized by IgG on wasp venom antigens) occurred concomitantly with early clinical tolerance and was seen within 12 hours of ultrarush VIT ($P < .001$).[51] 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 individuals.[52] This change in IgG specificity preceded the increase in IgG titers and was sustained for up to 6 months.[52]

Allergen-specific IgG induced from immunotherapy can block IgE-dependent histamine release and subsequent IgE-mediated antigen presentation to T cells.[53] This effect might be dependent on IgE, allergen concentration, and CD23, the low-affinity receptor for IgE.

Whereas 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.[37,53]

The relationship between these immunologic changes and immunotherapy efficacy is not completely understood.

ALLERGEN EXTRACTS

Summary Statement 6: 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 has 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.[2,18,54-56] 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.

United States–licensed extracts can be obtained in aqueous, glycerinated, lyophilized, and acetone-precipitated and alum-precipitated formulations. Some commonly used allergens are standardized. These include extracts for cat hair, cat pelt, *Dermatophagoides pteronyssinus*, *Dermatophagoides 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.[57] 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.

Most standardized extracts are labeled in BAU. Short ragweed potency units were originally based on the content of the major allergen Amb a 1. Ragweed potency is reported in FDA units and BAU. One FDA unit of Amb a 1 equals 1 μg of Amb a 1, and 350 units of Amb a 1/mL is equivalent to 100,000 BAU/mL. Cat extracts were also originally standardized based on the content of major allergen (Fel d 1), with 100,000 arbitrary units (AU) per milliliter containing between 10 to 19.9 FDA units of Fel d 1 per milliliter (1 FDA unit of Fel d 1 equals 2 to 4 μg of Fel d 1).[55,58,59] Subsequently, $ID_{50}EAL$ testing suggested that 100,000 AU/mL was equal to 10,000 BAU/mL.[60] Approximately 22% of individuals with cat allergy have specific IgE antibodies to cat albumin.[61] Cat pelt extracts have a greater amount of albumin than cat hair extracts.[60]

Dust mites were originally standardized in AU by means of inhibition radioimmunoassay (RIA), and subsequent $ID_{50}EAL$ testing indicated that the AU was bioequivalent to the BAU, and the original AU nomenclature was kept. Dust mite extracts are still labeled in AU.

Summary Statement 7: Nonstandardized extracts can vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Nonstandardized extracts are labeled as wt/vol, which expresses weight in grams per volume in milliliters; that is, a potency of 1:100 indicates that 1 g 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 with a particular wt/vol or PNU potency can have widely varying biologic activities.[62-64] Therefore they should not be considered equipotent.

Summary Statement 8: 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**

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. The major clinically relevant aeroallergens of North America are listed in Table III. Furthermore, nonrelevant allergens in such mixtures could act as sensitizers rather than as tolerogens.[65,66] The physician must therefore select only those aeroallergens for testing and treatment that are clinically relevant in a particular geographic area.

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, dog), insect (cockroach), and Hymenoptera venom source materials.

Cross-reactivity of allergen extract

Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

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. A summary of cross-reactivity patterns of the clinically relevant North American aeroallergens can be found in Fig 2. 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,[67] inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[68-75] Grasses in other subfamilies (eg, Bermuda, Bahia, and Johnson) show greater diversity and should be evaluated separately.[76-78] Bermuda and Johnson grasses are increasingly important in the South,

TABLE III. The major clinically relevant aeroallergens of North America*

- Tree pollen
  - Chinese elm *(Ulmus parvifolia)*†‡; Siberian elm *(Ulmus pumila)*†‡; American elm *(Ulmus Americana)*†‡
  - Red oak *(Quercus rubra)*†; White oak *(Quercus alba)*†
  - Paper birch *(Betula papyrifera)*
  - Alder *(Alnus rubra)*
  - Box elder *(Acer negundo)*†; Red maple *(Acer rubra)*†
  - Eastern cottonwood *(Populus deltoides)*
  - Sycamore *(Platanus occidentalis)*
  - White ash *(Fraxinus americana)*†; Olive *(Olea europaea)*†‡
  - Black walnut *(Juglans nigra)*
  - Mulberry *(Morus rubra)*
  - Mountain cedar *(Juniperus ashei)*
  - Pecan *(Carya illinoensis)*
- Grass pollen
  - Rye *(Lolium perenne)*§‖
  - Timothy *(Phleum pratense)*§‖
  - Meadow fescue *(Festuca elatior)*§‖
  - Bermuda *(Cynodon dactylon)*‖
  - Johnson *(Holcus halepensis)*
  - Bahia *(Paspalum notatum)*
- Weed pollen
  - Short ragweed *(Ambrosia artemisiifolia)*‖
  - English (narrow leaf) plantain *(Plantago lanceolata)*
  - Mugwort *(Artemisia vulgaris)*
  - Russian thistle *(Salsola kali)*
  - Burning bush *(Kochia scoparia)*
  - Sheet (red) sorrel *(Rumex asetosella)*
  - Red root pigweed *(Amaranthus retroflexus)*
- Indoor aeroallergens
  - Cat epithelium *(Felis domesticus)*‖
  - Dog epithelium *(Canis familiaris)*
  - Arthropods (domestic mites: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*)‖
  - Insects (German cockroach: *Blattella germanica*)
- Fungi
  - *Alternaria alternata*¶
  - *Cladosporium* (*C cladosporioides*, *C herbarum*)¶
  - *Penicillium* (*P chrysogenum*, *P expansum*)¶
  - *Aspergillus fumigatus*¶
  - *Epicoccum nigrum*, *Drechslera* or *Bipolaris* type (eg, *Helminthosporium solani*)¶

*Compiled and selected in collaboration with the AAAAI Immunotherapy Committee Allergen Subcommittee for the identification of 35 key allergens of North America.
†Extensive cross-reaction of species within the genus.
‡Apart from regional prevalence, they are limited to local sites with substantial stands of these trees.
§Extensively cross-react with one another and bluegrass, orchard, red top, and sweet vernal.
‖Allergens for which standardized extracts are commercially available.
¶Species that are widely distributed and clinically important.

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.[79-82] 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.[83-85] Significant cross-reactivity between Betulaceae pollens and oak of the Fagaceae family has been demonstrated with percutaneous skin testing.[75] RAST inhibition studies have shown cross-inhibition between oaks and other *Fagales* species.[86] IgE immunoblot inhibition experiments have demonstrated that the *Fagales* species might be strongly inhibited by birch species.[87] The use of one of the locally prevalent members (eg, birch and alder) should be adequate.[88]

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.[89,90] Maple and box elder trees are found throughout the United States, except for the arid southwest. Although in the same genus as maple, *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,[91,92] and there are allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.[93]

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.[94] Similarly, Chenopod-Amaranth families have wide ranges in the western regions but are present throughout North America.[95] Current information on cross-reactivity of these families is limited.[96-98] 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.[99] The use of a single Amaranth extract should be sufficient to cover this family.[100,101] Similarly, *Atriplex* species (eg, saltbushes and scales) show near identity, and use of a single member is adequate. 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,

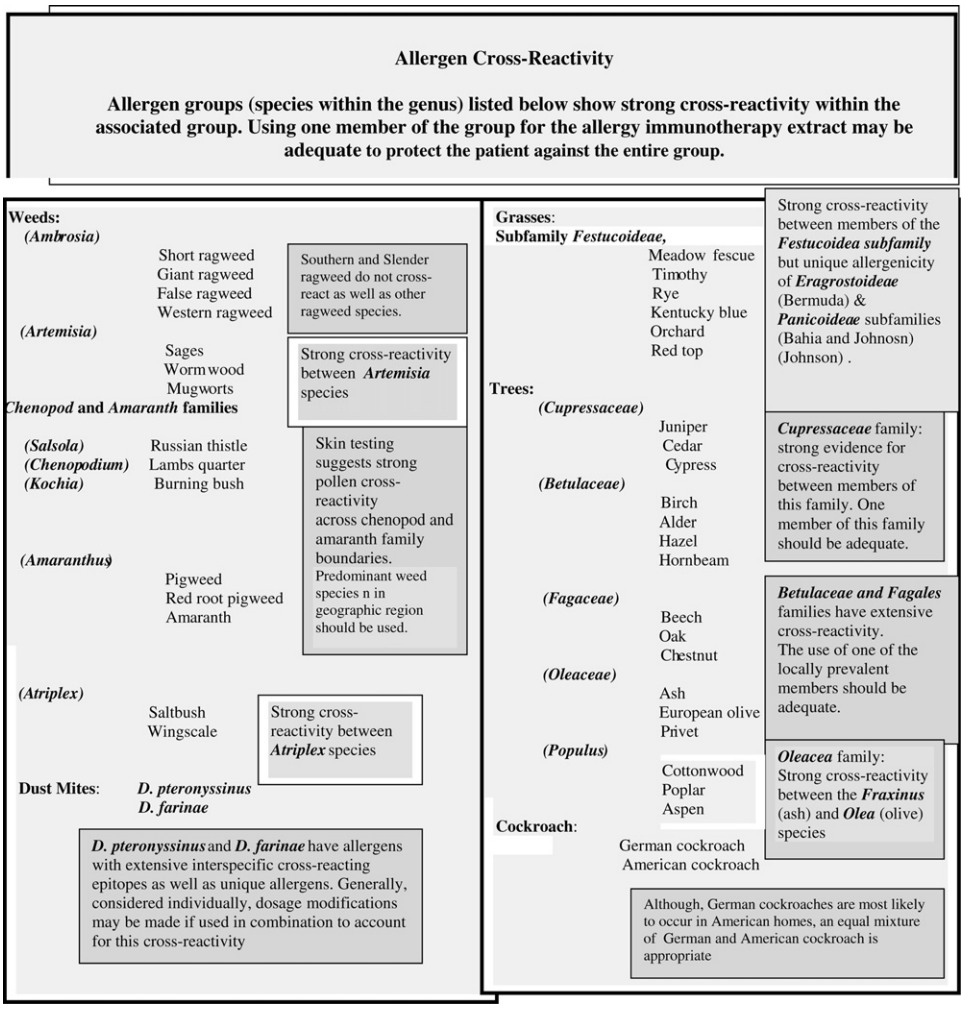


FIG 2. Patterns of allergen cross-reactivity.

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*).

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.[102,103] Stinging Hymenoptera insects occur throughout the United States; the fire ant is found only in Gulf Coast states, Texas, and some other southern and western states. Commercial venom extracts are available for some Hymenoptera species, except the fire ant, for which only whole-body extract is available.

EFFICACY OF IMMUNOTHERAPY

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity

Summary Statement 10: Immunotherapy is effective for 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.[104-111] Immunotherapy is effective for the treatment of allergic rhinitis[107] (including ocular symptoms[112,113]), allergic asthma,[104,109,111,114,115] and stinging insect hypersensitivity[108,116] and is effective in both adults and children.[117-124] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollens,[13,125-132] fungi,[133-138] animal allergens,[22,25,26,139-143] dust mite,[114,115,144-153] and cockroach.[154] There have been no controlled trials of fire ant whole-body extract, but it does appear to be effective in

TABLE IV. Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy

Outcome measure	House dust mite	Other allergens*†
Symptomatic improvement	2.7 (1.7-4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2-7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50)	5.5 (2.8-10.7)

Data are used with permission from Abramson et al.[104]
ND, Not done.
*Odds ratio (95% CI).
†Pollen, mold, or animal dander.

uncontrolled trials.[155-157] 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. A number of studies have also demonstrated a significant improvement in quality of life, as measured by using standardized questionnaires.[24,158-161] The magnitude of the effect depends on the outcome that is used (Table IV). For dust mite, the effect size ranges from a 2.7-fold improvement in symptoms to a 13.7-fold reduction in bronchial hyperresponsiveness. 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.[110] 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[107] and asthma[104,109,111] have been performed to deal with the issue of power. One review of 75 trials involving 3188 asthmatic patients found that, overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyperreactivity after immunotherapy, and it would have been necessary to treat 4 patients (95% CI, 3-5) with immunotherapy to avoid 1 deterioration in asthma symptoms and 5 (95% CI, 4-6) patients to avoid 1 requiring increased medication.[111] These meta-analyses strongly support the efficacy of allergen immunotherapy. Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued[13,162,163] and might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6,9,122,162-165] Allergen immunotherapy might also prevent the development of new allergen sensitivities in monosensitized patients.[120,166,167]

Food allergy, urticaria, and atopic dermatitis

Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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 use of allergen immunotherapy for individuals with the potential for IgE-mediated (anaphylaxis) reactions to foods should be regarded as investigational at this time.[168-171] There have been 2 investigational studies demonstrating efficacy in food hypersensitivity, the first using aqueous subcutaneous injections to peanut and the second using sublingual immunotherapy to hazelnut.[171-173]

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 a modified peanut extract is needed for clinical application of this method of treatment.[171] There is currently no FDA-approved formulation for sublingual immunotherapy, and this route of allergen immunotherapy is currently considered investigational at this time (see Summary Statement 73).

At the present time, there is not enough evidence to support food immunotherapy.

There is no evidence supporting the efficacy of immunotherapy for individuals with chronic urticaria, angioedema, or both.

There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[174-176] 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 ($P = .0379$) and topical corticosteroid use ($P = .0007$).[174]

The potential for benefit in symptoms related to oral allergy syndrome with the cross-reacting inhalant immunotherapy, which includes cross-reacting 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 subcutaneous immunotherapy directed against birch tree,[177] whereas another double-blind, double-dummy, placebo-controlled study comparing the effect of subcutaneous immunotherapy with sublingual immunotherapy 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, medication use, and decrease in IgE reactivity.[178] More investigation is required to substantiate the contention that benefits in oral symptoms will occur with immunotherapy.

Measures of efficacy

Summary Statement 12: 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. Objective measures, such as increase in allergen-specific IgG levels and decreased skin test reactivity, as measured by skin test titration, are changes generally associated with effective immunotherapy but, at present, are not practical for routine clinical use.[147] Nonquantitative skin testing or *in vitro* 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 are not very reliable given the strong placebo-like effect (Hawthorne effect) associated with any treatment. A more objective means for determining efficacy as validated in controlled clinical studies is the use of clinical symptom scores and the amount of medication required to control symptoms and maintain peak flow rates or pulmonary function tests within acceptable limits. Successful immunotherapy often results in a reduction in medication. Sequential measurement of disease-specific quality of life also might be helpful.

SAFETY OF IMMUNOTHERAPY

Reaction rates

Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Large local reactions associated with allergen immunotherapy are fairly common, with a frequency ranging from 26% to 86% of injections.[179] Two retrospective studies compared the effect of not adjusting immunotherapy dose based on large local reactions on the immunotherapy systemic reaction rate with dose-adjustment protocols.[179,180] There was a total of 12,464 injections administered with a dose-adjustment protocol in the 2 studies compared with 9542 injections administered with a no-dose-adjustment protocol. 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 for subsequent systemic reactions, 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 large local reactions, defined as 25 mm or larger, in patients who had experienced systemic reactions with age-, sex-, and allergen sensitivity–matched control subjects who had not had allergen immunotherapy systemic reactions found the rate of large local reactions was 4 times higher among the 258 patients who had subsequently experienced a systemic reaction compared with those who had never experienced a systemic reaction.[181] Patients who had experienced systemic reactions had 1573 large local reactions in 4460 visits (ie, 35.2% of visits) and 8081 injections (ie, 19.5% of injections) compared with the matched control group without systemic reactions who had 1388 large local reactions in 15,540 visits (8.9% per visit) and 26,259 injections (5.3% per injection; difference between groups, $P < .001$). Individual large local reactions were not predictive of future systemic reactions, but large local reactions preceded systemic reactions in approximately one third of the systemic reactions. These findings suggest that individuals with a greater frequency of large local reactions might be at greater risk for systemic reaction. Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy protocol modifications based on them are needed.

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

The prevalence of severe systemic reactions after allergen immunotherapy ranges from less than 1% of patients receiving conventional immunotherapy to greater than 36% of patients in some studies of patients receiving rush immunotherapy.[182,183]

In a recent survey of fatal and near-fatal reactions (NFRs) sent to physician members of the AAAAI, 273 of 646 respondents reported NFRs during the period of 1990-2001.[184]

The incidence of unconfirmed NFRs was 23 per year (5.4 events per million injections). Administration during the height of 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 angiotensin-converting enzyme 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 systemic reactions to subcutaneous immunotherapy over a 20-year period (1981-2000) during which 435,854 injections were administered to 4000 patients, 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.[185,186] In a prospective multicenter study there were 53 systemic reactions (0.3% of the doses) out of 17,526 administered doses in 18 (3.7%) of 423 patients.[187] 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 (21 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, there were 41 fatalities identified in the initial brief survey (20 directly reported and 17 with completed detailed questionnaire) from immunotherapy injections.[188] 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.[189,190] Therefore although severe systemic reactions to allergen immunotherapy are not common, serious systemic reactions (some fatal) can occur.

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

In the AAAAI survey of physician members on immunotherapy and skin testing, fatal reactions, and NFRs during the period of 1990-2001, 15 of the 17 fatalities had asthma, and in 9 patients asthma was considered the susceptibility factor that contributed to the fatal outcome.[188]

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.[184]

Administration during the peak pollen season (3 patients) and previous systemic reactions (4 patients) were cited as other contributing factors. Five fatalities occurred in outside medical facilities, and 2 fatalities occurred at home. No patients were receiving β-blockers; 1 patient was taking an angiotensin-converting enzyme inhibitor. In the most comprehensive evaluation of fatalities associated with allergen immunotherapy, from 1945-1987, there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[189] 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, with 73.3% of patients with an FEV_1 of less than 80% of predicted value experiencing 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 ($P < .0001$).[191] 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% of patients. These studies suggest that symptomatic asthma, severe asthma, or both might be a risk factor for immunotherapy.

In addition to symptomatic asthma and injections giving 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.[17] With the exception of dosing errors and 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 recent 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 or allergy symptom exacerbation, β-blocker use, change in health status (including pregnancy), or adverse reaction to previous allergen immunotherapy injection. The preinjection evaluation might also include a peak flow measurement to assess the airway function of asthmatic patients.

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 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

In a retrospective study the time to onset of a systemic reaction after an immunotherapy injection was less than 30 minutes in most cases.[189] A review of the literature indicates that 70% of systemic reactions occur within 30 minutes after an injection.[183] In the AAAAI 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.[184,188] 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.[190] 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 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.[192] In another prospective study 8% of systemic reactions occurred more than 2 hours after injection.[193]

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.[194]

Because most reactions that resulted from allergen immunotherapy occurred within 30 minutes after an injection, patients should remain in the physician's office for at least 30 minutes after receiving an injection, but longer waits are reasonable, as directed by the physician. In addition, patients who are at increased risk of a systemic reaction might need to carry injectable epinephrine. Such patients might also need to remain in the physician's office more than 30 minutes after an injection. 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.

β-Adrenergic blocking agents

Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

β-Blockade enhances pulmonary, cardiovascular, and dermatologic end-organ effects of mediators and increases mortality associated with experimental anaphylaxis induced by either immunologic or nonimmunologic mechanisms. Patients who are receiving β-adrenergic blocking medications might be at increased risk if they experience a systemic reaction to an allergen immunotherapy injection because the β-receptor blockade might attenuate the response to epinephrine.[195-202] Patients who are receiving β-blocking drugs were almost 9 times more likely to be hospitalized after an anaphylactoid reaction from radiocontrast media.[198] Although topical β-blockers have markedly less systemic β-antagonist effects than oral β-blockers, they still might exhibit some systemic β-antagonist effects. Whether topical β-blockers pose the same or a smaller risk than oral β-blockers in regard to the treatment of allergen immunotherapy–related systemic reactions is not known.

There have been very few studies that have examined the effect of β-blocker medications on allergen immunotherapy. A prospective 1-year study designed to determine whether patients taking β-blocker drugs were at increased risk of immunotherapy-induced systemic reactions found that there were 166 systemic reactions out of 56,105 injection visits in 3178 patients (68 were receiving a β-blocker).[203] The systemic reactions occurred in 144 (4.5%) patients, and only 1 of these patients was receiving a β-blocker medication. The authors calculated that by chance, 3.08 patients receiving the β-blocker medications drugs were expected to have had an systemic reaction and concluded that β-blocker medications did not increase the frequency of allergen immunotherapy systemic reactions ($P > .95$).

In another study of 1389 patients prescribed immunotherapy for Hymenoptera venom hypersensitivity who were followed for 34 months, there were 25 patients who received concomitant β-blocker medications.[204] Three (12%) of the 25 patients receiving β-blocker medications experienced systemic reactions during immunotherapy compared with 23 (16.7%) of 117 patients with cardiovascular disease not receiving β-blockers. Systemic reactions after a field sting or challenge occurred in 1 (14.3%) of 7 cardiovascular patients receiving β-blocker medications compared with 4 (13.8%) of 29 cardiovascular patients not receiving β-blocker medications. No severe reactions to immunotherapy or sting re-exposure were observed in patients receiving β-blockers medications.

Immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. In such cases, intravenous glucagon, which might reverse the refractory bronchospasm and hypotension by activating the adenyl cyclase directing and bypassing the β-adrenergic receptor, might be used if epinephrine has not been effective.[205,206] Prospective studies are necessary to clarify the magnitude of the risk of systemic reactions to allergens in patients who are receiving concomitant therapy with β-blockers, and a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy.

Contraindications

Summary Statement 18: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications

TABLE V. Actions to reduce the risk of anaphylaxis

- Assess the patient's general medical condition at the time of injection (eg, asthma exacerbation).
- Consider obtaining a PEFR before administration of the injection. If the PEFR is significantly less than the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.
- 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 with increased allergen sensitivity or those who have previously had a systemic reaction) might need to wait longer.
- Carefully evaluate any patient with a late reaction (eg, persistent large local reaction lasting >24 hours, systemic reaction occurring more than 30 minutes after the immunotherapy injection).
- 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.

PEFR, Peak expiratory flow rate measurement.

TABLE VI. Recommended equipment and medications to treat anaphylaxis

Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur. This should include at least the following equipment and medications:

- stethoscope and sphygmomanometer;
- tourniquet, syringes, hypodermic needles, and large-bore needles (14-gauge);
- aqueous epinephrine HCL 1:1000 wt/vol;
- equipment to administer oxygen by mask.
- intravenous fluid set-up;
- antihistamine for injection (second-line agents for anaphylaxis, but H_1 and H_2 antihistamines work better together than either one alone);
- corticosteroids for intravenous injection;
- vasopressor;
- equipment to maintain an airway appropriate for the supervising physician's expertise and skill.

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 venom hypersensitivity and cardiac disease being treated with β-blocker medications.

Reducing the risk of anaphylaxis to immunotherapy injections

Summary Statement 19: 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 extremely 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 or other health care professional appropriately trained in emergency treatment.

The 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. Epinephrine is the first-line treatment for anaphylaxis. 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.[12,207-213] It is important to administer epinephrine early in the management of anaphylaxis. 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 V and VI, respectively. Before allergen immunotherapy is chosen as a treatment, the physician should educate the patient about the benefits and risks of immunotherapy, as well as methods for minimizing risks. The patient also should be told that despite appropriate precautions, reactions might occur without warning signs or symptoms. Informed consent should include a discussion of the potential immunotherapy adverse reactions, and this discussion should be documented in the patient's medical record.

PATIENT SELECTION

Clinical indications

Summary Statement 20: Allergen immunotherapy should be considered for patients who have demonstrable

TABLE VII. Clinical indications for allergen immunotherapy

Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or both:
- symptoms of allergic rhinitis after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medications;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medication;
- coexisting allergic rhinitis and asthma;
- possible prevention of asthma in patients with allergic rhinitis

Symptoms of asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medication;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medications;
- coexisting allergic rhinitis and allergic asthma.

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);
- adults and children with a history of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.

evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic rhinitis.[107] Prospective, randomized, double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic asthma.[104,109,111]

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 proper identification and selection of component allergens on the basis of 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 (Table VII). The severity and duration of symptoms should also be considered in assessing the need for specific allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. In addition, specific allergen immunotherapy should be considered if the patient wishes to avoid long-term pharmacotherapy. Time lost from work, emergency department or physician's office visits, and responses to pharmacotherapy are important objective indicators of allergic disease severity.

Patients with allergic rhinitis who are unable to sleep because of symptoms or whose symptoms interfere with their work or school performance should be considered strong candidates for specific allergen immunotherapy. 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 considered. Unacceptable adverse effects of medications should also favor one's decision to initiate allergen immunotherapy. Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.[214]

Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued, and it might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6-9,122,162-165] These benefits of immunotherapy should be discussed with patients and might provide a clinical indication for immunotherapy for individual patients with allergic rhinitis.

Coexisting medical conditions should also be considered in the evaluation of a patient who might be a candidate for allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed with a combined aggressive regimen of allergen avoidance and pharmacotherapy and might also benefit from allergen immunotherapy.[215,216]

However, the patient's asthma must be stable before allergen immunotherapy is administered.[188,191]

Special precautions in patients with asthma

Summary Statement 21: 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 might be at increased risk for systemic reactions to immunotherapy injections.[182,188,191] Two surveys found that deaths from

immunotherapy were more common in symptomatic subjects with asthma.[188,189] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2,217]

Clinical indications for VIT

Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Systemic reactions to Hymenoptera stings, especially when associated with respiratory symptoms, cardiovascular symptoms, or both and positive skin test or *in vitro* test results for specific IgE antibodies, are a strong indication for allergen immunotherapy.[218] In the United States patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Several studies of patients with imported fire ant allergy have demonstrated the effectiveness of immunotherapy with whole-body extracts of fire ants.[155,156,219] 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. Patients younger than 16 years of age who present only with a cutaneous reaction to imported fire ant or Hymenoptera stings might not require immunotherapy.[218,220-222] In addition to allergen immunotherapy, patients with imported fire ant and Hymenoptera venom sensitivity should be instructed in how to best avoid insect stings, be prescribed epinephrine, and be taught how 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 the population that has not had a systemic reaction.[223] In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific IgE is recommended.[218] If the venom-specific IgE test result is also negative, it is recommended that the skin tests, venom-specific 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 IgE test result.[224] 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 re-stung. 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%).[225] 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 IgE test results who have had severe anaphylaxis to an insect sting.

Some patients who have negative venom skin test results and negative venom-specific IgE test results are reported to have had subsequent systemic reactions to stinging insects.[225-227] Controlled studies designed to evaluate the efficacy of immunotherapy in these patients have not been performed. There are very 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.[226] 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.

Summary Statement 23: 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.

ALLERGEN SELECTION AND HANDLING

Allergen selection

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

A careful history, noting environmental exposures and an understanding of the local and regional aerobiology of suspected allergens, such as pollen, fungi (mold), 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 skin or *in vitro* test results for specific IgE antibodies, provide good evidence that such exposures are relevant. Information concerning regional and local aerobiology is available on various Web sites or through the National Allergy Bureau at http://www.aaaai.org/nab. There are

no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma. 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 clinical history of an allergic disease.

There is no evidence to support the administration of immunotherapy based solely on results of specific *in vitro* 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.

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

The omission of clinically relevant allergens from an allergic patient's allergen immunotherapy extract contributes to decreased effectiveness of allergen immunotherapy. The 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 can make allergen immunotherapy less effective.

Knowledge of the total allergenic burden facing a patient and the realistic possibility of avoidance is important in determining whether allergen immunotherapy should be initiated. 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. Many individuals travel extensively for business or pleasure into different regions, and symptoms might worsen at these times. However, inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective. Determination of the significance of indoor allergens for a particular patient is harder because it is difficult to determine exposure in the home, school, and/or workplace. Historical factors, such as the presence of a furry animal in the home, a history of water damage and subsequent fungal exposure, or a history of insect infestation, might be helpful. However, such information is subjective and is often of uncertain reliability. In addition, some studies have demonstrated significant indoor levels of cat and dog allergen in households without pets[228] and significant levels of mouse allergen in suburban[229] and inner-city[230] homes 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 with increased asthma morbidity in inner-city children was found.[231] 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. Nevertheless, for most patients, determination of the clinical relevance of an allergen requires a strong correlation between the patient's history and evidence of allergen-specific IgE antibodies.

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted *in vitro* tests for specific IgE antibodies can also be used. **A**

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 the skin test results have demonstrated the efficacy of immunotherapy for relevant allergens.[25,26,112,130,134,135,140,141,149,154] 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 from skin testing in a highly sensitive individual.[232,233] In addition, skin tests might be difficult to perform in patients with dermatographism or atopic dermatitis. *In vitro* tests are particularly useful in such patients.

Studies indicate that skin testing is generally more sensitive than *in vitro* tests in detecting allergen-specific IgE.[234,235] Based on inhalation challenge test results, skin tests have shown specificity and sensitivity generally superior to those of *in vitro* tests. The comparability of skin tests and *in vitro* tests for specific IgE antibodies depends on the allergen being tested. For all of 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, prick testing is sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass[236] and cat,[237] are used. Intradermal/intracutaneous skin testing might be required for some allergen extracts. It is appropriate in some patients to use *in vitro* tests for specific IgE antibody as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. *In vitro* tests can also be used to define the allergens that should be used in allergen immunotherapy. If the allergy skin test result is negative and the *in vitro* test result is positive, a controlled challenge can be performed, and if the latter is positive, immunotherapy can be considered. 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 *in vitro* test results.

Specific allergens

Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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.[17,104,106,107,109] 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.[112,122] Because a particular pollen extract is a mixture of multiple glycoproteins, this suggests that mixing pollen allergens does not alter biologic activity.

Fungi (molds). Several studies with *Alternaria* and *Cladosporium* species suggest that allergen immunotherapy with fungi might be effective.[133-138] The allergen content of most mold extracts is highly variable.[238,239] However, there is evidence that proteolytic enzymes present in some mold extracts could digest other antigens, such as pollens, when combined in a mixture.[240] For this reason, it might be desirable to separate all pollen extracts from mold extracts when using mixtures.

Unfortunately, extracts for some potentially clinically important fungi are not available.[241] 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 distinguish 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.

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.

Because immunotherapy has been shown to be effective for cat[22,26,139-143,242] and dog,[25,141] the decision to include dog or cat allergen in an allergen immunotherapy extract should be considered in those circumstances in which there is exposure.

Dust mites and cockroach allergens. Crude house dust extract is generally an inappropriate substitute for house dust mite extract because the protein content measured is not restricted to dust mite allergens, nor does it necessarily guarantee inclusion of dust mite protein. Immunotherapy with standardized dust mite is generally more effective than that with crude house dust allergens. The house dust mites *D farinae* and *D 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, such as *Blomia tropicalis* and *Euroglyphus maynei*, partially cross-react with allergens from *Dermatophagoides* species. Only 50% of the projected amounts of each of the 2 house dust mites (*D pteronyssinus* and *D farinae*) need 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[144,147-149,151] 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. Dust mite hypersensitivity should particularly be considered in patients who have perennial symptoms exacerbated by a dusty environment at home, work, or both and periods of high humidity.

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. The major allergen of *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.[243] Immunotherapy with cockroach allergens is effective[154] and should 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.

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.[108,116,244] Efficacy has also been demonstrated with immunotherapy by using whole-body extracts of imported fire ants.[155,156]

Foods. Only a single clinical study accessing the efficacy and safety of subcutaneous immunotherapy with foods has been performed.[171,173] This study, which evaluated immunotherapy with peanut, found the incidence of systemic reactions, even during maintenance, was unacceptable. Thus there is no evidence to support the use of immunotherapy with food extracts. Currently, strict avoidance of the offending food is advisable, and subcutaneous immunotherapy for food allergy is not recommended.

Mixing of extracts

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Once the relevant allergens for each patient are identified, it is necessary to prepare a mixture that contains each of these allergens. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts. A number of 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 interactions between different types of allergens, when mixed, that could lead to degradation or unmasking of epitopes on exposure to proteolytic enzymes.

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Immunologic and 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.[71] 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 genera 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 the Allergen extract section, Fig 2, and the allergens and allergy diagnostic tests practice parameters).

Dose selection. Summary Statement 30: 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.[22-26,128,149,245] Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000 vol/vol).[28] A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy vaccine. Failure to do so might reduce the efficacy of immunotherapy. This occurs because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased (see the Immunotherapy schedules and doses section for further discussion and for recommended maintenance doses).

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as fungi (mold) and cockroach, from other extracts, such as pollens, is recommended. **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.[240,246,247] 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, and some weeds.[240,246,247] Cockroach had a similar deleterious effect on pollen extract potency.[246,248] Short ragweed appeared resistant to the effects of the proteolytic enzymes in one study,[240] 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.[247]

Dust mite extracts do not appear to have a deleterious effect on pollen extracts.[240,246,248] These studies suggest that pollen, dust mite, and cat extracts can be mixed together. 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. The evidence on mixing cockroach extract with other extracts is conflicting, and the clinical relevance of the changes is also unclear; therefore the clinician has the option of separating cockroach or not.

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 with lesser activities, such as pollen extracts.

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.

In this regard the number of separate injections that need to be given at each patient visit depends on whether all of the relevant extracts mixed into a single vial still deliver an optimal dose of each allergen. If mixing causes excessive dilution or if there are advantages to separating allergens into separate vials, then more than one vial might be necessary for successful immunotherapy.

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extracts are high-alert products that carry the risk for anaphylaxis. Policies, procedures, and processes intended for conventional drugs and medications might be highly 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 fatal anaphylactic reactions with allergenic products. 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. There are no reports of infection associated with allergen immunotherapy injections. Allergen vaccines are prepared by using sterile manufacturer's extracts and sterile diluents containing antibacterial constituents (usually phenol). A summary of the AAAAI/ACAAI/JCAAI proposed USP allergen immunotherapy extract preparation guidelines can be found in Table VIII.

TABLE VIII. AAAAI/ACAAI/JCAAI-proposed USP 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 below.*
   - 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.
2. **Physician responsibility**: A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in the preparation of immunotherapy using an aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files.
3. **Bacteriostasis**: Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if 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 the FDA-approved package insert 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 treatment with sanitizing agents containing alcohol and/or 70% isopropanol 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 the physical integrity of the vial.
10. **Labeling**: Immunotherapy vials are to be clearly labeled with the patient's name and 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.

*__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 media, such as from Valiteq (http://www.valiteq.com), 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.

Allergen immunotherapy extract handling

Storage. Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

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 a number of 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 extract, including reconstituted lyophilized extracts, should be stored at 4°C to minimize the rate of potency loss because storage at higher temperatures (eg, room temperature) can result in rapid deterioration.[249]

Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions (personal communication). These studies include actual shipments made by their carriers to places like

Phoenix in the summer and Alaska in the winter. 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.

Storing dilute extracts. Summary Statement 34a: More dilute concentrations of allergy immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than do more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: In determining the allergy vaccine expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of 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 allergen immunotherapy 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.[249,250]

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.[250] Phenol is a preservative added to extracts to prevent growth of microorganisms.

Phenol can denature proteins in allergen extracts.[251,252] Human serum albumin might protect against the deleterious effect of phenol on allergen extracts.[251] 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,[250,253] possibly through inhibition of the activity of proteolytic and glycosidic enzymes that are present in certain extracts. However, it is irritating when injected and should be diluted before beginning immunotherapy. Recommendations for extract stability are found in the manufacturers' product insert sheets. 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. The pain associated with glycerin increases in proportion to the glycerin concentration and injection volume, and the pain is proportional to the total injected dose of glycerin.[254] However, individual pain perception can vary substantially. Total glycerin doses of less than 0.05 mL rarely produce clinically important pain.

TABLE IX. Potency of selected manufacturer's extracts currently available

Extract	Potency
Cat hair and pelt	5000 and 10,000 BAU/mL
Dust mite	3000, 5000, 10,000, and 30,000 AU/mL
Bermuda grass	10,000 AU/mL
Short ragweed	1:10-1:20 wt/vol or 100,000 AU/mL
Other grasses*	10,000 and 100,000 BAU/mL
Other pollen	1:10 to 1:40 (wt/vol) or 10,000 PNU/mL
Molds	1:10 to 1:40 (wt/vol) or 20,000 to 100,000 PNU/mL

AU, Allergy unit; *BAU*, bioequivalent allergy unit; *PNU*, protein nitrogen unit.
*Perennial rye, Kentucky blue/June, timothy, sweet vernal, redtop, orchard, and meadow.

There have been few studies that have investigated the potency of dilutions of allergen extract mixture over time. Expiration dates for allergen extract dilutions are somewhat empiric and not strongly evidence based. A study undertaken by the AAAAI 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. Dust mite and cat at 1:10 and 1:100 vol/vol dilution were also stable in all conditions of storage over 12 months, as measured by an ELISA assay using 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.

IMMUNOTHERAPY SCHEDULES AND DOSES

Summary Statement 35: A customized individual 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 can be based on single or multiple allergens. **D**

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. Animal dander contains between 10 and 20 antigens,[255] house dust mites between 20 and 40 antigens,[256] and pollens between 30 and 50 antigens,[257,258] and fungal extract can contain as many as 80 antigens.[259]

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. This is designated as the patient's maintenance concentrate.

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. Standardized extracts are available with biologic potencies of 10,000 and 100,000 BAU for grasses; 5000 and 10,000 BAU for cat allergen; 5000, 10,000, or 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 wt/vol extracts (Table IX). 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.

Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

The highest concentration of an allergen extract mixture that is projected to be used as the therapeutically effective dose is called the maintenance concentrate. This should be prescribed individually for each patient by an allergist/immunologist. 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 individual manufacturer's extracts. Some patients might be unable to attain the projected therapeutically effective dose of the maintenance concentrate because of local reactions, systemic reactions, or both (eg, cat, 1000 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose]; see Table X for probable effective therapeutic dose range). Such patients might need weaker dilutions of their maintenance concentrate. Even so, 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 referred to as the maintenance dose. The consistent use of this nomenclature system is essential because errors in choosing the correct vial are a common cause of systemic reactions, especially when the patient transfers from one physician to another. Therefore it is important that standard terminology be adopted by all physicians who prescribe allergen immunotherapy.

Recommended doses

Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

The effective maintenance dose of immunotherapy for a particular patient must be individualized. To do this, the allergist/immunologist who prepares the allergen immunotherapy extract must balance the dose necessary to produce efficacy and the risk of reactions if such a dose is reached. The allergist/immunologist might need to prepare more than one maintenance concentrate to provide a therapeutic dose of each of the allergens for the polysensitized patient. Therapeutically effective doses for immunotherapy have been reported for some allergen extracts.[22,24,25,128,134,135,149,246,260,261] Effective doses have been determined for Hymenoptera venom, dust mite, cat allergen, dog, grass, and short ragweed (Table X).

Controlled studies demonstrate that the content of particular allergens in allergen immunotherapy extracts can be used to predict a therapeutic dose for those allergens, particularly when the extracts are standardized. For antigens 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. The therapeutically effective doses used in the most recent controlled clinical studies are the basis of the recommended dosage range of standardized extracts presented in Table X. 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 time that it is administered.[14]

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.[27] 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 risk of systemic reactions to immunotherapy injections with higher maintenance doses. The maintenance concentrate should be formulated to deliver a full therapeutic dose of each of its constituent components. However, some sensitive patients might not tolerate the targeted therapeutic dose, and their maintenance dose would be lower. Individuals 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 referred to as the maintenance dose.

Regardless of dose schedule, some patients are unable to progress to the predetermined maintenance dose because of large local or systemic reactions to the allergen

TABLE X. Probable effective dose range for allergen extracts US standardized units[a]

Antigen	Labeled potency or concentration[a,b]	Probable effective dose range
Dust mites: *D farinae* and *D pteronyssinus*[c]	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat[d]	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized[e]	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed[f]	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 μg of Amb a 1 1000-4000 AU Concentration of Amb a 1 is on the label of wt/vol extracts in FDA units[358]
Nonstandardized extract, dog[g]	1:10 to 1:100 wt/vol	15 μg of Can f 1
Nonstandardized extracts	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose

[a]Multiple studies have demonstrated that the efficacious dose for allergen immunotherapy is between 5 and 20 μg of the major allergen per injection. Only 2 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).

[b]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).

[c]There have been no dose-response studies with United States–licensed dust mite extracts, and dosing recommendations in AU value are extrapolated from published European studies that used aqueous[349] and alum-precipitated[149,151] extracts. 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.[149] The authors suggested the optimal maintenance dose was 7 μg of Der p 1. Corresponding doses were based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Extrapolating effective and safe doses in this manner might not be scientifically valid. *D farinae* and *D pteronyssinus* are similar in group 1 allergen content according to the FDA's current reference standards. 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*.

[d]The major cat allergen Fed d 1 is reported in FDA units, with 1 Fel d 1 unit equaling approximately 2 to 4 μg of Fel d 1.[55,58,59] The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 to 19.9 U/mL. One study demonstrated clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 dose in terms of decreased cat extract PD_{20}, titrated skin test results, and allergen-specific IgE and IgG levels.[350,351] In a recent study that investigated the efficacy in terms of immunologic changes of 3 doses of a United States–licensed cat extract (0.6, 3, and 15 μg) demonstrated that a significant effect on titrated skin prick test results, allergen-specific IgG4 levels, and $CD4^+$/IL-4 levels was only seen in the group treated with 15 μg of Fel d 1, although the 3-μg dose group did demonstrate a significant change in titrated skin test response and increase in cat-specific IgG4 levels.[22]

[e]There have been no dose-response studies with United States–licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,[130] alum-precipitated,[24,161] and calcium phosphate–precipitated grass pollen extracts.[352] One of these studies compared a dose of 2 μg with 20 μg of major timothy allergen (Phl p 5) and found clinical efficacy at both doses.[24] The efficacy was greater in the 20 μg of Phl p 5 dose, but the systemic reaction rate was also higher in the high-dose group. The package inserts for United States–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 BAU. Extrapolating effective and safe doses in this manner might not be scientifically valid. 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).

[f]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 suggested that 1 unit of Amb a 1 is equivalent to 1 μg of Amb a 1, and 350 Amb a 1 units/mL is equivalent to 100,000 BAU/mL.[60] The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2000 AU, with a range of 1000-4000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrated 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.[45] A ragweed dose-response study (0.6, 12.4, and 24.8 μg of Amb a 1) demonstrated efficacy, as measured by nasal challenge, at 12 and 24 μg of Amb a 1.[128] The efficacy of the 24-μg dose was not significantly better than the 12-μg dose, and the authors concluded that the optimal dose for ragweed extract was greater than 0.6 μg but not more than 12.4 μg of Amb a 1.

[g]Dog extracts are not standardized. However, one dose-response study with a United States–licensed acetone-precipitated dog extract investigated the efficacy of 3 doses (AP dog; Hollister-Stier, Spokane, Wash; 0.6, 3, and 15 μg) in terms of immunologic changes and found the dose of 15 μg of Can f 1 to be most efficacious.[25] 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 have assayed between 128 and 208 μg/mL (average Can f 1, 162 μg/mL [SD ± 26 μg/mL]; information provided by the extract manufacturer, Hollister-Stier).

immunotherapy extract. The evidence is not clear whether large local reactions are a potential risk for subsequent allergen immunotherapy systemic reactions.

Published studies do not indicate that an individual large local reaction is predictive of a subsequent systemic reaction.[179,180] However, one retrospective study found that individuals who have a history of repeated large local reactions (defined as >25 mm) might be at greater risk for a subsequent systemic reaction.[181]

The concept of highest tolerated dose does not apply for VIT, and all patients are expected to achieve the full recommended dose to achieve the necessary degree of protection. There are conflicting data over whether lower doses (50 μg) are less effective, but there are also data showing that 200 μg is more reliably effective.[245] In the case of VIT, patients are asked to tolerate more large local reactions to achieve the full dose, even though with inhalant immunotherapy the dose can be reduced for such large local reactions to minimize patient discomfort.

Effect of dilution on dose

Summary Statement 38: 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 vaccine, thereby limiting the ability to deliver a therapeutic effective dose for any given allergen.

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

Dilution from maintenance concentrate vaccine	Volume	Volume (mL)	Diluent volume (mL)	Final volume
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.

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 2000 BAU/mL, 2 mL of the manufacturer's extract (cat, 10,000 BAU/mL) can be added to 8 mL of diluent or 8 mL of other allergens, and the final concentration of cat will be 2000 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.

Dilutions of the maintenance concentrate

Summary Statement 39: 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 vol/vol 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, 1000 BAU or 100 BAU), but this system can be complicated if allergens with different potency units are used (eg, wt/vol, BAU, AU, or PNU) and make it difficult to easily interpret the vial label.

Instructions on how to prepare various allergen extracts 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.

Labeling dilutions

Summary Statement 40: 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, a number of 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 (vol/vol), a numbering system, a color-coding system, or an alphabetical system should be used. If this uniform labels 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.

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
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

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 3 and 4).

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 Appendix 2]).

Individualized treatment vials

Summary Statement 41: 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 (wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for 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). Labels on patient-specific vials can provide at least 2 patient identifiers (birth date and patient name), which would be consistent with the recommendations of the Joint Commission on Accreditation of Health Care Organizations National Patient Safety Goals: ''Goal 1: Improve the accuracy of patient identification by using at least two patient identifiers when providing care, treatment or services.''[5] 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 administration of the injection.[4,5]

In a survey of 1717 allergists endorsed by the AAAAI and JCAAI, 57% of the 476 respondents reported at least one wrong-patient injection, and 74% of the 473 respondents reported at least one wrong-dose injection.[4] 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 reasons why this might reduce incorrect injection errors. One reason was that patient-specific vials can be prepared in a quiet laboratory setting, which might provide substantially less distraction than the nurse in a room with a patient who is trying to concentrate only on drawing up the injection correctly. In addition, the specific components are mixed once with the preparation of individually prepared patient-labeled vials, whereas the mixing would be repeated on every injection visit if the allergen extract is withdrawn from different stock solutions, as it is in the off-the-board method. For safety reasons and to avoid cross-mixing of allergens removed from the manufacturer's extract, the mixing of antigens in the syringe (off the board) is not recommended.

Some allergists/immunologists prefer to administer immunotherapy doses drawn directly from a single stock dilution of individual allergens or common mixes (shared specific patient vials). In this way the immunotherapy dose is transferred to the patient without cross-contamination. If shared-patient (eg, mixed vespids and dust mite mix) vials are used, it is essential that policies and procedures are developed to verify that the correct dose from the correct vial is administered to the correct patient.

Starting doses

Summary Statement 42: The starting dose for build-up is usually a 1000- 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 slowly 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 1:1000 (vol/vol), although more diluted concentrations frequently are used for patients who are highly sensitive, as indicated by history or skin test reaction (see Appendix 3 for an example of a conventional immunotherapy schedule).

Frequency of build-up injections

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 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 2 times per week. 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 4 to 6 months, depending on the starting dilution and the occurrence of reactions. It is acceptable for patients to receive injections more frequently, provided there is adequate spacing between injections. The interval between injections is empiric but might be as short as 1 day without any increase in the occurrence of systemic reactions[262] if there is some urgency to achieve a maintenance dose (eg, allergy season is approaching) or for practical reasons (eg, patient's schedule). Alternatively, treatment schedules can be used that more rapidly achieve maintenance dosing. These cluster and rush dosing schedules are discussed in Summary Statements 47 through 49.

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 a number of 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).

Dose adjustments for systemic reactions

Summary Statement 44: 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 benefit/risk ratio justifies continuation of immunotherapy.

Reductions during periods of exacerbation of symptoms

Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Immunotherapy administered during periods of exacerbation of symptoms is considered a risk factor for immunotherapy.[17,184] Injections administered during periods when a patient is exposed to increased levels of allergen to which they are 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.[184] 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 sensitive, especially if their symptoms are poorly controlled.

Dose adjustments for late injections

Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

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 depends 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 Appendix 4 for an example of a dose-modification regimen for gaps in treatment).

Cluster schedules

Summary Statement 47: 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 (see Appendix 5).[22,26] 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. The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules.[145,263-266] The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.[267]

Rush schedules

Summary Statement 48: 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.[268] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.[191,269-272]

The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections over the course of 4 hours.[273] Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours.[274-276] 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 cluster[145,266] and rush[134,277] schedules.

Systemic reactions and rush schedules

Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

The advantages of rush immunotherapy come at a cost because there is an increased risk of local and systemic reactions. Systemic reaction rates have been reported to be

as high as 73% of patients, with the risk of such reactions reduced to 27% by premedication in one study.[272] Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing.[273]

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

Rush protocols for administration of Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions.[274-276,278,279]

Premedication and weekly immunotherapy

Summary Statement 50: Premedication can reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

There is concern that antihistamines taken before each injection with conventional immunotherapy might mask a minor reaction that would otherwise alert a physician to an impending systemic reaction. 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.[280] One study that compared terfenadine premedication with placebo premedication during rush VIT demonstrated greater clinical efficacy in the terfenadine-premedicated group in terms of subsequent responses to field stings or sting challenge.[281] There was also a significant difference in the systemic reaction rate between the 2 groups: 6 patients in the placebo-premedicated group had systemic reactions, whereas none of the patients in the terfenadine-premedicated group had systemic reactions ($P = .012$).

Unfortunately, patients might still have life-threatening anaphylaxis despite 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.

Premedication with cluster and rush immunotherapy

Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

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.[267] Premedication with a 3-day course of prednisone, an H_1 histamine receptor antagonist, and an H_2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.[272] In one study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on the safety and efficacy of rush immunotherapy, there was a 5-fold decrease in the risk of anaphylaxis in the group premedicated with omalizumab compared with the placebo premedication group.[282]

There are anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist, but there have been no published studies. Because the risk of a systemic reaction from rush VIT is relatively low, routine premedication before rush VIT is usually unnecessary.[274,276,278,279] In a study evaluating premedication with antihistamines and steroids for rush immunotherapy with imported fire ant venom, there was no statistically significant differences in the systemic reaction rates between the premedication and placebo premedication group (3.6% of the premedication group vs 6.7% of the placebo group, $P = .87$).[157]

Maintenance schedules

Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals 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 individuals might tolerate longer intervals between maintenance dose injections.

The interval between venom injections can be safely increased up to 8 weeks in some patients without loss of efficacy. 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.

Continuing care

Time course of improvement. Summary Statement 53: Clinical 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.[24,134,143,277] Improvement might not be observed for a number of reasons, including (1) failure to remove significant allergenic exposures (eg, a cat), (2) exposure to high levels of

allergen (eg, pollen or molds), (3) continued exposure to nonallergen triggers (eg, tobacco smoke), or (4) incomplete identification and treatment of clinically relevant allergens. 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 54: 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 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 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

The patient's response to immunotherapy should be evaluated on a regular basis. 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. 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.

There have been very 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 individuals.[283-285] However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported.[283,285] Nevertheless, systemic reactions to stings after discontinuing VIT were generally much milder than the pretreatment reactions and were rarely severe. Two studies did not find a difference in relapse rates between the patients treated for 3 years compared with those treated for 5 years,[283,286] but one of the studies noted that the small number of patients in the 3-year treatment group prevented them from making any conclusions about the risk of discontinuing treatment after 3 years.[283] However, one study found that patients who had experienced re-sting reactions after discontinuing VIT had received VIT for a significantly shorter duration (mean, 43.35 months) than those with continued protection (mean, 54.65 months; $P < .01$).[285] Another study reported that 5 years of VIT provided better immunologic and clinical outcomes than 2 to 4 years of treatment.[287]

Change in skin test reactivity did not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who experienced a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE.[286,288] Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment.[288] The relapse rate and the frequency of severe reactions were greater in patients who had a history of very severe reactions to stings before treatment, in patients who had systemic reactions during VIT (to a sting or a venom injection), in patients with honeybee allergy, and in those who had less than 5 years of treatment.

The duration of inhalant allergen immunotherapy efficacy has not been as extensively studied. Some studies have suggested 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 *(D pteronyssinus)* extract for 12 to 96 months.[14] 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.[13] There was a switch to placebo in half of 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. These studies demonstrate the uncertainty of the long-term benefit of inhalant immunotherapy after discontinuation.

Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained clinical remission after discontinuing inhalant immunotherapy, and 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 indication for continuation of immunotherapy can be found at http://www.aaaai.org or http://www.jcaai.org.

Documentation and record keeping. Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully 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 allergy immunotherapy and prescription forms can be found in the Appendix (Appendices 6-15), and these include examples of immunotherapy prescription and administration forms. These forms, along with examples of immunotherapy consent and instruction forms, can also be found at http://www.aaaai.org.

Injection techniques. Summary Statement 57: Allergen immunotherapy extract injections should be given using a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **C**

Immunotherapy should be given with a 26- to 27-gauge syringe with a half-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.[289-291]

If using shared specific patient vials (stock vials, such as mixed vespid or dust mite mix), a single dose should be drawn from each vial. Antigens from different vials should not be combined in a single syringe. Furthermore, extra care is needed to prevent using the wrong stock antigen.

Summary Statement 58: The injection should be given subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Each immunotherapy injection should be given in the posterior portion of the middle third of the upper 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.

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.

The syringe should be aspirated to check for blood return in the syringe before injecting. If blood is present, 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 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 syringe should be appropriately discarded. A fresh syringe and needle are necessary to determine whether a blood vessel has been entered.

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 could result in a local reaction.

LOCATION OF ALLERGEN IMMUNOTHERAPY ADMINISTRATION

Physician's office

Summary Statement 59: 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 to treat anaphylaxis should be in the immediate vicinity when immunotherapy injections are administered.

Summary Statement 60: 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.[292] 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.[184] 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 might be frequently necessary in the patient's immunotherapy schedule, as well as the patients total treatment program.

Other locations

Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **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.[292] The health care professional and staff 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, or allergy/asthma exacerbations at the time of allergen immunotherapy extract injection or poorly controlled asthma).

Appropriate adjustment of dose should be made as clinically indicated. The physician who prepared the patient's allergen immunotherapy extract should provide adequately labeled allergen immunotherapy extract vials, detailed directions regarding dosage schedule for build-up and maintenance, and instructions on adjustments that might be necessary under the following circumstances:

1. when providing patients with new vials;
2. during seasonal exposure to allergens that are in the patient's allergen vaccine, to which the patient is very sensitive, or both;
3. if the patient has missed injections; and
4. when reactions occur to the allergen immunotherapy extract.

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

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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 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 very 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 fully trained to administer the injection and to treat anaphylaxis if this should 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 supports (personnel, medications, supplies, and equipment) are more optimal for encouraging prompt recognition and treatment of anaphylaxis (Table V). 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.

Summary Statement 63: If a patient on 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for their immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extracts might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Patients often 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 brought from the previous physician (ie, an unchanged immunotherapy program) or one to be prepared by the current physician (ie, a new immunotherapy program).

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 full, clear, and detailed documentation of the patient's previous schedule and the contents of the allergen immunotherapy extract (see Appendices 7, 8, 11, 12, and 14 for examples of allergen immunotherapy prescription and administration forms and documentation guidelines for allergen immunotherapy forms). In addition, the patient's previous response to and compliance with this program 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 a schedule and the allergen immunotherapy extract, (2) the patient has shown significant improvement on this immunotherapy program, and (3) the contents of the allergen immunotherapy extract are appropriate for the area in which the patient is now living.

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, vaccine type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient's dose is not modified. This increased risk is due to the significant variability in content and potency of extracts and the variability in methods used by physicians to prepare the patient's maintenance concentrate and its dilutions. For example, the strength of a given concentration of nonstandardized extracts might vary significantly from vial to vial. The risk of systemic reactions in such a situation might be greater with nonstandardized extracts and allergen immunotherapy extracts that contain mixtures of allergens.

Therefore if the allergen immunotherapy extract is to be changed, the patient might need to be retested for specific IgE to the appropriate allergens 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 provided the interval of time since the last injection has not been too long. For lot changes from the same manufacturer, the physician can consider decreasing the dose by 50% to 90%. For changes in manufacturer and nonstandardized extracts, a greater decrease in dose might be necessary.

SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

Allergen immunotherapy in children

Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children

with allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Immunotherapy for children has been shown to be effective and often well tolerated,[137,242] although at least one study did not show efficacy.[293] 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.[294] In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (see the Patient selection section and Table VII). In recent studies children receiving allergen immunotherapy have demonstrated:

1. improvement in symptom control for asthma[117,119,121,122] and allergic rhinitis[118];
2. increased PC_{20} to histamine[121];
3. increased PC_{20} to cat and house dust mite allergens[121,149];
4. decreased risk of development of asthma[6,9,163-165];
5. decreased development of new sensitivities[120,166]; and
6. modification in release of mediators in children receiving immunotherapy that correlates with decreased clinical symptoms.[123]

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Although there is some disagreement about the role of allergen immunotherapy in children under the age of 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.[117,122] In children with allergic rhinitis, allergen immunotherapy might prevent the development of asthma.[6,9,163-165] However, allergen immunotherapy for inhalant allergens is usually not considered necessary in infants and toddlers because (1) there is 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 in pregnancy

Summary Statement 71: Allergen immunotherapy might be continued but is usually not initiated in the pregnant patient. **C**

The physician must be aware of the benefits and risks of immunotherapy in pregnant patients. The recommended precautions for prevention of adverse reactions are especially important in the pregnant patient. Allergen immunotherapy is effective in the pregnant patient. Thus allergen immunotherapy maintenance doses can be continued during pregnancy. Allergen immunotherapy is usually not initiated during pregnancy because of risks associated with systemic reactions and their treatment (ie, spontaneous abortion, premature labor, or fetal hypoxia). 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, and the patient is maintained on the dose that she is receiving at that time.

Immunotherapy in the elderly patient

Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy might be considered in the treatment of the elderly patient, but the benefit/risk assessment must be evaluated carefully in this population. Older 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. However, elderly patients may also benefit from allergen immunotherapy and age alone should not preclude the consideration of allergen immunotherapy.[295]

Immunotherapy in patients with immunodeficiency and autoimmune disorders

Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with immunodeficiency or autoimmune disorders. Therefore the decision to begin immunotherapy in patients with major humoral or cellular immune defects must be individualized. Concern about the increased risk of immunotherapy in such patients is largely hypothetical.

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

ALTERNATIVE ROUTES OF IMMUNOTHERAPY

Sublingual and oral immunotherapy

Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be

effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no FDA-approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **B**

Alternative routes of administration of allergen immunotherapy are ''a viable alternative to parenteral injection therapy'' in some cases.[106,296] Studies of oral immunotherapy have provided conflicting results for ragweed,[297] birch,[298] and cat[299] immunotherapy. The present dosage of oral immunotherapy extract is 20 to 200 times the parenteral injected dosage, which requires a cost assessment for this type of therapy. Furthermore, adverse effects have included gastrointestinal and oral reactions (50% in 1 study) that might preclude home therapy. Oral immunotherapy should be considered investigational at this time.

Optimal-dose (high-dose) sublingual swallow immunotherapy is effective in adults and children.[300-304] In a study of 855 patients with grass pollen allergy and allergic rhinitis randomized to placebo or one of 3 grass tablet doses, there was a significant reduction in symptom and medication scores in the highest-dose subgroup, who were treated for at least 8 weeks before the grass pollen season, compared with the placebo group (symptoms, 21%, $P = .0020$; medication use, 29%, $P = .0120$).[303]

Sublingual allergen studies have evaluated house dust, olive pollen, grass pollen, ragweed, birch, cat, latex, *Alternaria* species, and *Parietaria judaica*.[305-313] Sublingual immunotherapy has been shown to be effective in patients sensitized to 2 non–cross-reacting allergens, grass and birch.[314] It has been noted that the allergen is not degraded by saliva and that there is no direct sublingual absorption of allergen. Radiolabeled allergen has been detected after 48 hours in the sublingual region.[315,316] Alternative protocols, such as rush and ultra-rush (20 minutes) sublingual swallow[307,316,318] and no induction (build-up) phase,[301,303,317,319,320] have been studied. Several studies have suggested a relationship between dose and efficacy with sublingual immunotherapy,[303,310,321] but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. The majority of sublingual studies have demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both, but approximately 35% of the randomized, double-blind, placebo-controlled studies did not demonstrate efficacy in either parameter during the first year of treatment.[322] Further studies are needed to confirm the optimal dose for sublingual immunotherapy.

One of the potential advantages of sublingual immunotherapy is that it appears to be safe, even at very high doses (up to 500 times the usual monthly subcutaneous dose), and to be associated with a lower incidence of serious side effects.[310,320,323] This appears to apply to young children (<5 years), for whom there are prospective safety data[324,325] and a postmarketing survey.[326]



FIG 3. Sample of labels for allergen immunotherapy extract vials.

There have been no SLIT-related fatalities, but there have been 3 case reports of anaphylaxis caused by sublingual immunotherapy. One patient with latex hypersensitivity had anaphylactic shock 20 minutes after reaching the maximal dose on the fourth day of latex rush sublingual rush immunotherapy.[327]

The other 2 reported cases of SLIT anaphylaxis involved patients treated with multiple inhalant allergens. In one case a patient with allergic rhinitis and asthma who was prescribed a sublingual immunotherapy extract composed of multiple non–cross-reacting allergens (*Alternaria* species, dog, cat, ragweed mix, weed mix, and grass mix)[328] had generalized pruritis, followed by angioedema, shortness of breath, and dizziness, within a few minutes of administering 6 drops of the 1:100 vol/vol dilution on the third day of treatment. This episode was preceded by a milder systemic reaction the previous day (generalized pruritis). In the other case, a 13-year-old girl with allergic rhinitis and asthma had swelling of her lower lip 3 minutes after pollen drops, high fever, chest pain, nausea, and abdominal pain.[329] She was treated in the emergency department for anaphylaxis and hospitalized for observation. The reaction occurred 1 month after she had reached the maintenance dose during the peak of the spring season.

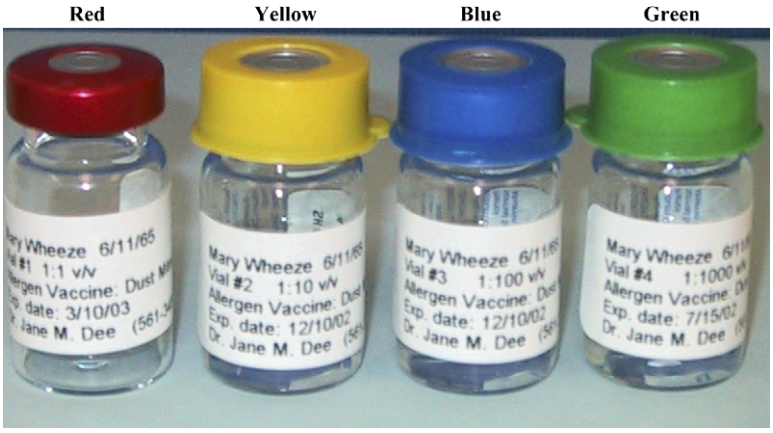


FIG 4. Sample set of color-coded vials of allergen vaccine.

There is currently no FDA-approved formulation for sublingual immunotherapy in the United States at this time, and this modality should be considered investigational. Current investigation of sublingual immunotherapy should not be confused with low-dose sublingual immunotherapy based on provocation neutralization testing or Rinkel-type skin testing.

Intranasal immunotherapy

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Based on controlled, well-designed studies, intranasal immunotherapy has been shown to improve the nasal symptoms of rhinitis.[330] Intranasal dry powder extract immunotherapy has been studied in grass,[330] birch,[331] *P judaica*,[332-334] and house dust mite[335] allergy. Clinical efficacy was noted in all of these studies. Nasal reactivity to allergen challenge was reduced, and only minor side effects were noted in 2 of the above studies. A 3-year study with *P judaica* reported to provide persistent benefits for up to 12 months after conclusion of allergen immunotherapy.[333] Local administration of nasal allergen in an aqueous solution for immunotherapy might be limited by the local side effects. Further studies in both pediatric and adult groups are needed. In human studies the antigen has been noted to appear in the serum within 15 to 30 minutes of administration, with a peak level occurring within 2 to 3 hours.[315] Some allergens have been reported to be retained in the nasal mucosa for up to 48 hours after administration. Intranasal immunotherapy is not currently available in the United States but has gained some acceptance in other parts of the world.

Immunotherapy techniques that are not recommended

Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

Low-dose regimens, including coseasonal low-dose immunotherapy for aeroallergens and the Rinkel low-dose titration techniques, are not effective.[27,28] Immunotherapy based on provocation–neutralization testing with food and aeroallergens and enzyme-potentiated desensitization is not effective.[336]

FUTURE TRENDS IN IMMUNOTHERAPY

Therapy with aeroallergen extracts will become more uniform (as is the current practice for insect venoms) as greater numbers of biologically standardized allergen extracts become available. The actual number of commercially available allergen extracts will be reduced based on consensus agreements about the regional prevalence of aeroallergens, their cross-allergenicity, and the relevance of their effect on human health in specific locales. Novel routes for more effective, convenient, and safer allergen immunotherapy are being investigated throughout the world.

For example, the sublingual route of administering allergen immunotherapy has been studied extensively in Europe. A meta-analysis confirmed its clinical effectiveness in allergic rhinitis,[302] and it has been reported to be effective in asthma as well.[337] Sublingual immunotherapy appears to have a very low risk of serious life-threatening systemic side effects, which might allow for home administration.[324,338] In some studies the clinical benefits of sublingual immunotherapy were not significant until the second year of treatment,[306,339] and comparisons suggest that the magnitude of the clinical benefit of sublingual immunotherapy might not be as great as that of subcutaneous immunotherapy.[311]

Trials with non–IgE-binding peptides containing T-cell stimulating peptides have been reported.[340] Site-directed mutagenesis has produced allergens with decreased IgE-binding capacity without decreased T-cell responses.[341,342]

Immunostimulatory sequences mimicking bacterial and viral DNA have been prepared that stimulate the innate immune system to direct T-cell responses toward

T_H1 rather than T_H2 phenotypes.[343] The results of clinical trials with a conjugate of the immunostimulatory sequence to the major allergen of ragweed, Amb a 1 (AIC), have been reported.[34,343] In a double-blind, placebo-controlled study of 25 adults who received 6 weekly injections of the AIC or placebo vaccine before ragweed season, the AIC group had better peak-season rhinitis scores on the visual analog scale ($P = .006$), peak-season daily nasal symptom diary scores ($P = .02$), and midseason overall quality-of-life scores ($P = .05$) than the placebo group during the first ragweed season, and this effect was observed in the subsequent ragweed season.[344]

Humanized anti-IgE mAb has been shown to have clinical effects in both allergic rhinitis and asthma.[345-348] Theoretically, this new therapeutic modality could be used as protective cover for clinical applications of rapid forms of immunotherapy. It is possible that preadministration of anti-IgE could provide a more effective protective effect than premedication with antihistamines and therefore permit a rush allergen immunotherapeutic regimen with reduced risk of serious systemic reactions.[282]

AUTHOR'S 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 2 systemic reaction grading systems (the European Academy of Allergy and Clinical Immunology's grading of severity for systemic side effects and the Portnoy method for numeric grading of reactions to allergen immunotherapy) can be found in the Appendix section. These forms can also be found along with examples of immunotherapy instruction and consent forms, preinjection health questionnaires, and indications for beginning and continuing immunotherapy forms at www.aaaai.org.

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APPENDIX 1. American College of Medical Quality's policy on the development and use of practice parameters for medical quality decision-making[1]

Practice parameters are strategies for patient management developed to assist health care professionals in clinical decision making. Practice parameters include standards, guidelines, and other patient management strategies. Standards are accepted principles for patient management. Guidelines are recommendations for patient management that identify a particular management strategy or a range of management strategies. Other strategies for patient management include practice policies and practice options. Practice parameters are to be used as screening tools to identify possible deviations from the applicable standards of care. Such parameters are not to be used as absolute standards or to profile or report on health care personnel. Parameters are designed to trigger a process in which possible deviations from the standard of care are identified as outlier practice patterns. Once a deviation from the parameter is identified, such a deviation should be referred to the appropriate qualified physician advisor or reviewer for a determination of medical necessity that conforms to the applicable standard of care. Parameters used in the day-to-day practice of clinical medicine should be clinically relevant. They should not be considered as substitutes for the standard of care but might contribute to its formulation.

Practice parameters must be developed, designed, and implemented only by board-certified, clinically practicing, specialty-matched physician advisors/reviewers with unrestricted medical licenses. Qualified nonphysicians might participate in the development of these parameters only in the areas in which their clinical expertise based on the standard of care is applicable. The health care personnel who develop these parameters should sign their names and date the final version as evidence of their participation and support. Practice parameters must be based on sound scientific research findings, professional literature, clinical experience and appropriate well-recognized methodologies and reflect professionally recognized national standards of care practiced in the clinical community of medicine. The development procedures followed, the participants involved, the evidence used, the assumptions and rationales accepted, and the analytic methods used should be meticulously documented, described, and made publicly available for national peer review. Parameters should be updated as needed.

Practice parameters are used as tools to enhance medical decision making but not as replacements for physicians' clinical judgment. They can be considered as means to enhance the performance of clinical and review personnel but not to replace them. It is below the standard of care of the medical review process to substitute qualified physician reviewer experts with unqualified reviewers who are using parameters.

APPENDIX 2. Examples of possible abbreviations for allergen immunotherapy extract 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

APPENDIX 3. 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

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

APPENDIX 4. Example of immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals (modification of the AAAAI skin testing and immunotherapy consent and instruction forms: immunotherapy administration instruction form, which can be found at http://www.aaaai.org)

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

- Up to 7 days, continue as scheduled (ie, if on weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection).
- Eight to 13 days after missed scheduled injection; repeat previous dose.
- Fourteen to 21 days after missed scheduled injection; reduce dose 25%.
- Twenty-one to 28 days after missed scheduled injection; reduce previous dose 50%.

Then increase dose each injection visit as directed on the immunotherapy schedule until therapeutic maintenance dose is reached.

This suggested approach to modification of doses of allergen immunotherapy because of gaps between treatment during the build-up phase is not based on retrospective or prospective published evidence, but it is presented as a sample for your consideration. The individual physician should use this or a similar protocol as a standard operating procedure for the specific clinical setting. A similar dose-reduction protocol should be developed for gaps in maintenance immunotherapy.

APPENDIX 5. Example of a cluster immunotherapy schedule[22,26]

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

APPENDIX 6. Recommended documentation for allergen immunotherapy prescription forms

The purpose of the allergen immunotherapy prescription form is to define the contents of the allergen immunotherapy extract in enough detail that it could be precisely duplicated. The following information should be on an immunotherapy prescription form:

Patient information:

- Patient name, patient number (if applicable), birth date, telephone number, and picture (if available) should be included.

Preparation information:

- Name of person and signature preparing the allergen immunotherapy extract should be included.
- Date of preparation should be recorded.
- Bottle name should be included (eg, trees and grass). If abbreviations are used, a 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 should be included.
- Volume of manufacturer's extract to add to achieve the projected effective concentration should be included. 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) should be included.
- Extract manufacturer should be included.
- Lot number should be included.
- Expiration date should be recorded and should not exceed the expiration date of any of the individual components.

APPENDIX 7. Allergen immunotherapy extract prescription 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:

_____
_____
_____
_____

_____ ____/____/____
Prescribing Physician Signature Date

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

APPENDIX 8. Maintenance concentrate prescription form

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: 6/10/06

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial **4** from Vial **1** on **8/30/06** Expiration date: **10/15/06**
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	Short ragweed	1:20 w/v G (150 Amb a1)	0.5ml	Greer	12345	1/01/08
2	Amaranthus Retroflexus	1:10 w/v G	0.5ml	H-S	6789	2/07/08
3	Ash	1:10 w/v G	0.5ml	Center	3333	3/17/08
4	Cat	10,000 BAU/ml G	2.00ml	ALO	9898	2/27/08
5	Timothy Grass	100,000 BAU/ml G	0.4ml	ALK	56789	7/09/08
6	Johnson Grass	1:10 w/v G	0.5ml	Greer	2434	7/20/08
7						
8						
9						
10						
Diluent	HSA		0.6ml	ALK	68597	12/08
Total Volume			5.00 ml			6/10/07

*** Components of mixes listed on a separate sheet**
**** Assumes 0.5 ml injection as target maintenance dose**

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

Specific Instructions:

_____

_____

Prescribing Physician Signature

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

APPENDIX 9. Labels for allergen immunotherapy extracts

Each vial of allergen immunotherapy extract should be labeled in a way that permits easy identification. Each label should include the following information (example in Figs 3 and 4):

- Appropriate patient identifiers might include the patient's name, patient's number, patient's picture, and birth date.
- The contents of the allergen immunotherapy extract in a general way should be included. The detail with which this can be identified depends on the size of the label and the number of allergens in the vial. Ideally, allergens should be identified as trees, grasses, weeds, mold, dust mite, cockroach, cat, and dog. Because of space limitations, it might be necessary to abbreviate the antigens (eg, T, G, W, M, DM, Cr, C, and D respectively [see Appendix 2]). A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate (vol/vol) should be recorded. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- The expiration date should be included.

APPENDIX 10. Allergen immunotherapy administration form recommended documentation

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

Patient information:

- Patient's name, date of birth, telephone number, and patient's picture (optional but helpful).

Allergen immunotherapy extract information:

- Allergen immunotherapy extract name and dilution from maintenance in vol/vol bottle letter (eg, A and B), bottle color, or number, if used.
- Expiration date of all dilutions.

Administration information in separate columns:

- Date of injection.
- Arm administered injection, which might facilitate determination of exact cause of local reaction.
- Projected build-up schedule.
- Delivered volume reported in milliliters.
- Description of any reactions. The details of any treatment given in response to a reaction would be documented elsewhere in the medical record and referenced on the administration form.
- *Patient's health before injection*. This can be performed through a verbal or written interview of the patient before administering the immunotherapy injection. The patient should be questioned about increased asthma or allergy symptoms, β-blocker use, change in health status (including pregnancy and recent infections), or an adverse reaction to a previous injection (including delayed large local reactions persisting through the next day). Patients with significant systemic illness generally should not receive an injection.
- *Antihistamine use*. Antihistamines are frequently a component of an allergy medication regimen, and it would be important to note whether a patient is taking an antihistamine on the day he or she receives his or her immunotherapy injection. For consistency in interpretation of reactions, it might be desirable for a patient to either take or avoid antihistamines on a regular basis on the days he or she receives immunotherapy. The physician should note on the form whether he or she recommends the patient consistently take an antihistamine on immunotherapy treatment days.
- *Peak flow reading*. Consider obtaining a peak expiratory flow rate measurement before administering an immunotherapy injection to asthmatic patients. Poorly controlled asthma is considered a risk factor for immunotherapy. Obtaining a peak expiratory flow rate measurement before the immunotherapy injection might help identify patients with symptomatic asthma. The patient's baseline peak expiratory flow rate should be provided on the form as a reference. Health care professionals administering immunotherapy injections should be provided with specific guidelines about the peak expiratory flow rate measurement for when an immunotherapy injection should be withheld and the patient referred for clinical evaluation.
- **Baseline blood pressure**. It might be useful to record the patient's blood pressure as a baseline for future reference.

APPENDIX 11. Allergen immunotherapy administration form

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 allergy or 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

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

Date to reorder: __/__/__

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 allergy or 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**	

APPENDIX 12. 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: _____
_____
Staff action taken (if any): _____

APPENDIX 13. 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.

APPENDIX 14. Allergen immunotherapy systemic reaction/anaphylaxis 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
__Epinephrine IM into 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	

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:
_____
_____
_____
_____

Clinical impression: True SR Questionable SR No SR

Systemic reaction severity classification: EAACI_____ **Portnoy** _____

Dosage adjustment? _____

Signatures_____ **RN** _____**MD/DO**

APPENDIX 15. Grading severity of allergen immunotherapy reactions: Two methods

1. **The European Academy of Allergy and Clinical Immunology grading of severity for systemic side effects***

Classification of systemic reactions

0 = No symptoms or nonspecific symptoms

I = Mild systemic reactions: symptoms—localized urticaria, rhinitis, or mild asthma (PF <20% decrease from baseline).

II = Moderate systemic reaction: symptoms—slow onset (>15 minutes) of generalized urticaria, moderate asthma, or both (PF < 40% decrease from baseline).

III = Severe (non–life-threatening) systemic reactions: symptoms—rapid onset (<15 minutes) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).

IV = Anaphylactic shock: symptoms—immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, and hypotension, for example.

2. **Portnoy method for numeric grading of reactions to allergen immunotherapy†**

Local

0+ = No significant reaction or small area of erythema less than the size of a half dollar without swelling or wheal formation

1+ = Erythema greater than the size of a half dollar, swelling or wheal formation, or both

Systemic

2+ = Systemic reactions: cutaneous only—might consist of a cutaneous eruption, such as urticaria

3+ = Systemic reaction: generalized pruritus, sneezing, or both—might consist of increased allergy symptoms, such as nasal congestion, sneezing, or pruritus, especially in the mouth or throat

4+ = Systemic reaction: pulmonary—consists of wheezing, shortness of breath, and tightness. Might be associated with decreased pulmonary function tests

5+ = Systemic reaction: anaphylaxis—a sensation of not feeling right is a frequent prelude; might consist of hypotension, laryngeal edema, severe wheezing, and cramping

6+ = Cardiopulmonary arrest

PF, Peak expiratory flow.

*Subcutaneous immunotherapy. Allergy 2006;61(suppl 82):5-13.

†Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80.

Allergen immunotherapy: A practice parameter second update

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

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the "Allergen immunotherapy: a practice parameter second 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 and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
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11. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999;83(suppl): S665–S700.
12. Diagnosis and management of urticaria: a practice parameter. Ann Allergy 2000;85(suppl):S521-S544.
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14. Symptom severity assessment of allergic rhinitis: part I. Ann Allergy 2003;91:105-14.
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16. Stinging insect hypersensitivity: a practice parameter update. J Allergy Clin Immunol 2004;114:869-86.
17. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol 2005;115(suppl):S483-S523.

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22. Contact dermatitis: a practice parameter. Ann Allergy Asthma Immunol 2006;97(suppl 2):S1-S38.

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

CONTRIBUTORS

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Allergen immunotherapy: A practice parameter second update

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PREFACE

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

The objective of ''Allergen immunotherapy: A practice parameter second update'' is to optimize the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. 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's ''Policy on development and use of practice parameters for medical quality decision-making'' (Appendix 1).[1]

This document builds on the previous Joint Task Force document, ''Allergen immunotherapy: a practice parameter'' published in the *Annals of Allergy, Asthma and Immunology* in 2003.[2] The updated practice parameters draft was prepared by Drs Linda Cox, James Li, Hal Nelson, and Richard Lockey. The Joint Task Force reworked the initial draft into a working draft of the document. The project was exclusively funded by the 3 allergy and immunology societies noted above.

In preparation for the 2003 ''Allergen immunotherapy: a practice parameter'' and the second update, a comprehensive search of the medical literature was conducted with various search engines, including PubMed; *immunotherapy*, *allergic rhinitis*, *asthma*, *stinging insect allergy*, and related search terms were used. 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 second update'' was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the ACAAI, AAAAI, and JCAAI. In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for review and comments from members of the sponsoring organizations. 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 allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. This document also contains recommendations for the safe practice of allergen immunotherapy, including specific recommendations on the prevention and management of 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 or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. Symptoms of allergic conjunctivitis (eg, itchy watery eyes) are often considered part of allergic rhinitis or are included in the diagnosis of rhinoconjunctivitis. Particularly good candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures, those in whom it is important to avoid the potential adverse effects of medications, and those who wish to reduce the long-term use of medications. Immunotherapy is recommended for patients with a history of systemic reaction to Hymenoptera stings and specific IgE antibodies to Hymenoptera venom.

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.[3]

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. 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 *maintenance concentrate* should be used to identify the allergen immunotherapy extract that contains a therapeutic effective dose for each of its individual constituents (see the Immunotherapy schedules and doses section).

The term *manufacturer's extract* refers to the allergy extract purchased from the manufacturer. The terms *stock*, *full-strength*, and *concentrate* are ambiguous and should not be used. 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).

Allergen immunotherapy is effective when appropriate doses of the allergens are administered. ''Allergen immunotherapy: A practice parameter'' recommends that vials of allergen immunotherapy extracts should be prepared individually for each patient to enhance the individualization of therapy, reduce the risk of allergen cross-contamination, and reduce the risk of error in administration.[4,5] This parameter recommends the use of standardized allergen immunotherapy prescription and administration forms to improve the safety, uniformity, and standardization of allergen immunotherapy practice.[4,5] The suggested forms are found in the Appendix (Appendices 7, 8, 11, 12, and 14) and in the members' section of the www.aaaai.org Web site. The routine use of these standardized forms should improve the quality of immunotherapy practice.

Members' feedback comments on the recommended allergen extract dilution dating in the 2003 ''Allergen immunotherapy: A practice parameter'' led to an allergen immunotherapy extract dilution stability study designed by the AAAAI Immunotherapy and Allergy Diagnostics Committee and funded by the AAAAI Board of Directors. The study was designed to investigate the effect of time, temperature, and dilution of standardized allergen extract potency, and the results of this study were considered in this update.

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 3 years after publication. Requests for information about or an interpretation of these practice parameters should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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. Allergen immunotherapy

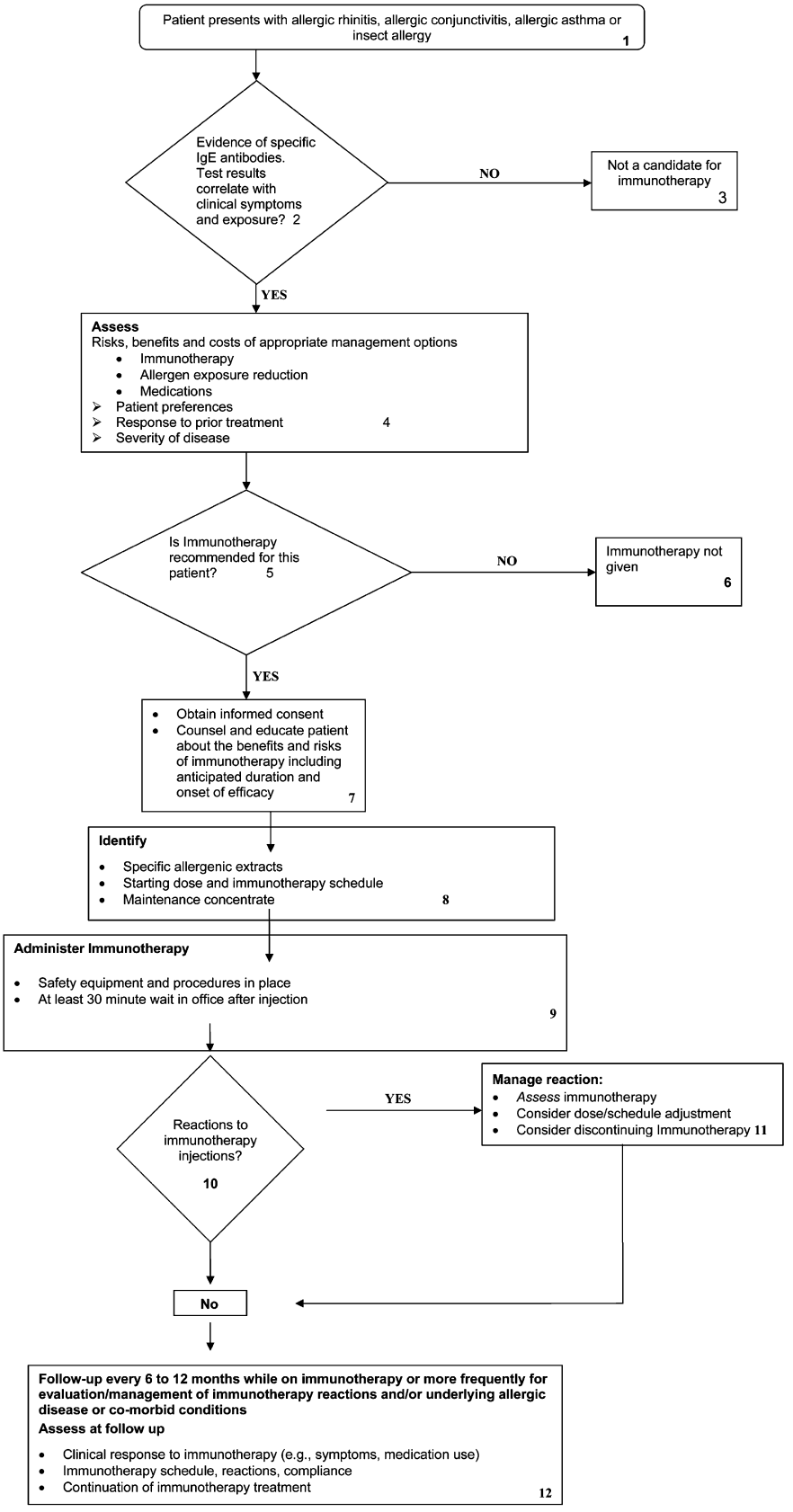


FIG 1. Algorithm for allergen immunotherapy.

might prevent the development of asthma in individuals with allergic rhinitis.[6-9] Evaluation of a patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic conjunctivitis, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for specific IgE antibody).[10]

Box 2

Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although *in vitro* testing for 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

Management of complex medical conditions, such as allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity, should include the careful evaluation of management 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 patient 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. On the basis of clinical considerations and patient 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 good candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy (VIT).

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 on the basis of 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 (see the Immunotherapy schedules and doses section). In general, the starting immunotherapy dose is 1000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 1000 to 4000 arbitrary units (AU; eg, for dust mite) or bioequivalent allergy units (BAU; eg, for grass) 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 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 referred to as *up-dosing*, *induction*, or the *dose-increase phase*) entails administration of gradually increasing doses during a period of approximately 14 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 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, in particular anaphylaxis. Patients should wait at the physician's office for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly, if they occur.

In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring 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. Some physicians recommend providing certain patients with epinephrine for self-administration in case of severe late reactions to immunotherapy injections.

Box 10

Injections of allergen immunotherapy extract can cause local or systemic reactions. Most severe reactions develop within 30 minutes after the immunotherapy injection, but reactions can occur after this time.

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 (anaphylaxis). Epinephrine is the treatment of choice in anaphylaxis, preferably when administered intramuscularly,[11] although subcutaneous administration is acceptable.[12]

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, see the practice parameters for anaphylaxis.[12]

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. After a severe systemic reaction, careful evaluation by the prescribing physician is recommended. For some patients, the immunotherapy maintenance dose might need to be reduced because of repeated systemic reactions to immunotherapy injections. The decision to continue immunotherapy should be re-evaluated after severe or repeated systemic reactions to allergen immunotherapy extracts.

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 doses, 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,[13] but others might experience a recurrence of their symptoms after discontinuation of allergen immunotherapy.[14] 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, and 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 on the basis of the patient's clinical response, disease severity, immunotherapy reaction history, and patient preference.

IMMUNOTHERAPY GLOSSARY

For more information on immunotherapy definitions, see the article by Kao.[15]

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 (pigments and salts; see the Allergen selection and handling section). Other terms used to describe the allergen immunotherapy extract include *allergen product*,[16] *allergy serum*, *allergen vaccine*,[17] 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.[18] Other terms that have been used for allergen immunotherapy include *hyposensitization*, *allergen-specific desensitization*, and the lay terms *allergy shots* or *allergy injections*.[15]

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

TABLE II. Allergen immunotherapy dose-calculation table

- Express weight per volume as a fraction: $\frac{1}{N}$ or 1:*N*.
- Calculate concentration of individual allergens in mixtures. If a mixture is made of equal amounts of N individual allergens to make a total concentration (C), the final concentration of an individual allergen (Ca) can be calculated by using the following equation:

$Ca = C \times \frac{1}{N} = \frac{C}{N}$ or *C*:*N*.

For example, if a mixture of equal amounts of 5 (N) allergens has a total concentration (C) of 100,000 BAU/mL, then the final concentration of each individual allergen (Ca) is: $Ca = \frac{C}{N} = \frac{100{,}000}{5} = 20{,}000\ BAU/mL$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{C}{N} = \frac{1/10}{5} = \frac{0.1}{5} = 0.02$ or $\frac{1}{50}$ or 1:50.

- Dilution of individual allergen: If an initial volume, Vi (in milliliters), of an individual antigen with concentration, Ci, is added to an allergen extract to make a final volume of Vf (in milliliters), the final allergen concentration (Ca) in the allergen extract mixture will be: $Ca = Ci \times \frac{Vi}{Vf}$.
- Final concentration of an allergen in a mixture of mixtures is determined by multiplying the initial concentration by the dilution factors from each mixing step.

For example, consider a mixture containing equal amounts of 5 (N) allergens with a total concentration (C) of 100,000 BAU/mL (first dilution). If an initial volume (Vi) of 0.5 mL of this mixture is further mixed with other components and diluent to make a final allergen extract mixture volume (Vf) of 5.0 mL (second dilution), the final concentration of an individual allergen (Ca) will be:

$$Ca = C \times \underbrace{\frac{1}{N}}_{\text{Mixture dilution}} \times \underbrace{\frac{Vi}{Vf}}_{\text{Allergen extract dilution}} = 100{,}000 \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{100{,}000}{50} = 2000\ BAU/mL$$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{1}{10} \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{1}{500}$ or 1:500.

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).

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 to 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-medicated 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 multiplied by volume of administered dose (see Table II for a dose-calculation table).

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, cat, 1000 BAU, [highest tolerated dose] vs 2000 BAU [projected effective dose]).

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 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 by a variety of immunologic transformations. Early definitions of the term immunotherapy included active and passive immunization for the purpose of improving 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 by means of induction of clonal deletion, anergy, immune tolerance, or immune deviation.

The *maintenance concentrate* is a preparation that contains individual 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 may not be the initially calculated projected effective dose.

The *maintenance goal* (or projected effective dose) is the allergen dose projected to provide therapeutic efficacy. The maintenance goal is based on published studies, but a projected effective dose has not been established for allergens. 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 the 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 large local reaction causing discomfort). The intervals between maintenance immunotherapy injections generally ranges 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 by means of immunoblotting or crossed allergoimmunoelectrophoresis.

For a definition of *projected effective dose*, see 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 test responses), and premedication with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similar high incidence of systemic reactions.

Off the board into one syringe is a phrase that describes a method of allergen immunotherapy preparation and administration that involves specifically mixing the patient's allergen immunotherapy injection in a single syringe, which is not recommended. This syringe might be inserted into more than one allergen extract vial, and this poses a risk of cross-contamination of the allergen extracts and might dull the needle with repeated penetration of the rubber stopper.

Shared specific patient vials is a method of allergen immunotherapy preparation and administration in which the allergy immunotherapy extract is withdrawn from a shared vial (eg, mixed vespids or dust mite mix). This is sometimes referred to as off the board, but it is distinct from the method of off the board into one syringe in that the syringe enters only one allergen extract vial.

INTRODUCTION

Immunity has been defined as protection against certain diseases. The initial immunotherapeutic interventions, which included the use of preventive vaccines and xenogenic 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 the field of allergen immunotherapy. From its humble empiric emergence in 1900, when ragweed injections were proposed as therapy for autumnal hay fever, allergen immunotherapy has progressed in both theory and practice from the passive immunologic approach to the active immunologic procedures pioneered by Noon[19] and Freeman.[20,21] 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 10 years. Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Some studies have suggested that allergen immunotherapy might prevent the development of asthma in individuals with allergic rhinitis.[6-9]

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,[22-26] and it should be differentiated from unproved methods, such as neutralization-provocation therapy and low-dose subcutaneous regimens based on the Rinkel technique, which have been found to ineffective in a double-blind placebo-controlled study.[27,28]

SUMMARY STATEMENTS

Mechanisms of immunotherapy

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, defined as a relative decrease in allergen-specific responsiveness and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

Allergen extracts

Summary Statement 6: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. **A**

Summary Statement 7: Nonstandardized extracts might vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Summary Statement 8: 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**

Cross-reactivity of allergen extract. Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

Efficacy of immunotherapy

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Summary Statement 10: Immunotherapy is effective for 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**

Food allergy, urticaria, and atopic dermatitis. Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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**

Measures of efficacy. Summary Statement 12: 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**

Safety of immunotherapy

Reaction rates. Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

Timing of anaphylactic reactions to immunotherapy injections. Summary Statement 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

β-*Adrenergic blocking agents.* Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

Contraindications. Summary Statement 18: 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**

Reducing the risk of anaphylaxis to immunotherapy injections. Summary Statement 19: 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**

Patient selection

Clinical indications. Summary Statement 20: 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 depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Special precautions in patients with asthma. Summary Statement 21: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. **C**

Clinical indications for VIT. Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Summary Statement 23: Patients selected for immunotherapy should be cooperative and compliant. **D**

Allergen selection and handling

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted in vitro tests for specific IgE antibodies can also be used. **A**

Specific allergens. Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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, supported by the presence of specific IgE antibodies. **A**

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Dose selection. Summary Statement 30: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. **A**

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens, is recommended. **B**

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extract handling

STORAGE

Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

STORING DILUTE EXTRACTS

Summary Statement 34a: More dilute concentrations of allergen immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: 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 a number of 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. **B**

Immunotherapy schedules and doses

Summary Statement 35: A customized individual 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 be based on single or multiple allergens. **D**

Maintenance concentrate. Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

Recommended doses. Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

Effect of dilution on dose. Summary Statement 38: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. **A**

Dilutions of the maintenance concentrate. Summary Statement 39: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. **D**

Labeling dilutions. Summary Statement 40: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. **D**

Individualized treatment vials. Summary Statement 41: 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. The mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. **C**

Starting doses. Summary Statement 42: The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. **D**

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

Dose adjustments for systemic reactions. Summary Statement 44: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. **D**

Reductions during periods of exacerbation of symptoms. Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Dose adjustments for late injections. Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

Cluster schedules. Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. **C**

Rush schedules. Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. **A**

Systemic reactions and rush schedules. Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

Premedication and weekly immunotherapy. Summary Statement 50: Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

Premedication with cluster and rush immunotherapy. Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

Maintenance schedules. Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. **A**

Continuing care

TIME COURSE OF IMPROVEMENT

Summary Statement 53: Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **A**

FOLLOW-UP VISITS

Summary Statement 54: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. **D**

DURATION OF TREATMENT

Summary Statement 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

DOCUMENTATION AND RECORD KEEPING

Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. **D**

INJECTION TECHNIQUES

Summary Statement 57: Allergen immunotherapy extract injections should be administered with a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **D**

Summary Statement 58: The injection should be administered subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Location of allergen immunotherapy administration

Physician's office. Summary Statement 59: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Summary Statement 60: 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**

Other locations. Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **D**

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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**

Summary Statement 63: 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for his or her immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extract might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Special considerations in immunotherapy

Allergen immunotherapy in children. Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Pregnancy. Summary Statement 71: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. **C**

Immunotherapy in the elderly patient. Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy in patients with immunodeficiency and autoimmune disorders. Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

Alternative routes of immunotherapy

Sublingual and oral immunotherapy. Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no US Food and Drug Administration (FDA)–approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **A**

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Immunotherapy techniques that are not recommended. Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

MECHANISMS OF IMMUNOTHERAPY

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, which is defined as a relative decrease in allergen-specific responsiveness, and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

The immunologic changes associated with immunotherapy are complex, and the exact mechanism or mechanisms responsible for its' clinical efficacy are continually being elucidated. Data support the concept that successful immunotherapy is associated with a change to a T_H1 $CD4^+$ cytokine profile.[29-34] Data indicate that increased production of IL-12, a strong inducer of T_H1 responses, contributes to this shift.[33] Clinically successful immunotherapy has been reported to be associated with immunologic tolerance, which is defined as a relative decrease in antigen-specific responsiveness, immune deviation, or anergy. For example, lymphoproliferative responses to allergen are reduced with immunotherapy.[32] Successful immunotherapy results in generation of a population of T regulatory cells, which are $CD4^+CD25^+$ T lymphocytes producing IL-10, TGF-β, or both.[35-39] Regulatory T-cell release has been described in allergen immunotherapy with Hymenoptera venom,[35] grass pollen extract,[37] and house dust mites.[38] IL-10 reduces B-cell antigen-specific IgE and increases IgG4 levels; reduces proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicits tolerance in T cells by means of selective inhibition of the CD28 costimulatory pathway.[36,37]

Allergen immunotherapy has been shown to block both the immediate and late-phase allergic response.[40] Allergen immunotherapy has been shown to decrease the recruitment of mast cells, basophils, and eosinophils in the skin, nose, eye, and bronchial mucosa after provocation or natural exposure to allergens.[41]

In patients receiving immunotherapy, initially there is an increase in specific IgE antibody levels, followed by a gradual decrease to a level that is still higher than that present before treatment. Clinical improvement in many patients develops before decreases in their IgE antibody levels occur or in other patients whose IgE antibody levels never decrease, thereby demonstrating that efficacy is not dependent on reductions in specific IgE levels.[42,43] Immunotherapy does diminish the seasonal increase in specific IgE levels.[44] Despite the persistence of significant levels of specific IgE antibody levels, immunotherapy usually causes a reduction in 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.[45-48]

An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, has also been associated with immunotherapy. The properties of allergen-specific IgA have yet to be determined, and there is a weak correlation between the increase in allergen-specific IgG levels and immunotherapy's clinical efficacy.[30,49,50]

Immunotherapy might alter the affinity and specificity of allergen-specific IgG.[51,52] During the initial phase of ultrarush VIT, a change in IgG specificity (ie, a change in the set of epitopes dominantly recognized by IgG on wasp venom antigens) occurred concomitantly with early clinical tolerance and was seen within 12 hours of ultrarush VIT ($P < .001$).[51] 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 individuals.[52] This change in IgG specificity preceded the increase in IgG titers and was sustained for up to 6 months.[52]

Allergen-specific IgG induced from immunotherapy can block IgE-dependent histamine release and subsequent IgE-mediated antigen presentation to T cells.[53] This effect might be dependent on IgE, allergen concentration, and CD23, the low-affinity receptor for IgE.

Whereas 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.[37,53]

The relationship between these immunologic changes and immunotherapy efficacy is not completely understood.

ALLERGEN EXTRACTS

Summary Statement 6: 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 has 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.[2,18,54-56] 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.

United States–licensed extracts can be obtained in aqueous, glycerinated, lyophilized, and acetone-precipitated and alum-precipitated formulations. Some commonly used allergens are standardized. These include extracts for cat hair, cat pelt, *Dermatophagoides pteronyssinus*, *Dermatophagoides 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.[57] 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.

Most standardized extracts are labeled in BAU. Short ragweed potency units were originally based on the content of the major allergen Amb a 1. Ragweed potency is reported in FDA units and BAU. One FDA unit of Amb a 1 equals 1 μg of Amb a 1, and 350 units of Amb a 1/mL is equivalent to 100,000 BAU/mL. Cat extracts were also originally standardized based on the content of major allergen (Fel d 1), with 100,000 arbitrary units (AU) per milliliter containing between 10 to 19.9 FDA units of Fel d 1 per milliliter (1 FDA unit of Fel d 1 equals 2 to 4 μg of Fel d 1).[55,58,59] Subsequently, $ID_{50}EAL$ testing suggested that 100,000 AU/mL was equal to 10,000 BAU/mL.[60] Approximately 22% of individuals with cat allergy have specific IgE antibodies to cat albumin.[61] Cat pelt extracts have a greater amount of albumin than cat hair extracts.[60]

Dust mites were originally standardized in AU by means of inhibition radioimmunoassay (RIA), and subsequent $ID_{50}EAL$ testing indicated that the AU was bioequivalent to the BAU, and the original AU nomenclature was kept. Dust mite extracts are still labeled in AU.

Summary Statement 7: Nonstandardized extracts can vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Nonstandardized extracts are labeled as wt/vol, which expresses weight in grams per volume in milliliters; that is, a potency of 1:100 indicates that 1 g 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 with a particular wt/vol or PNU potency can have widely varying biologic activities.[62-64] Therefore they should not be considered equipotent.

Summary Statement 8: 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**

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. The major clinically relevant aeroallergens of North America are listed in Table III. Furthermore, nonrelevant allergens in such mixtures could act as sensitizers rather than as tolerogens.[65,66] The physician must therefore select only those aeroallergens for testing and treatment that are clinically relevant in a particular geographic area.

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, dog), insect (cockroach), and Hymenoptera venom source materials.

Cross-reactivity of allergen extract

Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

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. A summary of cross-reactivity patterns of the clinically relevant North American aeroallergens can be found in Fig 2. 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,[67] inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[68-75] Grasses in other subfamilies (eg, Bermuda, Bahia, and Johnson) show greater diversity and should be evaluated separately.[76-78] Bermuda and Johnson grasses are increasingly important in the South,

TABLE III. The major clinically relevant aeroallergens of North America*

- Tree pollen
  - Chinese elm *(Ulmus parvifolia)*†‡; Siberian elm *(Ulmus pumila)*†‡; American elm *(Ulmus Americana)*†‡
  - Red oak *(Quercus rubra)*†; White oak *(Quercus alba)*†
  - Paper birch *(Betula papyrifera)*
  - Alder *(Alnus rubra)*
  - Box elder *(Acer negundo)*†; Red maple *(Acer rubra)*†
  - Eastern cottonwood *(Populus deltoides)*
  - Sycamore *(Platanus occidentalis)*
  - White ash *(Fraxinus americana)*†; Olive *(Olea europaea)*†‡
  - Black walnut *(Juglans nigra)*
  - Mulberry *(Morus rubra)*
  - Mountain cedar *(Juniperus ashei)*
  - Pecan *(Carya illinoensis)*
- Grass pollen
  - Rye *(Lolium perenne)*§‖
  - Timothy *(Phleum pratense)*§‖
  - Meadow fescue *(Festuca elatior)*§‖
  - Bermuda *(Cynodon dactylon)*‖
  - Johnson *(Holcus halepensis)*
  - Bahia *(Paspalum notatum)*
- Weed pollen
  - Short ragweed *(Ambrosia artemisiifolia)*‖
  - English (narrow leaf) plantain *(Plantago lanceolata)*
  - Mugwort *(Artemisia vulgaris)*
  - Russian thistle *(Salsola kali)*
  - Burning bush *(Kochia scoparia)*
  - Sheet (red) sorrel *(Rumex asetosella)*
  - Red root pigweed *(Amaranthus retroflexus)*
- Indoor aeroallergens
  - Cat epithelium *(Felis domesticus)*‖
  - Dog epithelium *(Canis familiaris)*
  - Arthropods (domestic mites: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*)‖
  - Insects (German cockroach: *Blattella germanica*)
- Fungi
  - *Alternaria alternata*¶
  - *Cladosporium* (*C cladosporioides*, *C herbarum*)¶
  - *Penicillium* (*P chrysogenum*, *P expansum*)¶
  - *Aspergillus fumigatus*¶
  - *Epicoccum nigrum*, *Drechslera* or *Bipolaris* type (eg, *Helminthosporium solani*)¶

*Compiled and selected in collaboration with the AAAAI Immunotherapy Committee Allergen Subcommittee for the identification of 35 key allergens of North America.
†Extensive cross-reaction of species within the genus.
‡Apart from regional prevalence, they are limited to local sites with substantial stands of these trees.
§Extensively cross-react with one another and bluegrass, orchard, red top, and sweet vernal.
‖Allergens for which standardized extracts are commercially available.
¶Species that are widely distributed and clinically important.

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.[79-82] 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.[83-85] Significant cross-reactivity between Betulaceae pollens and oak of the Fagaceae family has been demonstrated with percutaneous skin testing.[75] RAST inhibition studies have shown cross-inhibition between oaks and other *Fagales* species.[86] IgE immunoblot inhibition experiments have demonstrated that the *Fagales* species might be strongly inhibited by birch species.[87] The use of one of the locally prevalent members (eg, birch and alder) should be adequate.[88]

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.[89,90] Maple and box elder trees are found throughout the United States, except for the arid southwest. Although in the same genus as maple, *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,[91,92] and there are allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.[93]

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.[94] Similarly, Chenopod-Amaranth families have wide ranges in the western regions but are present throughout North America.[95] Current information on cross-reactivity of these families is limited.[96-98] 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.[99] The use of a single Amaranth extract should be sufficient to cover this family.[100,101] Similarly, *Atriplex* species (eg, saltbushes and scales) show near identity, and use of a single member is adequate. 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,

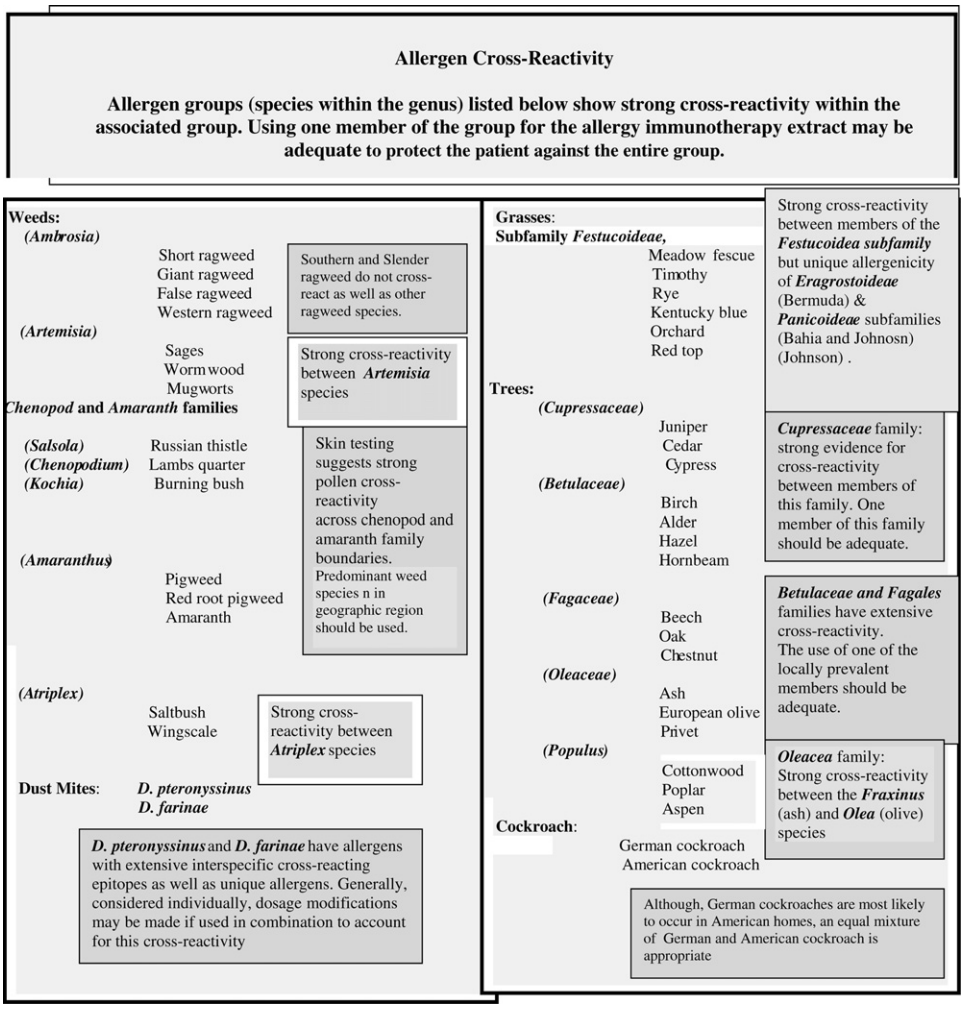


FIG 2. Patterns of allergen cross-reactivity.

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*).

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.[102,103] Stinging Hymenoptera insects occur throughout the United States; the fire ant is found only in Gulf Coast states, Texas, and some other southern and western states. Commercial venom extracts are available for some Hymenoptera species, except the fire ant, for which only whole-body extract is available.

EFFICACY OF IMMUNOTHERAPY

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity

Summary Statement 10: Immunotherapy is effective for 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.[104-111] Immunotherapy is effective for the treatment of allergic rhinitis[107] (including ocular symptoms[112,113]), allergic asthma,[104,109,111,114,115] and stinging insect hypersensitivity[108,116] and is effective in both adults and children.[117-124] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollens,[13,125-132] fungi,[133-138] animal allergens,[22,25,26,139-143] dust mite,[114,115,144-153] and cockroach.[154] There have been no controlled trials of fire ant whole-body extract, but it does appear to be effective in

TABLE IV. Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy

Outcome measure	House dust mite	Other allergens*†
Symptomatic improvement	2.7 (1.7-4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2-7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50)	5.5 (2.8-10.7)

Data are used with permission from Abramson et al.[104]
ND, Not done.
*Odds ratio (95% CI).
†Pollen, mold, or animal dander.

uncontrolled trials.[155-157] 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. A number of studies have also demonstrated a significant improvement in quality of life, as measured by using standardized questionnaires.[24,158-161] The magnitude of the effect depends on the outcome that is used (Table IV). For dust mite, the effect size ranges from a 2.7-fold improvement in symptoms to a 13.7-fold reduction in bronchial hyperresponsiveness. 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.[110] 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[107] and asthma[104,109,111] have been performed to deal with the issue of power. One review of 75 trials involving 3188 asthmatic patients found that, overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyperreactivity after immunotherapy, and it would have been necessary to treat 4 patients (95% CI, 3-5) with immunotherapy to avoid 1 deterioration in asthma symptoms and 5 (95% CI, 4-6) patients to avoid 1 requiring increased medication.[111] These meta-analyses strongly support the efficacy of allergen immunotherapy. Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued[13,162,163] and might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6,9,122,162-165] Allergen immunotherapy might also prevent the development of new allergen sensitivities in monosensitized patients.[120,166,167]

Food allergy, urticaria, and atopic dermatitis

Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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 use of allergen immunotherapy for individuals with the potential for IgE-mediated (anaphylaxis) reactions to foods should be regarded as investigational at this time.[168-171] There have been 2 investigational studies demonstrating efficacy in food hypersensitivity, the first using aqueous subcutaneous injections to peanut and the second using sublingual immunotherapy to hazelnut.[171-173]

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 a modified peanut extract is needed for clinical application of this method of treatment.[171] There is currently no FDA-approved formulation for sublingual immunotherapy, and this route of allergen immunotherapy is currently considered investigational at this time (see Summary Statement 73).

At the present time, there is not enough evidence to support food immunotherapy.

There is no evidence supporting the efficacy of immunotherapy for individuals with chronic urticaria, angioedema, or both.

There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[174-176] 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 ($P = .0379$) and topical corticosteroid use ($P = .0007$).[174]

The potential for benefit in symptoms related to oral allergy syndrome with the cross-reacting inhalant immunotherapy, which includes cross-reacting 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 subcutaneous immunotherapy directed against birch tree,[177] whereas another double-blind, double-dummy, placebo-controlled study comparing the effect of subcutaneous immunotherapy with sublingual immunotherapy 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, medication use, and decrease in IgE reactivity.[178] More investigation is required to substantiate the contention that benefits in oral symptoms will occur with immunotherapy.

Measures of efficacy

Summary Statement 12: 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. Objective measures, such as increase in allergen-specific IgG levels and decreased skin test reactivity, as measured by skin test titration, are changes generally associated with effective immunotherapy but, at present, are not practical for routine clinical use.[147] Nonquantitative skin testing or *in vitro* 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 are not very reliable given the strong placebo-like effect (Hawthorne effect) associated with any treatment. A more objective means for determining efficacy as validated in controlled clinical studies is the use of clinical symptom scores and the amount of medication required to control symptoms and maintain peak flow rates or pulmonary function tests within acceptable limits. Successful immunotherapy often results in a reduction in medication. Sequential measurement of disease-specific quality of life also might be helpful.

SAFETY OF IMMUNOTHERAPY

Reaction rates

Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Large local reactions associated with allergen immunotherapy are fairly common, with a frequency ranging from 26% to 86% of injections.[179] Two retrospective studies compared the effect of not adjusting immunotherapy dose based on large local reactions on the immunotherapy systemic reaction rate with dose-adjustment protocols.[179,180] There was a total of 12,464 injections administered with a dose-adjustment protocol in the 2 studies compared with 9542 injections administered with a no-dose-adjustment protocol. 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 for subsequent systemic reactions, 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 large local reactions, defined as 25 mm or larger, in patients who had experienced systemic reactions with age-, sex-, and allergen sensitivity–matched control subjects who had not had allergen immunotherapy systemic reactions found the rate of large local reactions was 4 times higher among the 258 patients who had subsequently experienced a systemic reaction compared with those who had never experienced a systemic reaction.[181] Patients who had experienced systemic reactions had 1573 large local reactions in 4460 visits (ie, 35.2% of visits) and 8081 injections (ie, 19.5% of injections) compared with the matched control group without systemic reactions who had 1388 large local reactions in 15,540 visits (8.9% per visit) and 26,259 injections (5.3% per injection; difference between groups, $P < .001$). Individual large local reactions were not predictive of future systemic reactions, but large local reactions preceded systemic reactions in approximately one third of the systemic reactions. These findings suggest that individuals with a greater frequency of large local reactions might be at greater risk for systemic reaction. Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy protocol modifications based on them are needed.

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

The prevalence of severe systemic reactions after allergen immunotherapy ranges from less than 1% of patients receiving conventional immunotherapy to greater than 36% of patients in some studies of patients receiving rush immunotherapy.[182,183]

In a recent survey of fatal and near-fatal reactions (NFRs) sent to physician members of the AAAAI, 273 of 646 respondents reported NFRs during the period of 1990-2001.[184]

The incidence of unconfirmed NFRs was 23 per year (5.4 events per million injections). Administration during the height of 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 angiotensin-converting enzyme 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 systemic reactions to subcutaneous immunotherapy over a 20-year period (1981-2000) during which 435,854 injections were administered to 4000 patients, 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.[185,186] In a prospective multicenter study there were 53 systemic reactions (0.3% of the doses) out of 17,526 administered doses in 18 (3.7%) of 423 patients.[187] 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 (21 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, there were 41 fatalities identified in the initial brief survey (20 directly reported and 17 with completed detailed questionnaire) from immunotherapy injections.[188] 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.[189,190] Therefore although severe systemic reactions to allergen immunotherapy are not common, serious systemic reactions (some fatal) can occur.

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

In the AAAAI survey of physician members on immunotherapy and skin testing, fatal reactions, and NFRs during the period of 1990-2001, 15 of the 17 fatalities had asthma, and in 9 patients asthma was considered the susceptibility factor that contributed to the fatal outcome.[188]

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.[184]

Administration during the peak pollen season (3 patients) and previous systemic reactions (4 patients) were cited as other contributing factors. Five fatalities occurred in outside medical facilities, and 2 fatalities occurred at home. No patients were receiving β-blockers; 1 patient was taking an angiotensin-converting enzyme inhibitor. In the most comprehensive evaluation of fatalities associated with allergen immunotherapy, from 1945-1987, there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[189] 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, with 73.3% of patients with an FEV_1 of less than 80% of predicted value experiencing 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 ($P < .0001$).[191] 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% of patients. These studies suggest that symptomatic asthma, severe asthma, or both might be a risk factor for immunotherapy.

In addition to symptomatic asthma and injections giving 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.[17] With the exception of dosing errors and 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 recent 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 or allergy symptom exacerbation, β-blocker use, change in health status (including pregnancy), or adverse reaction to previous allergen immunotherapy injection. The preinjection evaluation might also include a peak flow measurement to assess the airway function of asthmatic patients.

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 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

In a retrospective study the time to onset of a systemic reaction after an immunotherapy injection was less than 30 minutes in most cases.[189] A review of the literature indicates that 70% of systemic reactions occur within 30 minutes after an injection.[183] In the AAAAI 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.[184,188] 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.[190] 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 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.[192] In another prospective study 8% of systemic reactions occurred more than 2 hours after injection.[193]

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.[194]

Because most reactions that resulted from allergen immunotherapy occurred within 30 minutes after an injection, patients should remain in the physician's office for at least 30 minutes after receiving an injection, but longer waits are reasonable, as directed by the physician. In addition, patients who are at increased risk of a systemic reaction might need to carry injectable epinephrine. Such patients might also need to remain in the physician's office more than 30 minutes after an injection. 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.

β-Adrenergic blocking agents

Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

β-Blockade enhances pulmonary, cardiovascular, and dermatologic end-organ effects of mediators and increases mortality associated with experimental anaphylaxis induced by either immunologic or nonimmunologic mechanisms. Patients who are receiving β-adrenergic blocking medications might be at increased risk if they experience a systemic reaction to an allergen immunotherapy injection because the β-receptor blockade might attenuate the response to epinephrine.[195-202] Patients who are receiving β-blocking drugs were almost 9 times more likely to be hospitalized after an anaphylactoid reaction from radiocontrast media.[198] Although topical β-blockers have markedly less systemic β-antagonist effects than oral β-blockers, they still might exhibit some systemic β-antagonist effects. Whether topical β-blockers pose the same or a smaller risk than oral β-blockers in regard to the treatment of allergen immunotherapy–related systemic reactions is not known.

There have been very few studies that have examined the effect of β-blocker medications on allergen immunotherapy. A prospective 1-year study designed to determine whether patients taking β-blocker drugs were at increased risk of immunotherapy-induced systemic reactions found that there were 166 systemic reactions out of 56,105 injection visits in 3178 patients (68 were receiving a β-blocker).[203] The systemic reactions occurred in 144 (4.5%) patients, and only 1 of these patients was receiving a β-blocker medication. The authors calculated that by chance, 3.08 patients receiving the β-blocker medications drugs were expected to have had an systemic reaction and concluded that β-blocker medications did not increase the frequency of allergen immunotherapy systemic reactions ($P > .95$).

In another study of 1389 patients prescribed immunotherapy for Hymenoptera venom hypersensitivity who were followed for 34 months, there were 25 patients who received concomitant β-blocker medications.[204] Three (12%) of the 25 patients receiving β-blocker medications experienced systemic reactions during immunotherapy compared with 23 (16.7%) of 117 patients with cardiovascular disease not receiving β-blockers. Systemic reactions after a field sting or challenge occurred in 1 (14.3%) of 7 cardiovascular patients receiving β-blocker medications compared with 4 (13.8%) of 29 cardiovascular patients not receiving β-blocker medications. No severe reactions to immunotherapy or sting re-exposure were observed in patients receiving β-blockers medications.

Immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. In such cases, intravenous glucagon, which might reverse the refractory bronchospasm and hypotension by activating the adenyl cyclase directing and bypassing the β-adrenergic receptor, might be used if epinephrine has not been effective.[205,206] Prospective studies are necessary to clarify the magnitude of the risk of systemic reactions to allergens in patients who are receiving concomitant therapy with β-blockers, and a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy.

Contraindications

Summary Statement 18: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications

TABLE V. Actions to reduce the risk of anaphylaxis

- Assess the patient's general medical condition at the time of injection (eg, asthma exacerbation).
- Consider obtaining a PEFR before administration of the injection. If the PEFR is significantly less than the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.
- 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 with increased allergen sensitivity or those who have previously had a systemic reaction) might need to wait longer.
- Carefully evaluate any patient with a late reaction (eg, persistent large local reaction lasting >24 hours, systemic reaction occurring more than 30 minutes after the immunotherapy injection).
- 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.

PEFR, Peak expiratory flow rate measurement.

TABLE VI. Recommended equipment and medications to treat anaphylaxis

Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur. This should include at least the following equipment and medications:

- stethoscope and sphygmomanometer;
- tourniquet, syringes, hypodermic needles, and large-bore needles (14-gauge);
- aqueous epinephrine HCL 1:1000 wt/vol;
- equipment to administer oxygen by mask.
- intravenous fluid set-up;
- antihistamine for injection (second-line agents for anaphylaxis, but H_1 and H_2 antihistamines work better together than either one alone);
- corticosteroids for intravenous injection;
- vasopressor;
- equipment to maintain an airway appropriate for the supervising physician's expertise and skill.

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 venom hypersensitivity and cardiac disease being treated with β-blocker medications.

Reducing the risk of anaphylaxis to immunotherapy injections

Summary Statement 19: 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 extremely 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 or other health care professional appropriately trained in emergency treatment.

The 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. Epinephrine is the first-line treatment for anaphylaxis. 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.[12,207-213] It is important to administer epinephrine early in the management of anaphylaxis. 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 V and VI, respectively. Before allergen immunotherapy is chosen as a treatment, the physician should educate the patient about the benefits and risks of immunotherapy, as well as methods for minimizing risks. The patient also should be told that despite appropriate precautions, reactions might occur without warning signs or symptoms. Informed consent should include a discussion of the potential immunotherapy adverse reactions, and this discussion should be documented in the patient's medical record.

PATIENT SELECTION

Clinical indications

Summary Statement 20: Allergen immunotherapy should be considered for patients who have demonstrable

TABLE VII. Clinical indications for allergen immunotherapy

Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or both:
- symptoms of allergic rhinitis after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medications;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medication;
- coexisting allergic rhinitis and asthma;
- possible prevention of asthma in patients with allergic rhinitis

Symptoms of asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medication;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medications;
- coexisting allergic rhinitis and allergic asthma.

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);
- adults and children with a history of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.

evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic rhinitis.[107] Prospective, randomized, double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic asthma.[104,109,111]

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 proper identification and selection of component allergens on the basis of 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 (Table VII). The severity and duration of symptoms should also be considered in assessing the need for specific allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. In addition, specific allergen immunotherapy should be considered if the patient wishes to avoid long-term pharmacotherapy. Time lost from work, emergency department or physician's office visits, and responses to pharmacotherapy are important objective indicators of allergic disease severity.

Patients with allergic rhinitis who are unable to sleep because of symptoms or whose symptoms interfere with their work or school performance should be considered strong candidates for specific allergen immunotherapy. 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 considered. Unacceptable adverse effects of medications should also favor one's decision to initiate allergen immunotherapy. Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.[214]

Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued, and it might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6-9,122,162-165] These benefits of immunotherapy should be discussed with patients and might provide a clinical indication for immunotherapy for individual patients with allergic rhinitis.

Coexisting medical conditions should also be considered in the evaluation of a patient who might be a candidate for allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed with a combined aggressive regimen of allergen avoidance and pharmacotherapy and might also benefit from allergen immunotherapy.[215,216]

However, the patient's asthma must be stable before allergen immunotherapy is administered.[188,191]

Special precautions in patients with asthma

Summary Statement 21: 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 might be at increased risk for systemic reactions to immunotherapy injections.[182,188,191] Two surveys found that deaths from

immunotherapy were more common in symptomatic subjects with asthma.[188,189] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2,217]

Clinical indications for VIT

Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Systemic reactions to Hymenoptera stings, especially when associated with respiratory symptoms, cardiovascular symptoms, or both and positive skin test or *in vitro* test results for specific IgE antibodies, are a strong indication for allergen immunotherapy.[218] In the United States patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Several studies of patients with imported fire ant allergy have demonstrated the effectiveness of immunotherapy with whole-body extracts of fire ants.[155,156,219] 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. Patients younger than 16 years of age who present only with a cutaneous reaction to imported fire ant or Hymenoptera stings might not require immunotherapy.[218,220-222] In addition to allergen immunotherapy, patients with imported fire ant and Hymenoptera venom sensitivity should be instructed in how to best avoid insect stings, be prescribed epinephrine, and be taught how 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 the population that has not had a systemic reaction.[223] In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific IgE is recommended.[218] If the venom-specific IgE test result is also negative, it is recommended that the skin tests, venom-specific 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 IgE test result.[224] 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 re-stung. 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%).[225] 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 IgE test results who have had severe anaphylaxis to an insect sting.

Some patients who have negative venom skin test results and negative venom-specific IgE test results are reported to have had subsequent systemic reactions to stinging insects.[225-227] Controlled studies designed to evaluate the efficacy of immunotherapy in these patients have not been performed. There are very 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.[226] 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.

Summary Statement 23: 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.

ALLERGEN SELECTION AND HANDLING

Allergen selection

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

A careful history, noting environmental exposures and an understanding of the local and regional aerobiology of suspected allergens, such as pollen, fungi (mold), 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 skin or *in vitro* test results for specific IgE antibodies, provide good evidence that such exposures are relevant. Information concerning regional and local aerobiology is available on various Web sites or through the National Allergy Bureau at http://www.aaaai.org/nab. There are

no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma. 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 clinical history of an allergic disease.

There is no evidence to support the administration of immunotherapy based solely on results of specific *in vitro* 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.

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

The omission of clinically relevant allergens from an allergic patient's allergen immunotherapy extract contributes to decreased effectiveness of allergen immunotherapy. The 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 can make allergen immunotherapy less effective.

Knowledge of the total allergenic burden facing a patient and the realistic possibility of avoidance is important in determining whether allergen immunotherapy should be initiated. 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. Many individuals travel extensively for business or pleasure into different regions, and symptoms might worsen at these times. However, inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective. Determination of the significance of indoor allergens for a particular patient is harder because it is difficult to determine exposure in the home, school, and/or workplace. Historical factors, such as the presence of a furry animal in the home, a history of water damage and subsequent fungal exposure, or a history of insect infestation, might be helpful. However, such information is subjective and is often of uncertain reliability. In addition, some studies have demonstrated significant indoor levels of cat and dog allergen in households without pets[228] and significant levels of mouse allergen in suburban[229] and inner-city[230] homes 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 with increased asthma morbidity in inner-city children was found.[231] 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. Nevertheless, for most patients, determination of the clinical relevance of an allergen requires a strong correlation between the patient's history and evidence of allergen-specific IgE antibodies.

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted *in vitro* tests for specific IgE antibodies can also be used. **A**

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 the skin test results have demonstrated the efficacy of immunotherapy for relevant allergens.[25,26,112,130,134,135,140,141,149,154] 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 from skin testing in a highly sensitive individual.[232,233] In addition, skin tests might be difficult to perform in patients with dermatographism or atopic dermatitis. *In vitro* tests are particularly useful in such patients.

Studies indicate that skin testing is generally more sensitive than *in vitro* tests in detecting allergen-specific IgE.[234,235] Based on inhalation challenge test results, skin tests have shown specificity and sensitivity generally superior to those of *in vitro* tests. The comparability of skin tests and *in vitro* tests for specific IgE antibodies depends on the allergen being tested. For all of 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, prick testing is sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass[236] and cat,[237] are used. Intradermal/intracutaneous skin testing might be required for some allergen extracts. It is appropriate in some patients to use *in vitro* tests for specific IgE antibody as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. *In vitro* tests can also be used to define the allergens that should be used in allergen immunotherapy. If the allergy skin test result is negative and the *in vitro* test result is positive, a controlled challenge can be performed, and if the latter is positive, immunotherapy can be considered. 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 *in vitro* test results.

Specific allergens

Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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.[17,104,106,107,109] 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.[112,122] Because a particular pollen extract is a mixture of multiple glycoproteins, this suggests that mixing pollen allergens does not alter biologic activity.

Fungi (molds). Several studies with *Alternaria* and *Cladosporium* species suggest that allergen immunotherapy with fungi might be effective.[133-138] The allergen content of most mold extracts is highly variable.[238,239] However, there is evidence that proteolytic enzymes present in some mold extracts could digest other antigens, such as pollens, when combined in a mixture.[240] For this reason, it might be desirable to separate all pollen extracts from mold extracts when using mixtures.

Unfortunately, extracts for some potentially clinically important fungi are not available.[241] 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 distinguish 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.

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.

Because immunotherapy has been shown to be effective for cat[22,26,139-143,242] and dog,[25,141] the decision to include dog or cat allergen in an allergen immunotherapy extract should be considered in those circumstances in which there is exposure.

Dust mites and cockroach allergens. Crude house dust extract is generally an inappropriate substitute for house dust mite extract because the protein content measured is not restricted to dust mite allergens, nor does it necessarily guarantee inclusion of dust mite protein. Immunotherapy with standardized dust mite is generally more effective than that with crude house dust allergens. The house dust mites *D farinae* and *D 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, such as *Blomia tropicalis* and *Euroglyphus maynei*, partially cross-react with allergens from *Dermatophagoides* species. Only 50% of the projected amounts of each of the 2 house dust mites (*D pteronyssinus* and *D farinae*) need 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[144,147-149,151] 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. Dust mite hypersensitivity should particularly be considered in patients who have perennial symptoms exacerbated by a dusty environment at home, work, or both and periods of high humidity.

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. The major allergen of *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.[243] Immunotherapy with cockroach allergens is effective[154] and should 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.

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.[108,116,244] Efficacy has also been demonstrated with immunotherapy by using whole-body extracts of imported fire ants.[155,156]

Foods. Only a single clinical study accessing the efficacy and safety of subcutaneous immunotherapy with foods has been performed.[171,173] This study, which evaluated immunotherapy with peanut, found the incidence of systemic reactions, even during maintenance, was unacceptable. Thus there is no evidence to support the use of immunotherapy with food extracts. Currently, strict avoidance of the offending food is advisable, and subcutaneous immunotherapy for food allergy is not recommended.

Mixing of extracts

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Once the relevant allergens for each patient are identified, it is necessary to prepare a mixture that contains each of these allergens. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts. A number of 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 interactions between different types of allergens, when mixed, that could lead to degradation or unmasking of epitopes on exposure to proteolytic enzymes.

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Immunologic and 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.[71] 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 genera 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 the Allergen extract section, Fig 2, and the allergens and allergy diagnostic tests practice parameters).

Dose selection. Summary Statement 30: 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.[22-26,128,149,245] Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000 vol/vol).[28] A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy vaccine. Failure to do so might reduce the efficacy of immunotherapy. This occurs because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased (see the Immunotherapy schedules and doses section for further discussion and for recommended maintenance doses).

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as fungi (mold) and cockroach, from other extracts, such as pollens, is recommended. **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.[240,246,247] 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, and some weeds.[240,246,247] Cockroach had a similar deleterious effect on pollen extract potency.[246,248] Short ragweed appeared resistant to the effects of the proteolytic enzymes in one study,[240] 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.[247]

Dust mite extracts do not appear to have a deleterious effect on pollen extracts.[240,246,248] These studies suggest that pollen, dust mite, and cat extracts can be mixed together. 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. The evidence on mixing cockroach extract with other extracts is conflicting, and the clinical relevance of the changes is also unclear; therefore the clinician has the option of separating cockroach or not.

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 with lesser activities, such as pollen extracts.

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.

In this regard the number of separate injections that need to be given at each patient visit depends on whether all of the relevant extracts mixed into a single vial still deliver an optimal dose of each allergen. If mixing causes excessive dilution or if there are advantages to separating allergens into separate vials, then more than one vial might be necessary for successful immunotherapy.

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extracts are high-alert products that carry the risk for anaphylaxis. Policies, procedures, and processes intended for conventional drugs and medications might be highly 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 fatal anaphylactic reactions with allergenic products. 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. There are no reports of infection associated with allergen immunotherapy injections. Allergen vaccines are prepared by using sterile manufacturer's extracts and sterile diluents containing antibacterial constituents (usually phenol). A summary of the AAAAI/ACAAI/JCAAI proposed USP allergen immunotherapy extract preparation guidelines can be found in Table VIII.

TABLE VIII. AAAAI/ACAAI/JCAAI-proposed USP 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 below.*
   - 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.
2. **Physician responsibility**: A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in the preparation of immunotherapy using an aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files.
3. **Bacteriostasis**: Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if 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 the FDA-approved package insert 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 treatment with sanitizing agents containing alcohol and/or 70% isopropanol 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 the physical integrity of the vial.
10. **Labeling**: Immunotherapy vials are to be clearly labeled with the patient's name and 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.

*__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 media, such as from Valiteq (http://www.valiteq.com), 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.

Allergen immunotherapy extract handling

Storage. Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

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 a number of 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 extract, including reconstituted lyophilized extracts, should be stored at 4°C to minimize the rate of potency loss because storage at higher temperatures (eg, room temperature) can result in rapid deterioration.[249]

Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions (personal communication). These studies include actual shipments made by their carriers to places like

Phoenix in the summer and Alaska in the winter. 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.

Storing dilute extracts. Summary Statement 34a: More dilute concentrations of allergy immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than do more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: In determining the allergy vaccine expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of 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 allergen immunotherapy 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.[249,250]

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.[250] Phenol is a preservative added to extracts to prevent growth of microorganisms.

Phenol can denature proteins in allergen extracts.[251,252] Human serum albumin might protect against the deleterious effect of phenol on allergen extracts.[251] 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,[250,253] possibly through inhibition of the activity of proteolytic and glycosidic enzymes that are present in certain extracts. However, it is irritating when injected and should be diluted before beginning immunotherapy. Recommendations for extract stability are found in the manufacturers' product insert sheets. 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. The pain associated with glycerin increases in proportion to the glycerin concentration and injection volume, and the pain is proportional to the total injected dose of glycerin.[254] However, individual pain perception can vary substantially. Total glycerin doses of less than 0.05 mL rarely produce clinically important pain.

TABLE IX. Potency of selected manufacturer's extracts currently available

Extract	Potency
Cat hair and pelt	5000 and 10,000 BAU/mL
Dust mite	3000, 5000, 10,000, and 30,000 AU/mL
Bermuda grass	10,000 AU/mL
Short ragweed	1:10-1:20 wt/vol or 100,000 AU/mL
Other grasses*	10,000 and 100,000 BAU/mL
Other pollen	1:10 to 1:40 (wt/vol) or 10,000 PNU/mL
Molds	1:10 to 1:40 (wt/vol) or 20,000 to 100,000 PNU/mL

AU, Allergy unit; *BAU*, bioequivalent allergy unit; *PNU*, protein nitrogen unit.
*Perennial rye, Kentucky blue/June, timothy, sweet vernal, redtop, orchard, and meadow.

There have been few studies that have investigated the potency of dilutions of allergen extract mixture over time. Expiration dates for allergen extract dilutions are somewhat empiric and not strongly evidence based. A study undertaken by the AAAAI 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. Dust mite and cat at 1:10 and 1:100 vol/vol dilution were also stable in all conditions of storage over 12 months, as measured by an ELISA assay using 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.

IMMUNOTHERAPY SCHEDULES AND DOSES

Summary Statement 35: A customized individual 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 can be based on single or multiple allergens. **D**

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. Animal dander contains between 10 and 20 antigens,[255] house dust mites between 20 and 40 antigens,[256] and pollens between 30 and 50 antigens,[257,258] and fungal extract can contain as many as 80 antigens.[259]

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. This is designated as the patient's maintenance concentrate.

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. Standardized extracts are available with biologic potencies of 10,000 and 100,000 BAU for grasses; 5000 and 10,000 BAU for cat allergen; 5000, 10,000, or 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 wt/vol extracts (Table IX). 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.

Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

The highest concentration of an allergen extract mixture that is projected to be used as the therapeutically effective dose is called the maintenance concentrate. This should be prescribed individually for each patient by an allergist/immunologist. 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 individual manufacturer's extracts. Some patients might be unable to attain the projected therapeutically effective dose of the maintenance concentrate because of local reactions, systemic reactions, or both (eg, cat, 1000 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose]; see Table X for probable effective therapeutic dose range). Such patients might need weaker dilutions of their maintenance concentrate. Even so, 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 referred to as the maintenance dose. The consistent use of this nomenclature system is essential because errors in choosing the correct vial are a common cause of systemic reactions, especially when the patient transfers from one physician to another. Therefore it is important that standard terminology be adopted by all physicians who prescribe allergen immunotherapy.

Recommended doses

Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

The effective maintenance dose of immunotherapy for a particular patient must be individualized. To do this, the allergist/immunologist who prepares the allergen immunotherapy extract must balance the dose necessary to produce efficacy and the risk of reactions if such a dose is reached. The allergist/immunologist might need to prepare more than one maintenance concentrate to provide a therapeutic dose of each of the allergens for the polysensitized patient. Therapeutically effective doses for immunotherapy have been reported for some allergen extracts.[22,24,25,128,134,135,149,246,260,261] Effective doses have been determined for Hymenoptera venom, dust mite, cat allergen, dog, grass, and short ragweed (Table X).

Controlled studies demonstrate that the content of particular allergens in allergen immunotherapy extracts can be used to predict a therapeutic dose for those allergens, particularly when the extracts are standardized. For antigens 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. The therapeutically effective doses used in the most recent controlled clinical studies are the basis of the recommended dosage range of standardized extracts presented in Table X. 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 time that it is administered.[14]

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.[27] 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 risk of systemic reactions to immunotherapy injections with higher maintenance doses. The maintenance concentrate should be formulated to deliver a full therapeutic dose of each of its constituent components. However, some sensitive patients might not tolerate the targeted therapeutic dose, and their maintenance dose would be lower. Individuals 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 referred to as the maintenance dose.

Regardless of dose schedule, some patients are unable to progress to the predetermined maintenance dose because of large local or systemic reactions to the allergen

TABLE X. Probable effective dose range for allergen extracts US standardized units[a]

Antigen	Labeled potency or concentration[a,b]	Probable effective dose range
Dust mites: *D farinae* and *D pteronyssinus*[c]	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat[d]	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized[e]	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed[f]	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 μg of Amb a 1 1000-4000 AU Concentration of Amb a 1 is on the label of wt/vol extracts in FDA units[358]
Nonstandardized extract, dog[g]	1:10 to 1:100 wt/vol	15 μg of Can f 1
Nonstandardized extracts	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose

[a]Multiple studies have demonstrated that the efficacious dose for allergen immunotherapy is between 5 and 20 μg of the major allergen per injection. Only 2 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).

[b]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).

[c]There have been no dose-response studies with United States–licensed dust mite extracts, and dosing recommendations in AU value are extrapolated from published European studies that used aqueous[349] and alum-precipitated[149,151] extracts. 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.[149] The authors suggested the optimal maintenance dose was 7 μg of Der p 1. Corresponding doses were based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Extrapolating effective and safe doses in this manner might not be scientifically valid. *D farinae* and *D pteronyssinus* are similar in group 1 allergen content according to the FDA's current reference standards. 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*.

[d]The major cat allergen Fed d 1 is reported in FDA units, with 1 Fel d 1 unit equaling approximately 2 to 4 μg of Fel d 1.[55,58,59] The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 to 19.9 U/mL. One study demonstrated clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 dose in terms of decreased cat extract PD_{20}, titrated skin test results, and allergen-specific IgE and IgG levels.[350,351] In a recent study that investigated the efficacy in terms of immunologic changes of 3 doses of a United States–licensed cat extract (0.6, 3, and 15 μg) demonstrated that a significant effect on titrated skin prick test results, allergen-specific IgG4 levels, and $CD4^+$/IL-4 levels was only seen in the group treated with 15 μg of Fel d 1, although the 3-μg dose group did demonstrate a significant change in titrated skin test response and increase in cat-specific IgG4 levels.[22]

[e]There have been no dose-response studies with United States–licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,[130] alum-precipitated,[24,161] and calcium phosphate–precipitated grass pollen extracts.[352] One of these studies compared a dose of 2 μg with 20 μg of major timothy allergen (Phl p 5) and found clinical efficacy at both doses.[24] The efficacy was greater in the 20 μg of Phl p 5 dose, but the systemic reaction rate was also higher in the high-dose group. The package inserts for United States–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 BAU. Extrapolating effective and safe doses in this manner might not be scientifically valid. 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).

[f]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 suggested that 1 unit of Amb a 1 is equivalent to 1 μg of Amb a 1, and 350 Amb a 1 units/mL is equivalent to 100,000 BAU/mL.[60] The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2000 AU, with a range of 1000-4000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrated 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.[45] A ragweed dose-response study (0.6, 12.4, and 24.8 μg of Amb a 1) demonstrated efficacy, as measured by nasal challenge, at 12 and 24 μg of Amb a 1.[128] The efficacy of the 24-μg dose was not significantly better than the 12-μg dose, and the authors concluded that the optimal dose for ragweed extract was greater than 0.6 μg but not more than 12.4 μg of Amb a 1.

[g]Dog extracts are not standardized. However, one dose-response study with a United States–licensed acetone-precipitated dog extract investigated the efficacy of 3 doses (AP dog; Hollister-Stier, Spokane, Wash; 0.6, 3, and 15 μg) in terms of immunologic changes and found the dose of 15 μg of Can f 1 to be most efficacious.[25] 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 have assayed between 128 and 208 μg/mL (average Can f 1, 162 μg/mL [SD ± 26 μg/mL]; information provided by the extract manufacturer, Hollister-Stier).

immunotherapy extract. The evidence is not clear whether large local reactions are a potential risk for subsequent allergen immunotherapy systemic reactions.

Published studies do not indicate that an individual large local reaction is predictive of a subsequent systemic reaction.[179,180] However, one retrospective study found that individuals who have a history of repeated large local reactions (defined as >25 mm) might be at greater risk for a subsequent systemic reaction.[181]

The concept of highest tolerated dose does not apply for VIT, and all patients are expected to achieve the full recommended dose to achieve the necessary degree of protection. There are conflicting data over whether lower doses (50 μg) are less effective, but there are also data showing that 200 μg is more reliably effective.[245] In the case of VIT, patients are asked to tolerate more large local reactions to achieve the full dose, even though with inhalant immunotherapy the dose can be reduced for such large local reactions to minimize patient discomfort.

Effect of dilution on dose

Summary Statement 38: 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 vaccine, thereby limiting the ability to deliver a therapeutic effective dose for any given allergen.

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

Dilution from maintenance concentrate vaccine	Volume	Volume (mL)	Diluent volume (mL)	Final volume
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.

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 2000 BAU/mL, 2 mL of the manufacturer's extract (cat, 10,000 BAU/mL) can be added to 8 mL of diluent or 8 mL of other allergens, and the final concentration of cat will be 2000 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.

Dilutions of the maintenance concentrate

Summary Statement 39: 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 vol/vol 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, 1000 BAU or 100 BAU), but this system can be complicated if allergens with different potency units are used (eg, wt/vol, BAU, AU, or PNU) and make it difficult to easily interpret the vial label.

Instructions on how to prepare various allergen extracts 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.

Labeling dilutions

Summary Statement 40: 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, a number of 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 (vol/vol), a numbering system, a color-coding system, or an alphabetical system should be used. If this uniform labels 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.

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
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

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 3 and 4).

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 Appendix 2]).

Individualized treatment vials

Summary Statement 41: 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 (wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for 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). Labels on patient-specific vials can provide at least 2 patient identifiers (birth date and patient name), which would be consistent with the recommendations of the Joint Commission on Accreditation of Health Care Organizations National Patient Safety Goals: ''Goal 1: Improve the accuracy of patient identification by using at least two patient identifiers when providing care, treatment or services.''[5] 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 administration of the injection.[4,5]

In a survey of 1717 allergists endorsed by the AAAAI and JCAAI, 57% of the 476 respondents reported at least one wrong-patient injection, and 74% of the 473 respondents reported at least one wrong-dose injection.[4] 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 reasons why this might reduce incorrect injection errors. One reason was that patient-specific vials can be prepared in a quiet laboratory setting, which might provide substantially less distraction than the nurse in a room with a patient who is trying to concentrate only on drawing up the injection correctly. In addition, the specific components are mixed once with the preparation of individually prepared patient-labeled vials, whereas the mixing would be repeated on every injection visit if the allergen extract is withdrawn from different stock solutions, as it is in the off-the-board method. For safety reasons and to avoid cross-mixing of allergens removed from the manufacturer's extract, the mixing of antigens in the syringe (off the board) is not recommended.

Some allergists/immunologists prefer to administer immunotherapy doses drawn directly from a single stock dilution of individual allergens or common mixes (shared specific patient vials). In this way the immunotherapy dose is transferred to the patient without cross-contamination. If shared-patient (eg, mixed vespids and dust mite mix) vials are used, it is essential that policies and procedures are developed to verify that the correct dose from the correct vial is administered to the correct patient.

Starting doses

Summary Statement 42: The starting dose for build-up is usually a 1000- 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 slowly 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 1:1000 (vol/vol), although more diluted concentrations frequently are used for patients who are highly sensitive, as indicated by history or skin test reaction (see Appendix 3 for an example of a conventional immunotherapy schedule).

Frequency of build-up injections

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 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 2 times per week. 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 4 to 6 months, depending on the starting dilution and the occurrence of reactions. It is acceptable for patients to receive injections more frequently, provided there is adequate spacing between injections. The interval between injections is empiric but might be as short as 1 day without any increase in the occurrence of systemic reactions[262] if there is some urgency to achieve a maintenance dose (eg, allergy season is approaching) or for practical reasons (eg, patient's schedule). Alternatively, treatment schedules can be used that more rapidly achieve maintenance dosing. These cluster and rush dosing schedules are discussed in Summary Statements 47 through 49.

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 a number of 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).

Dose adjustments for systemic reactions

Summary Statement 44: 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 benefit/risk ratio justifies continuation of immunotherapy.

Reductions during periods of exacerbation of symptoms

Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Immunotherapy administered during periods of exacerbation of symptoms is considered a risk factor for immunotherapy.[17,184] Injections administered during periods when a patient is exposed to increased levels of allergen to which they are 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.[184] 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 sensitive, especially if their symptoms are poorly controlled.

Dose adjustments for late injections

Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

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 depends 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 Appendix 4 for an example of a dose-modification regimen for gaps in treatment).

Cluster schedules

Summary Statement 47: 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 (see Appendix 5).[22,26] 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. The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules.[145,263-266] The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.[267]

Rush schedules

Summary Statement 48: 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.[268] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.[191,269-272]

The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections over the course of 4 hours.[273] Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours.[274-276] 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 cluster[145,266] and rush[134,277] schedules.

Systemic reactions and rush schedules

Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

The advantages of rush immunotherapy come at a cost because there is an increased risk of local and systemic reactions. Systemic reaction rates have been reported to be

as high as 73% of patients, with the risk of such reactions reduced to 27% by premedication in one study.[272] Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing.[273]

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

Rush protocols for administration of Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions.[274-276,278,279]

Premedication and weekly immunotherapy

Summary Statement 50: Premedication can reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

There is concern that antihistamines taken before each injection with conventional immunotherapy might mask a minor reaction that would otherwise alert a physician to an impending systemic reaction. 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.[280] One study that compared terfenadine premedication with placebo premedication during rush VIT demonstrated greater clinical efficacy in the terfenadine-premedicated group in terms of subsequent responses to field stings or sting challenge.[281] There was also a significant difference in the systemic reaction rate between the 2 groups: 6 patients in the placebo-premedicated group had systemic reactions, whereas none of the patients in the terfenadine-premedicated group had systemic reactions ($P = .012$).

Unfortunately, patients might still have life-threatening anaphylaxis despite 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.

Premedication with cluster and rush immunotherapy

Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

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.[267] Premedication with a 3-day course of prednisone, an H_1 histamine receptor antagonist, and an H_2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.[272] In one study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on the safety and efficacy of rush immunotherapy, there was a 5-fold decrease in the risk of anaphylaxis in the group premedicated with omalizumab compared with the placebo premedication group.[282]

There are anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist, but there have been no published studies. Because the risk of a systemic reaction from rush VIT is relatively low, routine premedication before rush VIT is usually unnecessary.[274,276,278,279] In a study evaluating premedication with antihistamines and steroids for rush immunotherapy with imported fire ant venom, there was no statistically significant differences in the systemic reaction rates between the premedication and placebo premedication group (3.6% of the premedication group vs 6.7% of the placebo group, $P = .87$).[157]

Maintenance schedules

Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals 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 individuals might tolerate longer intervals between maintenance dose injections.

The interval between venom injections can be safely increased up to 8 weeks in some patients without loss of efficacy. 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.

Continuing care

Time course of improvement. Summary Statement 53: Clinical 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.[24,134,143,277] Improvement might not be observed for a number of reasons, including (1) failure to remove significant allergenic exposures (eg, a cat), (2) exposure to high levels of

allergen (eg, pollen or molds), (3) continued exposure to nonallergen triggers (eg, tobacco smoke), or (4) incomplete identification and treatment of clinically relevant allergens. 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 54: 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 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 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

The patient's response to immunotherapy should be evaluated on a regular basis. 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. 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.

There have been very 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 individuals.[283-285] However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported.[283,285] Nevertheless, systemic reactions to stings after discontinuing VIT were generally much milder than the pretreatment reactions and were rarely severe. Two studies did not find a difference in relapse rates between the patients treated for 3 years compared with those treated for 5 years,[283,286] but one of the studies noted that the small number of patients in the 3-year treatment group prevented them from making any conclusions about the risk of discontinuing treatment after 3 years.[283] However, one study found that patients who had experienced re-sting reactions after discontinuing VIT had received VIT for a significantly shorter duration (mean, 43.35 months) than those with continued protection (mean, 54.65 months; $P < .01$).[285] Another study reported that 5 years of VIT provided better immunologic and clinical outcomes than 2 to 4 years of treatment.[287]

Change in skin test reactivity did not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who experienced a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE.[286,288] Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment.[288] The relapse rate and the frequency of severe reactions were greater in patients who had a history of very severe reactions to stings before treatment, in patients who had systemic reactions during VIT (to a sting or a venom injection), in patients with honeybee allergy, and in those who had less than 5 years of treatment.

The duration of inhalant allergen immunotherapy efficacy has not been as extensively studied. Some studies have suggested 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 *(D pteronyssinus)* extract for 12 to 96 months.[14] 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.[13] There was a switch to placebo in half of 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. These studies demonstrate the uncertainty of the long-term benefit of inhalant immunotherapy after discontinuation.

Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained clinical remission after discontinuing inhalant immunotherapy, and 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 indication for continuation of immunotherapy can be found at http://www.aaaai.org or http://www.jcaai.org.

Documentation and record keeping. Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully 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 allergy immunotherapy and prescription forms can be found in the Appendix (Appendices 6-15), and these include examples of immunotherapy prescription and administration forms. These forms, along with examples of immunotherapy consent and instruction forms, can also be found at http://www.aaaai.org.

Injection techniques. Summary Statement 57: Allergen immunotherapy extract injections should be given using a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **C**

Immunotherapy should be given with a 26- to 27-gauge syringe with a half-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.[289-291]

If using shared specific patient vials (stock vials, such as mixed vespid or dust mite mix), a single dose should be drawn from each vial. Antigens from different vials should not be combined in a single syringe. Furthermore, extra care is needed to prevent using the wrong stock antigen.

Summary Statement 58: The injection should be given subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Each immunotherapy injection should be given in the posterior portion of the middle third of the upper 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.

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.

The syringe should be aspirated to check for blood return in the syringe before injecting. If blood is present, 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 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 syringe should be appropriately discarded. A fresh syringe and needle are necessary to determine whether a blood vessel has been entered.

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 could result in a local reaction.

LOCATION OF ALLERGEN IMMUNOTHERAPY ADMINISTRATION

Physician's office

Summary Statement 59: 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 to treat anaphylaxis should be in the immediate vicinity when immunotherapy injections are administered.

Summary Statement 60: 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.[292] 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.[184] 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 might be frequently necessary in the patient's immunotherapy schedule, as well as the patients total treatment program.

Other locations

Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **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.[292] The health care professional and staff 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, or allergy/asthma exacerbations at the time of allergen immunotherapy extract injection or poorly controlled asthma).

Appropriate adjustment of dose should be made as clinically indicated. The physician who prepared the patient's allergen immunotherapy extract should provide adequately labeled allergen immunotherapy extract vials, detailed directions regarding dosage schedule for build-up and maintenance, and instructions on adjustments that might be necessary under the following circumstances:

1. when providing patients with new vials;
2. during seasonal exposure to allergens that are in the patient's allergen vaccine, to which the patient is very sensitive, or both;
3. if the patient has missed injections; and
4. when reactions occur to the allergen immunotherapy extract.

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

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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 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 very 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 fully trained to administer the injection and to treat anaphylaxis if this should 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 supports (personnel, medications, supplies, and equipment) are more optimal for encouraging prompt recognition and treatment of anaphylaxis (Table V). 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.

Summary Statement 63: If a patient on 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for their immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extracts might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Patients often 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 brought from the previous physician (ie, an unchanged immunotherapy program) or one to be prepared by the current physician (ie, a new immunotherapy program).

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 full, clear, and detailed documentation of the patient's previous schedule and the contents of the allergen immunotherapy extract (see Appendices 7, 8, 11, 12, and 14 for examples of allergen immunotherapy prescription and administration forms and documentation guidelines for allergen immunotherapy forms). In addition, the patient's previous response to and compliance with this program 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 a schedule and the allergen immunotherapy extract, (2) the patient has shown significant improvement on this immunotherapy program, and (3) the contents of the allergen immunotherapy extract are appropriate for the area in which the patient is now living.

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, vaccine type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient's dose is not modified. This increased risk is due to the significant variability in content and potency of extracts and the variability in methods used by physicians to prepare the patient's maintenance concentrate and its dilutions. For example, the strength of a given concentration of nonstandardized extracts might vary significantly from vial to vial. The risk of systemic reactions in such a situation might be greater with nonstandardized extracts and allergen immunotherapy extracts that contain mixtures of allergens.

Therefore if the allergen immunotherapy extract is to be changed, the patient might need to be retested for specific IgE to the appropriate allergens 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 provided the interval of time since the last injection has not been too long. For lot changes from the same manufacturer, the physician can consider decreasing the dose by 50% to 90%. For changes in manufacturer and nonstandardized extracts, a greater decrease in dose might be necessary.

SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

Allergen immunotherapy in children

Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children

with allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Immunotherapy for children has been shown to be effective and often well tolerated,[137,242] although at least one study did not show efficacy.[293] 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.[294] In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (see the Patient selection section and Table VII). In recent studies children receiving allergen immunotherapy have demonstrated:

1. improvement in symptom control for asthma[117,119,121,122] and allergic rhinitis[118];
2. increased PC_{20} to histamine[121];
3. increased PC_{20} to cat and house dust mite allergens[121,149];
4. decreased risk of development of asthma[6,9,163-165];
5. decreased development of new sensitivities[120,166]; and
6. modification in release of mediators in children receiving immunotherapy that correlates with decreased clinical symptoms.[123]

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Although there is some disagreement about the role of allergen immunotherapy in children under the age of 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.[117,122] In children with allergic rhinitis, allergen immunotherapy might prevent the development of asthma.[6,9,163-165] However, allergen immunotherapy for inhalant allergens is usually not considered necessary in infants and toddlers because (1) there is 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 in pregnancy

Summary Statement 71: Allergen immunotherapy might be continued but is usually not initiated in the pregnant patient. **C**

The physician must be aware of the benefits and risks of immunotherapy in pregnant patients. The recommended precautions for prevention of adverse reactions are especially important in the pregnant patient. Allergen immunotherapy is effective in the pregnant patient. Thus allergen immunotherapy maintenance doses can be continued during pregnancy. Allergen immunotherapy is usually not initiated during pregnancy because of risks associated with systemic reactions and their treatment (ie, spontaneous abortion, premature labor, or fetal hypoxia). 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, and the patient is maintained on the dose that she is receiving at that time.

Immunotherapy in the elderly patient

Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy might be considered in the treatment of the elderly patient, but the benefit/risk assessment must be evaluated carefully in this population. Older 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. However, elderly patients may also benefit from allergen immunotherapy and age alone should not preclude the consideration of allergen immunotherapy.[295]

Immunotherapy in patients with immunodeficiency and autoimmune disorders

Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with immunodeficiency or autoimmune disorders. Therefore the decision to begin immunotherapy in patients with major humoral or cellular immune defects must be individualized. Concern about the increased risk of immunotherapy in such patients is largely hypothetical.

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

ALTERNATIVE ROUTES OF IMMUNOTHERAPY

Sublingual and oral immunotherapy

Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be

effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no FDA-approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **B**

Alternative routes of administration of allergen immunotherapy are ''a viable alternative to parenteral injection therapy'' in some cases.[106,296] Studies of oral immunotherapy have provided conflicting results for ragweed,[297] birch,[298] and cat[299] immunotherapy. The present dosage of oral immunotherapy extract is 20 to 200 times the parenteral injected dosage, which requires a cost assessment for this type of therapy. Furthermore, adverse effects have included gastrointestinal and oral reactions (50% in 1 study) that might preclude home therapy. Oral immunotherapy should be considered investigational at this time.

Optimal-dose (high-dose) sublingual swallow immunotherapy is effective in adults and children.[300-304] In a study of 855 patients with grass pollen allergy and allergic rhinitis randomized to placebo or one of 3 grass tablet doses, there was a significant reduction in symptom and medication scores in the highest-dose subgroup, who were treated for at least 8 weeks before the grass pollen season, compared with the placebo group (symptoms, 21%, $P = .0020$; medication use, 29%, $P = .0120$).[303]

Sublingual allergen studies have evaluated house dust, olive pollen, grass pollen, ragweed, birch, cat, latex, *Alternaria* species, and *Parietaria judaica*.[305-313] Sublingual immunotherapy has been shown to be effective in patients sensitized to 2 non–cross-reacting allergens, grass and birch.[314] It has been noted that the allergen is not degraded by saliva and that there is no direct sublingual absorption of allergen. Radiolabeled allergen has been detected after 48 hours in the sublingual region.[315,316] Alternative protocols, such as rush and ultra-rush (20 minutes) sublingual swallow[307,316,318] and no induction (build-up) phase,[301,303,317,319,320] have been studied. Several studies have suggested a relationship between dose and efficacy with sublingual immunotherapy,[303,310,321] but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. The majority of sublingual studies have demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both, but approximately 35% of the randomized, double-blind, placebo-controlled studies did not demonstrate efficacy in either parameter during the first year of treatment.[322] Further studies are needed to confirm the optimal dose for sublingual immunotherapy.

One of the potential advantages of sublingual immunotherapy is that it appears to be safe, even at very high doses (up to 500 times the usual monthly subcutaneous dose), and to be associated with a lower incidence of serious side effects.[310,320,323] This appears to apply to young children (<5 years), for whom there are prospective safety data[324,325] and a postmarketing survey.[326]



FIG 3. Sample of labels for allergen immunotherapy extract vials.

There have been no SLIT-related fatalities, but there have been 3 case reports of anaphylaxis caused by sublingual immunotherapy. One patient with latex hypersensitivity had anaphylactic shock 20 minutes after reaching the maximal dose on the fourth day of latex rush sublingual rush immunotherapy.[327]

The other 2 reported cases of SLIT anaphylaxis involved patients treated with multiple inhalant allergens. In one case a patient with allergic rhinitis and asthma who was prescribed a sublingual immunotherapy extract composed of multiple non–cross-reacting allergens (*Alternaria* species, dog, cat, ragweed mix, weed mix, and grass mix)[328] had generalized pruritis, followed by angioedema, shortness of breath, and dizziness, within a few minutes of administering 6 drops of the 1:100 vol/vol dilution on the third day of treatment. This episode was preceded by a milder systemic reaction the previous day (generalized pruritis). In the other case, a 13-year-old girl with allergic rhinitis and asthma had swelling of her lower lip 3 minutes after pollen drops, high fever, chest pain, nausea, and abdominal pain.[329] She was treated in the emergency department for anaphylaxis and hospitalized for observation. The reaction occurred 1 month after she had reached the maintenance dose during the peak of the spring season.

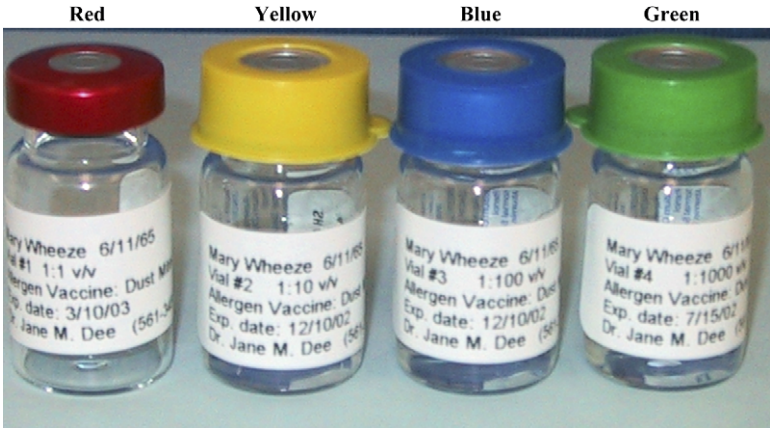


FIG 4. Sample set of color-coded vials of allergen vaccine.

There is currently no FDA-approved formulation for sublingual immunotherapy in the United States at this time, and this modality should be considered investigational. Current investigation of sublingual immunotherapy should not be confused with low-dose sublingual immunotherapy based on provocation neutralization testing or Rinkel-type skin testing.

Intranasal immunotherapy

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Based on controlled, well-designed studies, intranasal immunotherapy has been shown to improve the nasal symptoms of rhinitis.[330] Intranasal dry powder extract immunotherapy has been studied in grass,[330] birch,[331] *P judaica*,[332-334] and house dust mite[335] allergy. Clinical efficacy was noted in all of these studies. Nasal reactivity to allergen challenge was reduced, and only minor side effects were noted in 2 of the above studies. A 3-year study with *P judaica* reported to provide persistent benefits for up to 12 months after conclusion of allergen immunotherapy.[333] Local administration of nasal allergen in an aqueous solution for immunotherapy might be limited by the local side effects. Further studies in both pediatric and adult groups are needed. In human studies the antigen has been noted to appear in the serum within 15 to 30 minutes of administration, with a peak level occurring within 2 to 3 hours.[315] Some allergens have been reported to be retained in the nasal mucosa for up to 48 hours after administration. Intranasal immunotherapy is not currently available in the United States but has gained some acceptance in other parts of the world.

Immunotherapy techniques that are not recommended

Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

Low-dose regimens, including coseasonal low-dose immunotherapy for aeroallergens and the Rinkel low-dose titration techniques, are not effective.[27,28] Immunotherapy based on provocation–neutralization testing with food and aeroallergens and enzyme-potentiated desensitization is not effective.[336]

FUTURE TRENDS IN IMMUNOTHERAPY

Therapy with aeroallergen extracts will become more uniform (as is the current practice for insect venoms) as greater numbers of biologically standardized allergen extracts become available. The actual number of commercially available allergen extracts will be reduced based on consensus agreements about the regional prevalence of aeroallergens, their cross-allergenicity, and the relevance of their effect on human health in specific locales. Novel routes for more effective, convenient, and safer allergen immunotherapy are being investigated throughout the world.

For example, the sublingual route of administering allergen immunotherapy has been studied extensively in Europe. A meta-analysis confirmed its clinical effectiveness in allergic rhinitis,[302] and it has been reported to be effective in asthma as well.[337] Sublingual immunotherapy appears to have a very low risk of serious life-threatening systemic side effects, which might allow for home administration.[324,338] In some studies the clinical benefits of sublingual immunotherapy were not significant until the second year of treatment,[306,339] and comparisons suggest that the magnitude of the clinical benefit of sublingual immunotherapy might not be as great as that of subcutaneous immunotherapy.[311]

Trials with non–IgE-binding peptides containing T-cell stimulating peptides have been reported.[340] Site-directed mutagenesis has produced allergens with decreased IgE-binding capacity without decreased T-cell responses.[341,342]

Immunostimulatory sequences mimicking bacterial and viral DNA have been prepared that stimulate the innate immune system to direct T-cell responses toward

T_H1 rather than T_H2 phenotypes.[343] The results of clinical trials with a conjugate of the immunostimulatory sequence to the major allergen of ragweed, Amb a 1 (AIC), have been reported.[34,343] In a double-blind, placebo-controlled study of 25 adults who received 6 weekly injections of the AIC or placebo vaccine before ragweed season, the AIC group had better peak-season rhinitis scores on the visual analog scale ($P = .006$), peak-season daily nasal symptom diary scores ($P = .02$), and midseason overall quality-of-life scores ($P = .05$) than the placebo group during the first ragweed season, and this effect was observed in the subsequent ragweed season.[344]

Humanized anti-IgE mAb has been shown to have clinical effects in both allergic rhinitis and asthma.[345-348] Theoretically, this new therapeutic modality could be used as protective cover for clinical applications of rapid forms of immunotherapy. It is possible that preadministration of anti-IgE could provide a more effective protective effect than premedication with antihistamines and therefore permit a rush allergen immunotherapeutic regimen with reduced risk of serious systemic reactions.[282]

AUTHOR'S 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 2 systemic reaction grading systems (the European Academy of Allergy and Clinical Immunology's grading of severity for systemic side effects and the Portnoy method for numeric grading of reactions to allergen immunotherapy) can be found in the Appendix section. These forms can also be found along with examples of immunotherapy instruction and consent forms, preinjection health questionnaires, and indications for beginning and continuing immunotherapy forms at www.aaaai.org.

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352. Leynadier F, Banoun L, Dollois B, Terrier P, Epstein M, Guinnepain MT, 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.

APPENDIX 1. American College of Medical Quality's policy on the development and use of practice parameters for medical quality decision-making[1]

Practice parameters are strategies for patient management developed to assist health care professionals in clinical decision making. Practice parameters include standards, guidelines, and other patient management strategies. Standards are accepted principles for patient management. Guidelines are recommendations for patient management that identify a particular management strategy or a range of management strategies. Other strategies for patient management include practice policies and practice options. Practice parameters are to be used as screening tools to identify possible deviations from the applicable standards of care. Such parameters are not to be used as absolute standards or to profile or report on health care personnel. Parameters are designed to trigger a process in which possible deviations from the standard of care are identified as outlier practice patterns. Once a deviation from the parameter is identified, such a deviation should be referred to the appropriate qualified physician advisor or reviewer for a determination of medical necessity that conforms to the applicable standard of care. Parameters used in the day-to-day practice of clinical medicine should be clinically relevant. They should not be considered as substitutes for the standard of care but might contribute to its formulation.

Practice parameters must be developed, designed, and implemented only by board-certified, clinically practicing, specialty-matched physician advisors/reviewers with unrestricted medical licenses. Qualified nonphysicians might participate in the development of these parameters only in the areas in which their clinical expertise based on the standard of care is applicable. The health care personnel who develop these parameters should sign their names and date the final version as evidence of their participation and support. Practice parameters must be based on sound scientific research findings, professional literature, clinical experience and appropriate well-recognized methodologies and reflect professionally recognized national standards of care practiced in the clinical community of medicine. The development procedures followed, the participants involved, the evidence used, the assumptions and rationales accepted, and the analytic methods used should be meticulously documented, described, and made publicly available for national peer review. Parameters should be updated as needed.

Practice parameters are used as tools to enhance medical decision making but not as replacements for physicians' clinical judgment. They can be considered as means to enhance the performance of clinical and review personnel but not to replace them. It is below the standard of care of the medical review process to substitute qualified physician reviewer experts with unqualified reviewers who are using parameters.

APPENDIX 2. Examples of possible abbreviations for allergen immunotherapy extract 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

APPENDIX 3. 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

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

APPENDIX 4. Example of immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals (modification of the AAAAI skin testing and immunotherapy consent and instruction forms: immunotherapy administration instruction form, which can be found at http://www.aaaai.org)

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

- Up to 7 days, continue as scheduled (ie, if on weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection).
- Eight to 13 days after missed scheduled injection; repeat previous dose.
- Fourteen to 21 days after missed scheduled injection; reduce dose 25%.
- Twenty-one to 28 days after missed scheduled injection; reduce previous dose 50%.

Then increase dose each injection visit as directed on the immunotherapy schedule until therapeutic maintenance dose is reached.

This suggested approach to modification of doses of allergen immunotherapy because of gaps between treatment during the build-up phase is not based on retrospective or prospective published evidence, but it is presented as a sample for your consideration. The individual physician should use this or a similar protocol as a standard operating procedure for the specific clinical setting. A similar dose-reduction protocol should be developed for gaps in maintenance immunotherapy.

APPENDIX 5. Example of a cluster immunotherapy schedule[22,26]

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

APPENDIX 6. Recommended documentation for allergen immunotherapy prescription forms

The purpose of the allergen immunotherapy prescription form is to define the contents of the allergen immunotherapy extract in enough detail that it could be precisely duplicated. The following information should be on an immunotherapy prescription form:

Patient information:

- Patient name, patient number (if applicable), birth date, telephone number, and picture (if available) should be included.

Preparation information:

- Name of person and signature preparing the allergen immunotherapy extract should be included.
- Date of preparation should be recorded.
- Bottle name should be included (eg, trees and grass). If abbreviations are used, a 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 should be included.
- Volume of manufacturer's extract to add to achieve the projected effective concentration should be included. 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) should be included.
- Extract manufacturer should be included.
- Lot number should be included.
- Expiration date should be recorded and should not exceed the expiration date of any of the individual components.

APPENDIX 7. Allergen immunotherapy extract prescription 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:

_____
_____
_____
_____

_____ ____/____/____
Prescribing Physician Signature Date

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

APPENDIX 8. Maintenance concentrate prescription form

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: 6/10/06

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial **4** from Vial **1** on **8/30/06** Expiration date: **10/15/06**
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	Short ragweed	1:20 w/v G (150 Amb a1)	0.5ml	Greer	12345	1/01/08
2	Amaranthus Retroflexus	1:10 w/v G	0.5ml	H-S	6789	2/07/08
3	Ash	1:10 w/v G	0.5ml	Center	3333	3/17/08
4	Cat	10,000 BAU/ml G	2.00ml	ALO	9898	2/27/08
5	Timothy Grass	100,000 BAU/ml G	0.4ml	ALK	56789	7/09/08
6	Johnson Grass	1:10 w/v G	0.5ml	Greer	2434	7/20/08
7						
8						
9						
10						
Diluent	HSA		0.6ml	ALK	68597	12/08
Total Volume			5.00 ml			6/10/07

*** Components of mixes listed on a separate sheet**
**** Assumes 0.5 ml injection as target maintenance dose**

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

Specific Instructions:

_____

_____

Prescribing Physician Signature

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

APPENDIX 9. Labels for allergen immunotherapy extracts

Each vial of allergen immunotherapy extract should be labeled in a way that permits easy identification. Each label should include the following information (example in Figs 3 and 4):

- Appropriate patient identifiers might include the patient's name, patient's number, patient's picture, and birth date.
- The contents of the allergen immunotherapy extract in a general way should be included. The detail with which this can be identified depends on the size of the label and the number of allergens in the vial. Ideally, allergens should be identified as trees, grasses, weeds, mold, dust mite, cockroach, cat, and dog. Because of space limitations, it might be necessary to abbreviate the antigens (eg, T, G, W, M, DM, Cr, C, and D respectively [see Appendix 2]). A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate (vol/vol) should be recorded. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- The expiration date should be included.

APPENDIX 10. Allergen immunotherapy administration form recommended documentation

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

Patient information:

- Patient's name, date of birth, telephone number, and patient's picture (optional but helpful).

Allergen immunotherapy extract information:

- Allergen immunotherapy extract name and dilution from maintenance in vol/vol bottle letter (eg, A and B), bottle color, or number, if used.
- Expiration date of all dilutions.

Administration information in separate columns:

- Date of injection.
- Arm administered injection, which might facilitate determination of exact cause of local reaction.
- Projected build-up schedule.
- Delivered volume reported in milliliters.
- Description of any reactions. The details of any treatment given in response to a reaction would be documented elsewhere in the medical record and referenced on the administration form.
- *Patient's health before injection*. This can be performed through a verbal or written interview of the patient before administering the immunotherapy injection. The patient should be questioned about increased asthma or allergy symptoms, β-blocker use, change in health status (including pregnancy and recent infections), or an adverse reaction to a previous injection (including delayed large local reactions persisting through the next day). Patients with significant systemic illness generally should not receive an injection.
- *Antihistamine use*. Antihistamines are frequently a component of an allergy medication regimen, and it would be important to note whether a patient is taking an antihistamine on the day he or she receives his or her immunotherapy injection. For consistency in interpretation of reactions, it might be desirable for a patient to either take or avoid antihistamines on a regular basis on the days he or she receives immunotherapy. The physician should note on the form whether he or she recommends the patient consistently take an antihistamine on immunotherapy treatment days.
- *Peak flow reading*. Consider obtaining a peak expiratory flow rate measurement before administering an immunotherapy injection to asthmatic patients. Poorly controlled asthma is considered a risk factor for immunotherapy. Obtaining a peak expiratory flow rate measurement before the immunotherapy injection might help identify patients with symptomatic asthma. The patient's baseline peak expiratory flow rate should be provided on the form as a reference. Health care professionals administering immunotherapy injections should be provided with specific guidelines about the peak expiratory flow rate measurement for when an immunotherapy injection should be withheld and the patient referred for clinical evaluation.
- **Baseline blood pressure**. It might be useful to record the patient's blood pressure as a baseline for future reference.

APPENDIX 11. Allergen immunotherapy administration form

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 allergy or 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

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

Date to reorder: __/__/__

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 allergy or 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**	

APPENDIX 12. 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: _____
_____
Staff action taken (if any): _____

APPENDIX 13. 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.

APPENDIX 14. Allergen immunotherapy systemic reaction/anaphylaxis 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
__Epinephrine IM into 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	

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:
_____
_____
_____
_____

Clinical impression: True SR Questionable SR No SR

Systemic reaction severity classification: EAACI_____ **Portnoy** _____

Dosage adjustment? _____

Signatures_____ **RN** _____**MD/DO**

APPENDIX 15. Grading severity of allergen immunotherapy reactions: Two methods

1. **The European Academy of Allergy and Clinical Immunology grading of severity for systemic side effects***

Classification of systemic reactions

0 = No symptoms or nonspecific symptoms

I = Mild systemic reactions: symptoms—localized urticaria, rhinitis, or mild asthma (PF <20% decrease from baseline).

II = Moderate systemic reaction: symptoms—slow onset (>15 minutes) of generalized urticaria, moderate asthma, or both (PF < 40% decrease from baseline).

III = Severe (non–life-threatening) systemic reactions: symptoms—rapid onset (<15 minutes) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).

IV = Anaphylactic shock: symptoms—immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, and hypotension, for example.

2. **Portnoy method for numeric grading of reactions to allergen immunotherapy†**

Local

0+ = No significant reaction or small area of erythema less than the size of a half dollar without swelling or wheal formation

1+ = Erythema greater than the size of a half dollar, swelling or wheal formation, or both

Systemic

2+ = Systemic reactions: cutaneous only—might consist of a cutaneous eruption, such as urticaria

3+ = Systemic reaction: generalized pruritus, sneezing, or both—might consist of increased allergy symptoms, such as nasal congestion, sneezing, or pruritus, especially in the mouth or throat

4+ = Systemic reaction: pulmonary—consists of wheezing, shortness of breath, and tightness. Might be associated with decreased pulmonary function tests

5+ = Systemic reaction: anaphylaxis—a sensation of not feeling right is a frequent prelude; might consist of hypotension, laryngeal edema, severe wheezing, and cramping

6+ = Cardiopulmonary arrest

PF, Peak expiratory flow.

*Subcutaneous immunotherapy. Allergy 2006;61(suppl 82):5-13.

†Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80.

Allergen immunotherapy: A practice parameter second update

Supplement Editor: **Linda Cox, MD**
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These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology.

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the "Allergen immunotherapy: a practice parameter second 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 and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
5. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
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11. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999;83(suppl): S665–S700.
12. Diagnosis and management of urticaria: a practice parameter. Ann Allergy 2000;85(suppl):S521-S544.
13. Allergen immunotherapy: a practice parameter. Ann Allergy 2003;90(suppl):SI-S540.
14. Symptom severity assessment of allergic rhinitis: part I. Ann Allergy 2003;91:105-14.
15. Disease management of atopic dermatitis: an updated practice parameter. Ann Allergy 2004;93(suppl): S1-S21.
16. Stinging insect hypersensitivity: a practice parameter update. J Allergy Clin Immunol 2004;114:869-86.
17. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol 2005;115(suppl):S483-S523.

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22. Contact dermatitis: a practice parameter. Ann Allergy Asthma Immunol 2006;97(suppl 2):S1-S38.

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

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Allergen immunotherapy: A practice parameter second update

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PREFACE

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

The objective of ''Allergen immunotherapy: A practice parameter second update'' is to optimize the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. 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's ''Policy on development and use of practice parameters for medical quality decision-making'' (Appendix 1).[1]

This document builds on the previous Joint Task Force document, ''Allergen immunotherapy: a practice parameter'' published in the *Annals of Allergy, Asthma and Immunology* in 2003.[2] The updated practice parameters draft was prepared by Drs Linda Cox, James Li, Hal Nelson, and Richard Lockey. The Joint Task Force reworked the initial draft into a working draft of the document. The project was exclusively funded by the 3 allergy and immunology societies noted above.

In preparation for the 2003 ''Allergen immunotherapy: a practice parameter'' and the second update, a comprehensive search of the medical literature was conducted with various search engines, including PubMed; *immunotherapy*, *allergic rhinitis*, *asthma*, *stinging insect allergy*, and related search terms were used. 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 second update'' was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the ACAAI, AAAAI, and JCAAI. In addition, the draft was posted on the ACAAI and AAAAI Web sites with an invitation for review and comments from members of the sponsoring organizations. 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 allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. This document also contains recommendations for the safe practice of allergen immunotherapy, including specific recommendations on the prevention and management of 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 or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. Symptoms of allergic conjunctivitis (eg, itchy watery eyes) are often considered part of allergic rhinitis or are included in the diagnosis of rhinoconjunctivitis. Particularly good candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures, those in whom it is important to avoid the potential adverse effects of medications, and those who wish to reduce the long-term use of medications. Immunotherapy is recommended for patients with a history of systemic reaction to Hymenoptera stings and specific IgE antibodies to Hymenoptera venom.

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.[3]

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. 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 *maintenance concentrate* should be used to identify the allergen immunotherapy extract that contains a therapeutic effective dose for each of its individual constituents (see the Immunotherapy schedules and doses section).

The term *manufacturer's extract* refers to the allergy extract purchased from the manufacturer. The terms *stock*, *full-strength*, and *concentrate* are ambiguous and should not be used. 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).

Allergen immunotherapy is effective when appropriate doses of the allergens are administered. ''Allergen immunotherapy: A practice parameter'' recommends that vials of allergen immunotherapy extracts should be prepared individually for each patient to enhance the individualization of therapy, reduce the risk of allergen cross-contamination, and reduce the risk of error in administration.[4,5] This parameter recommends the use of standardized allergen immunotherapy prescription and administration forms to improve the safety, uniformity, and standardization of allergen immunotherapy practice.[4,5] The suggested forms are found in the Appendix (Appendices 7, 8, 11, 12, and 14) and in the members' section of the www.aaaai.org Web site. The routine use of these standardized forms should improve the quality of immunotherapy practice.

Members' feedback comments on the recommended allergen extract dilution dating in the 2003 ''Allergen immunotherapy: A practice parameter'' led to an allergen immunotherapy extract dilution stability study designed by the AAAAI Immunotherapy and Allergy Diagnostics Committee and funded by the AAAAI Board of Directors. The study was designed to investigate the effect of time, temperature, and dilution of standardized allergen extract potency, and the results of this study were considered in this update.

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 3 years after publication. Requests for information about or an interpretation of these practice parameters should be directed to the Executive Offices of the AAAAI, ACAAI, and JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

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. Allergen immunotherapy

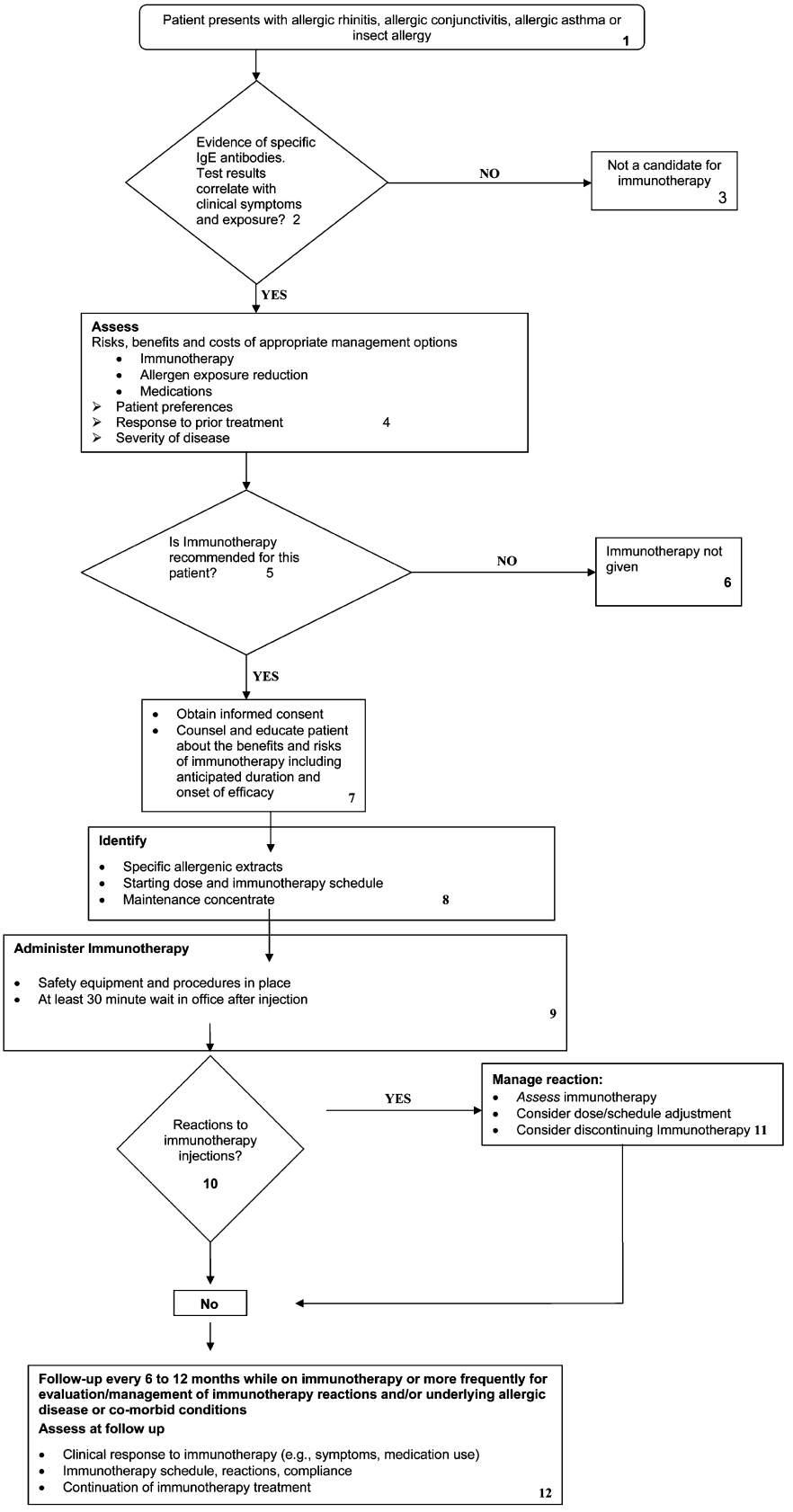


FIG 1. Algorithm for allergen immunotherapy.

might prevent the development of asthma in individuals with allergic rhinitis.[6-9] Evaluation of a patient with suspected allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic conjunctivitis, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or *in vitro* tests for specific IgE antibody).[10]

Box 2

Immediate hypersensitivity skin testing is generally the preferred method of testing for specific IgE antibodies, although *in vitro* testing for 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

Management of complex medical conditions, such as allergic asthma, allergic rhinitis/conjunctivitis, and stinging insect hypersensitivity, should include the careful evaluation of management 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 patient 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. On the basis of clinical considerations and patient 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 good candidates for immunotherapy. However, asthma must be controlled at the time the immunotherapy injection is administered. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy (VIT).

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 on the basis of 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 (see the Immunotherapy schedules and doses section). In general, the starting immunotherapy dose is 1000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose might be lower. The maintenance dose is generally 1000 to 4000 arbitrary units (AU; eg, for dust mite) or bioequivalent allergy units (BAU; eg, for grass) 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 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 referred to as *up-dosing*, *induction*, or the *dose-increase phase*) entails administration of gradually increasing doses during a period of approximately 14 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 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, in particular anaphylaxis. Patients should wait at the physician's office for at least 30 minutes after the immunotherapy injection or injections so that reactions can be recognized and treated promptly, if they occur.

In general, immunotherapy injections should be withheld if the patient presents with an acute asthma exacerbation. For patients with asthma, consider measuring 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. Some physicians recommend providing certain patients with epinephrine for self-administration in case of severe late reactions to immunotherapy injections.

Box 10

Injections of allergen immunotherapy extract can cause local or systemic reactions. Most severe reactions develop within 30 minutes after the immunotherapy injection, but reactions can occur after this time.

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 (anaphylaxis). Epinephrine is the treatment of choice in anaphylaxis, preferably when administered intramuscularly,[11] although subcutaneous administration is acceptable.[12]

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, see the practice parameters for anaphylaxis.[12]

The immunotherapy dose and schedule, as well as the benefits and risks of continuing immunotherapy, should be evaluated after any immunotherapy-induced systemic reaction. After a severe systemic reaction, careful evaluation by the prescribing physician is recommended. For some patients, the immunotherapy maintenance dose might need to be reduced because of repeated systemic reactions to immunotherapy injections. The decision to continue immunotherapy should be re-evaluated after severe or repeated systemic reactions to allergen immunotherapy extracts.

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 doses, 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,[13] but others might experience a recurrence of their symptoms after discontinuation of allergen immunotherapy.[14] 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, and 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 on the basis of the patient's clinical response, disease severity, immunotherapy reaction history, and patient preference.

IMMUNOTHERAPY GLOSSARY

For more information on immunotherapy definitions, see the article by Kao.[15]

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 (pigments and salts; see the Allergen selection and handling section). Other terms used to describe the allergen immunotherapy extract include *allergen product*,[16] *allergy serum*, *allergen vaccine*,[17] 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.[18] Other terms that have been used for allergen immunotherapy include *hyposensitization*, *allergen-specific desensitization*, and the lay terms *allergy shots* or *allergy injections*.[15]

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

TABLE II. Allergen immunotherapy dose-calculation table

- Express weight per volume as a fraction: $\frac{1}{N}$ or 1:*N*.
- Calculate concentration of individual allergens in mixtures. If a mixture is made of equal amounts of N individual allergens to make a total concentration (C), the final concentration of an individual allergen (Ca) can be calculated by using the following equation:

$Ca = C \times \frac{1}{N} = \frac{C}{N}$ or *C*:*N*.

For example, if a mixture of equal amounts of 5 (N) allergens has a total concentration (C) of 100,000 BAU/mL, then the final concentration of each individual allergen (Ca) is: $Ca = \frac{C}{N} = \frac{100{,}000}{5} = 20{,}000\ BAU/mL$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{C}{N} = \frac{1/10}{5} = \frac{0.1}{5} = 0.02$ or $\frac{1}{50}$ or 1:50.

- Dilution of individual allergen: If an initial volume, Vi (in milliliters), of an individual antigen with concentration, Ci, is added to an allergen extract to make a final volume of Vf (in milliliters), the final allergen concentration (Ca) in the allergen extract mixture will be: $Ca = Ci \times \frac{Vi}{Vf}$.
- Final concentration of an allergen in a mixture of mixtures is determined by multiplying the initial concentration by the dilution factors from each mixing step.

For example, consider a mixture containing equal amounts of 5 (N) allergens with a total concentration (C) of 100,000 BAU/mL (first dilution). If an initial volume (Vi) of 0.5 mL of this mixture is further mixed with other components and diluent to make a final allergen extract mixture volume (Vf) of 5.0 mL (second dilution), the final concentration of an individual allergen (Ca) will be:

$$Ca = C \times \underbrace{\frac{1}{N}}_{\text{Mixture dilution}} \times \underbrace{\frac{Vi}{Vf}}_{\text{Allergen extract dilution}} = 100{,}000 \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{100{,}000}{50} = 2000\ BAU/mL$$

Likewise, if C = 1:10 (wt/vol), then: $Ca = \frac{1}{10} \times \frac{1}{5} \times \frac{0.5}{5.0} = \frac{1}{500}$ or 1:500.

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).

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 to 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-medicated 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 multiplied by volume of administered dose (see Table II for a dose-calculation table).

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, cat, 1000 BAU, [highest tolerated dose] vs 2000 BAU [projected effective dose]).

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 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 by a variety of immunologic transformations. Early definitions of the term immunotherapy included active and passive immunization for the purpose of improving 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 by means of induction of clonal deletion, anergy, immune tolerance, or immune deviation.

The *maintenance concentrate* is a preparation that contains individual 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 may not be the initially calculated projected effective dose.

The *maintenance goal* (or projected effective dose) is the allergen dose projected to provide therapeutic efficacy. The maintenance goal is based on published studies, but a projected effective dose has not been established for allergens. 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 the 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 large local reaction causing discomfort). The intervals between maintenance immunotherapy injections generally ranges 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 by means of immunoblotting or crossed allergoimmunoelectrophoresis.

For a definition of *projected effective dose*, see 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 test responses), and premedication with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similar high incidence of systemic reactions.

Off the board into one syringe is a phrase that describes a method of allergen immunotherapy preparation and administration that involves specifically mixing the patient's allergen immunotherapy injection in a single syringe, which is not recommended. This syringe might be inserted into more than one allergen extract vial, and this poses a risk of cross-contamination of the allergen extracts and might dull the needle with repeated penetration of the rubber stopper.

Shared specific patient vials is a method of allergen immunotherapy preparation and administration in which the allergy immunotherapy extract is withdrawn from a shared vial (eg, mixed vespids or dust mite mix). This is sometimes referred to as off the board, but it is distinct from the method of off the board into one syringe in that the syringe enters only one allergen extract vial.

INTRODUCTION

Immunity has been defined as protection against certain diseases. The initial immunotherapeutic interventions, which included the use of preventive vaccines and xenogenic 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 the field of allergen immunotherapy. From its humble empiric emergence in 1900, when ragweed injections were proposed as therapy for autumnal hay fever, allergen immunotherapy has progressed in both theory and practice from the passive immunologic approach to the active immunologic procedures pioneered by Noon[19] and Freeman.[20,21] 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 10 years. Numerous well-designed controlled studies have demonstrated that allergen immunotherapy is efficacious in the treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Some studies have suggested that allergen immunotherapy might prevent the development of asthma in individuals with allergic rhinitis.[6-9]

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,[22-26] and it should be differentiated from unproved methods, such as neutralization-provocation therapy and low-dose subcutaneous regimens based on the Rinkel technique, which have been found to ineffective in a double-blind placebo-controlled study.[27,28]

SUMMARY STATEMENTS

Mechanisms of immunotherapy

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, defined as a relative decrease in allergen-specific responsiveness and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

Allergen extracts

Summary Statement 6: When possible, standardized extracts should be used to prepare the allergen immunotherapy extract treatment sets. **A**

Summary Statement 7: Nonstandardized extracts might vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Summary Statement 8: 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**

Cross-reactivity of allergen extract. Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

Efficacy of immunotherapy

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Summary Statement 10: Immunotherapy is effective for 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**

Food allergy, urticaria, and atopic dermatitis. Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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**

Measures of efficacy. Summary Statement 12: 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**

Safety of immunotherapy

Reaction rates. Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

Timing of anaphylactic reactions to immunotherapy injections. Summary Statement 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

β-*Adrenergic blocking agents.* Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

Contraindications. Summary Statement 18: 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**

Reducing the risk of anaphylaxis to immunotherapy injections. Summary Statement 19: 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**

Patient selection

Clinical indications. Summary Statement 20: 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 depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Special precautions in patients with asthma. Summary Statement 21: Allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. **C**

Clinical indications for VIT. Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Summary Statement 23: Patients selected for immunotherapy should be cooperative and compliant. **D**

Allergen selection and handling

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted in vitro tests for specific IgE antibodies can also be used. **A**

Specific allergens. Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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, supported by the presence of specific IgE antibodies. **A**

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Dose selection. Summary Statement 30: The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract. **A**

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as mold/fungi and cockroach, from other extracts, such as pollens, is recommended. **B**

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extract handling

STORAGE

Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

STORING DILUTE EXTRACTS

Summary Statement 34a: More dilute concentrations of allergen immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: 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 a number of 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. **B**

Immunotherapy schedules and doses

Summary Statement 35: A customized individual 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 be based on single or multiple allergens. **D**

Maintenance concentrate. Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

Recommended doses. Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

Effect of dilution on dose. Summary Statement 38: Dilution limits the number of antigens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. **A**

Dilutions of the maintenance concentrate. Summary Statement 39: Serial dilutions of the maintenance concentrate should be made in preparation for the build-up phase of immunotherapy. **D**

Labeling dilutions. Summary Statement 40: A consistent uniform labeling system for dilutions from the maintenance concentrate might reduce errors in administration and therefore is recommended. **D**

Individualized treatment vials. Summary Statement 41: 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. The mixing of antigens in a syringe is not recommended because of the potential for cross-contamination of extracts. **C**

Starting doses. Summary Statement 42: The starting dose for build-up is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose might be advisable for highly sensitive patients. **D**

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 injections per week. **D**

Dose adjustments for systemic reactions. Summary Statement 44: The dose of allergen immunotherapy extract should be appropriately reduced after a systemic reaction if immunotherapy is continued. **D**

Reductions during periods of exacerbation of symptoms. Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Dose adjustments for late injections. Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

Cluster schedules. Summary Statement 47: With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. **C**

Rush schedules. Summary Statement 48: Rush schedules can achieve a maintenance dose more quickly than weekly schedules. **A**

Systemic reactions and rush schedules. Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

Premedication and weekly immunotherapy. Summary Statement 50: Premedication might reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

Premedication with cluster and rush immunotherapy. Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

Maintenance schedules. Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals might tolerate longer intervals between maintenance dose injections. **A**

Continuing care

TIME COURSE OF IMPROVEMENT

Summary Statement 53: Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose. **A**

FOLLOW-UP VISITS

Summary Statement 54: Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. **D**

DURATION OF TREATMENT

Summary Statement 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

DOCUMENTATION AND RECORD KEEPING

Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully documented. **D**

INJECTION TECHNIQUES

Summary Statement 57: Allergen immunotherapy extract injections should be administered with a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **D**

Summary Statement 58: The injection should be administered subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Location of allergen immunotherapy administration

Physician's office. Summary Statement 59: The preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract. **D**

Summary Statement 60: 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**

Other locations. Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **D**

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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**

Summary Statement 63: 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for his or her immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extract might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Special considerations in immunotherapy

Allergen immunotherapy in children. Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Pregnancy. Summary Statement 71: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. **C**

Immunotherapy in the elderly patient. Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy in patients with immunodeficiency and autoimmune disorders. Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

Alternative routes of immunotherapy

Sublingual and oral immunotherapy. Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no US Food and Drug Administration (FDA)–approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **A**

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Immunotherapy techniques that are not recommended. Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

MECHANISMS OF IMMUNOTHERAPY

Summary Statement 1: Immunologic changes during immunotherapy are complex. **D**

Summary Statement 2: Successful immunotherapy is associated with a change toward a T_H1 $CD4^+$ cytokine profile. **A**

Summary Statement 3: Allergen immunotherapy is also associated with immunologic tolerance, which is defined as a relative decrease in allergen-specific responsiveness, and by the generation of $CD4^+CD25^+$ regulatory T lymphocytes. **A**

Summary Statement 4: Efficacy from immunotherapy is not dependent on reduction in specific IgE levels. **A**

Summary Statement 5: Increases in allergen-specific IgG antibody titers are not predictive of the duration and degree of efficacy of immunotherapy. However, alterations in the allergen-specific IgG specificity with immunotherapy might play a role in determining clinical efficacy. **A**

The immunologic changes associated with immunotherapy are complex, and the exact mechanism or mechanisms responsible for its' clinical efficacy are continually being elucidated. Data support the concept that successful immunotherapy is associated with a change to a T_H1 $CD4^+$ cytokine profile.[29-34] Data indicate that increased production of IL-12, a strong inducer of T_H1 responses, contributes to this shift.[33] Clinically successful immunotherapy has been reported to be associated with immunologic tolerance, which is defined as a relative decrease in antigen-specific responsiveness, immune deviation, or anergy. For example, lymphoproliferative responses to allergen are reduced with immunotherapy.[32] Successful immunotherapy results in generation of a population of T regulatory cells, which are $CD4^+CD25^+$ T lymphocytes producing IL-10, TGF-β, or both.[35-39] Regulatory T-cell release has been described in allergen immunotherapy with Hymenoptera venom,[35] grass pollen extract,[37] and house dust mites.[38] IL-10 reduces B-cell antigen-specific IgE and increases IgG4 levels; reduces proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicits tolerance in T cells by means of selective inhibition of the CD28 costimulatory pathway.[36,37]

Allergen immunotherapy has been shown to block both the immediate and late-phase allergic response.[40] Allergen immunotherapy has been shown to decrease the recruitment of mast cells, basophils, and eosinophils in the skin, nose, eye, and bronchial mucosa after provocation or natural exposure to allergens.[41]

In patients receiving immunotherapy, initially there is an increase in specific IgE antibody levels, followed by a gradual decrease to a level that is still higher than that present before treatment. Clinical improvement in many patients develops before decreases in their IgE antibody levels occur or in other patients whose IgE antibody levels never decrease, thereby demonstrating that efficacy is not dependent on reductions in specific IgE levels.[42,43] Immunotherapy does diminish the seasonal increase in specific IgE levels.[44] Despite the persistence of significant levels of specific IgE antibody levels, immunotherapy usually causes a reduction in 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.[45-48]

An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, has also been associated with immunotherapy. The properties of allergen-specific IgA have yet to be determined, and there is a weak correlation between the increase in allergen-specific IgG levels and immunotherapy's clinical efficacy.[30,49,50]

Immunotherapy might alter the affinity and specificity of allergen-specific IgG.[51,52] During the initial phase of ultrarush VIT, a change in IgG specificity (ie, a change in the set of epitopes dominantly recognized by IgG on wasp venom antigens) occurred concomitantly with early clinical tolerance and was seen within 12 hours of ultrarush VIT ($P < .001$).[51] 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 individuals.[52] This change in IgG specificity preceded the increase in IgG titers and was sustained for up to 6 months.[52]

Allergen-specific IgG induced from immunotherapy can block IgE-dependent histamine release and subsequent IgE-mediated antigen presentation to T cells.[53] This effect might be dependent on IgE, allergen concentration, and CD23, the low-affinity receptor for IgE.

Whereas 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.[37,53]

The relationship between these immunologic changes and immunotherapy efficacy is not completely understood.

ALLERGEN EXTRACTS

Summary Statement 6: 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 has 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.[2,18,54-56] 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.

United States–licensed extracts can be obtained in aqueous, glycerinated, lyophilized, and acetone-precipitated and alum-precipitated formulations. Some commonly used allergens are standardized. These include extracts for cat hair, cat pelt, *Dermatophagoides pteronyssinus*, *Dermatophagoides 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.[57] 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.

Most standardized extracts are labeled in BAU. Short ragweed potency units were originally based on the content of the major allergen Amb a 1. Ragweed potency is reported in FDA units and BAU. One FDA unit of Amb a 1 equals 1 μg of Amb a 1, and 350 units of Amb a 1/mL is equivalent to 100,000 BAU/mL. Cat extracts were also originally standardized based on the content of major allergen (Fel d 1), with 100,000 arbitrary units (AU) per milliliter containing between 10 to 19.9 FDA units of Fel d 1 per milliliter (1 FDA unit of Fel d 1 equals 2 to 4 μg of Fel d 1).[55,58,59] Subsequently, $ID_{50}EAL$ testing suggested that 100,000 AU/mL was equal to 10,000 BAU/mL.[60] Approximately 22% of individuals with cat allergy have specific IgE antibodies to cat albumin.[61] Cat pelt extracts have a greater amount of albumin than cat hair extracts.[60]

Dust mites were originally standardized in AU by means of inhibition radioimmunoassay (RIA), and subsequent $ID_{50}EAL$ testing indicated that the AU was bioequivalent to the BAU, and the original AU nomenclature was kept. Dust mite extracts are still labeled in AU.

Summary Statement 7: Nonstandardized extracts can vary widely in biologic activity and, regardless of a particular wt/vol or PNU potency, should not be considered equipotent. **B**

Nonstandardized extracts are labeled as wt/vol, which expresses weight in grams per volume in milliliters; that is, a potency of 1:100 indicates that 1 g 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 with a particular wt/vol or PNU potency can have widely varying biologic activities.[62-64] Therefore they should not be considered equipotent.

Summary Statement 8: 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**

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. The major clinically relevant aeroallergens of North America are listed in Table III. Furthermore, nonrelevant allergens in such mixtures could act as sensitizers rather than as tolerogens.[65,66] The physician must therefore select only those aeroallergens for testing and treatment that are clinically relevant in a particular geographic area.

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, dog), insect (cockroach), and Hymenoptera venom source materials.

Cross-reactivity of allergen extract

Summary Statement 9: Knowledge of allergen cross-reactivity is important in the selection of allergens for immunotherapy because limiting the number of allergens in a treatment vial is necessary to attain optimal therapeutic doses for the individual patient. **B**

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. A summary of cross-reactivity patterns of the clinically relevant North American aeroallergens can be found in Fig 2. 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,[67] inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[68-75] Grasses in other subfamilies (eg, Bermuda, Bahia, and Johnson) show greater diversity and should be evaluated separately.[76-78] Bermuda and Johnson grasses are increasingly important in the South,

TABLE III. The major clinically relevant aeroallergens of North America*

- Tree pollen
  - Chinese elm *(Ulmus parvifolia)*†‡; Siberian elm *(Ulmus pumila)*†‡; American elm *(Ulmus Americana)*†‡
  - Red oak *(Quercus rubra)*†; White oak *(Quercus alba)*†
  - Paper birch *(Betula papyrifera)*
  - Alder *(Alnus rubra)*
  - Box elder *(Acer negundo)*†; Red maple *(Acer rubra)*†
  - Eastern cottonwood *(Populus deltoides)*
  - Sycamore *(Platanus occidentalis)*
  - White ash *(Fraxinus americana)*†; Olive *(Olea europaea)*†‡
  - Black walnut *(Juglans nigra)*
  - Mulberry *(Morus rubra)*
  - Mountain cedar *(Juniperus ashei)*
  - Pecan *(Carya illinoensis)*
- Grass pollen
  - Rye *(Lolium perenne)*§‖
  - Timothy *(Phleum pratense)*§‖
  - Meadow fescue *(Festuca elatior)*§‖
  - Bermuda *(Cynodon dactylon)*‖
  - Johnson *(Holcus halepensis)*
  - Bahia *(Paspalum notatum)*
- Weed pollen
  - Short ragweed *(Ambrosia artemisiifolia)*‖
  - English (narrow leaf) plantain *(Plantago lanceolata)*
  - Mugwort *(Artemisia vulgaris)*
  - Russian thistle *(Salsola kali)*
  - Burning bush *(Kochia scoparia)*
  - Sheet (red) sorrel *(Rumex asetosella)*
  - Red root pigweed *(Amaranthus retroflexus)*
- Indoor aeroallergens
  - Cat epithelium *(Felis domesticus)*‖
  - Dog epithelium *(Canis familiaris)*
  - Arthropods (domestic mites: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*)‖
  - Insects (German cockroach: *Blattella germanica*)
- Fungi
  - *Alternaria alternata*¶
  - *Cladosporium* (*C cladosporioides*, *C herbarum*)¶
  - *Penicillium* (*P chrysogenum*, *P expansum*)¶
  - *Aspergillus fumigatus*¶
  - *Epicoccum nigrum*, *Drechslera* or *Bipolaris* type (eg, *Helminthosporium solani*)¶

*Compiled and selected in collaboration with the AAAAI Immunotherapy Committee Allergen Subcommittee for the identification of 35 key allergens of North America.
†Extensive cross-reaction of species within the genus.
‡Apart from regional prevalence, they are limited to local sites with substantial stands of these trees.
§Extensively cross-react with one another and bluegrass, orchard, red top, and sweet vernal.
‖Allergens for which standardized extracts are commercially available.
¶Species that are widely distributed and clinically important.

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.[79-82] 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.[83-85] Significant cross-reactivity between Betulaceae pollens and oak of the Fagaceae family has been demonstrated with percutaneous skin testing.[75] RAST inhibition studies have shown cross-inhibition between oaks and other *Fagales* species.[86] IgE immunoblot inhibition experiments have demonstrated that the *Fagales* species might be strongly inhibited by birch species.[87] The use of one of the locally prevalent members (eg, birch and alder) should be adequate.[88]

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.[89,90] Maple and box elder trees are found throughout the United States, except for the arid southwest. Although in the same genus as maple, *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,[91,92] and there are allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.[93]

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.[94] Similarly, Chenopod-Amaranth families have wide ranges in the western regions but are present throughout North America.[95] Current information on cross-reactivity of these families is limited.[96-98] 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.[99] The use of a single Amaranth extract should be sufficient to cover this family.[100,101] Similarly, *Atriplex* species (eg, saltbushes and scales) show near identity, and use of a single member is adequate. 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,

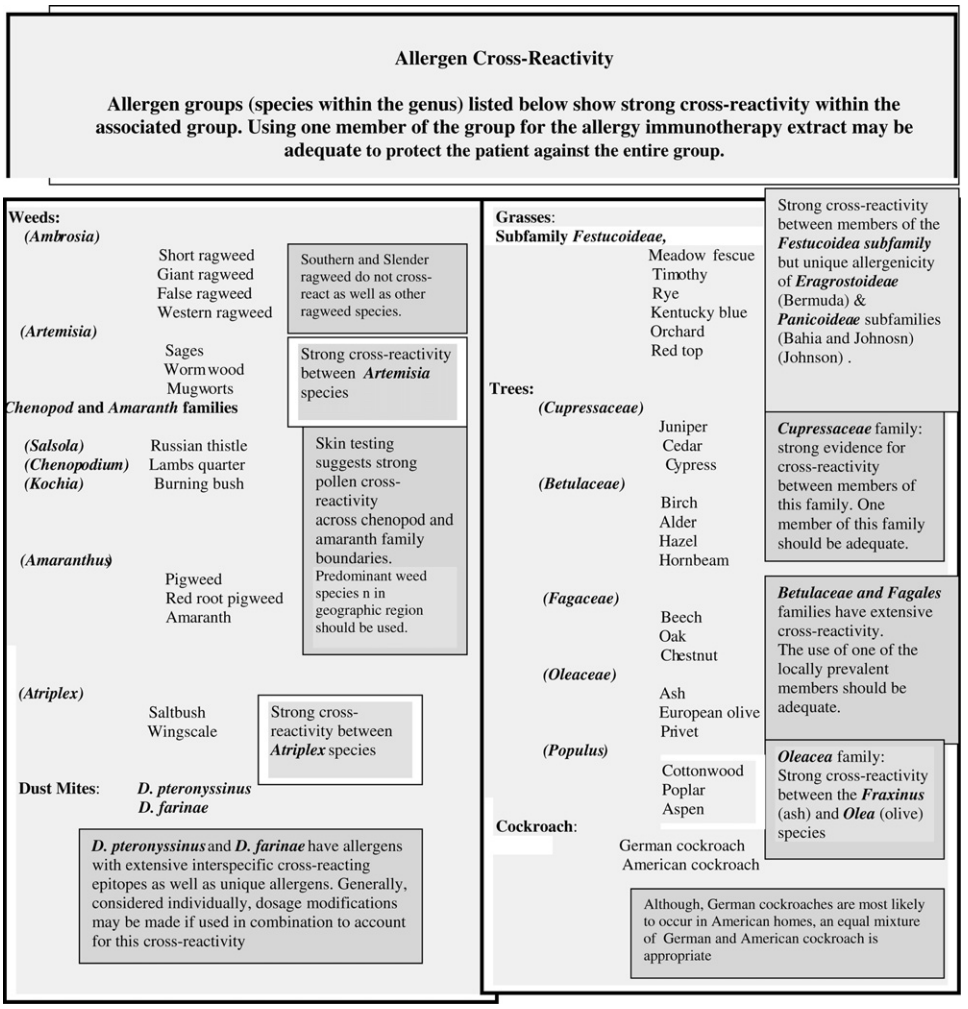


FIG 2. Patterns of allergen cross-reactivity.

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*).

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.[102,103] Stinging Hymenoptera insects occur throughout the United States; the fire ant is found only in Gulf Coast states, Texas, and some other southern and western states. Commercial venom extracts are available for some Hymenoptera species, except the fire ant, for which only whole-body extract is available.

EFFICACY OF IMMUNOTHERAPY

Allergic rhinitis, allergic asthma, and stinging insect hypersensitivity

Summary Statement 10: Immunotherapy is effective for 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.[104-111] Immunotherapy is effective for the treatment of allergic rhinitis[107] (including ocular symptoms[112,113]), allergic asthma,[104,109,111,114,115] and stinging insect hypersensitivity[108,116] and is effective in both adults and children.[117-124] Its efficacy is confirmed for the treatment of inhalant allergy caused by pollens,[13,125-132] fungi,[133-138] animal allergens,[22,25,26,139-143] dust mite,[114,115,144-153] and cockroach.[154] There have been no controlled trials of fire ant whole-body extract, but it does appear to be effective in

TABLE IV. Improvement of symptoms and reduction in medication and bronchial hyperresponsiveness after immunotherapy

Outcome measure	House dust mite	Other allergens*†
Symptomatic improvement	2.7 (1.7-4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2-7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50)	5.5 (2.8-10.7)

Data are used with permission from Abramson et al.[104]
ND, Not done.
*Odds ratio (95% CI).
†Pollen, mold, or animal dander.

uncontrolled trials.[155-157] 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. A number of studies have also demonstrated a significant improvement in quality of life, as measured by using standardized questionnaires.[24,158-161] The magnitude of the effect depends on the outcome that is used (Table IV). For dust mite, the effect size ranges from a 2.7-fold improvement in symptoms to a 13.7-fold reduction in bronchial hyperresponsiveness. 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.[110] 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[107] and asthma[104,109,111] have been performed to deal with the issue of power. One review of 75 trials involving 3188 asthmatic patients found that, overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyperreactivity after immunotherapy, and it would have been necessary to treat 4 patients (95% CI, 3-5) with immunotherapy to avoid 1 deterioration in asthma symptoms and 5 (95% CI, 4-6) patients to avoid 1 requiring increased medication.[111] These meta-analyses strongly support the efficacy of allergen immunotherapy. Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued[13,162,163] and might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6,9,122,162-165] Allergen immunotherapy might also prevent the development of new allergen sensitivities in monosensitized patients.[120,166,167]

Food allergy, urticaria, and atopic dermatitis

Summary Statement 11: Clinical studies do not support the use of allergen immunotherapy for food hypersensitivity or chronic urticaria, angioedema, or both at this time. Therefore allergen immunotherapy for patients with food hypersensitivity or chronic urticaria, angioedema, or both is not recommended. **D**

Summary Statement 11b: There are limited data indicating that immunotherapy can be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity. **C**

Summary Statement 11c: 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 use of allergen immunotherapy for individuals with the potential for IgE-mediated (anaphylaxis) reactions to foods should be regarded as investigational at this time.[168-171] There have been 2 investigational studies demonstrating efficacy in food hypersensitivity, the first using aqueous subcutaneous injections to peanut and the second using sublingual immunotherapy to hazelnut.[171-173]

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 a modified peanut extract is needed for clinical application of this method of treatment.[171] There is currently no FDA-approved formulation for sublingual immunotherapy, and this route of allergen immunotherapy is currently considered investigational at this time (see Summary Statement 73).

At the present time, there is not enough evidence to support food immunotherapy.

There is no evidence supporting the efficacy of immunotherapy for individuals with chronic urticaria, angioedema, or both.

There are limited data indicating that immunotherapy might be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[174-176] 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 ($P = .0379$) and topical corticosteroid use ($P = .0007$).[174]

The potential for benefit in symptoms related to oral allergy syndrome with the cross-reacting inhalant immunotherapy, which includes cross-reacting 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 subcutaneous immunotherapy directed against birch tree,[177] whereas another double-blind, double-dummy, placebo-controlled study comparing the effect of subcutaneous immunotherapy with sublingual immunotherapy 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, medication use, and decrease in IgE reactivity.[178] More investigation is required to substantiate the contention that benefits in oral symptoms will occur with immunotherapy.

Measures of efficacy

Summary Statement 12: 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. Objective measures, such as increase in allergen-specific IgG levels and decreased skin test reactivity, as measured by skin test titration, are changes generally associated with effective immunotherapy but, at present, are not practical for routine clinical use.[147] Nonquantitative skin testing or *in vitro* 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 are not very reliable given the strong placebo-like effect (Hawthorne effect) associated with any treatment. A more objective means for determining efficacy as validated in controlled clinical studies is the use of clinical symptom scores and the amount of medication required to control symptoms and maintain peak flow rates or pulmonary function tests within acceptable limits. Successful immunotherapy often results in a reduction in medication. Sequential measurement of disease-specific quality of life also might be helpful.

SAFETY OF IMMUNOTHERAPY

Reaction rates

Summary Statement 13: Published studies indicate that individual local reactions do not appear to be predictive of subsequent systemic reactions. However, some patients with greater frequency of large local reactions might be at an increased risk for future systemic reactions. **C**

Large local reactions associated with allergen immunotherapy are fairly common, with a frequency ranging from 26% to 86% of injections.[179] Two retrospective studies compared the effect of not adjusting immunotherapy dose based on large local reactions on the immunotherapy systemic reaction rate with dose-adjustment protocols.[179,180] There was a total of 12,464 injections administered with a dose-adjustment protocol in the 2 studies compared with 9542 injections administered with a no-dose-adjustment protocol. 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 for subsequent systemic reactions, 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 large local reactions, defined as 25 mm or larger, in patients who had experienced systemic reactions with age-, sex-, and allergen sensitivity–matched control subjects who had not had allergen immunotherapy systemic reactions found the rate of large local reactions was 4 times higher among the 258 patients who had subsequently experienced a systemic reaction compared with those who had never experienced a systemic reaction.[181] Patients who had experienced systemic reactions had 1573 large local reactions in 4460 visits (ie, 35.2% of visits) and 8081 injections (ie, 19.5% of injections) compared with the matched control group without systemic reactions who had 1388 large local reactions in 15,540 visits (8.9% per visit) and 26,259 injections (5.3% per injection; difference between groups, $P < .001$). Individual large local reactions were not predictive of future systemic reactions, but large local reactions preceded systemic reactions in approximately one third of the systemic reactions. These findings suggest that individuals with a greater frequency of large local reactions might be at greater risk for systemic reaction. Prospective studies investigating the sensitivity and specificity of large local reactions and the effect of immunotherapy protocol modifications based on them are needed.

Summary Statement 14: Although there is a low risk of severe systemic reactions with appropriately administered allergen immunotherapy, life-threatening and fatal reactions do occur. **C**

The prevalence of severe systemic reactions after allergen immunotherapy ranges from less than 1% of patients receiving conventional immunotherapy to greater than 36% of patients in some studies of patients receiving rush immunotherapy.[182,183]

In a recent survey of fatal and near-fatal reactions (NFRs) sent to physician members of the AAAAI, 273 of 646 respondents reported NFRs during the period of 1990-2001.[184]

The incidence of unconfirmed NFRs was 23 per year (5.4 events per million injections). Administration during the height of 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 angiotensin-converting enzyme 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 systemic reactions to subcutaneous immunotherapy over a 20-year period (1981-2000) during which 435,854 injections were administered to 4000 patients, 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.[185,186] In a prospective multicenter study there were 53 systemic reactions (0.3% of the doses) out of 17,526 administered doses in 18 (3.7%) of 423 patients.[187] 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 (21 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, there were 41 fatalities identified in the initial brief survey (20 directly reported and 17 with completed detailed questionnaire) from immunotherapy injections.[188] 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.[189,190] Therefore although severe systemic reactions to allergen immunotherapy are not common, serious systemic reactions (some fatal) can occur.

Summary Statement 15: 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 recent health changes that might require modifying or withholding that patient's immunotherapy treatment. Risk factors for severe immunotherapy reactions include symptomatic asthma and injections administered during periods of symptom exacerbation. Before the administration of the allergy injection, the patient should be evaluated for the presence of asthma or allergy symptom exacerbation. One might also consider an objective measure of airway function (eg, peak flow) for the asthmatic patient before allergy injections. **B**

In the AAAAI survey of physician members on immunotherapy and skin testing, fatal reactions, and NFRs during the period of 1990-2001, 15 of the 17 fatalities had asthma, and in 9 patients asthma was considered the susceptibility factor that contributed to the fatal outcome.[188]

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.[184]

Administration during the peak pollen season (3 patients) and previous systemic reactions (4 patients) were cited as other contributing factors. Five fatalities occurred in outside medical facilities, and 2 fatalities occurred at home. No patients were receiving β-blockers; 1 patient was taking an angiotensin-converting enzyme inhibitor. In the most comprehensive evaluation of fatalities associated with allergen immunotherapy, from 1945-1987, there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[189] 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, with 73.3% of patients with an FEV_1 of less than 80% of predicted value experiencing 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 ($P < .0001$).[191] 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% of patients. These studies suggest that symptomatic asthma, severe asthma, or both might be a risk factor for immunotherapy.

In addition to symptomatic asthma and injections giving 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.[17] With the exception of dosing errors and 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 recent 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 or allergy symptom exacerbation, β-blocker use, change in health status (including pregnancy), or adverse reaction to previous allergen immunotherapy injection. The preinjection evaluation might also include a peak flow measurement to assess the airway function of asthmatic patients.

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 16: Because most systemic reactions that result from allergen immunotherapy occur within 30 minutes after an injection, patients should remain in the physician's office at least 30 minutes after an injection. **C**

In a retrospective study the time to onset of a systemic reaction after an immunotherapy injection was less than 30 minutes in most cases.[189] A review of the literature indicates that 70% of systemic reactions occur within 30 minutes after an injection.[183] In the AAAAI 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.[184,188] 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.[190] 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 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.[192] In another prospective study 8% of systemic reactions occurred more than 2 hours after injection.[193]

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.[194]

Because most reactions that resulted from allergen immunotherapy occurred within 30 minutes after an injection, patients should remain in the physician's office for at least 30 minutes after receiving an injection, but longer waits are reasonable, as directed by the physician. In addition, patients who are at increased risk of a systemic reaction might need to carry injectable epinephrine. Such patients might also need to remain in the physician's office more than 30 minutes after an injection. 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.

β-Adrenergic blocking agents

Summary Statement 17: β-Adrenergic blocking agents might make allergen immunotherapy–related systemic reactions more difficult to treat and delay the recovery. Therefore a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy. However, immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. **C**

β-Blockade enhances pulmonary, cardiovascular, and dermatologic end-organ effects of mediators and increases mortality associated with experimental anaphylaxis induced by either immunologic or nonimmunologic mechanisms. Patients who are receiving β-adrenergic blocking medications might be at increased risk if they experience a systemic reaction to an allergen immunotherapy injection because the β-receptor blockade might attenuate the response to epinephrine.[195-202] Patients who are receiving β-blocking drugs were almost 9 times more likely to be hospitalized after an anaphylactoid reaction from radiocontrast media.[198] Although topical β-blockers have markedly less systemic β-antagonist effects than oral β-blockers, they still might exhibit some systemic β-antagonist effects. Whether topical β-blockers pose the same or a smaller risk than oral β-blockers in regard to the treatment of allergen immunotherapy–related systemic reactions is not known.

There have been very few studies that have examined the effect of β-blocker medications on allergen immunotherapy. A prospective 1-year study designed to determine whether patients taking β-blocker drugs were at increased risk of immunotherapy-induced systemic reactions found that there were 166 systemic reactions out of 56,105 injection visits in 3178 patients (68 were receiving a β-blocker).[203] The systemic reactions occurred in 144 (4.5%) patients, and only 1 of these patients was receiving a β-blocker medication. The authors calculated that by chance, 3.08 patients receiving the β-blocker medications drugs were expected to have had an systemic reaction and concluded that β-blocker medications did not increase the frequency of allergen immunotherapy systemic reactions ($P > .95$).

In another study of 1389 patients prescribed immunotherapy for Hymenoptera venom hypersensitivity who were followed for 34 months, there were 25 patients who received concomitant β-blocker medications.[204] Three (12%) of the 25 patients receiving β-blocker medications experienced systemic reactions during immunotherapy compared with 23 (16.7%) of 117 patients with cardiovascular disease not receiving β-blockers. Systemic reactions after a field sting or challenge occurred in 1 (14.3%) of 7 cardiovascular patients receiving β-blocker medications compared with 4 (13.8%) of 29 cardiovascular patients not receiving β-blocker medications. No severe reactions to immunotherapy or sting re-exposure were observed in patients receiving β-blockers medications.

Immunotherapy is indicated in patients with life-threatening stinging insect hypersensitivity who also require β-blocker medications because the risk of the stinging insect hypersensitivity is greater than the risk of an immunotherapy-related systemic reaction. In such cases, intravenous glucagon, which might reverse the refractory bronchospasm and hypotension by activating the adenyl cyclase directing and bypassing the β-adrenergic receptor, might be used if epinephrine has not been effective.[205,206] Prospective studies are necessary to clarify the magnitude of the risk of systemic reactions to allergens in patients who are receiving concomitant therapy with β-blockers, and a cautious attitude should be adopted toward the concomitant use of β-blocker agents and inhalant allergen immunotherapy.

Contraindications

Summary Statement 18: Medical conditions that reduce the patient's ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications

TABLE V. Actions to reduce the risk of anaphylaxis

- Assess the patient's general medical condition at the time of injection (eg, asthma exacerbation).
- Consider obtaining a PEFR before administration of the injection. If the PEFR is significantly less than the patient's baseline value, the clinical condition of the patient should be evaluated before administration of the injection.
- 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 with increased allergen sensitivity or those who have previously had a systemic reaction) might need to wait longer.
- Carefully evaluate any patient with a late reaction (eg, persistent large local reaction lasting >24 hours, systemic reaction occurring more than 30 minutes after the immunotherapy injection).
- 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.

PEFR, Peak expiratory flow rate measurement.

TABLE VI. Recommended equipment and medications to treat anaphylaxis

Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur. This should include at least the following equipment and medications:

- stethoscope and sphygmomanometer;
- tourniquet, syringes, hypodermic needles, and large-bore needles (14-gauge);
- aqueous epinephrine HCL 1:1000 wt/vol;
- equipment to administer oxygen by mask.
- intravenous fluid set-up;
- antihistamine for injection (second-line agents for anaphylaxis, but H_1 and H_2 antihistamines work better together than either one alone);
- corticosteroids for intravenous injection;
- vasopressor;
- equipment to maintain an airway appropriate for the supervising physician's expertise and skill.

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 venom hypersensitivity and cardiac disease being treated with β-blocker medications.

Reducing the risk of anaphylaxis to immunotherapy injections

Summary Statement 19: 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 extremely 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 or other health care professional appropriately trained in emergency treatment.

The 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. Epinephrine is the first-line treatment for anaphylaxis. 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.[12,207-213] It is important to administer epinephrine early in the management of anaphylaxis. 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 V and VI, respectively. Before allergen immunotherapy is chosen as a treatment, the physician should educate the patient about the benefits and risks of immunotherapy, as well as methods for minimizing risks. The patient also should be told that despite appropriate precautions, reactions might occur without warning signs or symptoms. Informed consent should include a discussion of the potential immunotherapy adverse reactions, and this discussion should be documented in the patient's medical record.

PATIENT SELECTION

Clinical indications

Summary Statement 20: Allergen immunotherapy should be considered for patients who have demonstrable

TABLE VII. Clinical indications for allergen immunotherapy

Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or both:
- symptoms of allergic rhinitis after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medications;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medication;
- coexisting allergic rhinitis and asthma;
- possible prevention of asthma in patients with allergic rhinitis

Symptoms of asthma after natural exposure to aeroallergens and demonstrable evidence of clinically relevant specific IgE AND (one of the following)
- poor response to pharmacotherapy, allergen avoidance, or both;
- unacceptable adverse effects of medication;
- wish to reduce or avoid long-term pharmacotherapy and the cost of medications;
- coexisting allergic rhinitis and allergic asthma.

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);
- adults and children with a history of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies.

evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. **A**

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic rhinitis.[107] Prospective, randomized, double-blind, placebo-controlled studies demonstrate the effectiveness of specific immunotherapy in the treatment of allergic asthma.[104,109,111]

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 proper identification and selection of component allergens on the basis of 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 (Table VII). The severity and duration of symptoms should also be considered in assessing the need for specific allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. In addition, specific allergen immunotherapy should be considered if the patient wishes to avoid long-term pharmacotherapy. Time lost from work, emergency department or physician's office visits, and responses to pharmacotherapy are important objective indicators of allergic disease severity.

Patients with allergic rhinitis who are unable to sleep because of symptoms or whose symptoms interfere with their work or school performance should be considered strong candidates for specific allergen immunotherapy. 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 considered. Unacceptable adverse effects of medications should also favor one's decision to initiate allergen immunotherapy. Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.[214]

Allergen immunotherapy for allergic rhinitis might have persistent benefits after immunotherapy is discontinued, and it might reduce the risk for the future development of asthma in patients with allergic rhinitis.[6-9,122,162-165] These benefits of immunotherapy should be discussed with patients and might provide a clinical indication for immunotherapy for individual patients with allergic rhinitis.

Coexisting medical conditions should also be considered in the evaluation of a patient who might be a candidate for allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed with a combined aggressive regimen of allergen avoidance and pharmacotherapy and might also benefit from allergen immunotherapy.[215,216]

However, the patient's asthma must be stable before allergen immunotherapy is administered.[188,191]

Special precautions in patients with asthma

Summary Statement 21: 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 might be at increased risk for systemic reactions to immunotherapy injections.[182,188,191] Two surveys found that deaths from

immunotherapy were more common in symptomatic subjects with asthma.[188,189] Thus allergen immunotherapy should not be initiated in patients with poorly controlled asthma symptoms.[2,217]

Clinical indications for VIT

Summary Statement 22: VIT should be strongly 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 antibodies. **A**

Systemic reactions to Hymenoptera stings, especially when associated with respiratory symptoms, cardiovascular symptoms, or both and positive skin test or *in vitro* test results for specific IgE antibodies, are a strong indication for allergen immunotherapy.[218] In the United States patients older than 16 years with a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Several studies of patients with imported fire ant allergy have demonstrated the effectiveness of immunotherapy with whole-body extracts of fire ants.[155,156,219] 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. Patients younger than 16 years of age who present only with a cutaneous reaction to imported fire ant or Hymenoptera stings might not require immunotherapy.[218,220-222] In addition to allergen immunotherapy, patients with imported fire ant and Hymenoptera venom sensitivity should be instructed in how to best avoid insect stings, be prescribed epinephrine, and be taught how 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 the population that has not had a systemic reaction.[223] In patients with negative venom skin test results who have a severe systemic reaction, further evaluation for the presence of venom-specific IgE is recommended.[218] If the venom-specific IgE test result is also negative, it is recommended that the skin tests, venom-specific 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 IgE test result.[224] 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 re-stung. 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%).[225] 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 IgE test results who have had severe anaphylaxis to an insect sting.

Some patients who have negative venom skin test results and negative venom-specific IgE test results are reported to have had subsequent systemic reactions to stinging insects.[225-227] Controlled studies designed to evaluate the efficacy of immunotherapy in these patients have not been performed. There are very 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.[226] 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.

Summary Statement 23: 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.

ALLERGEN SELECTION AND HANDLING

Allergen selection

Clinical evaluation. Summary Statement 24: The selection of the components of an allergen immunotherapy extract that are most likely to be effective should be based on a careful history of relevant symptoms with knowledge of possible environmental exposures and correlation with positive test results for specific IgE antibodies. **A**

A careful history, noting environmental exposures and an understanding of the local and regional aerobiology of suspected allergens, such as pollen, fungi (mold), 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 skin or *in vitro* test results for specific IgE antibodies, provide good evidence that such exposures are relevant. Information concerning regional and local aerobiology is available on various Web sites or through the National Allergy Bureau at http://www.aaaai.org/nab. There are

no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma. 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 clinical history of an allergic disease.

There is no evidence to support the administration of immunotherapy based solely on results of specific *in vitro* 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.

Clinical correlation. Summary Statement 25: The allergen immunotherapy extract should contain only clinically relevant allergens. **A**

The omission of clinically relevant allergens from an allergic patient's allergen immunotherapy extract contributes to decreased effectiveness of allergen immunotherapy. The 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 can make allergen immunotherapy less effective.

Knowledge of the total allergenic burden facing a patient and the realistic possibility of avoidance is important in determining whether allergen immunotherapy should be initiated. 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. Many individuals travel extensively for business or pleasure into different regions, and symptoms might worsen at these times. However, inclusion of allergens to which IgE antibodies are present but that are not clinically relevant might dilute the essential allergen components of the allergen immunotherapy extract so that immunotherapy might be less effective. Determination of the significance of indoor allergens for a particular patient is harder because it is difficult to determine exposure in the home, school, and/or workplace. Historical factors, such as the presence of a furry animal in the home, a history of water damage and subsequent fungal exposure, or a history of insect infestation, might be helpful. However, such information is subjective and is often of uncertain reliability. In addition, some studies have demonstrated significant indoor levels of cat and dog allergen in households without pets[228] and significant levels of mouse allergen in suburban[229] and inner-city[230] homes 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 with increased asthma morbidity in inner-city children was found.[231] 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. Nevertheless, for most patients, determination of the clinical relevance of an allergen requires a strong correlation between the patient's history and evidence of allergen-specific IgE antibodies.

Skin tests and in vitro IgE antibody tests. Summary Statement 26: 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 specific IgE antibodies. Appropriately interpreted *in vitro* tests for specific IgE antibodies can also be used. **A**

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 the skin test results have demonstrated the efficacy of immunotherapy for relevant allergens.[25,26,112,130,134,135,140,141,149,154] 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 from skin testing in a highly sensitive individual.[232,233] In addition, skin tests might be difficult to perform in patients with dermatographism or atopic dermatitis. *In vitro* tests are particularly useful in such patients.

Studies indicate that skin testing is generally more sensitive than *in vitro* tests in detecting allergen-specific IgE.[234,235] Based on inhalation challenge test results, skin tests have shown specificity and sensitivity generally superior to those of *in vitro* tests. The comparability of skin tests and *in vitro* tests for specific IgE antibodies depends on the allergen being tested. For all of 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, prick testing is sensitive enough to detect clinically relevant IgE antibodies when potent extracts, such as grass[236] and cat,[237] are used. Intradermal/intracutaneous skin testing might be required for some allergen extracts. It is appropriate in some patients to use *in vitro* tests for specific IgE antibody as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. *In vitro* tests can also be used to define the allergens that should be used in allergen immunotherapy. If the allergy skin test result is negative and the *in vitro* test result is positive, a controlled challenge can be performed, and if the latter is positive, immunotherapy can be considered. 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 *in vitro* test results.

Specific allergens

Summary Statement 27: Immunotherapy is effective for pollen, mold, animal allergens, cockroach, dust mite, 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.[17,104,106,107,109] 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.[112,122] Because a particular pollen extract is a mixture of multiple glycoproteins, this suggests that mixing pollen allergens does not alter biologic activity.

Fungi (molds). Several studies with *Alternaria* and *Cladosporium* species suggest that allergen immunotherapy with fungi might be effective.[133-138] The allergen content of most mold extracts is highly variable.[238,239] However, there is evidence that proteolytic enzymes present in some mold extracts could digest other antigens, such as pollens, when combined in a mixture.[240] For this reason, it might be desirable to separate all pollen extracts from mold extracts when using mixtures.

Unfortunately, extracts for some potentially clinically important fungi are not available.[241] 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 distinguish 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.

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.

Because immunotherapy has been shown to be effective for cat[22,26,139-143,242] and dog,[25,141] the decision to include dog or cat allergen in an allergen immunotherapy extract should be considered in those circumstances in which there is exposure.

Dust mites and cockroach allergens. Crude house dust extract is generally an inappropriate substitute for house dust mite extract because the protein content measured is not restricted to dust mite allergens, nor does it necessarily guarantee inclusion of dust mite protein. Immunotherapy with standardized dust mite is generally more effective than that with crude house dust allergens. The house dust mites *D farinae* and *D 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, such as *Blomia tropicalis* and *Euroglyphus maynei*, partially cross-react with allergens from *Dermatophagoides* species. Only 50% of the projected amounts of each of the 2 house dust mites (*D pteronyssinus* and *D farinae*) need 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[144,147-149,151] 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. Dust mite hypersensitivity should particularly be considered in patients who have perennial symptoms exacerbated by a dusty environment at home, work, or both and periods of high humidity.

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. The major allergen of *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.[243] Immunotherapy with cockroach allergens is effective[154] and should 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.

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.[108,116,244] Efficacy has also been demonstrated with immunotherapy by using whole-body extracts of imported fire ants.[155,156]

Foods. Only a single clinical study accessing the efficacy and safety of subcutaneous immunotherapy with foods has been performed.[171,173] This study, which evaluated immunotherapy with peanut, found the incidence of systemic reactions, even during maintenance, was unacceptable. Thus there is no evidence to support the use of immunotherapy with food extracts. Currently, strict avoidance of the offending food is advisable, and subcutaneous immunotherapy for food allergy is not recommended.

Mixing of extracts

Principles of mixing. Summary Statement 28: Consideration of the following principles is necessary when mixing allergen extract: (1) cross-reactivity of allergens, (2) optimization of the dose of each constituent, and (3) enzymatic degradation of allergens. **B**

Once the relevant allergens for each patient are identified, it is necessary to prepare a mixture that contains each of these allergens. Standardized extracts should be used, when available, and can be mixed with nonstandardized extracts. A number of 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 interactions between different types of allergens, when mixed, that could lead to degradation or unmasking of epitopes on exposure to proteolytic enzymes.

Mixing cross-reactive extracts. Summary Statement 29: The selection of allergens for immunotherapy should be based (in part) on the cross-reactivity of clinically relevant allergens. 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**

Immunologic and 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.[71] 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 genera 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 the Allergen extract section, Fig 2, and the allergens and allergy diagnostic tests practice parameters).

Dose selection. Summary Statement 30: 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.[22-26,128,149,245] Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000 vol/vol).[28] A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy vaccine. Failure to do so might reduce the efficacy of immunotherapy. This occurs because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased (see the Immunotherapy schedules and doses section for further discussion and for recommended maintenance doses).

Proteolytic enzymes and mixing. Summary Statement 31: Separation of extracts with high proteolytic enzyme activities, such as fungi (mold) and cockroach, from other extracts, such as pollens, is recommended. **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.[240,246,247] 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, and some weeds.[240,246,247] Cockroach had a similar deleterious effect on pollen extract potency.[246,248] Short ragweed appeared resistant to the effects of the proteolytic enzymes in one study,[240] 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.[247]

Dust mite extracts do not appear to have a deleterious effect on pollen extracts.[240,246,248] These studies suggest that pollen, dust mite, and cat extracts can be mixed together. 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. The evidence on mixing cockroach extract with other extracts is conflicting, and the clinical relevance of the changes is also unclear; therefore the clinician has the option of separating cockroach or not.

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 with lesser activities, such as pollen extracts.

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.

In this regard the number of separate injections that need to be given at each patient visit depends on whether all of the relevant extracts mixed into a single vial still deliver an optimal dose of each allergen. If mixing causes excessive dilution or if there are advantages to separating allergens into separate vials, then more than one vial might be necessary for successful immunotherapy.

Summary Statement 32: Allergen immunotherapy extract preparation should be performed by individuals experienced and trained in handling allergenic products. **D**

Allergen immunotherapy extracts are high-alert products that carry the risk for anaphylaxis. Policies, procedures, and processes intended for conventional drugs and medications might be highly 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 fatal anaphylactic reactions with allergenic products. 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. There are no reports of infection associated with allergen immunotherapy injections. Allergen vaccines are prepared by using sterile manufacturer's extracts and sterile diluents containing antibacterial constituents (usually phenol). A summary of the AAAAI/ACAAI/JCAAI proposed USP allergen immunotherapy extract preparation guidelines can be found in Table VIII.

TABLE VIII. AAAAI/ACAAI/JCAAI-proposed USP 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 below.*
   - 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.
2. **Physician responsibility**: A physician with training and expertise in allergen immunotherapy is responsible for ensuring that compounding personnel are instructed and trained in the preparation of immunotherapy using an aseptic technique as defined below and that they meet the requirements of these guidelines. Evidence of such compliance shall be documented and maintained in personnel files.
3. **Bacteriostasis**: Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if 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 the FDA-approved package insert 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 treatment with sanitizing agents containing alcohol and/or 70% isopropanol 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 the physical integrity of the vial.
10. **Labeling**: Immunotherapy vials are to be clearly labeled with the patient's name and 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.

*__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 media, such as from Valiteq (http://www.valiteq.com), 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.

Allergen immunotherapy extract handling

Storage. Summary Statement 33a: Allergen immunotherapy extracts should be stored at 4°C to reduce the rate of potency loss. **B**

Summary statement 33b: 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**

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 a number of 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 extract, including reconstituted lyophilized extracts, should be stored at 4°C to minimize the rate of potency loss because storage at higher temperatures (eg, room temperature) can result in rapid deterioration.[249]

Extract manufacturers conduct stability studies with standardized extracts that expose them to various shipping conditions (personal communication). These studies include actual shipments made by their carriers to places like

Phoenix in the summer and Alaska in the winter. 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.

Storing dilute extracts. Summary Statement 34a: More dilute concentrations of allergy immunotherapy extracts (diluted greater than 1:10 vol/vol) are more sensitive to the effects of temperature and lose potency more rapidly than do more concentrated allergen immunotherapy extracts. The expiration date for more dilute concentrations should reflect this shorter shelf life. **B**

Summary Statement 34b: In determining the allergy vaccine expiration date, consideration must be given to the fact that the rate of potency loss over time is influenced by a number of 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 allergen immunotherapy 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.[249,250]

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.[250] Phenol is a preservative added to extracts to prevent growth of microorganisms.

Phenol can denature proteins in allergen extracts.[251,252] Human serum albumin might protect against the deleterious effect of phenol on allergen extracts.[251] 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,[250,253] possibly through inhibition of the activity of proteolytic and glycosidic enzymes that are present in certain extracts. However, it is irritating when injected and should be diluted before beginning immunotherapy. Recommendations for extract stability are found in the manufacturers' product insert sheets. 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. The pain associated with glycerin increases in proportion to the glycerin concentration and injection volume, and the pain is proportional to the total injected dose of glycerin.[254] However, individual pain perception can vary substantially. Total glycerin doses of less than 0.05 mL rarely produce clinically important pain.

TABLE IX. Potency of selected manufacturer's extracts currently available

Extract	Potency
Cat hair and pelt	5000 and 10,000 BAU/mL
Dust mite	3000, 5000, 10,000, and 30,000 AU/mL
Bermuda grass	10,000 AU/mL
Short ragweed	1:10-1:20 wt/vol or 100,000 AU/mL
Other grasses*	10,000 and 100,000 BAU/mL
Other pollen	1:10 to 1:40 (wt/vol) or 10,000 PNU/mL
Molds	1:10 to 1:40 (wt/vol) or 20,000 to 100,000 PNU/mL

AU, Allergy unit; *BAU*, bioequivalent allergy unit; *PNU*, protein nitrogen unit.
*Perennial rye, Kentucky blue/June, timothy, sweet vernal, redtop, orchard, and meadow.

There have been few studies that have investigated the potency of dilutions of allergen extract mixture over time. Expiration dates for allergen extract dilutions are somewhat empiric and not strongly evidence based. A study undertaken by the AAAAI 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. Dust mite and cat at 1:10 and 1:100 vol/vol dilution were also stable in all conditions of storage over 12 months, as measured by an ELISA assay using 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.

IMMUNOTHERAPY SCHEDULES AND DOSES

Summary Statement 35: A customized individual 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 can be based on single or multiple allergens. **D**

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. Animal dander contains between 10 and 20 antigens,[255] house dust mites between 20 and 40 antigens,[256] and pollens between 30 and 50 antigens,[257,258] and fungal extract can contain as many as 80 antigens.[259]

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. This is designated as the patient's maintenance concentrate.

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. Standardized extracts are available with biologic potencies of 10,000 and 100,000 BAU for grasses; 5000 and 10,000 BAU for cat allergen; 5000, 10,000, or 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 wt/vol extracts (Table IX). 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.

Summary Statement 36: The highest-concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial) that is used for the projected effective dose is called the maintenance concentrate vial. 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. **D**

The highest concentration of an allergen extract mixture that is projected to be used as the therapeutically effective dose is called the maintenance concentrate. This should be prescribed individually for each patient by an allergist/immunologist. 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 individual manufacturer's extracts. Some patients might be unable to attain the projected therapeutically effective dose of the maintenance concentrate because of local reactions, systemic reactions, or both (eg, cat, 1000 BAU [highest tolerated dose] vs 2000 BAU [projected effective dose]; see Table X for probable effective therapeutic dose range). Such patients might need weaker dilutions of their maintenance concentrate. Even so, 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 referred to as the maintenance dose. The consistent use of this nomenclature system is essential because errors in choosing the correct vial are a common cause of systemic reactions, especially when the patient transfers from one physician to another. Therefore it is important that standard terminology be adopted by all physicians who prescribe allergen immunotherapy.

Recommended doses

Summary Statement 37: The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The projected effective dose is referred to as the maintenance goal. Some individuals unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The effective therapeutic dose is referred to as the maintenance dose. **A**

The effective maintenance dose of immunotherapy for a particular patient must be individualized. To do this, the allergist/immunologist who prepares the allergen immunotherapy extract must balance the dose necessary to produce efficacy and the risk of reactions if such a dose is reached. The allergist/immunologist might need to prepare more than one maintenance concentrate to provide a therapeutic dose of each of the allergens for the polysensitized patient. Therapeutically effective doses for immunotherapy have been reported for some allergen extracts.[22,24,25,128,134,135,149,246,260,261] Effective doses have been determined for Hymenoptera venom, dust mite, cat allergen, dog, grass, and short ragweed (Table X).

Controlled studies demonstrate that the content of particular allergens in allergen immunotherapy extracts can be used to predict a therapeutic dose for those allergens, particularly when the extracts are standardized. For antigens 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. The therapeutically effective doses used in the most recent controlled clinical studies are the basis of the recommended dosage range of standardized extracts presented in Table X. 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 time that it is administered.[14]

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.[27] 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 risk of systemic reactions to immunotherapy injections with higher maintenance doses. The maintenance concentrate should be formulated to deliver a full therapeutic dose of each of its constituent components. However, some sensitive patients might not tolerate the targeted therapeutic dose, and their maintenance dose would be lower. Individuals 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 referred to as the maintenance dose.

Regardless of dose schedule, some patients are unable to progress to the predetermined maintenance dose because of large local or systemic reactions to the allergen

TABLE X. Probable effective dose range for allergen extracts US standardized units[a]

Antigen	Labeled potency or concentration[a,b]	Probable effective dose range
Dust mites: *D farinae* and *D pteronyssinus*[c]	3000, 5000, 10,000, and 30,000 AU/mL	500-2000 AU
Cat[d]	5000-10,000 BAU/mL	1000-4000 BAU
Grass, standardized[e]	10,000-100,000 BAU/mL	1000-4000 BAU
Short ragweed[f]	1:10 to 1:20 wt/vol 100,000 AU/mL	6-12 μg of Amb a 1 1000-4000 AU Concentration of Amb a 1 is on the label of wt/vol extracts in FDA units[358]
Nonstandardized extract, dog[g]	1:10 to 1:100 wt/vol	15 μg of Can f 1
Nonstandardized extracts	1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL	Highest tolerated dose

[a]Multiple studies have demonstrated that the efficacious dose for allergen immunotherapy is between 5 and 20 μg of the major allergen per injection. Only 2 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).

[b]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).

[c]There have been no dose-response studies with United States–licensed dust mite extracts, and dosing recommendations in AU value are extrapolated from published European studies that used aqueous[349] and alum-precipitated[149,151] extracts. 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.[149] The authors suggested the optimal maintenance dose was 7 μg of Der p 1. Corresponding doses were based on specific allergen measurements of US commercially available standardized extracts provided by manufacturers. Extrapolating effective and safe doses in this manner might not be scientifically valid. *D farinae* and *D pteronyssinus* are similar in group 1 allergen content according to the FDA's current reference standards. 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*.

[d]The major cat allergen Fed d 1 is reported in FDA units, with 1 Fel d 1 unit equaling approximately 2 to 4 μg of Fel d 1.[55,58,59] The amount of Fel d 1 in 10,000 BAU/mL ranges from 10 to 19.9 U/mL. One study demonstrated clinical efficacy of a maintenance dose of 4.56 FDA units of Fel d 1 dose in terms of decreased cat extract PD_{20}, titrated skin test results, and allergen-specific IgE and IgG levels.[350,351] In a recent study that investigated the efficacy in terms of immunologic changes of 3 doses of a United States–licensed cat extract (0.6, 3, and 15 μg) demonstrated that a significant effect on titrated skin prick test results, allergen-specific IgG4 levels, and $CD4^+$/IL-4 levels was only seen in the group treated with 15 μg of Fel d 1, although the 3-μg dose group did demonstrate a significant change in titrated skin test response and increase in cat-specific IgG4 levels.[22]

[e]There have been no dose-response studies with United States–licensed standardized grass extracts. Recommended doses are extrapolated from published European studies that have used aqueous,[130] alum-precipitated,[24,161] and calcium phosphate–precipitated grass pollen extracts.[352] One of these studies compared a dose of 2 μg with 20 μg of major timothy allergen (Phl p 5) and found clinical efficacy at both doses.[24] The efficacy was greater in the 20 μg of Phl p 5 dose, but the systemic reaction rate was also higher in the high-dose group. The package inserts for United States–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 BAU. Extrapolating effective and safe doses in this manner might not be scientifically valid. 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).

[f]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 suggested that 1 unit of Amb a 1 is equivalent to 1 μg of Amb a 1, and 350 Amb a 1 units/mL is equivalent to 100,000 BAU/mL.[60] The package insert of the short ragweed 100,000 AU/mL extract states the optimal immunotherapy dose is 2000 AU, with a range of 1000-4000 AU. One open study of patients with ragweed-induced allergic rhinitis demonstrated 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.[45] A ragweed dose-response study (0.6, 12.4, and 24.8 μg of Amb a 1) demonstrated efficacy, as measured by nasal challenge, at 12 and 24 μg of Amb a 1.[128] The efficacy of the 24-μg dose was not significantly better than the 12-μg dose, and the authors concluded that the optimal dose for ragweed extract was greater than 0.6 μg but not more than 12.4 μg of Amb a 1.

[g]Dog extracts are not standardized. However, one dose-response study with a United States–licensed acetone-precipitated dog extract investigated the efficacy of 3 doses (AP dog; Hollister-Stier, Spokane, Wash; 0.6, 3, and 15 μg) in terms of immunologic changes and found the dose of 15 μg of Can f 1 to be most efficacious.[25] 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 have assayed between 128 and 208 μg/mL (average Can f 1, 162 μg/mL [SD ± 26 μg/mL]; information provided by the extract manufacturer, Hollister-Stier).

immunotherapy extract. The evidence is not clear whether large local reactions are a potential risk for subsequent allergen immunotherapy systemic reactions.

Published studies do not indicate that an individual large local reaction is predictive of a subsequent systemic reaction.[179,180] However, one retrospective study found that individuals who have a history of repeated large local reactions (defined as >25 mm) might be at greater risk for a subsequent systemic reaction.[181]

The concept of highest tolerated dose does not apply for VIT, and all patients are expected to achieve the full recommended dose to achieve the necessary degree of protection. There are conflicting data over whether lower doses (50 μg) are less effective, but there are also data showing that 200 μg is more reliably effective.[245] In the case of VIT, patients are asked to tolerate more large local reactions to achieve the full dose, even though with inhalant immunotherapy the dose can be reduced for such large local reactions to minimize patient discomfort.

Effect of dilution on dose

Summary Statement 38: 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 vaccine, thereby limiting the ability to deliver a therapeutic effective dose for any given allergen.

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

Dilution from maintenance concentrate vaccine	Volume	Volume (mL)	Diluent volume (mL)	Final volume
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.

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 2000 BAU/mL, 2 mL of the manufacturer's extract (cat, 10,000 BAU/mL) can be added to 8 mL of diluent or 8 mL of other allergens, and the final concentration of cat will be 2000 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.

Dilutions of the maintenance concentrate

Summary Statement 39: 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 vol/vol 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, 1000 BAU or 100 BAU), but this system can be complicated if allergens with different potency units are used (eg, wt/vol, BAU, AU, or PNU) and make it difficult to easily interpret the vial label.

Instructions on how to prepare various allergen extracts 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.

Labeling dilutions

Summary Statement 40: 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, a number of 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 (vol/vol), a numbering system, a color-coding system, or an alphabetical system should be used. If this uniform labels 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.

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
1000-fold	1:1000	4	Green
10,000-fold	1:10,000	5	Silver

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 3 and 4).

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 Appendix 2]).

Individualized treatment vials

Summary Statement 41: 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 (wrong patient) injection. The mixing of antigens in a syringe is not recommended because of the potential for 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). Labels on patient-specific vials can provide at least 2 patient identifiers (birth date and patient name), which would be consistent with the recommendations of the Joint Commission on Accreditation of Health Care Organizations National Patient Safety Goals: ''Goal 1: Improve the accuracy of patient identification by using at least two patient identifiers when providing care, treatment or services.''[5] 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 administration of the injection.[4,5]

In a survey of 1717 allergists endorsed by the AAAAI and JCAAI, 57% of the 476 respondents reported at least one wrong-patient injection, and 74% of the 473 respondents reported at least one wrong-dose injection.[4] 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 reasons why this might reduce incorrect injection errors. One reason was that patient-specific vials can be prepared in a quiet laboratory setting, which might provide substantially less distraction than the nurse in a room with a patient who is trying to concentrate only on drawing up the injection correctly. In addition, the specific components are mixed once with the preparation of individually prepared patient-labeled vials, whereas the mixing would be repeated on every injection visit if the allergen extract is withdrawn from different stock solutions, as it is in the off-the-board method. For safety reasons and to avoid cross-mixing of allergens removed from the manufacturer's extract, the mixing of antigens in the syringe (off the board) is not recommended.

Some allergists/immunologists prefer to administer immunotherapy doses drawn directly from a single stock dilution of individual allergens or common mixes (shared specific patient vials). In this way the immunotherapy dose is transferred to the patient without cross-contamination. If shared-patient (eg, mixed vespids and dust mite mix) vials are used, it is essential that policies and procedures are developed to verify that the correct dose from the correct vial is administered to the correct patient.

Starting doses

Summary Statement 42: The starting dose for build-up is usually a 1000- 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 slowly 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 1:1000 (vol/vol), although more diluted concentrations frequently are used for patients who are highly sensitive, as indicated by history or skin test reaction (see Appendix 3 for an example of a conventional immunotherapy schedule).

Frequency of build-up injections

Summary Statement 43: The frequency of allergen immunotherapy administration during the build-up phase is usually 1 to 2 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 2 times per week. 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 4 to 6 months, depending on the starting dilution and the occurrence of reactions. It is acceptable for patients to receive injections more frequently, provided there is adequate spacing between injections. The interval between injections is empiric but might be as short as 1 day without any increase in the occurrence of systemic reactions[262] if there is some urgency to achieve a maintenance dose (eg, allergy season is approaching) or for practical reasons (eg, patient's schedule). Alternatively, treatment schedules can be used that more rapidly achieve maintenance dosing. These cluster and rush dosing schedules are discussed in Summary Statements 47 through 49.

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 a number of 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).

Dose adjustments for systemic reactions

Summary Statement 44: 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 benefit/risk ratio justifies continuation of immunotherapy.

Reductions during periods of exacerbation of symptoms

Summary Statement 45: Immunotherapy given during periods when the patient is exposed to increased levels of allergen to which they are sensitive might be associated with an increased risk of a systemic reaction. Consider not increasing or even reducing the immunotherapy dose in highly sensitive patients during the time period when they are exposed to increased levels of allergen, especially if they are experiencing an exacerbation of their symptoms. **C**

Immunotherapy administered during periods of exacerbation of symptoms is considered a risk factor for immunotherapy.[17,184] Injections administered during periods when a patient is exposed to increased levels of allergen to which they are 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.[184] 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 sensitive, especially if their symptoms are poorly controlled.

Dose adjustments for late injections

Summary Statement 46: It is customary to reduce the dose of allergen immunotherapy extract when the interval between injections is prolonged. **D**

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 depends 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 Appendix 4 for an example of a dose-modification regimen for gaps in treatment).

Cluster schedules

Summary Statement 47: 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 (see Appendix 5).[22,26] 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. The cluster schedule is associated with the same or a slightly increased frequency of systemic reactions compared with immunotherapy administered with more conventional schedules.[145,263-266] The occurrence of both local and systemic reactions to cluster immunotherapy can be reduced with administration of an antihistamine 2 hours before dosing.[267]

Rush schedules

Summary Statement 48: 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.[268] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.[191,269-272]

The most accelerated schedule that has been described for inhalant allergens involves administering 7 injections over the course of 4 hours.[273] Ultrarush immunotherapy schedules have been described for stinging insect hypersensitivity to achieve a maintenance dose in as little as 3.5 to 4 hours.[274-276] 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 cluster[145,266] and rush[134,277] schedules.

Systemic reactions and rush schedules

Summary Statement 49: Rush schedules are associated with an increased risk of systemic reactions. However, rush protocols for administration of Hymenoptera VIT have not been associated with a similarly high incidence of systemic reactions. **A**

The advantages of rush immunotherapy come at a cost because there is an increased risk of local and systemic reactions. Systemic reaction rates have been reported to be

as high as 73% of patients, with the risk of such reactions reduced to 27% by premedication in one study.[272] Most reactions to rush immunotherapy are not severe, and the most common systemic reaction is usually flushing.[273]

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

Rush protocols for administration of Hymenoptera venom have not been associated with a similarly high incidence of systemic reactions.[274-276,278,279]

Premedication and weekly immunotherapy

Summary Statement 50: Premedication can reduce the frequency of systemic reactions caused by conventional immunotherapy. **A**

There is concern that antihistamines taken before each injection with conventional immunotherapy might mask a minor reaction that would otherwise alert a physician to an impending systemic reaction. 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.[280] One study that compared terfenadine premedication with placebo premedication during rush VIT demonstrated greater clinical efficacy in the terfenadine-premedicated group in terms of subsequent responses to field stings or sting challenge.[281] There was also a significant difference in the systemic reaction rate between the 2 groups: 6 patients in the placebo-premedicated group had systemic reactions, whereas none of the patients in the terfenadine-premedicated group had systemic reactions ($P = .012$).

Unfortunately, patients might still have life-threatening anaphylaxis despite 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.

Premedication with cluster and rush immunotherapy

Summary Statement 51: Premedication should be given before cluster and rush immunotherapy with aeroallergens to reduce the rate of systemic reactions. **A**

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.[267] Premedication with a 3-day course of prednisone, an H_1 histamine receptor antagonist, and an H_2 histamine receptor antagonist before rush immunotherapy with inhalant allergens reduced the risk of a systemic reaction from approximately 73% to 27% of patients.[272] In one study designed to investigate the effect of 12 weeks of premedication with a humanized monoclonal anti-IgE antibody (omalizumab) on the safety and efficacy of rush immunotherapy, there was a 5-fold decrease in the risk of anaphylaxis in the group premedicated with omalizumab compared with the placebo premedication group.[282]

There are anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist, but there have been no published studies. Because the risk of a systemic reaction from rush VIT is relatively low, routine premedication before rush VIT is usually unnecessary.[274,276,278,279] In a study evaluating premedication with antihistamines and steroids for rush immunotherapy with imported fire ant venom, there was no statistically significant differences in the systemic reaction rates between the premedication and placebo premedication group (3.6% of the premedication group vs 6.7% of the placebo group, $P = .87$).[157]

Maintenance schedules

Summary Statement 52: Once a patient reaches a maintenance dose, the interval between injections often can be progressively increased as tolerated up to an interval of up to 4 weeks for inhalant allergens and up to 8 weeks for venom. Some individuals 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 individuals might tolerate longer intervals between maintenance dose injections.

The interval between venom injections can be safely increased up to 8 weeks in some patients without loss of efficacy. 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.

Continuing care

Time course of improvement. Summary Statement 53: Clinical 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.[24,134,143,277] Improvement might not be observed for a number of reasons, including (1) failure to remove significant allergenic exposures (eg, a cat), (2) exposure to high levels of

allergen (eg, pollen or molds), (3) continued exposure to nonallergen triggers (eg, tobacco smoke), or (4) incomplete identification and treatment of clinically relevant allergens. 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 54: 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 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 55a: 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 benefits and risks associated with discontinuing or continuing immunotherapy. **D**

Summary Statement 55b: 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 very severe reaction to a sting, a systemic reaction during VIT (to a sting or a venom injection), honeybee venom allergy, and treatment duration of less than 5 years. **C**

Summary Statement 55c: 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 up to 5 years of treatment. **D**

Summary Statement 55d: 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**

Summary Statement 55e: Some patients might experience sustained clinical remission of their allergic disease after discontinuing immunotherapy, but others might relapse. **B**

The patient's response to immunotherapy should be evaluated on a regular basis. 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. 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.

There have been very 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 individuals.[283-285] However, relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported.[283,285] Nevertheless, systemic reactions to stings after discontinuing VIT were generally much milder than the pretreatment reactions and were rarely severe. Two studies did not find a difference in relapse rates between the patients treated for 3 years compared with those treated for 5 years,[283,286] but one of the studies noted that the small number of patients in the 3-year treatment group prevented them from making any conclusions about the risk of discontinuing treatment after 3 years.[283] However, one study found that patients who had experienced re-sting reactions after discontinuing VIT had received VIT for a significantly shorter duration (mean, 43.35 months) than those with continued protection (mean, 54.65 months; $P < .01$).[285] Another study reported that 5 years of VIT provided better immunologic and clinical outcomes than 2 to 4 years of treatment.[287]

Change in skin test reactivity did not appear to predict persistent efficacy after discontinuation because the skin test response was negative in some of the patients who experienced a systemic sting reaction. However, no relapses were observed among patients without detectable venom-specific IgE.[286,288] Some of the patients who experienced systemic sting reactions after discontinuing VIT had experienced systemic reactions during the VIT treatment.[288] The relapse rate and the frequency of severe reactions were greater in patients who had a history of very severe reactions to stings before treatment, in patients who had systemic reactions during VIT (to a sting or a venom injection), in patients with honeybee allergy, and in those who had less than 5 years of treatment.

The duration of inhalant allergen immunotherapy efficacy has not been as extensively studied. Some studies have suggested 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 *(D pteronyssinus)* extract for 12 to 96 months.[14] 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.[13] There was a switch to placebo in half of 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. These studies demonstrate the uncertainty of the long-term benefit of inhalant immunotherapy after discontinuation.

Currently, there are inadequate diagnostic tools available to identify which patients will experience a sustained clinical remission after discontinuing inhalant immunotherapy, and 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 indication for continuation of immunotherapy can be found at http://www.aaaai.org or http://www.jcaai.org.

Documentation and record keeping. Summary Statement 56: The allergen immunotherapy extract contents, informed consent for immunotherapy, and administration of extracts should be carefully 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 allergy immunotherapy and prescription forms can be found in the Appendix (Appendices 6-15), and these include examples of immunotherapy prescription and administration forms. These forms, along with examples of immunotherapy consent and instruction forms, can also be found at http://www.aaaai.org.

Injection techniques. Summary Statement 57: Allergen immunotherapy extract injections should be given using a 1-mL syringe with a 26- to 27-gauge half-inch nonremovable needle. **C**

Immunotherapy should be given with a 26- to 27-gauge syringe with a half-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.[289-291]

If using shared specific patient vials (stock vials, such as mixed vespid or dust mite mix), a single dose should be drawn from each vial. Antigens from different vials should not be combined in a single syringe. Furthermore, extra care is needed to prevent using the wrong stock antigen.

Summary Statement 58: The injection should be given subcutaneously in the posterior portion of the middle third of the upper arm. **D**

Each immunotherapy injection should be given in the posterior portion of the middle third of the upper 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.

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.

The syringe should be aspirated to check for blood return in the syringe before injecting. If blood is present, 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 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 syringe should be appropriately discarded. A fresh syringe and needle are necessary to determine whether a blood vessel has been entered.

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 could result in a local reaction.

LOCATION OF ALLERGEN IMMUNOTHERAPY ADMINISTRATION

Physician's office

Summary Statement 59: 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 to treat anaphylaxis should be in the immediate vicinity when immunotherapy injections are administered.

Summary Statement 60: 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.[292] 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.[184] 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 might be frequently necessary in the patient's immunotherapy schedule, as well as the patients total treatment program.

Other locations

Summary Statement 61: Regardless of the location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. **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.[292] The health care professional and staff 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, or allergy/asthma exacerbations at the time of allergen immunotherapy extract injection or poorly controlled asthma).

Appropriate adjustment of dose should be made as clinically indicated. The physician who prepared the patient's allergen immunotherapy extract should provide adequately labeled allergen immunotherapy extract vials, detailed directions regarding dosage schedule for build-up and maintenance, and instructions on adjustments that might be necessary under the following circumstances:

1. when providing patients with new vials;
2. during seasonal exposure to allergens that are in the patient's allergen vaccine, to which the patient is very sensitive, or both;
3. if the patient has missed injections; and
4. when reactions occur to the allergen immunotherapy extract.

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

Home administration. Summary Statement 62: 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 patients' health (eg, VIT for a patient living in a remote area), very careful consideration of potential benefits and risks of at-home administration of allergen immunotherapy should be made on an individual patient 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 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 very 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 fully trained to administer the injection and to treat anaphylaxis if this should 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 supports (personnel, medications, supplies, and equipment) are more optimal for encouraging prompt recognition and treatment of anaphylaxis (Table V). 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.

Summary Statement 63: If a patient on 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. If immunotherapy is continued, a decision must then be made about whether to continue an unchanged immunotherapy program initiated by the previous physician or to prepare a new immunotherapy program. **D**

Summary Statement 64: If a patient transfers from one physician to another and continues on an immunotherapy program without changes to either the schedule or allergen immunotherapy extract, the risk of a systemic reaction is not substantially increased. **D**

Summary Statement 65: A full, clear, and detailed documentation of the patient's schedule must accompany a patient when he or she transfers responsibility for their immunotherapy program 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**

Summary Statement 66: An allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the extract. These include changes in the lot, manufacturer, allergen extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and/or components or relative amounts in the mixture. **D**

Summary Statement 67: There is an increased risk of a systemic reaction in a patient who transfers from one physician to another if the immunotherapy extract is changed because of the significant variability in content and potency of allergen extracts. The risk of a systemic reaction with a different extracts might be greater with nonstandardized extracts and with extracts that contain mixtures of allergens. **D**

Summary Statement 68: Immunotherapy with a different extract should be conducted cautiously. If there is inadequate information to support continuing with the previous immunotherapy program, re-evaluation might be necessary, and a new schedule and allergen immunotherapy extract might need to be prepared. **D**

Patients often 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 brought from the previous physician (ie, an unchanged immunotherapy program) or one to be prepared by the current physician (ie, a new immunotherapy program).

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 full, clear, and detailed documentation of the patient's previous schedule and the contents of the allergen immunotherapy extract (see Appendices 7, 8, 11, 12, and 14 for examples of allergen immunotherapy prescription and administration forms and documentation guidelines for allergen immunotherapy forms). In addition, the patient's previous response to and compliance with this program 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 a schedule and the allergen immunotherapy extract, (2) the patient has shown significant improvement on this immunotherapy program, and (3) the contents of the allergen immunotherapy extract are appropriate for the area in which the patient is now living.

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, vaccine type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient's dose is not modified. This increased risk is due to the significant variability in content and potency of extracts and the variability in methods used by physicians to prepare the patient's maintenance concentrate and its dilutions. For example, the strength of a given concentration of nonstandardized extracts might vary significantly from vial to vial. The risk of systemic reactions in such a situation might be greater with nonstandardized extracts and allergen immunotherapy extracts that contain mixtures of allergens.

Therefore if the allergen immunotherapy extract is to be changed, the patient might need to be retested for specific IgE to the appropriate allergens 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 provided the interval of time since the last injection has not been too long. For lot changes from the same manufacturer, the physician can consider decreasing the dose by 50% to 90%. For changes in manufacturer and nonstandardized extracts, a greater decrease in dose might be necessary.

SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

Allergen immunotherapy in children

Summary Statement 69: Immunotherapy for children is effective and often well tolerated. Therefore immunotherapy should be considered (along with pharmacotherapy and allergen avoidance) in the management of children

with allergic rhinitis, allergic rhinoconjunctivitis, allergic asthma, and stinging insect hypersensitivity. It might prevent the new onset of allergen sensitivities or progression to asthma. **A**

Immunotherapy for children has been shown to be effective and often well tolerated,[137,242] although at least one study did not show efficacy.[293] 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.[294] In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (see the Patient selection section and Table VII). In recent studies children receiving allergen immunotherapy have demonstrated:

1. improvement in symptom control for asthma[117,119,121,122] and allergic rhinitis[118];
2. increased PC_{20} to histamine[121];
3. increased PC_{20} to cat and house dust mite allergens[121,149];
4. decreased risk of development of asthma[6,9,163-165];
5. decreased development of new sensitivities[120,166]; and
6. modification in release of mediators in children receiving immunotherapy that correlates with decreased clinical symptoms.[123]

Summary Statement 70: Children under 5 years of age can have difficulty cooperating with an immunotherapy program. Therefore the physician who evaluates the patient must consider the benefits and risks of immunotherapy and individualize treatment in patients under the age of 5 years. **A**

Although there is some disagreement about the role of allergen immunotherapy in children under the age of 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.[117,122] In children with allergic rhinitis, allergen immunotherapy might prevent the development of asthma.[6,9,163-165] However, allergen immunotherapy for inhalant allergens is usually not considered necessary in infants and toddlers because (1) there is 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 in pregnancy

Summary Statement 71: Allergen immunotherapy might be continued but is usually not initiated in the pregnant patient. **C**

The physician must be aware of the benefits and risks of immunotherapy in pregnant patients. The recommended precautions for prevention of adverse reactions are especially important in the pregnant patient. Allergen immunotherapy is effective in the pregnant patient. Thus allergen immunotherapy maintenance doses can be continued during pregnancy. Allergen immunotherapy is usually not initiated during pregnancy because of risks associated with systemic reactions and their treatment (ie, spontaneous abortion, premature labor, or fetal hypoxia). 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, and the patient is maintained on the dose that she is receiving at that time.

Immunotherapy in the elderly patient

Summary Statement 72: Comorbid medical conditions and certain medication use might increase the risk from immunotherapy in elderly patients. Therefore special consideration must be given to the benefits and risks of immunotherapy in this patient population. **D**

Immunotherapy might be considered in the treatment of the elderly patient, but the benefit/risk assessment must be evaluated carefully in this population. Older 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. However, elderly patients may also benefit from allergen immunotherapy and age alone should not preclude the consideration of allergen immunotherapy.[295]

Immunotherapy in patients with immunodeficiency and autoimmune disorders

Summary Statement 73: Immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. **D**

There are no controlled studies about the effectiveness or risks associated with immunotherapy in patients with immunodeficiency or autoimmune disorders. Therefore the decision to begin immunotherapy in patients with major humoral or cellular immune defects must be individualized. Concern about the increased risk of immunotherapy in such patients is largely hypothetical.

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

ALTERNATIVE ROUTES OF IMMUNOTHERAPY

Sublingual and oral immunotherapy

Summary Statement 74: Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation in the United States. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be

effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. However, there is no FDA-approved formulation for sublingual or oral immunotherapy in the United States. Therefore sublingual and oral immunotherapy should be considered investigational at this time. **B**

Alternative routes of administration of allergen immunotherapy are ''a viable alternative to parenteral injection therapy'' in some cases.[106,296] Studies of oral immunotherapy have provided conflicting results for ragweed,[297] birch,[298] and cat[299] immunotherapy. The present dosage of oral immunotherapy extract is 20 to 200 times the parenteral injected dosage, which requires a cost assessment for this type of therapy. Furthermore, adverse effects have included gastrointestinal and oral reactions (50% in 1 study) that might preclude home therapy. Oral immunotherapy should be considered investigational at this time.

Optimal-dose (high-dose) sublingual swallow immunotherapy is effective in adults and children.[300-304] In a study of 855 patients with grass pollen allergy and allergic rhinitis randomized to placebo or one of 3 grass tablet doses, there was a significant reduction in symptom and medication scores in the highest-dose subgroup, who were treated for at least 8 weeks before the grass pollen season, compared with the placebo group (symptoms, 21%, $P = .0020$; medication use, 29%, $P = .0120$).[303]

Sublingual allergen studies have evaluated house dust, olive pollen, grass pollen, ragweed, birch, cat, latex, *Alternaria* species, and *Parietaria judaica*.[305-313] Sublingual immunotherapy has been shown to be effective in patients sensitized to 2 non–cross-reacting allergens, grass and birch.[314] It has been noted that the allergen is not degraded by saliva and that there is no direct sublingual absorption of allergen. Radiolabeled allergen has been detected after 48 hours in the sublingual region.[315,316] Alternative protocols, such as rush and ultra-rush (20 minutes) sublingual swallow[307,316,318] and no induction (build-up) phase,[301,303,317,319,320] have been studied. Several studies have suggested a relationship between dose and efficacy with sublingual immunotherapy,[303,310,321] but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. The majority of sublingual studies have demonstrated some evidence of clinical efficacy in the form of either improved symptom scores, medication scores, or both, but approximately 35% of the randomized, double-blind, placebo-controlled studies did not demonstrate efficacy in either parameter during the first year of treatment.[322] Further studies are needed to confirm the optimal dose for sublingual immunotherapy.

One of the potential advantages of sublingual immunotherapy is that it appears to be safe, even at very high doses (up to 500 times the usual monthly subcutaneous dose), and to be associated with a lower incidence of serious side effects.[310,320,323] This appears to apply to young children (<5 years), for whom there are prospective safety data[324,325] and a postmarketing survey.[326]



FIG 3. Sample of labels for allergen immunotherapy extract vials.

There have been no SLIT-related fatalities, but there have been 3 case reports of anaphylaxis caused by sublingual immunotherapy. One patient with latex hypersensitivity had anaphylactic shock 20 minutes after reaching the maximal dose on the fourth day of latex rush sublingual rush immunotherapy.[327]

The other 2 reported cases of SLIT anaphylaxis involved patients treated with multiple inhalant allergens. In one case a patient with allergic rhinitis and asthma who was prescribed a sublingual immunotherapy extract composed of multiple non–cross-reacting allergens (*Alternaria* species, dog, cat, ragweed mix, weed mix, and grass mix)[328] had generalized pruritis, followed by angioedema, shortness of breath, and dizziness, within a few minutes of administering 6 drops of the 1:100 vol/vol dilution on the third day of treatment. This episode was preceded by a milder systemic reaction the previous day (generalized pruritis). In the other case, a 13-year-old girl with allergic rhinitis and asthma had swelling of her lower lip 3 minutes after pollen drops, high fever, chest pain, nausea, and abdominal pain.[329] She was treated in the emergency department for anaphylaxis and hospitalized for observation. The reaction occurred 1 month after she had reached the maintenance dose during the peak of the spring season.

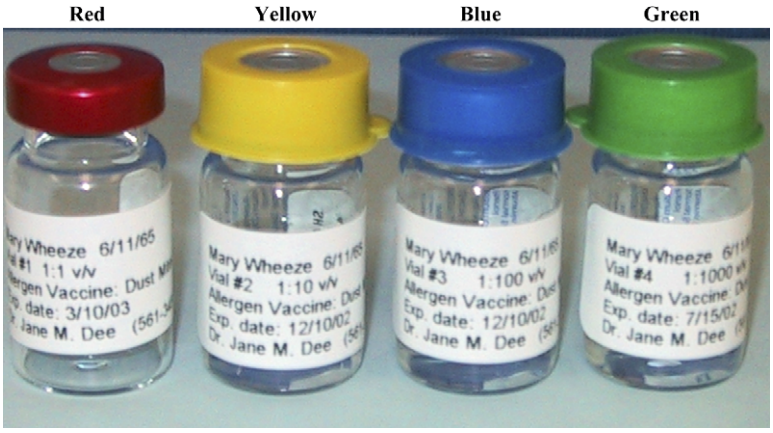


FIG 4. Sample set of color-coded vials of allergen vaccine.

There is currently no FDA-approved formulation for sublingual immunotherapy in the United States at this time, and this modality should be considered investigational. Current investigation of sublingual immunotherapy should not be confused with low-dose sublingual immunotherapy based on provocation neutralization testing or Rinkel-type skin testing.

Intranasal immunotherapy

Summary Statement 75: Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality in the United States. **B**

Based on controlled, well-designed studies, intranasal immunotherapy has been shown to improve the nasal symptoms of rhinitis.[330] Intranasal dry powder extract immunotherapy has been studied in grass,[330] birch,[331] *P judaica*,[332-334] and house dust mite[335] allergy. Clinical efficacy was noted in all of these studies. Nasal reactivity to allergen challenge was reduced, and only minor side effects were noted in 2 of the above studies. A 3-year study with *P judaica* reported to provide persistent benefits for up to 12 months after conclusion of allergen immunotherapy.[333] Local administration of nasal allergen in an aqueous solution for immunotherapy might be limited by the local side effects. Further studies in both pediatric and adult groups are needed. In human studies the antigen has been noted to appear in the serum within 15 to 30 minutes of administration, with a peak level occurring within 2 to 3 hours.[315] Some allergens have been reported to be retained in the nasal mucosa for up to 48 hours after administration. Intranasal immunotherapy is not currently available in the United States but has gained some acceptance in other parts of the world.

Immunotherapy techniques that are not recommended

Summary Statement 76: Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not recommended. **D**

Low-dose regimens, including coseasonal low-dose immunotherapy for aeroallergens and the Rinkel low-dose titration techniques, are not effective.[27,28] Immunotherapy based on provocation–neutralization testing with food and aeroallergens and enzyme-potentiated desensitization is not effective.[336]

FUTURE TRENDS IN IMMUNOTHERAPY

Therapy with aeroallergen extracts will become more uniform (as is the current practice for insect venoms) as greater numbers of biologically standardized allergen extracts become available. The actual number of commercially available allergen extracts will be reduced based on consensus agreements about the regional prevalence of aeroallergens, their cross-allergenicity, and the relevance of their effect on human health in specific locales. Novel routes for more effective, convenient, and safer allergen immunotherapy are being investigated throughout the world.

For example, the sublingual route of administering allergen immunotherapy has been studied extensively in Europe. A meta-analysis confirmed its clinical effectiveness in allergic rhinitis,[302] and it has been reported to be effective in asthma as well.[337] Sublingual immunotherapy appears to have a very low risk of serious life-threatening systemic side effects, which might allow for home administration.[324,338] In some studies the clinical benefits of sublingual immunotherapy were not significant until the second year of treatment,[306,339] and comparisons suggest that the magnitude of the clinical benefit of sublingual immunotherapy might not be as great as that of subcutaneous immunotherapy.[311]

Trials with non–IgE-binding peptides containing T-cell stimulating peptides have been reported.[340] Site-directed mutagenesis has produced allergens with decreased IgE-binding capacity without decreased T-cell responses.[341,342]

Immunostimulatory sequences mimicking bacterial and viral DNA have been prepared that stimulate the innate immune system to direct T-cell responses toward

T_H1 rather than T_H2 phenotypes.[343] The results of clinical trials with a conjugate of the immunostimulatory sequence to the major allergen of ragweed, Amb a 1 (AIC), have been reported.[34,343] In a double-blind, placebo-controlled study of 25 adults who received 6 weekly injections of the AIC or placebo vaccine before ragweed season, the AIC group had better peak-season rhinitis scores on the visual analog scale ($P = .006$), peak-season daily nasal symptom diary scores ($P = .02$), and midseason overall quality-of-life scores ($P = .05$) than the placebo group during the first ragweed season, and this effect was observed in the subsequent ragweed season.[344]

Humanized anti-IgE mAb has been shown to have clinical effects in both allergic rhinitis and asthma.[345-348] Theoretically, this new therapeutic modality could be used as protective cover for clinical applications of rapid forms of immunotherapy. It is possible that preadministration of anti-IgE could provide a more effective protective effect than premedication with antihistamines and therefore permit a rush allergen immunotherapeutic regimen with reduced risk of serious systemic reactions.[282]

AUTHOR'S 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 2 systemic reaction grading systems (the European Academy of Allergy and Clinical Immunology's grading of severity for systemic side effects and the Portnoy method for numeric grading of reactions to allergen immunotherapy) can be found in the Appendix section. These forms can also be found along with examples of immunotherapy instruction and consent forms, preinjection health questionnaires, and indications for beginning and continuing immunotherapy forms at www.aaaai.org.

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APPENDIX 1. American College of Medical Quality's policy on the development and use of practice parameters for medical quality decision-making[1]

Practice parameters are strategies for patient management developed to assist health care professionals in clinical decision making. Practice parameters include standards, guidelines, and other patient management strategies. Standards are accepted principles for patient management. Guidelines are recommendations for patient management that identify a particular management strategy or a range of management strategies. Other strategies for patient management include practice policies and practice options. Practice parameters are to be used as screening tools to identify possible deviations from the applicable standards of care. Such parameters are not to be used as absolute standards or to profile or report on health care personnel. Parameters are designed to trigger a process in which possible deviations from the standard of care are identified as outlier practice patterns. Once a deviation from the parameter is identified, such a deviation should be referred to the appropriate qualified physician advisor or reviewer for a determination of medical necessity that conforms to the applicable standard of care. Parameters used in the day-to-day practice of clinical medicine should be clinically relevant. They should not be considered as substitutes for the standard of care but might contribute to its formulation.

Practice parameters must be developed, designed, and implemented only by board-certified, clinically practicing, specialty-matched physician advisors/reviewers with unrestricted medical licenses. Qualified nonphysicians might participate in the development of these parameters only in the areas in which their clinical expertise based on the standard of care is applicable. The health care personnel who develop these parameters should sign their names and date the final version as evidence of their participation and support. Practice parameters must be based on sound scientific research findings, professional literature, clinical experience and appropriate well-recognized methodologies and reflect professionally recognized national standards of care practiced in the clinical community of medicine. The development procedures followed, the participants involved, the evidence used, the assumptions and rationales accepted, and the analytic methods used should be meticulously documented, described, and made publicly available for national peer review. Parameters should be updated as needed.

Practice parameters are used as tools to enhance medical decision making but not as replacements for physicians' clinical judgment. They can be considered as means to enhance the performance of clinical and review personnel but not to replace them. It is below the standard of care of the medical review process to substitute qualified physician reviewer experts with unqualified reviewers who are using parameters.

APPENDIX 2. Examples of possible abbreviations for allergen immunotherapy extract 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

APPENDIX 3. 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

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

APPENDIX 4. Example of immunotherapy dose adjustments for unscheduled gaps in allergen immunotherapy injection intervals (modification of the AAAAI skin testing and immunotherapy consent and instruction forms: immunotherapy administration instruction form, which can be found at http://www.aaaai.org)

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

- Up to 7 days, continue as scheduled (ie, if on weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection).
- Eight to 13 days after missed scheduled injection; repeat previous dose.
- Fourteen to 21 days after missed scheduled injection; reduce dose 25%.
- Twenty-one to 28 days after missed scheduled injection; reduce previous dose 50%.

Then increase dose each injection visit as directed on the immunotherapy schedule until therapeutic maintenance dose is reached.

This suggested approach to modification of doses of allergen immunotherapy because of gaps between treatment during the build-up phase is not based on retrospective or prospective published evidence, but it is presented as a sample for your consideration. The individual physician should use this or a similar protocol as a standard operating procedure for the specific clinical setting. A similar dose-reduction protocol should be developed for gaps in maintenance immunotherapy.

APPENDIX 5. Example of a cluster immunotherapy schedule[22,26]

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

APPENDIX 6. Recommended documentation for allergen immunotherapy prescription forms

The purpose of the allergen immunotherapy prescription form is to define the contents of the allergen immunotherapy extract in enough detail that it could be precisely duplicated. The following information should be on an immunotherapy prescription form:

Patient information:

- Patient name, patient number (if applicable), birth date, telephone number, and picture (if available) should be included.

Preparation information:

- Name of person and signature preparing the allergen immunotherapy extract should be included.
- Date of preparation should be recorded.
- Bottle name should be included (eg, trees and grass). If abbreviations are used, a 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 should be included.
- Volume of manufacturer's extract to add to achieve the projected effective concentration should be included. 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) should be included.
- Extract manufacturer should be included.
- Lot number should be included.
- Expiration date should be recorded and should not exceed the expiration date of any of the individual components.

APPENDIX 7. Allergen immunotherapy extract prescription 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:

_____
_____
_____
_____

_____ ____/____/____
Prescribing Physician Signature Date

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

APPENDIX 8. Maintenance concentrate prescription form

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: 6/10/06

Dates of subsequent dilutions from maintenance concentration with expiration dates
Vial **4** from Vial **1** on **8/30/06** Expiration date: **10/15/06**
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	Short ragweed	1:20 w/v G (150 Amb a1)	0.5ml	Greer	12345	1/01/08
2	Amaranthus Retroflexus	1:10 w/v G	0.5ml	H-S	6789	2/07/08
3	Ash	1:10 w/v G	0.5ml	Center	3333	3/17/08
4	Cat	10,000 BAU/ml G	2.00ml	ALO	9898	2/27/08
5	Timothy Grass	100,000 BAU/ml G	0.4ml	ALK	56789	7/09/08
6	Johnson Grass	1:10 w/v G	0.5ml	Greer	2434	7/20/08
7						
8						
9						
10						
Diluent	HSA		0.6ml	ALK	68597	12/08
Total Volume			5.00 ml			6/10/07

*** Components of mixes listed on a separate sheet**
**** Assumes 0.5 ml injection as target maintenance dose**

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

Specific Instructions:

_____

_____

Prescribing Physician Signature

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

APPENDIX 9. Labels for allergen immunotherapy extracts

Each vial of allergen immunotherapy extract should be labeled in a way that permits easy identification. Each label should include the following information (example in Figs 3 and 4):

- Appropriate patient identifiers might include the patient's name, patient's number, patient's picture, and birth date.
- The contents of the allergen immunotherapy extract in a general way should be included. The detail with which this can be identified depends on the size of the label and the number of allergens in the vial. Ideally, allergens should be identified as trees, grasses, weeds, mold, dust mite, cockroach, cat, and dog. Because of space limitations, it might be necessary to abbreviate the antigens (eg, T, G, W, M, DM, Cr, C, and D respectively [see Appendix 2]). A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate (vol/vol) should be recorded. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- The expiration date should be included.

APPENDIX 10. Allergen immunotherapy administration form recommended documentation

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

Patient information:

- Patient's name, date of birth, telephone number, and patient's picture (optional but helpful).

Allergen immunotherapy extract information:

- Allergen immunotherapy extract name and dilution from maintenance in vol/vol bottle letter (eg, A and B), bottle color, or number, if used.
- Expiration date of all dilutions.

Administration information in separate columns:

- Date of injection.
- Arm administered injection, which might facilitate determination of exact cause of local reaction.
- Projected build-up schedule.
- Delivered volume reported in milliliters.
- Description of any reactions. The details of any treatment given in response to a reaction would be documented elsewhere in the medical record and referenced on the administration form.
- *Patient's health before injection*. This can be performed through a verbal or written interview of the patient before administering the immunotherapy injection. The patient should be questioned about increased asthma or allergy symptoms, β-blocker use, change in health status (including pregnancy and recent infections), or an adverse reaction to a previous injection (including delayed large local reactions persisting through the next day). Patients with significant systemic illness generally should not receive an injection.
- *Antihistamine use*. Antihistamines are frequently a component of an allergy medication regimen, and it would be important to note whether a patient is taking an antihistamine on the day he or she receives his or her immunotherapy injection. For consistency in interpretation of reactions, it might be desirable for a patient to either take or avoid antihistamines on a regular basis on the days he or she receives immunotherapy. The physician should note on the form whether he or she recommends the patient consistently take an antihistamine on immunotherapy treatment days.
- *Peak flow reading*. Consider obtaining a peak expiratory flow rate measurement before administering an immunotherapy injection to asthmatic patients. Poorly controlled asthma is considered a risk factor for immunotherapy. Obtaining a peak expiratory flow rate measurement before the immunotherapy injection might help identify patients with symptomatic asthma. The patient's baseline peak expiratory flow rate should be provided on the form as a reference. Health care professionals administering immunotherapy injections should be provided with specific guidelines about the peak expiratory flow rate measurement for when an immunotherapy injection should be withheld and the patient referred for clinical evaluation.
- **Baseline blood pressure**. It might be useful to record the patient's blood pressure as a baseline for future reference.

APPENDIX 11. Allergen immunotherapy administration form

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 allergy or 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

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

Date to reorder: __/__/__

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 allergy or 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**	

APPENDIX 12. 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: _____
_____
Staff action taken (if any): _____

APPENDIX 13. 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.

APPENDIX 14. Allergen immunotherapy systemic reaction/anaphylaxis 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
__Epinephrine IM into 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	

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:
_____
_____
_____
_____

Clinical impression: True SR Questionable SR No SR

Systemic reaction severity classification: EAACI_____ **Portnoy** _____

Dosage adjustment? _____

Signatures_____ **RN** _____**MD/DO**

APPENDIX 15. Grading severity of allergen immunotherapy reactions: Two methods

1. **The European Academy of Allergy and Clinical Immunology grading of severity for systemic side effects***

Classification of systemic reactions

0 = No symptoms or nonspecific symptoms

I = Mild systemic reactions: symptoms—localized urticaria, rhinitis, or mild asthma (PF <20% decrease from baseline).

II = Moderate systemic reaction: symptoms—slow onset (>15 minutes) of generalized urticaria, moderate asthma, or both (PF < 40% decrease from baseline).

III = Severe (non–life-threatening) systemic reactions: symptoms—rapid onset (<15 minutes) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).

IV = Anaphylactic shock: symptoms—immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, and hypotension, for example.

2. **Portnoy method for numeric grading of reactions to allergen immunotherapy†**

Local

0+ = No significant reaction or small area of erythema less than the size of a half dollar without swelling or wheal formation

1+ = Erythema greater than the size of a half dollar, swelling or wheal formation, or both

Systemic

2+ = Systemic reactions: cutaneous only—might consist of a cutaneous eruption, such as urticaria

3+ = Systemic reaction: generalized pruritus, sneezing, or both—might consist of increased allergy symptoms, such as nasal congestion, sneezing, or pruritus, especially in the mouth or throat

4+ = Systemic reaction: pulmonary—consists of wheezing, shortness of breath, and tightness. Might be associated with decreased pulmonary function tests

5+ = Systemic reaction: anaphylaxis—a sensation of not feeling right is a frequent prelude; might consist of hypotension, laryngeal edema, severe wheezing, and cramping

6+ = Cardiopulmonary arrest

PF, Peak expiratory flow.

*Subcutaneous immunotherapy. Allergy 2006;61(suppl 82):5-13.

†Sharkey P, Portnoy J. Rush immunotherapy: experience with a one-day schedule. Ann Allergy Asthma Immunol 1996;76:175-80.

Correction

With regard to the 2007 supplement *Allergen Immunotherapy: A Practice Parameter Second Update* (J Allergy Clin Immunol 2007;120:S25-S85), there have been some modifications to the Practice Parameter's Table VIII, "AAAAI/ACAAI/JCAAI-proposed USP Allergen Immunotherapy Extract Preparation Guidelines," which is now entitled "Allergen Immunotherapy Extract Preparation Guidelines." At the time of the Practice Parameter's publication, the USP's <797> Pharmaceutical Compounding–Sterile Preparations guidelines were still being developed. Since the publication, these guidelines have been finalized.

The changes are additions and refer to the qualifications of the compounding personnel and responsibilities of the supervising physician:

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 physician is responsible for providing general oversight and supervision of compounding, although it is not required that the physician be in the office when allergy immunotherapy extracts are prepared.

TABLE VIII. 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 test 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, physician 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 using aseptic technique 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, although it is not required that the physician be in the office when allergy immunotherapy extracts are prepared.
3. **Bacteriostasis:** Allergen extract dilutions must be bacteriostatic, meaning that they must contain phenol concentrations of at least 0.25%, or if 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 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 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 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 the FDA-approved package insert or accepted standards of clinical practice permit another route of administration.
9. **Aseptic technique:** Preparation of allergy immunotherapy shall follow aseptic manipulations defined as:
   - 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 may contribute to microbial contamination (eg, eating, food preparation, placement of used diagnostic devices, 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 treatment with sanitizing agents containing alcohol and/or 70% isopropanol 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 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 media such as from Valiteq is transferred in ten 0.5-mL increments with a sterile syringe to a sterile 10-cc vial. Five mL of sterile water (preservative free) is added. This is the "concentrate." The vial is incubated within a range of 20-35°C for 14 days. Failure is indicated by visible turbidity in the medium on or before 14 days.