# Allergen immunotherapy: a practice parameter

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"Allergen immunotherapy: a practice parameter" has been reviewed and endorsed by the American Academy of Pediatrics.

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The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) jointly accept responsibility for this publication. 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, the ACAAI, and the Joint Council of Allergy, Asthma and Immunology (JCAAI). These parameters are not designed for use by pharmaceutical companies in drug promotion.

*Practice Parameters Published by the Joint Task Force on Practice Parameters*

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

## I. PREFACE

The objective of "Allergen immunotherapy: a practice parameter" is to improve the practice of allergen immunotherapy for patients with allergic rhinitis, allergic asthma, and Hymenoptera sensitivity. This parameter is intended to increase the appropriate use of allergen immunotherapy; reduce the underuse, overuse, and misuse of allergen immunotherapy; and establish guidelines for the safe and effective use of allergen immunotherapy, while reducing unwanted and unneeded variation in immunotherapy practice.

"Allergen immunotherapy: a practice parameter" was developed by the Joint Task Force on Practice Parameters. The three major allergy and immunology societies—the ACAAI, the AAAAI, and the JCAAI—charged the Task Force with

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the development of practice guidelines for allergen immunotherapy. The document "Allergen immunotherapy: a practice parameter" builds on the "Practice parameters for allergen immunotherapy" previously published by the Joint Task Force.[1] "Allergen immunotherapy: a practice parameter" was written and reviewed by subspecialists in allergy and immunology. The project was exclusively funded by the three allergy and immunology societies noted above.

A work group chaired by Dr. Richard Lockey prepared the initial draft. The Joint Task Force reworked the initial draft into a working draft of the document. 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 1).[2] Laboratory-based studies were not rated.

The working draft of "Allergen immunotherapy: a practice parameter" was reviewed by a large number of experts in immunotherapy, allergy, and immunology. These experts included reviewers appointed by the ACAAI, AAAAI, and JCAAI. More than 1,000 copies of the working draft were distributed at the ACAAI annual meeting in the fall of 2001. The authors carefully considered additional comments from these reviewers. The draft summary statements were distributed and presented at a symposium during the 2002 AAAAI annual meeting. Approximately 1,000 physicians attended this symposium. The authors reviewed comments from these participants also. The revised final document presented here was approved by the sponsoring organizations and represents an evidence-based, broadly accepted consensus opinion.

Table 1. 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 quasi-experimental 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 or clinical experience of respected authorities, or both |
| LB | Evidence from laboratory-based studies† |
| **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 |
| E | Directly based on category LB evidence† |
| F | Based on consensus of the Joint Task Force on Practice Parameters† |

* From Shekelle et al.[2] By permission of British Medical Journal.
† Added by current authors.

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 category I 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 immunoglobulin (Ig)E antibodies to relevant allergens. Symptoms of allergic conjunctivitis (eg, itchy, watery eyes) are often considered part of allergic rhinitis or are included in the diagnosis of rhinoconjunctivitis. Thus, in this document the term *allergic rhinitis* also applies in cases of allergic conjunctivitis. 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 and specific IgE antibodies to Hymenoptera venom.

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.

Physicians are using various immunotherapy buildup and maintenance doses, schedules, and procedures. The terminology of immunotherapy is sometimes ambiguous. This parameter recommends a more uniform and standardized terminology and provides specific recommendations for immunotherapy maintenance doses, schedules, and procedures.

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 term *allergy serum* is outmoded and should not be used. In 1998 the World Health Organization proposed changing the designation *allergen extract* to *allergen vaccine* to reflect the protective effect of allergen immunotherapy.[3] The term *vaccine* refers to an agent that is "given to induce a state of protection against a disease."[4]

*Allergen vaccine* is the recommended term for the therapeutic agent used in allergen immunotherapy. This term is used in the document when the therapeutic use of the preparation is clear. The terms *allergen extract* or *extract* (*vac-*

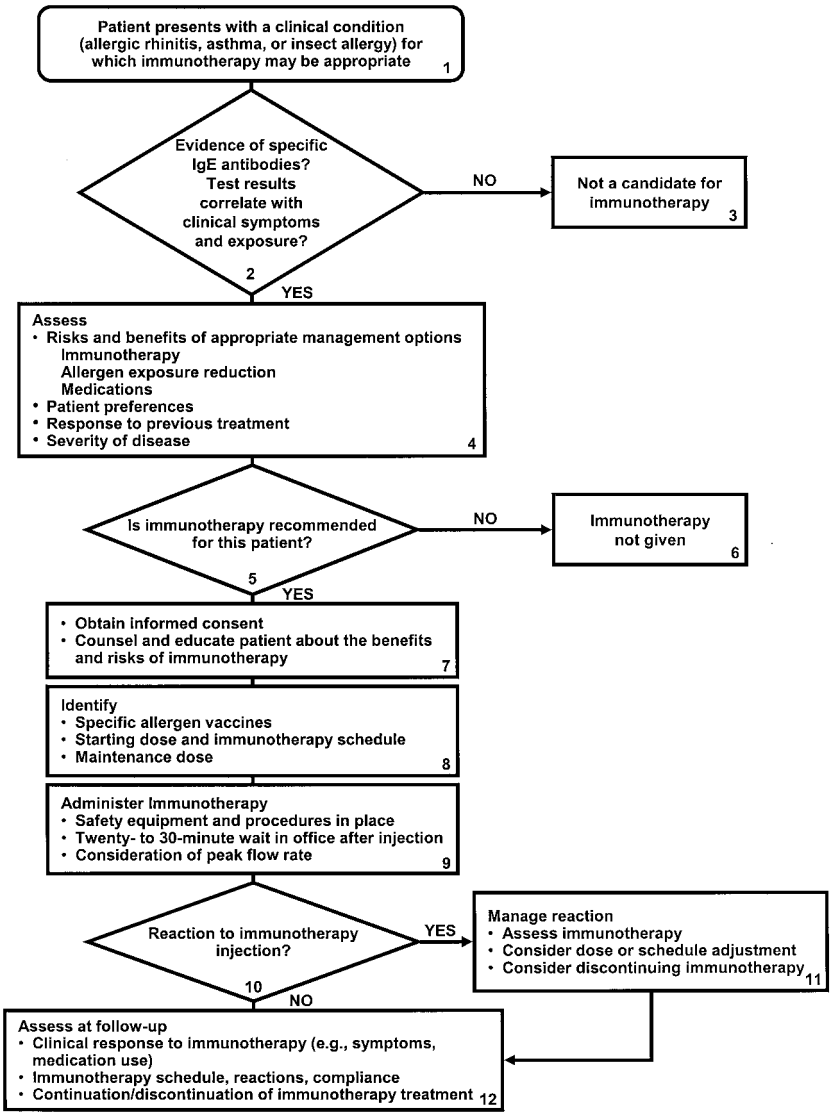


Figure 1. Algorithm for allergen immunotherapy. IgE, immunoglobulin E.

*cine*) are used in text where the nontherapeutic aspects of the allergen preparation are important.

The term *maintenance concentrate* should be used to identify the vaccine that the physician plans to use as the maintenance dose of immunotherapy (see Section XII). The term *manufacturer's extract* (*vaccine*) simply refers to the vaccine 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 (vol/vol) dilution (eg, 1:100 vol/vol dilution of a maintenance concentrate).

Allergen immunotherapy is effective when appropriate doses of allergen vaccine are administered. Recommended doses for common allergens are found in Section XII.

"Allergen immunotherapy: a practice parameter" recommends that vials of allergen vaccines *not* be shared among patients (the so-called off-the-table method). Vials of allergen vaccine should be prepared individually for each patient to enhance individualization of therapy, reduce the risk of allergen cross-contamination, and reduce the risk of error in administration.

To improve the uniformity and standardization of immunotherapy practice, this parameter recommends the use of standard vaccine prescription forms, vaccine content forms, and immunotherapy administration forms. Suggested forms are found in Section XII. The routine use of these standardized forms should improve the quality of immunotherapy practice.

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## RELATED GUIDELINES

For more disease-specific information, the reader is referred to related guidelines on allergy diagnostic testing,[5] asthma,[6,7] allergic rhinitis,[8] and stinging insect hypersensitivity.[9] "Allergen immunotherapy: a practice parameter" provides an update for the immunotherapy sections of these guidelines.

## II. ALGORITHM AND ANNOTATIONS

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

1) Immunotherapy is effective in the management of allergic asthma, allergic rhinitis, and stinging insect hypersensitivity. Allergen immunotherapy may prevent the development of asthma in children with allergic rhinitis. Evaluation of a patient with suspected allergic rhinitis, asthma, or stinging insect allergy includes a detailed history, an appropriate physical examination, and selected laboratory tests. A definitive diagnosis of allergic asthma, allergic rhinitis, or stinging insect hypersensitivity depends on the results of allergy testing (immediate hypersensitivity skin tests or well performed in vitro tests for specific IgE antibody). Immediate hypersensitivity skin tests are preferred for most patients. For additional details, see the practice parameters on asthma,[6,7] rhinitis,[8] allergy diagnostic testing,[3] stinging insect hypersensitivity,[9] and anaphylaxis.[10]

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 tests for specific IgE antibodies correlate with suspected triggers and patient exposure.

3) Immunotherapy should not be given to patients with negative tests for specific IgE antibody or those with positive tests for specific IgE antibody 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.

4) Management of complex medical conditions such as allergic asthma, allergic rhinitis, and stinging insect hypersensitivity should include the careful evaluation of management options. Each of the three major management approaches (immunotherapy, allergen exposure reduction, and pharmacotherapy) has benefits, risks, and costs. Further, 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.

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, immunotherapy may or may not be recommended. In general, patients with allergic rhinitis or allergic asthma whose symptoms are not well controlled by medications or avoidance may 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. In general, patients with stinging insect hypersensitivity who are at risk for anaphylaxis should receive venom immunotherapy.

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

7) Before immunotherapy is started, patients should understand its benefits and risks. The risk of anaphylaxis and the importance of adhering to the immunotherapy schedule should be discussed.

8) The physician prescribing immunotherapy should be trained and experienced in prescribing and administering immunotherapy. The prescribing physician must select the appropriate allergen vaccines on the basis of that particular patient's clinical history, allergen exposure history, and the results of tests for specific IgE antibodies. The quality of the allergen extracts (vaccines) available is an important consideration. When preparing mixtures of allergen extracts (vaccines), the prescribing physician must take into account the cross-reactivity of allergen extracts (vaccines) 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 (Section XII). In general, the starting immunotherapy dose is 1,000-fold to 10,000-fold less than the maintenance dose. For highly sensitive patients, the starting dose may be lower. The maintenance dose is generally 600 allergy units (AU; eg, for dust mite) or 4,000 bioequivalent allergy units (BAU; eg, grass) for standardized allergen vaccines. For nonstandardized extracts (vaccines), a suggested maintenance dose is 3,000 to 5,000 protein nitrogen units (PNU) or 0.5 mL of a 1:100 weight/volume dilution of manufacturer's extract (vaccine). If the major allergen concentration of the vaccine is known, a range between 5 and 20 $\mu$g is a recommended maintenance dose. In general, the immunotherapy schedule to reach maintenance consists of gradually increasing doses during approximately 14 to 28 weeks varying between twice-weekly injections for 14 weeks and weekly injections for 28 weeks. Rush, modified-rush, or cluster immunotherapy schedules are also appropriate for some patients.

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 may receive immunotherapy injections at another health care fa-

cility if the physician and staff at that location are equipped to recognize and manage immunotherapy reactions, in particular, anaphylaxis. Patients should wait at the physician's office for at least 20 to 30 minutes after the immunotherapy injection(s) 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, some physicians recommend measuring peak expiratory flow rate (PEFR) before administering an immunotherapy injection and withholding an immunotherapy injection if the PEFR 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.

10) Injections of allergen vaccine can cause local or systemic reactions. Most severe reactions develop within 20 to 30 minutes after the immunotherapy injection, but reactions can occur after this time.

11) Local reactions can be managed with local treatment (eg, cool compresses or topical corticosteroids) or antihistamines. Systemic reactions (anaphylaxis) can be mild or severe. Management of systemic reactions should include epinephrine, preferably given intramuscularly, although subcutaneous administration is acceptable. Antihistamines and systemic corticosteroids may help to modify systemic reactions, but should never replace epinephrine because of their slow onset of action and lack of immediate vascular effect. Intravenous saline or supplemental oxygen may be required in severe cases. For additional details, see the practice parameters for anaphylaxis.[10]

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

12) Patients receiving maintenance immunotherapy should have followup visits at least every 6 to 12 months. Periodic visits may 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, the reaction history, and patient compliance should also be evaluated. The physician may at this time make adjustments to the immunotherapy schedule or dose as clinically indicated.

For many patients, the recommended duration of allergen immunotherapy is 3 to 5 years. However, the duration of immunotherapy should be individualized on the basis of clinical response, disease severity, immunotherapy reaction history, and patient preference.

## III. IMMUNOTHERAPY GLOSSARY

*Allergen immunotherapy* is the repeated administration of a specific allergen(s) to patients with IgE-mediated conditions for the purpose of providing protection against the allergic symptoms and inflammatory reactions associated with natural exposure to the allergen(s).[1] Other terms that have been used for allergen immunotherapy are *hyposensitization*, *allergen-specific desensitization*, and the common terms *allergy shots* or *injections*.[11]

*Anaphylaxis* is an immediate systemic reaction occurring after exposure to an allergen. It is caused by the rapid, IgE-mediated release of vasoactive mediators from tissue mast cells and peripheral blood basophils.

*Cluster immunotherapy* is the administration of two or more injections per visit to achieve a maintenance dose more rapidly than is achieved with conventional schedules. It is a type of rush immunotherapy characterized by the giving of several allergen injections in a single day of treatment. (See other forms of rush immunotherapy, below.)

*Desensitization* is a process by which effector cells are rendered less reactive or nonreactive to IgE-mediated immune responses by the rapid administration of incremental doses of an allergenic substance. In some cases, the skin test response to the agent is reduced or is negative after desensitization.

*Extracts*, or *allergen extracts*, are solutions of proteins and glycoproteins extracted from source materials such as pollen, mold cultures, and pelt. The terms *allergen extract* and *extract (vaccine)* are used in this document where the nontherapeutic aspects of the allergen preparation are important. (See *Vaccine*.)

*Hyposensitization* was formerly used interchangeably with *allergen immunotherapy*. It was introduced to distinguish allergen immunotherapy from classic experimental animal desensitization. Because complete desensitization can rarely be accomplished by allergen immunotherapy, it was proposed that hyposensitization would appropriately denote this state of incomplete desensitization.

*Immunomodulation* is a global term that refers to a wide range of drug or immunologic interventions that alter normal or abnormal immune responses by deletion of specific T or B cells, immune deviation, anergic induction of peripheral or central tolerance, or modification of various inflammatory pathways (eg, chemotaxis, adhesins, or intracytoplasmic signaling).

*Immunotherapy* is a treatment method that appeared soon after the discovery of adaptive immune responses. It has evolved to encompass any intervention that may improve immune-induced aberrant conditions by various immunologic transformations. Early definitions of immunotherapy included active and passive immunization for the purpose of improving a host's defenses against microorganisms. Originally, allergen immunotherapy was conceived as a form of active immunization for the purpose of altering a host's abnormal immune responses rather than improving defense

against microorganisms. Today, immunotherapy includes all methods that attempt to overcome abnormal immune responses by inducing clonal deletion, anergy, immune tolerance, or immune deviation.

*Major allergen* refers to any antigen that binds to human IgE sera in >50% of patients in a clinically sensitive group. Binding reactions are detected by immunoblotting or crossed allergoimmunoelectrophoretic techniques, indicating that >50% of the patients have high specific IgE-binding capacity to the antigen.

*Modified rush immunotherapy* is a form of intensive immunotherapy in which subcutaneous allergen injections are administered at 24-hour intervals. Depending upon the sensitivity of the patient and the potency of the allergens being administered, premedication may or may not be necessary.

*Rush immunotherapy* is a form of allergen immunotherapy in which incremental doses of allergen are administered at intervals varying between 15 to 30 minutes and 24 hours, until the optimal effective dose is achieved. Very sensitive patients (eg, those with markedly positive prick or puncture tests) may experience various degrees of systemic reaction during this procedure. Therefore, physicians who use this method frequently premedicate patients with both antihistamines and corticosteroids to minimize the risk of systemic reaction.

*Vaccine, or allergen vaccine,* is the recommended term for the therapeutic preparations used in allergen immunotherapy. This term is used in the document when the therapeutic use of the preparation is clear. (See *extracts*.)

## IV. 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 empirical 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[12] and Freeman.[13] 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. Allergen immunotherapy may prevent the development of asthma in children with allergic rhinitis.

The subcutaneous administration of allergen vaccines should be differentiated from unproven methods such as neutralization-provocation therapy and subtherapeutic sublingual treatment (low-dose regimens based on Rinkel titration). Allergen vaccine therapy should also be differentiated from the process of desensitization, which usually refers to the rapid progressive administration of an allergenic substance (protein or simple chemical) to render effector cells less reactive.

## V. SUMMARY STATEMENTS

After each statement is a letter in parentheses. This letter indicates the strength of the recommendation. Letters are explained in Table 1.

### *Mechanisms of Immunotherapy*

Summary Statement 1. Immunologic changes during immunotherapy are complex. Successful immunotherapy is often associated with a shift from $TH_2$ to $TH_1$ CD4+ lymphocyte immune response to allergen. (A)

Summary Statement 2. Successful immunotherapy is also associated with immunologic tolerance, defined as a relative decline in allergen-specific responsiveness. (A)

Summary Statement 3. The relationship between immunotherapy efficacy and specific IgE antibody levels is variable. (A)

Summary Statement 4. Increases in allergen-specific IgG blocking antibody titer are not predictive of the duration and degree of efficacy of immunotherapy. (A)

### *Allergen Extracts (Vaccines)*

Summary Statement 5. Whenever possible, standardized extracts (vaccines) should be used to prepare vaccine treatment sets. (A)

Summary Statement 6. Nonstandardized extracts (vaccines) may vary widely in biologic activity. (B)

Summary Statement 7. In choosing the components for a clinically relevant vaccine, 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)

Summary Statement 8. 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*

Summary Statement 9. Immunotherapy is effective for treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Therefore, immunotherapy merits consideration in patients with these disorders. (A)

Summary Statement 10. Clinical studies to date do not support the use of allergen immunotherapy for food hypersensitivity, chronic urticaria, and/or angioedema. Therefore, allergen immunotherapy for patients with these conditions is not recommended. (B)

Summary Statement 11. Clinical parameters, such as symptom scores and medication use, may be useful measures

of the efficacy of immunotherapy in a clinical setting. Routine periodic skin testing or in vitro IgE antibody testing of patients receiving immunotherapy is not recommended. (A)

*Safety of Immunotherapy*

Summary Statement 12. In the United States severe systemic reactions occur rarely after appropriately administered allergen immunotherapy. (C)

Summary Statement 13. Because most systemic reactions that result from allergen immunotherapy occur 20 to 30 minutes after an injection, patients should remain in the physician's office at least 20 to 30 minutes after an injection. (C)

Summary Statement 14. Patients taking $\beta$-adrenergic blocking agents may be at increased risk when receiving allergen immunotherapy, because $\beta$-receptor blockade can make treatment of anaphylaxis more difficult. Therefore, $\beta$-adrenergic blocking agents are relative contraindications for immunotherapy. (C)

Summary Statement 15. Medical conditions that reduce the patient's ability to survive a systemic reaction are relative contraindications for allergen immunotherapy. Examples include severe asthma uncontrolled by pharmacotherapy and significant cardiovascular disease. (F)

Summary Statement 16. 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 are assured. (D)

*Patient Selection*

Summary Statement 17. 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. Patients who wish to avoid or reduce the long-term use of medications are good candidates for immunotherapy. (A)

Summary Statement 18. Patients with severe, poorly controlled asthma are at higher risk for systemic reactions to immunotherapy injections. (C)

Summary Statement 19. Venom immunotherapy should be strongly considered in patients with a history of a systemic reaction to a Hymenoptera sting (especially if the reaction was associated with respiratory or cardiovascular symptoms) and patients with demonstrable evidence of specific IgE antibodies. (A)

Summary Statement 20. Patients selected for immunotherapy should be cooperative and compliant. (A)

*Allergen Selection and Handling*

Summary Statement 21. The components of a clinically relevant vaccine (and therefore a vaccine that is most likely to be effective) should be selected on the basis of a careful history of relevant symptoms, knowledge of possible environmental exposures, and correlation with positive tests for specific IgE antibodies. (A)

Summary Statement 22. The immunotherapy vaccine should contain only clinically relevant allergens. (A)

Summary Statement 23. Immediate-type 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 and well performed in vitro tests for specific IgE antibodies may also be used. (A)

Summary Statement 24. Immunotherapy is effective for pollen, fungi (molds), animal dander, dust mite, cockroach, and Hymenoptera sensitivity. Therefore, immunotherapy should be considered as part of the management program in patients who have symptoms related to exposure to these allergens and in whom the presence of specific IgE antibodies has been established. (A)

Summary Statement 25. In the mixing of an allergen vaccine, the following factors must be considered: 1) the cross-reactivity of the allergens, 2) the optimal dose of each constituent, and 3) enzymatic degradation of the allergens. (E)

Summary Statement 26. The selection of allergens for immunotherapy should be based in part on the cross-reactivity of clinically relevant allergens. Many related pollen contain allergens that are cross-reactive. When pollen allergens are substantially cross-reactive, selection of a single pollen within the cross-reactive genus or subfamily may suffice. When pollen allergens are not substantially cross-reactive, testing for and treatment with multiple locally prevalent pollen may be necessary. (B)

Summary Statement 27. The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the clinically relevant constituents in the vaccine. (A)

Summary Statement 28. Separation of aqueous extracts (vaccines) with high proteolytic enzyme activities (eg, fungi, dust mites, cockroach, and insect venoms) from other extracts (vaccines) is recommended. (E)

Summary Statement 29. Extracts (vaccines) should be stored at 4° C to reduce the rate of potency loss. Dilute concentrations are more sensitive to temperature and lose potency more rapidly than do more concentrated preparations. The expiration date for dilute concentrations should reflect their shorter shelf life. (E)

*Immunotherapy Schedules and Doses*

Summary Statement 30. A commercially available allergen extract (vaccine) may be used alone or combined to prepare a customized allergen mixture for an individual patient. (F)

Summary Statement 31. The highest concentration of a vaccine projected as the therapeutically effective dose is called the maintenance concentrate. (F)

Summary Statement 32. The maintenance concentrate should be selected to deliver a dose considered to be a therapeutically effective dose for each of its constituent components. (A)

Summary Statement 33. Serial dilutions of the maintenance concentrate should be made in preparation for the buildup phase of immunotherapy. (F)

Summary Statement 34. Use of a consistent, uniform labeling system for dilutions from the maintenance concentrate may reduce errors in administration. (F)

Summary Statement 35. The maintenance concentrate and serial dilutions, whether a single vaccine or a mixture of vaccines, should be prepared and labeled for each patient. (F)

Summary Statement 36. The starting dose for buildup is usually a 1,000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose may be advisable for highly sensitive patients. (A)

Summary Statement 37. During the buildup phase, the usual frequency of vaccine administration is one to two injections per week, at least 2 days apart. (A)

Summary Statement 38. If immunotherapy is continued after a systemic reaction, the dose of vaccine should be appropriately reduced. (D)

Summary Statement 39. It is usual practice to reduce the dose of vaccine when the interval between injections is prolonged. (F)

Summary Statement 40. With cluster immunotherapy, two or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. (A)

Summary Statement 41. Rush schedules can achieve a maintenance dose more quickly than weekly schedules, but are associated with an increased risk of systemic reaction. Premedication can reduce the rate of systemic reaction. (B)

Summary Statement 42. Routine premedication before allergen immunotherapy injections administered on a conventional schedule is not necessary and may mask the early signs of systemic reaction. (F)

Summary Statement 43. When the patient has reached a maintenance dose, the interval between injections can often be progressively increased as tolerated to 4 to 6 weeks. (A)

Summary Statement 44. Clinical improvement usually is observed within 1 year after the patient reaches a maintenance dose. (A)

Summary Statement 45. Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. (F)

Summary Statement 46. A decision to continue or stop immunotherapy should be made after 3 to 5 years. (A)

Summary Statement 47. The vaccine contents, informed consent for immunotherapy, and administration of vaccines should be carefully documented. (F)

*Special Considerations in Immunotherapy*

Summary Statement 48. The preferred location for the administration of allergen immunotherapy is the office of the physician who prepared the patient's vaccine. (D)

Summary Statement 49. Generally, patients at high risk of systemic reaction should receive immunotherapy in the office of the physician who prepared the patient's vaccine. (D)

Summary Statement 50. Regardless of location, allergen immunotherapy should be administered under the supervision of an appropriately trained physician and personnel. (D)

Summary Statement 51. Immunotherapy injections should not be administered at home because of the risk of inadequate recognition and treatment of systemic reactions. (F)

Summary Statement 52. Immunotherapy for children is effective and often well tolerated. Therefore, immunotherapy is appropriate (as is pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Allergen immunotherapy may prevent the development of asthma in children with allergic rhinitis. (A)

Summary Statement 53. Children $<5$ years of age may have difficulty cooperating with an immunotherapy program. Therefore, the physician should carefully consider the benefits and risks of immunotherapy and individualize treatment in patients younger than 5 years of age. (A)

Summary Statement 54. Allergen immunotherapy may be continued in the pregnant patient, but it is customary to delay the commencement of allergen immunotherapy until the patient is no longer pregnant. (C)

Summary Statement 55. In older adults, medications and co-morbid medical conditions may increase the risk from immunotherapy. Therefore, special consideration must be given to the benefits and risks of immunotherapy in older adults. (D)

Summary Statement 56. Allergen immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. (D)

Summary Statement 57. High-dose sublingual-swallow, high-dose sublingual-spit, and oral immunotherapy are under clinical investigation. Efficacy has been demonstrated for high-dose sublingual-swallow therapy, but the results of oral immunotherapy are equivocal. Sublingual-spit therapy requires further study. These therapies are not currently in general use in the United States, and no vaccines intended for sublingual or oral use are available in the United States. (A)

Summary Statement 58. Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but this modality is currently not used in the United States. (B)

Summary Statement 59. Low-dose immunotherapy, enzyme-potentiated immunotherapy and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing are not effective and are not recommended. (D)

Summary Statement 60. If a patient receiving immunotherapy transfers from one physician to another, the new physician and the patient should decide whether to continue the immunotherapy program initiated by the previous physician or to prepare a new program. (F)

Summary Statement 61. If a patient transfers from one physician to another and no change is made in either the immunotherapy schedule or the vaccine, the risk of systemic reaction is not substantially increased. (F)

Summary Statement 62. A full, clear, and detailed documentation of the patient's immunotherapy schedule must accompany the patient when he or she transfers from one physician to another. Also, a record of previous responses to and compliance with the program should be communicated to the new physician. Finally, a detailed record of the results of the patient's specific IgE antibody tests (immediate-type skin tests or in vitro tests) should be provided. (F)

Summary Statement 63. An immunotherapy vaccine must be considered changed if there is any change in the constituents of the vaccine. This includes any change in the lot, manufacturer, vaccine type (eg, aqueous, glycerinated, standardized, nonstandardized), components, or relative amounts of the components in the mixture. (E)

Summary Statement 64. If a patient transfers from one physician to another, there is an increased risk of systemic reaction if the immunotherapy vaccine is changed because of the marked variability in the content and potency of vaccines. The risk of systemic reaction with a different vaccine is greater with nonstandardized vaccines and with vaccines containing mixtures of allergens. (F)

Summary Statement 65. Immunotherapy with a different vaccine should be conducted cautiously. If there is inadequate information to support continuation of the previous immunotherapy program (including tests for specific IgE antibodies), reevaluation may be necessary and a new schedule and vaccine prepared. (F)

## VI. MECHANISMS OF IMMUNOTHERAPY

**Summary Statement 1. Immunologic changes during immunotherapy are complex. Successful immunotherapy is often associated with a shift from $TH_2$ to $TH_1$ CD4+ lymphocyte immune response to allergen. (A)**

Successful immunotherapy is often associated with a shift from a predominant $TH_2$ to a $TH_1$ CD4+ lymphocyte immune response to allergen.[14–16] Studies show that increased production of interleukin (IL)-12, a strong inducer of $TH_1$ responses, contributes to this shift.[17–19] The high concentrations of antigens administered during immunotherapy may lead to extensive T cell receptor and co-receptor ligation, known to promote $TH_1$ cytokine responses[14,20]

**Summary Statement 2. Successful immunotherapy is also associated with immunologic tolerance, defined as a relative decline in allergen-specific responsiveness. (A)**

Clinically successful immunotherapy may be associated with immunologic tolerance, defined as a relative decline in antigen-specific responsiveness, immune deviation, or anergy. For example, lymphoproliferative responses to allergen are reduced with immunotherapy, and levels of some T cell-derived cytokines (eg, IL-4, IL-5, IL-13) decline during the course of immunotherapy.[16,21–24] A study in patients who received insect venom immunotherapy found that IL-10 was a critical factor in inducing this tolerance.[17] Evidence suggests that this is also true for inhalant allergen immunotherapy.[15,25–28]

**Summary Statement 3. The relationship between immunotherapy efficacy and specific IgE antibody levels is variable. (A)**

In patients receiving immunotherapy, there is an increase in specific IgE antibody levels, followed by a gradual decrease to a level that is still higher than the level present before treatment. Clinical improvement occurs in many patients before declines in their IgE antibody levels occur, and in other patients IgE antibody levels never decline; thus, efficacy is not dependent on reductions in specific IgE levels.[14,29,30] Despite persistence of increased specific IgE antibody levels, immunotherapy usually causes a reduction in the release of mediators such as histamine from basophils and mast cells, a phenomenon most pronounced during the immediate phase of allergic reaction. In general, suppression of late-phase inflammatory responses in the skin and respiratory tract also occurs with immunotherapy.[14,31–34]

**Summary Statement 4. Increases in allergen-specific IgG blocking antibody titer are not predictive of the duration and degree of efficacy of immunotherapy. (A)**

Although numerous immunologic changes occur in patients treated with allergen immunotherapy, many of these changes may not be clinically relevant.[14,35] For example, titers of allergen-specific IgG antibody, the so-called blocking antibody that theoretically competes with IgE, characteristically increase in patients during immunotherapy.[14,16,36,37] However, increases in specific IgG antibody do not correlate with clinical response to immunotherapy. Further, clinical improvement with immunotherapy may persist even though specific IgG levels decline to pretreatment levels after immunotherapy is discontinued.

## VII. ALLERGEN VACCINES

*Standardized Vaccines*

**Summary Statement 5. Whenever possible, standardized extracts (vaccines) should be used to prepare vaccine treatment sets. (A)**

Allergen extracts (vaccines) are commercially available for most of the commonly recognized allergens. Whenever possible, standardized extracts (vaccines) should be used to prepare vaccine treatment sets.[3,38–40]

The catalogs of manufacturers that produce allergen extracts and vaccines list a wide range of pollen, molds, animals, arthropods, and insects for which allergen immunotherapy is available. Extracts (vaccines) can be obtained in aqueous, glycerinated, lyophilized, and alum-precipitated formulations. Similar allergens can be purchased in different concentrations from different companies (eg, dust mite allergens in concentrations of 5,000 and 10,000 allergy units [AU]).

Some commonly used allergens are standardized. These include extracts (vaccines) for cat hair, cat pelt, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, short ragweed, Bermuda grass, Kentucky bluegrass, perennial ryegrass, 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, many are not yet standardized. In the United States, standardized extracts and vaccines first were labeled in potency units (AU), on the basis of major allergen content (eg, ragweed) but now are labeled on the basis of comparative skin test potency (bioequivalent allergy units; BAU). Most standardized extracts (vaccines) are labeled in BAU; dust mite extracts (vaccines) are still labeled in AU. Nonstandardized extracts (vaccines) are labeled as either weight-to-volume (wt/vol), which expresses weight in grams per volume in milliliters, or in protein nitrogen units (PNU), where 1 PNU equals 0.01 $\mu$g of protein nitrogen. International units (IU) are based on in vitro assays relative to World Health Organization standard allergens. Nonstandardized extracts (vaccines) labeled as wt/vol or in PNU show no consistent association between the quantity on the label and the biologic activity of the product. Because nonstandardized extracts (vaccines) may have a wide range of potency, it is essential that appropriate concentration nomenclature be used in the labeling of vials.

The advantages of standardized vaccines are that biologic activity is more consistent, and therefore risk of adverse reaction is diminished. Standardization focuses exclusively on total potency and does not account for immunochemical variations in individual extract (vaccine) constituents that may exist between manufacturers or between lots produced by the same manufacturers.

**Summary Statement 6. Nonstandardized extracts (vaccines) may vary widely in biologic activity. (B)**

For nonstandardized extracts (vaccines), the most common designation of potency currently in use is wt/vol. Nonstandardized extracts (vaccines) are also available in PNU. The wt/vol unit indicates how the extract or vaccine was produced. A potency of 1:100 indicates that 1 g of dry allergen (eg, ragweed) was added to 100 cc of a buffer for extraction. Pollen grains are eluted for a time, and then the solid material is filtered out, leaving an aqueous solution. Extracts (vaccines) with a particular wt/vol potency may have widely varying biologic activities.[41–43] Therefore, they should not be considered equipotent.

**Summary Statement 7. In choosing the components for a clinically relevant vaccine, 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 demographically diverse, it is not possible to devise a list of appropriate allergen extracts and vaccines for each practice location. Further, it is impractical to keep every available extract (vaccine) in the medical facility. 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.

There are few generally reliable sources that can help physicians make rational choices for individual patients. This has led to nonuniform allergen mixtures within specific geographic regions, often formulated without regard to environmental sampling, changes in ecologic diversity, and cross-allergenicity. Further, nonrelevant allergens in such mixtures could act as sensitizers rather than as tolerogens. The primary allergens used for immunotherapy are derived from plant (grasses, trees, weeds), arthropod (house-dust mites), fungus, animal (cat, dog), insect (cockroach), and Hymenoptera venom source materials.

*Cross-Reactivity of Allergen Extract (Vaccines)*

**Summary Statement 8. 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)**

The major clinically relevant aeroallergens of North America are listed in Table 2. 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-allergenicity is variable for many grass and weed pollen, their intrinsic allergenicity, prevalence, and aerobiologic characteristics within a specific region should be considered. Because many temperate pasture grasses (subfamily Poaceae; eg, fescue, rye, timothy, blue, orchard), which are widely distributed throughout the United States, share major allergens[44]; inclusion of a representative member (eg, perennial rye, meadow fescue, or timothy) generally provides efficacy against the entire group.[45–52] Grasses in other subfamilies (eg, Bermuda, Bahia, Johnson) show greater diversity and should be evaluated separately.[53] Bermuda and Johnson grasses are increasingly important in the South, and Bahia has become an important allergenic grass in the lower southern states. Because the ability of palms, sedges, and cattails to trigger allergic symptoms is uncertain, immunotherapy with these allergens is generally not recommended.

Although cross-allergenicity among tree pollen is limited, it does occur. Pollen from members of the cypress family (Cupressaceae; eg, juniper, cedar, cypress) strongly cross-react. Therefore, pollen from one member of this family should be adequate for skin testing and immunotherapy.[54–57] The closely related birch family (Betulaceae; eg, birch, alder, hazel, hornbeam, hop hornbeam) and beech (Fagaceae; eg, beech, oak, chestnut) have strong cross-allergenicity.[58–60] The use of one of the locally prevalent birch members (eg, birch, alder) should be adequate.[61–63] In areas where oaks predominate, the use of a single oak should provide coverage for the other oaks. Ash and European olive trees are strongly cross-reactive; the extract (vaccine) that correlates best with symp-

Table 2. The Major Clinically Relevant Aeroallergens of North America*

| |
|---|
| **Tree pollen** |
| Chinese elm (*Ulmus parvifolia*);†,‡ Siberian elm (*Ulmus pumila*);†,‡ 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 (*Moras 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 American Academy of Allergy, Asthma, and Immunology Immunotherapy committee and Allergen subcommittee for the identification of 35 key allergens in North America.

† Extensive cross-reaction of species within the genus.

‡ Apart from regional prevalences, 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.

‖ Like all ragweeds, extensively cross-react with other species within their genus.

** Species that are widely distributed and clinically important.

toms and is prevalent in the region could be used.[64,65] 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 stands) 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.

Strong cross-allergenicity between major allergens of common ragweed species (eg, short, giant, false, western) permits the use of a single pollen in this botanical group. Southern and slender ragweed do not cross-react as well.[66,67] 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 gives adequate coverage of the group.[68] Similarly, Chenopod-Amaranth families have wide ranges in the western regions. *Amaranthus* species have essentially the same allergenic identity, and use of a single extract (vaccine), such as redroot pigweed, is adequate.[69,70] Similarly, *Atriplex* species (eg, saltbushes, scales) show near identity; 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 semi-arid climates and regions of higher altitudes. *D. pteronyssinus* and *D. farinae* are members of the same family and genus. They have allergens with extensive cross-reacting epitopes as well as unique allergenic epitopes. Generally, *D. pteronyssinus* and *D. farinae* are considered individually.

Establishing the practical importance of various allergenic fungi involves many of the same problems encountered in treating pollen allergy. In general, the genera of Deuteromycetes occur in all but the coldest regions. For clinical purposes, molds often are characterized as outdoor (eg, *Alternaria*, *Cladosporium*, *Drechslera* [*Helminthosporium*] species) or indoor (eg, *Aspergillus*, *Penicillium*).

Immunotherapy with standardized extracts (vaccines) 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 or vaccine representing an equal mixture of German and American cockroaches may be appropriate for immunotherapy.[71]

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 (vaccines) are available for all Hymenoptera except the fire ant, for which only whole-body extract (vaccine) is available. The whole-body fire ant vaccine appears to be effective.[72,73]

## VIII. EFFICACY OF IMMUNOTHERAPY

*Allergic Rhinitis, Allergic Asthma, and Stinging Insect Hypersensitivity*

**Summary Statement 9. Immunotherapy is effective for treatment of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Therefore, immunotherapy merits consideration in patients with these disorders. (A)**

Many double-blind, placebo-controlled, randomized clinical trials have found a beneficial effect of immunotherapy under various conditions.[3,38,39,74–78] Immunotherapy is effective for the treatment of allergic rhinitis, including ocular symptoms,[79,80] allergic asthma, and stinging insect hypersensitivity,[77,81,82] and is effective in both adults and children.[83–91] Its efficacy is confirmed for the treatment of inhalant allergy attributable to pollen,[79,92–100] fungi,[101–106] animal allergens,[107–112] arthropods such as dust mites,[80,113–121] and insects such as cockroaches.[122] Various types of vaccine have been evaluated in these clinical trials, including aqueous and modified vaccines. Outcomes used to measure the efficacy of immunotherapy include symptom and medication scores, organ challenge, immunologic change in cell markers, and cytokine profiles. The magnitude of the effect depends on the outcome measure used (Table 3). 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 some studies have demonstrated efficacy for immunotherapy, others have not. A review of the studies that did not demonstrate efficacy failed to identify a systematic deficiency.[78] 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 efficacy was present (a type II error). To handle the issue of statistical power, meta-analyses of the efficacy of immunotherapy for rhinitis[76] and asthma[74,75] have been performed. These meta-analyses strongly support the efficacy of immunotherapy. Allergen immunotherapy for allergic rhinitis may have persistent benefits after immunotherapy is discontinued[100,123] and may reduce the risk for the development of asthma in children.[124–126]

Table 3. Improvement of Symptoms and Reduction in Medication and Bronchial Hyperresponsiveness after Immunotherapy*

| Outcome measure | Immunotherapy target | |
|---|---|---|
| | House-dust mite* | Other allergens*,† |
| Symptom 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 (3.8–50.0) | 5.5 (2.8–10.7) |

ND, not done.
* Odds ratios (95% confidence intervals).
† Pollen, mold, or animal dander.
Data from Abramson et al.[74]

*Food Allergy, Urticaria, and Atopic Dermatitis*

**Summary Statement 10. Clinical studies to date do not support the use of allergen immunotherapy for food hypersensitivity, chronic urticaria, or angioedema. Therefore, allergen immunotherapy for patients with these conditions is not recommended. (B)**

The use of allergen immunotherapy for individuals with the potential for IgE-mediated (allergic or anaphylactic) reactions to foods should be regarded as investigational.[127–130] No data demonstrate the efficacy of immunotherapy for individuals with chronic urticaria or angioedema. Limited data indicate that immunotherapy may be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity.[131]

*Measures of Efficacy*

**Summary Statement 11. Clinical parameters such as symptom scores and medication use may be useful measures of the efficacy of immunotherapy in a clinical setting. Routine periodic skin testing or in vitro IgE antibody testing of patients receiving immunotherapy is not recommended. (A)**

The clinical effectiveness of immunotherapy can be measured by both objective and subjective means. Although it is preferable to monitor the effectiveness of immunotherapy using objective measurements, many objective measurements are not practical for routine clinical use. Therefore, most allergists rely on subjective assessments, such as the patient's report that he or she feels better during a season previously associated with symptoms. Although subjective assessments are the most common means by which physicians judge the result of immunotherapy, they are not reliable, given the strong placebo effect associated with any treatment. More objective measures of efficacy, as validated in controlled clinical studies, are clinical symptom scores and the amount of medication required to control symptoms and keep PEFRs or pulmonary function test results within acceptable limits. Successful immunotherapy often leads to a reduction in medication use. Sequential measurement of disease-specific quality of life also may be helpful. Repeated 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 or specific IgE antibody levels closely correlate with a patient's clinical response.[118]

## IX. SAFETY OF IMMUNOTHERAPY

*Reaction Rates*

**Summary Statement 12. In the United States, severe systemic reactions are rare after appropriately administered allergen immunotherapy. (C)**

In the United States, the frequency of severe systemic reaction after allergen immunotherapy ranges from <1% of patients receiving conventional immunotherapy to >36% of patients in some studies of patients receiving rush immunotherapy.[132,133] In a study of 628 patients receiving conventional immunotherapy, 7% had a systemic reaction that oc-

curred within 6 hours after an injection.[134] In another study, however, only 0.5% of allergy injections resulted in a systemic reaction.[135] In the most comprehensive evaluation of fatalities associated with allergen immunotherapy, from 1945 to 1987 there were 40 fatalities during allergen immunotherapy and 6 fatalities during skin testing.[136] Therefore, although severe systemic reactions to allergen immunotherapy are not common, serious systemic reactions (some fatal) can occur. Risk factors for serious systemic reactions include 1) a medical condition that reduces the ability to survive a systemic reaction, 2) compromised pulmonary function, 3) poorly controlled asthma, and 4) concurrent use of β-adrenergic blocking agents.

*Timing of Anaphylactic Reactions to Immunotherapy Injections*

**Summary Statement 13. Because most systemic reactions that result from allergen immunotherapy occur 20 to 30 minutes after an injection, patients should remain in the physician's office at least 20 to 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.[136] A review of the literature indicates that 70% of systemic reactions occur within 30 minutes after an injection.[133] In a prospective study, systemic reactions occurring from 30 minutes to 6 hours after an allergen immunotherapy injection accounted for 38% of all systemic reactions.[134] In another prospective study, 8% of systemic reactions occurred more than 2 hours after injection.[135] Because most reactions that result from allergen immunotherapy occur 20 to 30 minutes after an injection, patients should remain in the physician's office at least 20 to 30 minutes after receiving an injection. In addition, patients who are at increased risk of systemic reaction, particularly if they previously have had a systemic reaction more than 30 minutes after an injection, may need to carry injectable epinephrine. These patients should be instructed in the use of epinephrine to treat a systemic reaction that occurs after they have left the physician's office or other location where the injection was given. Such patients may also need to remain in the physician's office more than 30 minutes after an injection.

*β-Adrenergic Blocking Agents*

**Summary Statement 14. Patients taking β-adrenergic blocking agents may be at increased risk when receiving allergen immunotherapy because β-receptor blockade can make treatment of anaphylaxis more difficult. Therefore, β-adrenergic blocking agents are relative contraindications for immunotherapy. (C)**

Patients who are receiving β-adrenergic blocking agents may be at increased risk if they experience a systemic reaction to an allergen immunotherapy injection because the reaction may be more severe and β-receptor blockade may attenuate the response to epinephrine.[137–144] In such cases, intravenous glucagon may be used if epinephrine has not been effective. An increased risk of hospitalization attributable to anaphylaxis has been found in patients receiving β-adrenergic blocking agents.[138] Among patients with reactions to radiographic contrast media, 61% have severe reactions if they have cardiovascular disease or are taking a β-blocker, as compared with 35% in whom these risk factors are not present.[139] In unusual circumstances, such as life-threatening stinging insect hypersensitivity, allergen immunotherapy may be considered even if the patient is taking β-blocking agents.

*Contraindications*

**Summary Statement 15. Medical conditions that reduce the patient's ability to survive a systemic reaction are relative contraindications for allergen immunotherapy. Examples include severe asthma uncontrolled by pharmacotherapy and significant cardiovascular disease. (F)**

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, uncontrolled hypertension, or failure of a major organ system.

Under some circumstances, immunotherapy may be indicated for a high-risk patient; however, the relative risks and benefits must be considered carefully. An example is a patient who has hypertension that is successfully controlled with a β-blocker and who is also sensitive to stinging insects. If, after consultation with the physician managing the patient's hypertension, it is agreed that stopping use of the β-blocker is not in the patient's best interest, it may be appropriate to initiate immunotherapy with venom vaccine.

*Reducing the Risk of Anaphylaxis to Immunotherapy Injections*

**Summary Statement 16. 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 assured. (D)**

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 the early symptoms and signs of anaphylaxis and administer emergency treatment if necessary (see Summary Statements 48 to 51). Epinephrine is the treatment of choice 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.[10,145–148] It is impor-

tant to administer epinephrine early in the management of anaphylaxis. Suggested actions to reduce the risk of anaphylaxis are listed in Table 4. 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 may occur without warning signs or symptoms. Documentation of informed consent is important.

## X. PATIENT SELECTION

*Clinical Indications*

**Summary Statement 17. 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. Patients who wish to avoid or reduce the long-term use of medications are good candidates for immunotherapy. (A)**

Clinical indications for allergen immunotherapy are given in Table 5.

Randomized, prospective, single- or double-blind, placebo-controlled studies demonstrate effectiveness of specific immunotherapy in the treatment of allergic rhinitis. Prospective, randomized, double-blind, placebo-controlled studies demonstrate effectiveness of specific immunotherapy in the treatment of allergic asthma (see Section VIII).

Table 4. Actions to Reduce the Risk of Anaphylaxis

| |
|---|
| Assessment of the patient's general medical condition at the time of injection (eg, asthma exacerbation). |
| Adjustment of the vaccine dose or injection frequency if symptoms of anaphylaxis occur and immunotherapy is continued. |
| Use of appropriately diluted initial vaccines in patients who appear to have increased sensitivity on the basis of history or tests for specific immunoglobulin E antibodies. |
| Instruction that patients wait in the physician's office for 20 to 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) may need to wait longer. |
| Careful evaluation of any patient with a late reaction (ie, local or systemic reaction more than 30 minutes after the immunotherapy injection). |
| Procedures to avoid clerical or nursing errors (eg, careful checking of patient identification). |
| Recognition that dosage adjustments are usually necessary with a newly prepared vaccine or a patient who has had a significant interruption in the immunotherapy schedule. |
| Adequate equipment and medications should be immediately available to treat anaphylaxis, should it occur.[149] This should include at least the following equipment and reagents: 1) stethoscope, 2) sphygmomanometer, 3) tourniquets, 4) syringes, 5) hypodermic needles, 6) large-bore (14-gauge) needles, 7) epinephrine 1:1,000, 8) oxygen, 9) equipment for administering intravenous fluids, 10) oral airway, 11) antihistamine for injection, 12) corticosteroid for intravenous injection, and 13) vasopressor. |

Table 5. Clinical Indications for Allergen Immunotherapy

| |
|---|
| **In patients with allergic rhinitis** |
| **Symptoms of allergic rhinitis after natural exposure to aeroallergens, demonstrable evidence of clinically relevant specific immunoglobulin (Ig)E antibodies, and one of the following:** |
| Poor response to pharmacotherapy or allergen avoidance |
| Unacceptable adverse effects of medications |
| Desire to avoid long-term pharmacotherapy and reduce the cost of medication |
| Coexisting allergic rhinitis and asthma |
| Possible prevention of asthma in children |
| **In patients with allergic asthma** |
| **Symptoms of asthma after natural exposure to aeroallergens, demonstrable evidence of clinically relevant specific IgE antibodies, and one of the following:** |
| Poor response to pharmacotherapy or allergen avoidance |
| Unacceptable adverse effects of medication |
| Desire to avoid long-term pharmacotherapy and reduce the cost of medication |
| Coexisting allergic rhinitis and allergic asthma |
| **In patients with reactions to Hymenoptera stings** |
| History of a systemic reaction to a Hymenoptera sting (especially if the reaction was associated with respiratory or cardiovascular symptoms) and demonstrable evidence of clinically relevant specific IgE antibodies* |
| Age >16 years, history of a systemic reaction limited to the skin, and demonstrable evidence of clinically relevant specific IgE antibodies |
| History of a systemic reaction to imported fire ant and demonstrable evidence of clinically relevant specific IgE antibodies |

* Patients younger than 16 years who present with a history of only cutaneous symptoms to Hymenoptera stings may not require immunotherapy.

Allergen immunotherapy is an effective form of treatment for many allergic patients, provided they have undergone an appropriate allergy evaluation. The expected response to allergen immunotherapy is antigen-specific and depends on the proper identification and selection of component allergens on the basis of the patient's history, allergen exposures, and diagnostic test results.

Aeroallergen immunotherapy should be considered for patients who have symptoms of allergic rhinitis or asthma after natural exposure to allergens and who demonstrate specific IgE antibodies to relevant allergens. Evaluation of the patient should include a medical history and an appropriate physical examination. The severity and duration of symptoms also should be considered in evaluating the need for specific allergen immunotherapy. Symptom severity can be defined by subjective as well as objective means. In addition, specific allergen immunotherapy should be considered if the patient wishes to avoid long-term pharmacotherapy. Time lost from work, visits to the emergency department or physician's

office, and response to conventional medications are also important objective indicators of disease severity.

Patients with allergic rhinitis who can not sleep because of symptoms or whose daytime 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 the patient's responsiveness to other forms of therapy, such as allergen avoidance or medication, should also be considered. Adverse effects of medication also should favor a decision to initiate allergen immunotherapy. Immunotherapy is usually not more costly than pharmacotherapy over the projected course of treatment.

Allergen immunotherapy for allergic rhinitis may have benefits that continue after immunotherapy is stopped. Preliminary results suggest that it may reduce the risk for the development of asthma in children.[123–126] These benefits of immunotherapy should be discussed with patients and may provide a clinical indication for initiating immunotherapy in selected patients with allergic rhinitis.

Coexisting medical conditions should also be considered in selecting patients who may benefit from allergen immunotherapy. Patients with moderate or severe allergic asthma and allergic rhinitis should be managed aggressively with a combined regimen of allergen avoidance and pharmacotherapy; these patients may also benefit from allergen immunotherapy.[6,7] Patients with severe or uncontrolled asthma may be at increased risk for systemic reactions to immunotherapy injections.[150]

*Special Precautions in Patients With Asthma*

**Summary Statement 18. Patients with severe, poorly controlled asthma are at higher risk for systemic reactions to immunotherapy injections. (C)**

Patients with severe, poorly controlled asthma are at higher risk for systemic reactions to immunotherapy injections than patients with stable, well controlled asthma.[132,150] One survey found that deaths from immunotherapy were more common in symptomatic (as compared with asymptomatic) patients with asthma.[136]

*Clinical Indications for Venom Immunotherapy*

**Summary Statement 19. Venom immunotherapy should be strongly considered in patients with a history of a systemic reaction to a Hymenoptera sting (especially if the reaction was associated with respiratory or cardiovascular symptoms) and patients with demonstrable evidence of specific IgE antibodies. (A)**

Systemic reactions to Hymenoptera stings, especially when associated with respiratory or cardiovascular symptoms, and positive skin tests or specific IgE antibodies are strong indications for allergen immunotherapy.[77,81,82] In the United States, patients older than 16 years of age who have a systemic reaction limited to the skin are also candidates for allergen immunotherapy. Patients younger than 16 years of age who present with only a cutaneous reaction to Hymenoptera stings may not require immunotherapy.[3,77] Adults and children with a history of systemic reactions to fire ants (*Solenopsis* species) and those with positive skin tests or specific IgE antibodies should be treated with allergen immunotherapy. Several studies of fire ant-allergic patients have demonstrated effectiveness of immunotherapy with whole-body extracts of fire ants.[73,151] In addition to allergen immunotherapy, patients with Hymenoptera venom sensitivity should be instructed in how to avoid insect stings and prescribed epinephrine (and taught how to use it). Some patients who have skin test results negative for IgE-mediated conditions are reported to have had subsequent systemic reactions to stinging insects.[152] However, there is no evidence that venom immunotherapy is effective in such patients. There are no published data of the effectiveness of venom immunotherapy in patients with negative skin tests and positive in vitro tests who have experienced moderate to severe anaphylaxis resulting from a Hymenoptera sting. However, there are data to indicate that these patients may have another episode of anaphylaxis if they are stung again while not receiving venom immunotherapy.[152] Therefore, the physician must consider the potential risk of future anaphylactic reactions; venom immunotherapy may be appropriate for such patients.[153]

**Summary Statement 20. Patients selected for immunotherapy should be cooperative and compliant. (A)**

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

## XI. ALLERGEN SELECTION AND HANDLING

*Allergen Selection*

*Clinical Evaluation.* **Summary Statement 21. The components of a clinically relevant vaccine (and therefore a vaccine that is most likely to be effective) should be selected on the basis of a careful history of relevant symptoms, knowledge of possible environmental exposures, and correlation with positive tests for specific IgE antibodies. (A)**

A careful history that notes environmental exposures and reflects an understanding of the local and regional aerobiology of suspected allergens is required for the selection of the components of a clinically relevant vaccine.[3,38] The prescribing physician must understand the local and regional suspected allergens, such as pollen, fungi (mold), animal (dander), arthropod (dust mite), and insect (cockroach) aeroallergen sources. Although the relationship between day-to-day outdoor pollen and fungi exposure and the development of clinical symptoms is not always clear, symptoms that consistently occur during periods of increased exposure to allergens, in association with positive results on skin tests or in vitro tests for specific IgE antibodies, provide good evidence that such

exposures are clinically relevant. Information concerning regional and local aerobiology is available on various web sites or through the Pollen and Mold Network at *http://www.aaaai.org*.

There are no data to support allergen immunotherapy as a treatment for non–IgE-mediated symptoms of rhinitis or asthma. Although in vitro tests may be helpful in the decision to administer immunotherapy, there is very limited evidence to support the administration of immunotherapy based solely on the results of specific in vitro testing. As is the case in interpreting positive immediate hypersensitivity skin tests, there must be a clinical correlation between the demonstration of in vitro allergen-specific IgE and the clinical history of the patient.

*Clinical Correlation.* **Summary Statement 22. The immunotherapy vaccine should contain only clinically relevant allergens. (A)**

The omission of clinically relevant allergens from an allergic patient's vaccine 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, dilutes the content of other allergens in the vaccine and can make allergen immunotherapy less effective.

A knowledge of the patient's total allergen burden and the realistic possibility of avoidance are important in determining whether allergen immunotherapy should be initiated. A patient's lifestyle may result in exposure to a wide variety of aeroallergens from different regions, necessitating inclusion of several allergens from different geographic areas in the vaccine. Many individuals travel extensively into various regions, and symptoms may worsen at these times. However, inclusion of allergens to which IgE antibodies are present but which are not clinically relevant dilutes the essential allergen components of the vaccine so that immunotherapy may be less effective. Determining the significance of indoor allergens for a particular patient is more difficult because it is difficult to determine exposure in the home or workplace. The identification of historical factors such as the presence of a furry animal in the home, an episode of water damage and subsequent fungal exposure, or a history of insect infestation may be helpful. However, such information is subjective and often of uncertain reliability. Commercial immunoassays to measure the presence of indoor allergens (eg, dust mite, cockroach, cat, dog) in settled house dust may 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 antibody.

*Skin Tests and In Vitro IgE Antibody Tests.* **Summary Statement 23. Immediate-type allergy 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 and well performed in vitro tests for specific IgE antibodies also may be used. (A)**

The use of standardized allergens has greatly increased the consistency of skin test results for antigens that have been standardized. Controlled studies in which the clinical history has been correlated with skin test results demonstrate the efficacy of immunotherapy for relevant allergens.[3,38,74–77] Skin testing also provides the physician with information about the appropriate starting dose of selected allergens. On rare occasions, systemic reactions occur from skin testing in a highly sensitive individual. In addition, skin tests may 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 testing to detect allergen-specific IgE.[154–157] As shown by inhalation challenge test results, skin tests have 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 selecting allergens to include in immunotherapy and for determining the starting dose in an immunotherapy program. Among the skin testing techniques available, a properly applied percutaneous test (prick or puncture) consistently produces reproducible results. Generally, prick testing is sensitive enough to detect clinically relevant IgE antibodies in 80% of patients. If a high concentration of diagnostic allergen extract is used for intracutaneous (intradermal) testing (ie, 1:100 wt/vol or greater), false-positive reactions (similar to an irritant response) may occur and have no clinical relevance.

In some patients it is appropriate to use in vitro tests for specific IgE antibodies as an alternative to skin tests in the diagnosis of allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. In vitro tests also can be used to define the allergens that should be used in allergen immunotherapy. If both skin tests and in vitro tests are performed, and the patient has negative results on percutaneous skin tests but positive results on in vitro tests for IgE, allergen immunotherapy should be instituted only after careful consideration.

*Specific Allergens*

**Summary Statement 24. Immunotherapy is effective for pollen, fungi (molds), animal dander, dust mite, cockroach, and Hymenoptera sensitivity. Therefore, immunotherapy should be considered as part of the management program in patients who have symptoms related to exposure to these allergens and in whom the presence of specific IgE antibodies has been established. (A)**

*Pollen.* Pollen vaccines have been shown to be safe and effective in many controlled clinical trials.[3,38,74,76]

*Fungi (Molds).* Several studies, specifically with *Alternaria* and *Cladosporium*, suggest that allergen immunotherapy with fungi may be effective.[101–106] The allergen content of most mold extract (vaccine) is highly variable.[158] However,

there is evidence that proteolytic enzymes present in some mold extracts (vaccines) could digest pollen allergen (except ragweed vaccine in glycerin) when combined in a mixture.[159,160] For this reason, it may be desirable to separate all pollen vaccines (except ragweed) from mold vaccines when using mixtures.

There are thousands of species of fungi, and vaccines for some potentially clinically important fungi are not available. For example, there are no commercially available extracts (vaccines) for many fungal ascospores, although they are frequently the dominant type of airborne bioparticulate during certain seasons. Another example is the lack of basidiospore (mushroom) extracts (vaccines), especially given the evidence that such exposures may be associated with epidemics of asthma in the late fall. It is important that the physician distinguish between molds that are predominantly found indoors (eg, *Penicillium* and *Aspergillus* genera), those found exclusively outdoors, or those found both indoors and outdoors, and be able to evaluate the potential clinical impact of each.

*Animal dander.* The best treatment for animal allergy is avoidance, but this is not always possible. Because immunotherapy has been shown to be effective for cat allergy,[109,110] the inclusion of cat allergen in a vaccine should be considered in those circumstances where there is exposure. Exposure to cat allergen has been shown to be ubiquitous and may occur even without a cat in the home, making avoidance even more difficult. Evidence for the efficacy of immunotherapy for dog allergy is not robust.[107,108,112]

*Dust mite (arthropod) and cockroach allergens.* House dust vaccine is generally an inappropriate substitute for house-dust mite vaccine. Immunotherapy with standardized dust mite is generally more effective than crude house dust allergens. The house-dust mites *D. farinae* and *D. pteronyssinus* contain two major allergen groups that are immunologically cross-reactive: Der p 1 and Der f 1 and Der p 2 and Der f 2. At least 60% of mite-sensitive patients react to these two groups. Allergens from other species of mites, *Blomia tropicalis* and *Euroglyphus maynei*, cross-react partially with allergens from *Dermatophagoides* species. For patients sensitive to both *D. pteronyssinus* and *D. farinae*, only 50% of the projected amounts of each of these two house-dust mites must be included in the vaccine because of the high degree of cross-allergenicity between the major allergens in these two species. Immunotherapy for dust mites is effective[113–121] and should be considered in conjunction with avoidance measures in patients who have symptoms consistent with dust mite allergy and IgE antibodies specific for dust mite allergens. Dust mite hypersensitivity should be considered particularly in patients who have perennial symptoms exacerbated by periods of high humidity and a dusty environment at home or work.

Inhalant insect aeroallergens frequently cause allergic rhinitis and asthma. In dwellings, the most common cockroach species are the German cockroach, *Blattella 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 vaccine. Immunotherapy with cockroach allergens is effective[122] 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 using Hymenoptera venom is effective in dramatically reducing the risk of anaphylaxis to honeybee, yellow-jacket, hornet, and wasp stings.[77,81,82]

*Food.* Allergen immunotherapy for food allergy is investigational at this time. Currently, strict avoidance of the offending food is advisable; immunotherapy for food allergy is not recommended.

### *Mixing of Vaccines*

*Principles of mixing.* **Summary Statement 25. In the mixing of an allergen vaccine, the following factors must be considered: 1) the cross-reactivity of the allergens, 2) the optimal dose of each constituent, and 3) enzymatic degradation of the allergens. (E)**

After the allergens relevant for the patient in question have been identified, it is often necessary to prepare a mixture that contains each of the allergens. When available, standardized extracts (vaccines) should be used and may be mixed with nonstandardized extracts (vaccines). Although current data neither support nor reject the practice of combining allergens in one vial, this practice is widely accepted. Many factors must be considered when combining extracts (vaccines), including the cross-reactivity of the allergens, the need to include the optimal dose of each constituent, and potential interactions between allergens that could lead to degradation or the unmasking of epitopes upon exposure to proteolytic enzymes.

*Mixing cross-reactive extracts (vaccines).* **Summary Statement 26. The selection of allergens for immunotherapy should be based in part on the cross-reactivity of clinically relevant allergens. Many related pollen contain cross-reactive allergens. When pollen allergens are substantially cross-reactive, selection of a single pollen within the cross-reactive genus or subfamily may suffice. When pollen allergens are not substantially cross-reactive, testing for and treatment with multiple locally prevalent pollen may be necessary. (B)**

Immunologic and allergenic cross-reactivity is the recognition of different vaccine constituents as the same or similar by the patient's immune system. 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. Such a practice may result in the addition of too much of a given allergen, which could lead to an adverse reaction as well as to the unnecessary dilution of

other allergens and resultant reduction in efficacy. Knowledge of each allergen's classification according to species and the immunologic cross-reactivity within allergens of the same genera or subfamily allows one to select vaccine components that are maximally effective. In general, the patterns of allergenic cross-reactivities among pollen follow their taxonomic relationships (see Section VII for further discussion and references).

*Dose selection.* **Summary Statement 27. The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the clinically relevant constituents in the vaccine. (A)**

The maintenance dose of allergen immunotherapy must be adequate.[39,161,162] Low maintenance doses (eg, dilutions of 1:1,000,000) of allergen immunotherapy are not effective.[162] Another consideration when mixing or combining extract (vaccine) into the same treatment vial is the need to deliver an optimal therapeutically effective dose of each constituent within the vaccine. Failure to do so may reduce the efficacy of immunotherapy. Reduced efficacy may occur because of a dilution effect, ie, as one mixes multiple vaccines, the concentration of each one in the final mixture is decreased (see Section XII for further discussion and recommended maintenance doses).

*Proteolytic enzymes and mixing.* **Summary Statement 28. Separation of aqueous extracts (vaccines) with high proteolytic enzyme activities (eg, fungi, dust mites, cockroach, and insect venoms) from other extracts (vaccines) is recommended. (E)**

Many allergen extracts (vaccines) contain mixtures of proteins and glycoproteins. There have been reports of interactions between extracts (vaccines) when mixed together.[159,160,163] When mixed together, extracts (vaccines) such as those against *Alternaria* species have been shown to reduce the IgE-binding activity of timothy grass extract (vaccine). This effect was not demonstrated when *Alternaria* was mixed with ragweed in glycerin. All interactions between extracts have not been delineated fully; therefore, extracts (vaccines) that have higher proteolytic enzyme activities, such as those originating from fungi, arthropods (dust mites), and insects, should generally be kept separate from those with lesser enzyme activities such as pollen-based extracts (vaccines; Table 6). In this regard, the number of injections to be given at each patient visit depends on whether all of the relevant extracts (vaccines) mixed into a single vial can 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 may be necessary for successful immunotherapy.

Table 6. Allergens Compatible for Mixing Together

| |
|---|
| Allergens with high protease activity (may be mixed together) |
| Arthropods (dust mites) |
| Fungi (mold spores) |
| Insects (cockroach) |
| Allergens with low protease activity (may be mixed together) |
| Grass pollen |
| Tree pollen |
| Weed pollen |
| Animals (cat and dog allergens) |
| Other allergens |
| Ragweed (may be mixed with either group above) |
| Insect venoms (require a separate vial and a separate injection) |

*Extract and Vaccine Handling*

**Summary Statement 29. Extracts (vaccines) should be stored at 4° C to reduce the rate of potency loss. Dilute concentrations are more sensitive to temperature and lose potency more rapidly than do more concentrated vaccines. The expiration date for dilute concentrations should reflect their shorter shelf life. (E)**

Because the efficacy and safety of immunotherapy depend on the use of vaccines with predictable biologic activity, it is important that they be stored under conditions that preserve such activity. Vaccine potency is affected by many factors, including the passage of time, temperature, concentration, number of allergens in the storage vial, volume of the storage vial, and the presence of stabilizers and preservatives.[164] To minimize the rate of potency loss, extracts and vaccines, including reconstituted lyophilized extracts and vaccines, should be stored at 4° C; storage at higher temperatures (eg, room temperature) results in rapid allergen deterioration.[165]

The potency of concentrated vaccines (1:10 to 1:100 wt/vol) kept at 4° C is relatively constant, allowing the vaccine to be used until the expiration date printed on the label. Less concentrated vaccine is more sensitive to the effects of temperature and may not maintain its potency until the expiration date. Thus, highly concentrated vaccines are more stable than dilute vaccines. Extracts and vaccines 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; however, after the vaccine is reconstituted, stabilizing agents such as human serum albumin (0.03%) are needed to maintain potency. Stabilizers (human serum albumin and glycerol) help prevent the loss of potency within storage vials by preventing absorption of allergen on the inner surface of the glass vial. Glycerin at a concentration of 50% may inhibit the activity of proteolytic and glycosidic enzymes that are present in certain extracts and vaccines. However, glycerin is irritating when injected and should be diluted before initiation of immunotherapy. An antibacterial agent such as phenol also should be included as a preservative.

## XII. IMMUNOTHERAPY SCHEDULES AND DOSES

*Immunotherapy Vaccines*

*Manufacturer's extract (vaccine).* **Summary Statement 30. A commercially available allergen extract (vaccine) may be used alone or combined to prepare a customized allergen mixture for an individual patient. (F)**

An allergen extract (vaccine) is a solution of elutable materials derived from allergen source materials such as pollen or mold. The solution contains complex mixtures of proteins and glycoproteins, some of which bind to antibodies.

Allergen extracts used for immunotherapy are also referred to as vaccines, a term that more accurately describes their functional immune effects. Allergen extracts can be purchased in high concentration and subsequently diluted or mixed in a physician's office. These extracts obtained from a company should be referred to as the *manufacturer's extract* (or *vaccine*).

Nonstandardized manufacturer's extracts (vaccines) are usually available at concentrations of between 1:10 and 1:50 wt/vol or 20,000 to 100,000 PNU. Standardized extracts (vaccines) are available with biologic potencies of 10,000 and 100,000 BAU for grasses, 5,000 and 10,000 BAU for cat allergen, and 5,000, 10,000, and 30,000 AU for dust mite (Table 7). An important factor that limits a vaccine's concentration is the tendency of precipitates to develop in highly concentrated antigen solutions. This phenomenon is unpredictable and poorly understood. Although there is no evidence that such precipitates adversely affect vaccine efficacy and safety, the FDA currently does not permit a manufacturer to ship extract with precipitates.

*Maintenance concentrate.* **Summary Statement 31. The highest concentration of a vaccine projected as the therapeutically effective dose is called the maintenance concentrate. (F)**

The highest concentration of a vaccine that is projected to be used as the therapeutically effective dose is called the *maintenance concentrate*. The composition of the maintenance concentrate should be determined by the prescribing physician before immunotherapy is initiated. The maintenance concentrate consists of an allergen or allergens that have been determined to be clinically relevant for the patient. They should be prepared individually for each patient by an allergist/immunologist. If a mixture of allergens, the maintenance concentrate should be obtained from the manufacturer as a customized mixture or prepared by the physician under sterile conditions by adding an appropriate volume of individual extracts (vaccines). In some patients, local or systemic reactions may prevent the attainment of the projected therapeutically effective dose of the maintenance concentrate. These patients may need weaker dilutions of their maintenance concentrate. Even so, the originally projected maintenance concentration of vaccine is still referred to as the maintenance concentrate. The consistent use of this term is important because an error in choosing the correct vial is a common cause of systemic reaction, especially when the patient has transferred physicians, and because there are currently differing terms for the concentration of a maintenance vial. Therefore, it is important that standard terminology be adopted by all physicians who prescribe allergen immunotherapy.

Table 7. Potency of Extracts (Vaccines) Currently Available from Selected Manufacturers

| Vaccine | Potency |
|---|---|
| Cat hair and pelt | 5,000 and 10,000 BAU/mL |
| Dust mite | 5,000, 10,000, and 30,000 AU/mL |
| Bermuda grass | 10,000 AU/mL |
| Other grasses* | 10,000 and 100,000 BAU/mL |
| Other pollen | 1:10–1:40 (wt/vol) or 10,000–40,000 PNU/mL |
| Molds | 1:10–1:40 (wt/vol) or 20,000 to 100,000 PNU/mL |

AU, allergy unit; BAU, bioequivalent allergy unit; PNU, protein nitrogen unit.

* Perennial rye, Kentucky bluegrass, timothy, sweet vernal, red top, orchard, and meadow fescue.

*Recommended doses.* **Summary Statement 32. The maintenance concentrate should be selected to deliver a dose considered to be a therapeutically effective dose for each of its constituent components. (A)**

The effective maintenance dose of immunotherapy must be individualized for each patient. To do this, the allergist or immunologist who prepares the vaccine must balance the dose necessary to produce efficacy and the risk of reaction if that dose is reached. 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 shown to be effective in controlled studies. In general, however, low doses are less likely to be effective and very low doses are usually ineffective. Although administration of a higher maintenance dose of immunotherapy increases the likelihood of clinical effectiveness, it also increases the risk of systemic reaction. In particular, highly sensitive patients may be at risk of systemic reactions to immunotherapy injections with higher maintenance doses. Therapeutically effective doses for immunotherapy have been reported.[41,159,166] The maintenance concentrate should deliver a full therapeutic dose of each of its constituent components. In some sensitive patients, it may not be possible to reach the targeted therapeutic dose.

Controlled studies demonstrate that the content of particular allergens in vaccines can be used to predict a therapeutic dose for those allergens, particularly when the vaccines are standardized.[39,161] Effective doses have been determined for dust mite, cat allergen, grass, and short ragweed. 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 vaccine, including final dilutions of each of its constituents. The ranges of therapeutically effective doses (in micrograms, allergy units, bioequivalent allergy units, and weight per volume) are presented in Table 8.[39] Although early improvement in symptoms has been documented with use of immunotherapy, long-term benefit appears related to the cumulative dose of vaccine given over time.

Regardless of dose schedule, some patients can not progress to the predetermined maintenance dose because of large local or systemic reaction to the allergen vaccine. Pub-

Table 8. Recommended Maintenance Doses of Allergen Immunotherapy

| Allergen | Dose, standardized units | Dose, major allergen | Maintenance concentrate, wt/vol* |
|---|---|---|---|
| *Dermatophagoides pteronyssinus* | 600 AU | 7–12 μg Der p 1 | NA |
| *Dermatophagoides farinae* | 2,000 AU | 10 μg Der f 1 | NA |
| Cat | 2,000–3,000 BAU | 11–17 μg Fel d 1 | NA |
| Grass (e.g., timothy) | 4,000 BAU | 7 μg Phl p 5 | NA |
| Short ragweed (standardized) | NA | 6–24 μg Amb a 1 | 1:100–1:30 |
| Other pollen (nonstandardized) | NA | ND | 1:100–1:30 |
| Fungi/mold (nonstandardized) | NA | ND | 1:100–1:50 |

AU, allergy unit; BAU, bioequivalent allergy unit; NA, not applicable; ND, not determined.
* Based on a maintenance injection of 0.5 mL.

lished studies do not indicate that large local reactions are always predictive of subsequent systemic reactions.[167,168] Nevertheless, in the experience of some experts, a correlation between large local reactions and subsequent systemic reactions can be made in some patients. Patients who have systemic reactions with doses that are below the therapeutic effective dose should be maintained on the highest tolerated dose, as long as that dose is effective.

Dilution limits the number of allergens that can be added to a maintenance concentrate if a therapeutic dose is to be delivered. As the number of allergens added to an individual patient's maintenance concentrate increases, the concentration of each decreases because of a dilution effect. This limits the ability to deliver a therapeutic effective dose for any given allergen. The final concentration can be calculated by dividing the initial concentration of each component by the total number of components added (Table 9).

*Dilutions of the maintenance concentrate.* **Summary Statement 33. Serial dilutions of the maintenance concentrate should be made in preparation for the buildup phase of immunotherapy. (F)**

In preparation for the buildup phase of immunotherapy, serial dilutions should be produced from each maintenance concentrate vaccine. Typically, these are 10-fold dilutions, although other dilutions are occasionally used. These dilutions should be labeled in terms of volume per volume to indicate that they are dilutions derived from the maintenance concentrate. For example, serial 10-fold dilutions from the maintenance concentrate would be labeled as 1:10 (vol/vol), 1:100 (vol/vol), and so on. Various dilutions are shown in Table 10. If the final volume of the diluted vaccine to be produced is 10 mL, then 10% of that volume, or 1.0 mL, should be removed from the concentrated extract (vaccine) and added to a new bottle containing 9.0 mL of diluent.

*Labeling dilutions.* **Summary Statement 34. Use of consistent, uniform labeling system for dilutions from the maintenance concentrate may reduce errors in administration. (F)**

During the buildup phase of immunotherapy, dilutions of the patient's maintenance concentrate are needed. Use of a universally accepted labeling system to indicate dilutions may help to avoid administration errors (Table 11). In addition to the labeled dilution from the maintenance concentrate (in volume per volume), a numbering system, color-coding system, or alphabetical system should be used. If a uniform labeling system is used, it would be best if all physicians used the same system. Figure 2 provides an example of a set of labels for vials containing allergen vaccine. Figure 3 shows color-coded vials.

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 vaccines, 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; for example, the highest concentration should be red, the next highest yellow, followed by blue, green, and silver, in that order.

Regardless of whether a multiple labeling system for indicating dilutions from the maintenance concentrate is used, the contents of each vaccine should be listed separately, includ-

Table 9. Dilution Effect*

| Initial concentration† | Components, no. | Final concentration |
|---|---|---|
| 1:10 wt/vol | 1 | 1:10 wt/vol |
| | 5 | 1:50 wt/vol |
| | 10 | 1:100 wt/vol |
| 10,000 BAU/mL | 1 | 10,000 BAU/mL |
| | 5 | 2,000 BAU/mL |
| | 10 | 1,000 BAU/mL |

BAU, bioequivalent allergy unit.
* Assuming that an equal volume of each component is added to the maintenance concentrate vaccine, as more components are added, the more dilute each becomes.
† In the manufacturer's vaccine.

Table 10. Preparation of Dilutions from the Maintenance Concentrate Vaccine

| Dilution from maintenance concentrate vaccine, vol/vol | Volume, mL | Diluent volume, mL | Final volume, mL | Final concentration, vol/vol |
|---|---|---|---|---|
| 1:1 | 1.0 | 0.0 | 1.0 | 1:1 |
| 1:1 | 2.0 | 8.0 | 10.0 | 1:5 |
| 1:1 | 1.0 | 9.0 | 10.0 | 1:10 |
| 1:10 | 1.0 | 9.0 | 10.0 | 1:100 |
| 1:100 | 1.0 | 9.0 | 10.0 | 1:1,000 |
| 1:1,000 | 1.0 | 9.0 | 10.0 | 1:10,000 |

Table 11. Suggested Methods for Labeling Dilutions from the Maintenance Dose Vaccine

| Dilution from maintenance concentrate | Label | | |
|---|---|---|---|
| | Vol/vol | Number | Color |
| Undiluted | 1:1 | 1 | Red |
| 10-fold | 1:10 | 2 | Yellow |
| 100-fold | 1:100 | 3 | Blue |
| 1,000-fold | 1:1,000 | 4 | Green |
| 10,000-fold | 1:10,000 | 5 | Silver |

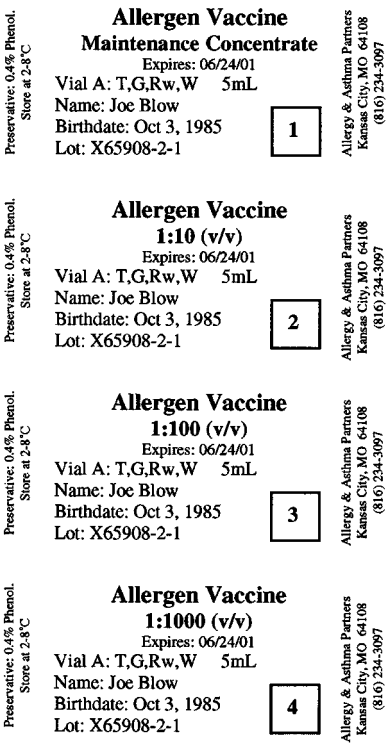


Figure 2. Sample set of labels for vials containing allergen vaccine.

ing the final concentration of each of its constituents. Consistency is essential as a basis for adopting a standardized system. Some allergists and immunologists, however, have found it helpful to use letters to designate component mixtures of extracts and vaccines (eg, T, trees; G, grasses; M, molds) rather than an alphabet system for dilutions.

*Individualized treatment vials.* **Summary Statement 35. The maintenance concentrate and serial dilutions, whether a single vaccine or a mixture of vaccines, should be prepared and labeled for each patient. (F)**

The use of individually prepared and labeled vials is recommended because it has several advantages over the use of shared vials (ie, vials of vaccine used for multiple patients). The risk of error of administration is reduced. The risk of allergen cross-contamination is eliminated. Premixing vaccines in a glass vial is more precise than premixing vaccines

Figure 3. Sample set of color-coded vials of allergen vaccine.

in a syringe. The off-the-table method of sharing vials among different patients is not recommended.

*Immunotherapy Schedules*

*Starting doses.* **Summary Statement 36. The starting dose for buildup is usually a 1,000- or 10,000-fold dilution of the maintenance concentrate, although a lower starting dose may be advisable for highly sensitive patients. (A)**

Allergen immunotherapy administration has two phases: the initial buildup, when the dose and concentration of vaccine are slowly increased, and the maintenance phase, when the patient receives an effective therapeutic dose over a period of time.[3,38,74–77] If the starting dose is too dilute, an unnecessarily large number of injections will be needed, delaying the achievement of a therapeutically effective dose. However, if the starting dose is too concentrated, the patient may be at increased risk of a systemic reaction.

When choosing the starting dose, most allergists and immunologists start at a dilution of the maintenance concentrate that is appropriate based on the sensitivity of the patient to the allergens in the vaccine, which in turn is based on the history and skin test reactivity. Alternatively, when evaluating patients for immunotherapy, some allergists and immunologists perform intracutaneous tests using several higher dilutions of the maintenance concentrate vaccine to determine the starting dose. A dilution resulting in a wheal $<10$ mm in diameter is considered an appropriate starting dose. Each approach is acceptable; therefore, the physician may choose the approach with which he or she feels more comfortable. Common starting dilutions from the maintenance concentrate are 1:10,000 (vol/vol) or 1:1,000 (vol/vol), although more dilute concentrations are used for patients who are highly sensitive as indicated by history or skin test reaction.

*Frequency of buildup injections.* **Summary Statement 37. During the buildup phase, the usual frequency of vaccine administration is one to two injections per week, at least 2 days apart. (A)**

Many schedules are used for the buildup phase of immunotherapy.[3,38,74–77] According to the most commonly used schedule, increasing doses of vaccine are administered one to two times per week. This schedule is recommended in most of the vaccine package inserts. With this schedule, a patient typically reaches 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 may be as short as 1 or 2 days if there is urgency to achieve a maintenance dose (eg, allergy season is approaching) or if there are practical reasons (eg, injections can only be given 2 days apart, such as Tuesdays and Thursdays).

Vaccines used during the buildup phase usually consist of three or four 10-fold dilutions of the maintenance dose vaccine. The volume generally is increased by 0.05 to 0.10 mL per dose depending on a number of factors, including the patient's sensitivity to the vaccine, the patient's history of previous reactions, and the concentration being delivered (with smaller increments being given at higher concentrations). The volume administered often starts at 0.05 mL and increases to 0.5 to 1.0 mL. The next injection, given from a bottle with a 10-fold higher concentration of vaccine, is usually 0.05 to 0.1 mL, to ensure that there is no initial increase in the total dose of allergen administered when progressing from the lower concentration to the next higher concentration. This practice reduces the potential risk of a systemic reaction when progressing to a higher concentration.

Table 12 shows a sample buildup schedule for weekly immunotherapy using a 0.5-mL maintenance concentrate goal. Similar buildup schedules can be used for a 1.0-mL maintenance goal.

Table 12. Sample Buildup Schedule for Weekly Immunotherapy*

| Dilution, vol/vol | Volume, mL |
|---|---|
| 1:1,000 | 0.05 |
| | 0.10 |
| | 0.30 |
| | 0.50 |
| 1:100 | 0.05 |
| | 0.10 |
| | 0.20 |
| | 0.30 |
| | 0.40 |
| | 0.50 |
| 1:10 | 0.05 |
| | 0.10 |
| | 0.20 |
| | 0.30 |
| | 0.35 |
| | 0.40 |
| | 0.45 |
| | 0.50 |
| Maintenance concentrate | 0.05 |
| | 0.10 |
| | 0.15 |
| | 0.20 |
| | 0.25 |
| | 0.30 |
| | 0.35 |
| | 0.40 |
| | 0.45 |
| | 0.50 |

* Dilutions are expressed as volume per volume from the maintenance concentrate vaccine.

*Dose adjustments for systemic reactions.* **Summary Statement 38. If immunotherapy is continued after a systemic reaction, the dose of vaccine should be appropriately reduced. (D)**

If a systemic reaction has occurred, it is usual practice to reduce the dose or consider discontinuation of immunotherapy, especially if the reaction was severe. Although there are no evidence-based guidelines on dose adjustment after a systemic reaction, many allergists and immunologists reduce the dose to one that was previously tolerated or to an even lower dose if the reaction was severe. When the reduced dose is tolerated, a cautious increase in subsequent doses can be attempted. It is important for the physician who prescribed the vaccine to review the course of immunotherapy to determine whether the benefits of continued immunotherapy justify the risks.

*Dose adjustments for late injections.* **Summary Statement 39. It is usual practice to reduce the dose of vaccine when the interval between injections is prolonged. (F)**

During the buildup phase, it is customary to repeat or even reduce the dose of vaccine if there has been a substantial time interval between injections. Factors in this decision are the concentration of vaccine to be given, whether the patient has a history of systemic reaction, and the degree of variation from the prescribed interval of time (longer intervals since the last injection lead to greater reductions in the dose to be given).

Injections given during periods when the patient is exposed to increased levels of allergen to which he or she is sensitive are associated with an increased risk of systemic reaction, especially if the patient is experiencing a marked exacerbation of symptoms, particularly asthma symptoms. Therefore, it is reasonable to maintain or reduce the dose of vaccine during seasons when the patient is exposed to increased levels of allergen to which he or she is sensitive, especially if symptoms are poorly controlled.

*Cluster schedules.* **Summary Statement 40. With cluster immunotherapy, two or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules. (A)**

Rush schedules are designed to accelerate the buildup phase of immunotherapy. Cluster immunotherapy is usually characterized by visits for administration of vaccine one or two times per week, with two or more buildup injections given per visit. Typically, these are given at 30- to 120-minute intervals. Although this schedule can permit a patient to reach a maintenance dose in as brief a time as 2 to 4 weeks,

the cluster schedule is associated with a greater possibility of systemic reaction than is immunotherapy given using more conventional schedules.[169,170]

*Rush schedules.* **Summary Statement 41. Rush schedules can achieve a maintenance dose more quickly than weekly schedules but are associated with an increased risk of systemic reaction. Premedication can reduce the rate of systemic reaction. (B)**

Rush schedules that are more rapid than cluster immunotherapy schedules may be used. Initially, the use of rush schedules was inhibited by concern about systemic reactions. 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.[171] As experience with accelerated forms of immunotherapy was acquired, schedules were developed to reach a maintenance dose more rapidly.

The most accelerated schedule that has been described for inhalant allergens involves giving eight injections over the course of 6 hours.[172] Rush immunotherapy schedules for stinging insect hypersensitivity can achieve a maintenance dose in as little as 90 minutes.[173] Such schedules are labor-intensive and can be difficult for both patients and medical staff. Conventional schedules in which injections are given two or three times per week are more practical.

The advantage of a rush schedule is that patients can attain a therapeutically effective maintenance dose more rapidly than with a conventional schedule. There are anecdotal reports of, but no controlled studies documenting, more rapid symptomatic improvement with rush schedules for inhalant allergens.

The advantage of rush immunotherapy comes at a cost: accelerated schedules are associated with an increased risk of local or systemic reaction.[174,175] Systemic reaction rates have been reported to be as high as 55%,[176] although the risk of such reactions is considerably lower (27%) after premedication.[177]

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

Premedication with prednisone, an $H_1$ histamine receptor antagonist, with or without an $H_2$ histamine receptor antagonist before rush immunotherapy reduces the risk of systemic reaction.[177,178] Anecdotal reports of reductions in systemic reaction rates with the addition of a leukotriene receptor antagonist have not been confirmed by published studies. Because the risk of systemic reaction from venom rush immunotherapy is relatively low, premedication before venom rush immunotherapy is optional.[173]

*Premedication and weekly immunotherapy.* **Summary Statement 42. Routine premedication before allergen immunotherapy injections administered on a conventional schedule is not necessary and may mask the early signs of systemic reaction (F).**

There is concern that antihistamines taken before each injection in conventional immunotherapy may mask the early signs of an impending systemic reaction. Further, except in the case of rush schedules, it is unclear whether an antihistamine taken before each injection reduces the risk of systemic reaction. Because many patients take an antihistamine as part of their overall allergy management, it is important to determine whether the patient has taken an antihistamine on the day of a vaccine injection. The addition of epinephrine to the vaccine or the routine use of premedication with corticosteroids is not recommended.

*Maintenance schedules.* **Summary Statement 43. When the patient has reached a maintenance dose, the interval between injections often can be progressively increased as tolerated to 4 to 6 weeks. (A)**

When a patient who is receiving inhalant allergen immunotherapy has reached a maintenance dose, an interval of 2 to 4 weeks between injections is recommended, provided clinical improvement is maintained. In some patients, the interval between injections can safely be increased to 6 weeks without loss of efficacy. In other patients, greater efficacy or fewer reactions may 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 44. Clinical improvement is usually observed within 1 year after the patient reaches a maintenance dose. (A)**

Clinical improvement usually occurs within 1 year after the patient reaches a maintenance dose.[121] Improvement may not be observed for several reasons, including failure to remove significant allergenic exposures (eg, a cat), exposure to high levels of pollen or molds, continued exposure to nonallergenic triggers (eg, tobacco smoke), incomplete identification and treatment of clinically relevant allergens, and misdiagnosis. 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 or modification of immunotherapy should be considered and other treatment options pursued.

*Followup visits.* **Summary Statement 45. Patients should be evaluated at least every 6 to 12 months while they receive immunotherapy. (F)**

Patients should be evaluated at least every 6 to 12 months while receiving immunotherapy. The purposes of evaluation are to evaluate efficacy, implement and reinforce the safe administration of immunotherapy, monitor adverse reactions, ensure patient compliance, determine whether immunotherapy can be discontinued, and determine whether adjustments in the dosing schedule or allergen content are necessary. Patients may need more frequent office visits for evaluation and management of immunotherapy (eg, treatment of local or systemic reaction, changes in immunotherapy vials or lots) or of the underlying allergic disease.

*Duration of treatment.* **Summary Statement 46. A decision to continue or stop immunotherapy should be made after 3 to 5 years. (A)**

If allergen immunotherapy is effective, treatment may be continued for longer than 3 to 5 years, depending on the patient's ongoing response to treatment. Whether to continue immunotherapy should be discussed each time the patient is evaluated, particularly after 3 to 5 years of treatment. Although some patients experience a prolonged remission after discontinuation, others do not. Therefore, the decision to continue or stop immunotherapy must be individualized.

In a controlled study in which immunotherapy for grass-pollen allergy was discontinued after 3 to 4 years of successful treatment, 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.[100] It is unclear whether such prolonged improvement applies to other allergens or persists for longer than 3 to 4 years.

*Documentation and Record Keeping*

**Summary Statement 47. The vaccine contents, informed consent for immunotherapy, and administration of vaccines should be carefully documented. (F)**

The allergen immunotherapy treatment should be accurately and carefully documented. This documentation must include the information listed in Appendix 1. An immunotherapy vaccine administration form is shown in Appendix 2. Immunotherapy prescription/content forms (1 blank, 1 filled out) are shown in Appendix 3. Recommended vaccine expiration times are given in Table 13.

## XIII. SPECIAL CONSIDERATIONS IN IMMUNOTHERAPY

*Location of Allergen Immunotherapy Administration*

*Physician's office.* **Summary Statement 48. The preferred location for the administration of allergen immunotherapy is the office of the physician who prepared the patient's vaccine. (D)**

The preferred location of allergen immunotherapy administration is the office of the physician who prepared the patient's vaccine. 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 may be appropriate to administer the allergen vaccine in another physician's office. Wherever it is administered, immunotherapy should be administered with care. A physician qualified to treat anaphylaxis should be in the vicinity when immunotherapy injections are given.

Table 13. Recommended Vaccine Expiration Times for Dilutions from Maintenance Concentrate when Diluted in Buffered Saline

| Dilution | Recommended expiration time |
|---|---|
| Maintenance concentrate, vol/vol | 6–12 months* |
| 1:10 | 6 months |
| 1:100 | 6 months |
| 1:1,000 | 6 weeks |
| 1:10,000 | Unknown |

* The expiration date of the maintenance dose should be the expiration date of the earliest expiring constituent that is added to the mixture.

**Summary Statement 49. Generally, patients at high risk for systemic reaction should receive immunotherapy in the office of the physician who prepared the patient's vaccine. (D)**

Generally, patients at high risk for systemic reaction (those who are highly sensitive or have severe symptoms, co-morbid conditions, or a history of recurrent reactions) should receive immunotherapy in the office of the allergist/immunologist. The allergist/immunologist who prepared the patient's vaccine and the support staff should have experience and procedures in place for administering immunotherapy to high-risk patients. The physician who prescribed allergen immunotherapy and who prepared the patient's vaccine is usually best equipped to manage reactions and to manage the patient's immunotherapy program.[179]

*Other locations.* **Summary Statement 50. Regardless of 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 appropriately trained in the technical aspects of the procedure (Appendix 4) and have available resuscitative equipment and medicines and storage facilities for allergen extract and vaccine. 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 factors that place the patient at greater risk of systemic reaction (eg, the use of concomitant medications, such as $\beta$-blockers, which can interfere with emergency treatment; allergy or asthma exacerbations; poorly controlled asthma).

Appropriate adjustment of the dose should be made as clinically indicated. The physician who prepared the patient's vaccine should provide adequately labeled vials, detailed directions regarding the dosage schedule for buildup and maintenance, plus instructions on adjustments that may 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 or to which the patient is very sensitive; 3) when the patient has missed injections; and 4) when reactions to the allergen vaccine occur.

Any systemic reaction to allergen immunotherapy should be treated immediately, and the physician who prepared the allergen vaccine should be informed. This may require a return to the office of the allergist or immunologist for treatment reevaluation.

*Home administration.* **Summary Statement 51. Immunotherapy injections should not be administered at home because of the risk of inadequate recognition and treatment of systemic reactions. (F)**

Allergen immunotherapy should be administered by health care professionals, under the supervision of an appropriately trained physician, in a health care facility with appropriate equipment. At-home administration of allergen vaccines is not recommended because serious systemic reactions may not be adequately recognized or treated. Further, without the supervision of a trained physician and personnel, appropriate dose adjustments and modifications can not be made. In the home setting, patient compliance with the immunotherapy schedule and accurate documentation of immunotherapy injections are not ensured. The package insert (approved by the United States FDA) that accompanies all allergen extracts implies that allergy injections should be given in a clinical setting under the supervision of a physician, with the patient remaining in the area for at least 20 minutes after the injection. No published studies have compared the safety of allergen immunotherapy administered at home with the safety of immunotherapy administered in a health care facility. It may be appropriate to consider venom immunotherapy for the rare patient with life-threatening anaphylaxis to Hymenoptera who can not avoid Hymenoptera exposure and can not receive venom immunotherapy in a health care facility and for whom self-administered epinephrine is not an adequate management strategy.

*Immunotherapy in Children*

**Summary Statement 52. Immunotherapy for children is effective and often well tolerated. Therefore, immunotherapy is appropriate (as is pharmacotherapy and allergen avoidance) in the management of children with allergic rhinitis, allergic asthma, and stinging insect hypersensitivity. Allergen immunotherapy may prevent the development of asthma in children with allergic rhinitis. (A)**

Immunotherapy for children has been shown to be effective and often well tolerated,[83,84] although one study[85] did not show efficacy. In general, the clinical indications for immunotherapy for allergic rhinitis and asthma are similar for adults and children (see Section X). Studies of children receiving allergen immunotherapy have found the following: 1) improvement in symptom control for asthma[83,84,86,87] and allergic rhinitis[91]; 2) increased concentration of methacholine necessary to provoke a decrease in forced expiratory volume in 1 second in children <5 years of age[86]; 3) increased concentration necessary to provoke a decrease in forced expiratory volume in 1 second to cat and house-dust mite allergens[87]; 4) decreased risk of developing asthma[123–126]; 5) decreased development of new sensitivities[88,180]; and 6) a modification in the release of mediators that correlates with a decrease in clinical symptoms.[89]

**Summary Statement 53. Children <5 years of age may have difficulty cooperating with an immunotherapy program. Therefore, the physician should carefully consider the benefits and risks of immunotherapy and individualize treatment in patients <5 years of age. (A)**

Although there is some disagreement about the role of allergen immunotherapy in children <5 years of age, some studies have found allergen immunotherapy to be effective in this age group.[83,84] In children with rhinoconjunctivitis, allergen immunotherapy may prevent the development of asthma.[124–126] However, allergen immunotherapy for inhalant allergens is usually not considered necessary in infants and toddlers because pollen sensitivities often develop later in childhood; symptoms and signs of systemic reaction may be difficult to recognize; and injections can be traumatic to very young children. Therefore, each case should be considered individually by weighing the benefits and risks. For children with severe allergic disease or a history of anaphylaxis to stinging insects, the benefits of allergen immunotherapy may outweigh the risks.

*Immunotherapy in Pregnant Patients*

**Summary Statement 54. Allergen immunotherapy may be continued in the pregnant patient, but it is customary to delay the commencement of allergen immunotherapy until the patient is no longer pregnant. (C)**

The physician must be aware of the benefits and risks of immunotherapy in the pregnant patient. The recommended precautions for preventing adverse reactions are especially important in the pregnant patient.

Allergen immunotherapy is effective in the pregnant patient. Allergen immunotherapy maintenance doses may be continued during pregnancy. When a patient receiving immunotherapy reports that she is pregnant, the dose of immunotherapy usually is not increased; rather, the patient is maintained on the dose she is receiving at that time. Allergen immunotherapy is usually not initiated during pregnancy because of risks associated with systemic reaction and its treatment. Possible complications include spontaneous abortion, premature labor, and fetal hypoxia. The initiation of immunotherapy may be considered during pregnancy for the rare pregnant patient with life-threatening Hymenoptera sensitivity.

*Immunotherapy in Older Patients*

**Summary Statement 55. In older adults, medications and co-morbid medical conditions may increase the risk from immunotherapy. Therefore, special consideration must be given to the benefits and risks of immunotherapy in older adults. (D)**

Immunotherapy may be appropriate in the treatment of elderly patients, but the benefits and risks must be evaluated more carefully in this population. Older patients may be taking medications (such as $\beta$-blockers) that could make treatment of anaphylaxis with epinephrine more difficult, or they may have a significant co-morbid medical condition (such as hypertension, coronary artery disease, cerebrovascular disease, or cardiac arrhythmias).

*Immunotherapy in Patients with Immunodeficiency and Autoimmune Disorders*

**Summary Statement 56. Allergen immunotherapy can be considered in patients with immunodeficiency and autoimmune disorders. (D)**

There are no data on the effectiveness or risks associated with allergen immunotherapy in patients with immunodeficiency or autoimmune disorders. Concern about the increased risk of immunotherapy in such patients is largely theoretical.

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

*Alternative Routes of Immunotherapy*

The efficacy of allergen immunotherapy by other routes (sublingual, oral, nasal) has been evaluated in double-blinded, placebo-controlled studies over the past 2 decades. Methods that have been evaluated include high-dose sublingual-swallow, high-dose sublingual-spit, oral, and nasal. Various allergen formulations, including aqueous, gluteraldehyde polymers, powders, and tablets, have been used. Some of these modalities are currently used in Europe, but none are generally accepted in the United States.

**Summary Statement 57. High-dose sublingual-swallow, high-dose sublingual-spit, and oral immunotherapy are under clinical investigation. Efficacy has been demonstrated for high-dose sublingual-swallow therapy, but the results of oral immunotherapy are equivocal. Sublingual-spit therapy requires further study. These therapies are not currently in general use in the United States, and no vaccines intended for sublingual or oral use are available in the United States. (A)**

Sublingual-swallow immunotherapy. High-dose sublingual-swallow immunotherapy using 50 to 100 times the dose used in subcutaneous immunotherapy has been studied extensively in the past decade. An international workshop group[38] has concluded that this modality may be indicated in the following situations:

1) some patients with rhinitis, conjunctivitis, and/or asthma caused by pollen and mite allergy;

2) patients who are not sufficiently controlled by conventional pharmacotherapy;

3) patients who have systemic reactions associated with injection immunotherapy; and

4) patients who are poorly compliant and refuse injections.

For the present, these recommendations are limited to European countries because formulations intended for high-dose sublingual-swallow use are not available in the United States, nor has sublingual administration received regulatory approval by the United States FDA.

Optimal-dose sublingual-swallow immunotherapy has been found effective in adults but is not yet recommended for children.[38] Sublingual-swallow immunotherapy under current investigation should not be confused with low-dose sublingual therapy based on provocation neutralization testing or Rinkel-type skin testing, which is not recommended. Other studies have evaluated house dust, olive pollen, grass pollen, and *Parietaria judaica*.[181–183] It has been noted that allergen is not degraded by saliva. Radiolabeled allergen has been detected after 48 hours in the sublingual region.[184,185] Other studies using rush sublingual, sublingual-swallow,[182] and sublingual-spit[186] therapies have been published. Further studies are needed to confirm the efficacy and safety of optimal dose sublingual-swallow immunotherapy in children and adults. Sublingual therapy in pediatric patients has been evaluated in several studies.[181,187,188] However, reports of these studies have limitations, including small number of patients, failure to describe the patients who withdrew, minimal characterization of local adverse reactions, and limitation to monotherapy.

*Oral immunotherapy.* Studies of oral immunotherapy for birch,[189] ragweed,[190] and cat allergy[191] have yielded conflicting results. The current dosage of oral immunotherapy is 20 to 200 times the parenteral injected dosage; this type of therapy requires a cost evaluation. Adverse effects have included gastrointestinal and oral reactions, which may preclude home therapy. For these reasons, oral immunotherapy should be considered investigational at this time.

*Intranasal immunotherapy.* **Summary Statement 58. Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but this modality currently is not used in the United States. (B)**

Controlled, well designed studies have shown intranasal immunotherapy to improve nasal symptoms of rhinitis.[192] Intranasal dry powder allergen immunotherapy has been studied in patients allergic to grass,[192] birch,[193,194] *P. judaica* ,[195,196] and house-dust mite.[197] Clinical efficacy was noted in all of these studies, and adverse effects were minor. Three-year studies with *P. judaica* have reported benefits for up to 12 months after the conclusion of allergen immunotherapy.[198] The local administration of nasal allergen in an aqueous solution may be limited by local side effects. Additional studies in both children and adults are needed. In human studies, antigen has been noted to appear in the serum within 15 to 30 minutes of administration, with the peak level occurring within 2 to 3 hours.[185] Some allergens have been reported to be retained in the nasal mucosa for as long as 48 hours after administration. Currently, intranasal immunotherapy is not used in the United States, but it has gained acceptance in other parts of the world. Current recommendations by the ARIA group[38] regarding nasal immunotherapy are similar to those for high-dose sublingual immunotherapy.

*Immunotherapy Techniques That Are Not Recommended*

**Summary Statement 59. Low-dose immunotherapy, enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutral-**

**ization testing are not effective and are not recommended. (D)**

Low-dose regimens, including co-seasonal low-dose immunotherapy for aeroallergens and the Rinkel low-dose titration techniques, have not been shown effective.[162] Similarly, immunotherapy based on provocation-neutralization testing with food and aeroallergens and enzyme-potentiated desensitization have not been shown effective.

**Summary Statement 60. If a patient receiving immunotherapy transfers from one physician to another, the new physician and the patient should decide whether to continue the immunotherapy program initiated by the previous physician or to prepare a new program. (F)**

**Summary Statement 61. If a patient transfers from one physician to another and no change is made in either the immunotherapy schedule or the vaccine, the risk of systemic reaction is not substantially increased. (F)**

**Summary Statement 62. A full, clear, and detailed documentation of the patient's immunotherapy schedule must accompany the patient when he or she transfers from one physician to another. Also, a record of previous responses to and compliance with the program should be communicated to the new physician. Finally, a detailed record of the results of the patient's specific IgE antibody tests (immediate-type skin tests or in vitro tests) should be provided. (F)**

**Summary Statement 63. An immunotherapy vaccine must be considered changed if there is any change in the constituents of the vaccine. This includes *any* change in the lot, manufacturer, vaccine type (eg, aqueous, glycerinated, standardized, nonstandardized), components, or relative amounts of the components in the mixture. (E)**

**Summary Statement 64. If a patient transfers from one physician to another, there is an increased risk of systemic reaction if the immunotherapy vaccine is changed, because of the marked variability in the content and potency of vaccines. The risk of systemic reaction with a different vaccine is greater with nonstandardized vaccines and with vaccines containing mixtures of allergens. (F)**

**Summary Statement 65. Immunotherapy with a different vaccine should be conducted cautiously. If there is inadequate information to support continuation of the previous immunotherapy program (including tests for specific IgE antibodies), reevaluation may be necessary and a new schedule and vaccine prepared. (F)**

Patients often transfer from one physician to another while receiving allergen immunotherapy. When this occurs, the new physician and the patient must decide whether to continue immunotherapy and, if so, which vaccine and schedule should be used (the one that the patient brought from the previous physician or one to be prepared by the new physician).

If the patient transfers to another physician and continues the immunotherapy program without changing either the schedule or vaccine (ie, uses vaccine provided by the previous physician), he or she is not at substantially increased risk of systemic reactions, provided there is full, clear, and detailed documentation of the patient's previous immunotherapy schedule and the vaccine contents. In addition, the patient's previous response to and compliance with the immunotherapy program must accompany the patient when responsibility for the program is transferred from one physician to another. Documentation should include a record of any reactions to immunotherapy and how they were managed as well as the patient's improvement or lack of improvement while receiving immunotherapy. Under these circumstances, immunotherapy can be continued with the vaccine that the patient was previously receiving if 1) the previous physician is willing and able to continue providing the patient with a schedule and vaccine; 2) the patient has shown clinical improvement while receiving the immunotherapy program; and 3) the contents of the vaccine are appropriate for the area in which the patient is now residing.

An immunotherapy vaccine must be considered changed if there is any change in the constituents of the vaccine. This includes any change in the lot, manufacturer, vaccine type (eg, aqueous, glycerinated, standardized, nonstandardized), component allergens, or the respective concentrations of the components in the vaccine. There is increased risk of systemic reaction if the immunotherapy vaccine is changed. This increased risk is attributable to the marked variability in content and potency of vaccines. For example, the strength of a given concentration of nonstandardized extract (vaccine) may vary by a factor of 1,000 from vial to vial. In such a situation, the risk of systemic reaction is greater with nonstandardized vaccines and vaccines that contain mixtures of allergens.

Therefore, if the vaccine is to be changed, the patient may need to be retested for specific IgE antibodies to the appropriate allergens and started on an immunotherapy schedule and vaccine that the current physician believes is appropriate and safe. On occasion, the information that accompanies the patient may be so thorough that it is possible for the current physician to develop a schedule and vaccine identical or almost identical to that provided by the previous physician. In this situation, it may be appropriate to decrease the dose from the patient's previous injection, provided that the interval of time since the previous injection is not too great. 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 much greater decrease in dose may be necessary. Serial intradermal immediate-type skin tests may be helpful to compare vaccine potency. All changes in immunotherapy dose and schedule should be conducted cautiously.

## XIV. FUTURE TRENDS IN IMMUNOTHERAPY

As more biologically standardized allergen extracts become available, therapy with aeroallergenic vaccines will become more uniform (as is the current practice for allergy to insect venoms). The number of commercially available allergen vaccines will decrease after consensus agreement about re-

gional prevalences of aeroallergens, their cross-allergenicity, and the relevance of their effect on human health in specific locales.

Novel routes for more effective, more convenient, and safer allergen immunotherapy are being investigated throughout the world. For example, oral, sublingual-swallow, or nasal routes of administering allergen vaccines may prove to be safe and more effective. Preformed soluble antigen-antibody complexes have been shown effective in patients with house-dust mite allergy, but whether they will be clinically feasible is controversial.[199] The uses of immunogenic but nonallergic overlapping synthetic peptides (short and long) and large recombinant allergen peptide fragments are being explored on an experimental basis.[24] In animal models, both antigen-dependent and antigen-independent gene-based vaccines have been shown to downregulate IgG and IgE production with concurrent modulation of cytokines.[200–204] Some of this benefit is attributable to nonspecific immunostimulatory oligodeoxynucleotides (CpG, cytosine phosphate guanine) with tolerizing motifs.[205]

This research has already led to conjugation of short-chain tolerizing oligodeoxynucleotides (CpG) to protein allergens (ie, ragweed allergen). Humanized anti-IgE monoclonal antibody has already been shown to have modest clinical effects in both allergic rhinitis and asthma.[206,207] Theoretically, this new therapeutic modality could be used as protective cover for future clinical applications of rapid rush forms of immunotherapy. As presently applied, rapid rush immunotherapy requires significant premedication with antihistamines and corticosteroids to prevent systemic reaction. It is anticipated that the preadministration of anti-IgE could provide a more predictable protective effect and therefore permit a full-dose allergen immunotherapeutic regimen within a few hours with minimal systemic effects. Cytokine and cytokine receptor modulation are active areas of current clinical research. The most promising candidates are monoclonal anti-interleukin (IL)-5 and anti-IL-13 antibodies, but antagonists to IL-4 (ie, soluble IL-4 receptor $\alpha$) are also promising treatments.[208–210] As yet, the clinical application of these immunomodulative approaches remains to be determined.

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*Requests for reprints should be addressed to:*
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## Appendix 1. Documentation of allergen immunotherapy

***Immunotherapy Content Form***

The purpose of this form is to define the contents of the vaccine in enough detail that it could be duplicated if necessary.

This form should include the following:

- Appropriate patient identifiers, including patient name, number, and birth date
- Vaccine contents, including common name or genus and species of individual allergens and detailed description of all mixtures
- Extract (vaccine) manufacturer and catalog number or lot number of each component
- Volume of individual components of manufacturer's vaccine and final concentration of each
- Type of diluent used (if any)
- Vaccine expiration date

***Documentation of Informed Consent***

Informed consent is a process by which a patient and physician discuss various aspects of a proposed treatment. Though 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 a record of the following:

- Treatment proposed and its alternatives
- Benefits expected from the treatment
- Risks, including a fair description of how frequently adverse outcomes (including death) occur
- Anticipated duration of treatment
- Office policies that affect treatment

Since the informed consent process is complex and details may vary from state to state, each allergist/immunologist should decide how to document informed consent. Legal advice may be useful.

***Immunotherapy Vaccine Administration Form***

This form (example in Appendix 2) should be used to document the administration of vaccine 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 permit documentation in enough detail to allow later determination of what was done. The form should contain the following:

- Appropriate patient identifiers, including patient name, number, and birth date. Placement of the patient's picture on the form may be helpful, particularly when more than 1 patient has the same name. If 2 or more patients have the same name, that fact should be noted on the form as well, as should a means of distinguishing the 2 individuals.
- Name of the vaccine, including an indication of the dilution from the maintenance concentrate in volume per volume. Other identifiers, such as cap color, number, or letter, may help to reduce the risk of an administration error.
- Dates and times of vaccine injection
- Volume of vaccine administered in milliliters (mL) with each injection. If a dose adjustment is required, it may be useful to note the next dose to be administered. During the buildup phase, the dose can be determined using a standard schedule.
- Arm in which the injection was given (left or right). This may facilitate determination of which vaccine causes local reactions. Because local reactions do not correlate reliably with systemic reactions, the presence of an immediate local reaction may not be a useful way to determine which vaccine caused a systemic reaction. Although it is a common practice to alternate the arm into which a particular vaccine is given, there is no evidence that this is necessary.
- In patients with asthma (unstable asthma in particular), peak expiratory flow rate measurements may be considered before an injection. If done repeatedly over time, this permits better determination of baseline peak expiratory flow rate. If a patient's peak expiratory flow rate is significantly below baseline, the clinical condition of the patient should be evaluated before administration of the injection.
- Description of any reactions. Dose adjustments may be necessary if reactions are frequent or severe.
- Details of any treatment given in response to a reaction should be documented in the medical record and referenced on the administration form.
- Any adjustment from the standard schedule and the reason for the adjustment (eg, missed appointments).
- Clinical status of the patient before the injection. In general, patients who have high fever or any significant systemic illness should not receive an injection. It is desirable to document the patient's clinical condition before each injection, particularly if the patient is symptomatic.
- Whether the patient has taken an antihistamine that day
- Whether any new medication has been taken since the last immunotherapy injection

***Labels for Vaccine Vials***

Each vial of vaccine should be labeled in a way that permits easy identification. Each label should include the following information:

- Appropriate patient identifiers, including patient name, medical record, number, and birth date
- General description of the vaccine contents. The detail with which the contents can be identified depends on the size of the label and the number of allergens in the vial. Because of space limitations, it may be necessary to abbreviate the antigens. Possible abbreviations are as follows: 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. A full and detailed description of vial contents should be recorded on the prescription/content form.
- The dilution from the maintenance concentrate in volume per volume. If colors, numbers, or letters are used to identify the dilution, they also should be included.
- Vaccine expiration date

***Instruction Form for Use at an Outside Facility***

An instruction form should accompany all patients who go to an outside facility for immunotherapy injections. It should include:

- General instructions for administration of immunotherapy
- Directions for adjusting the dose if there is a reaction
- Directions for adjusting the dose after an unexpected interval between injections
- Instructions for treating reactions if they occur

## Appendix 2.—Immunotherapy Vaccine Administration Form

**Patient Name:**
**Date of Birth:**
**Patient Number:**
**Telephone:**
**Diagnosis:**

**Prescribing Physician:**
**Address:**

**Telephone:**
**Fax:**

| Vial | Extract Name |
|---|---|
| A | _____ |
| B | _____ |

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

**Best Baseline Peak Flow:** _____

| | | | | | | Vial A | | | | Vial B | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Date | Time | Health screen abnormal[1] | Anti-histamine taken?[2] | Peak Flow | Arm | Vial Number or Dilution | Delivered Volume | Local Reaction[3] | Arm | Vial Number or Dilution | Delivered Volume | Local 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 | _____ | _____ | _____ | _____ |
| 25. | ___/___/___ | _____ | Y N | Y N | _____ | R L | _____ | _____ | _____ | R L | _____ | _____ | _____ | _____ |

[1]The health screen is a written or verbal interview of the patient before administration of the allergy injection. The interview covers the presence of increased allergy or asthma symptoms, symptoms of respiratory tract infection, β-blocker use, change in health status (including pregnancy), or adverse reaction to a previous injection. A "yes" answer during this health screen may require further evaluation.
[2]To improve consistency in interpretation of reactions, it should be noted whether the patient has taken an antihistamine on the injection day. The physician also may request that antihistamines always be taken on injection days.
[3]This column is a record of local reactions. The details of treatment of a systemic reaction (noted as SR) would be recorded elsewhere in the medical record.

## Appendix 3.—Maintenance Concentrate Prescription/Content Form

**Patient Name:**
**Patient Number:**
**Birth Date:**
**Telephone:**

**Prescribing physician:**
**Address:**

**Telephone:**
**Fax:**

**Vial 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 |

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

| Allergen Number | Allergen (Common name or *Genus,species*) | Projected effective concentration (AU, BAU, W/V, PNU) | Conc. of available manufacturer's extract (AU, BAU, W/V, PNU) | Volume of manufacturer's extract to add | Manufacturer Lot Number | Expiration date |
|---|---|---|---|---|---|---|
| 1 | | | | | | |
| 2 | | | | | | |
| 3 | | | | | | |
| 4 | | | | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| Diluent | | | | | | |
| Total Volume | | | | | | |

**Specific Instructions**:

$$\text{Volume to add} = \frac{\text{Projected Effective Concentration}}{\text{Conc. of Manufacturer's Extract}} \times \text{total volume}$$

_____ ____/____/____
Signature Date

| Allergen | Projected Effective Concentration 0.5mL injected | 1.0mL injected |
|---|---|---|
| Dust mite (*D. pteronyssinus*) | 1,200 AU/mL | 600 AU/mL |
| Dust mite (*D. farinae*) | 4,000 AU/mL | 2,000 AU/mL |
| Dust mite (equal mix) | 1,500-2,000 AU/mL | 750-1,000 AU/mL |
| Cat | 4,000-6,000 BAU/mL | 2,000-3,000 BAU/mL |
| Grass | 8,000 BAU/mL | 4,000 BAU/mL |
| Short ragweed | 1:100 – 1:30 (w/v) | 1:200 – 1:60 (w/v) |
| Other pollen | 1:100 – 1:30 | 1:200 – 1:60 |
| Molds | 1:100 – 1:50 | 1:200 – 1:100 |

Appendix 3.—continued

**Patient Name:**
**Patient Number:**
**Birth Date:**
**Telephone:**

**Prescribing physician:**
**Address:**

**Telephone:**
**Fax:**

**Vial Name: TGR**

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

| Allergen Number | Allergen (Common name or *Genus,species*) | Projected effective concentration (AU, BAU, W/V, PNU) | Conc. of available manufacturer's extract (AU, BAU, W/V, PNU) | Volume of manufacturer's extract to add | Manufacturer Lot Number | Expiration date |
|---|---|---|---|---|---|---|
| 1 | Timothy grass | 8,000 BAU/mL | 100,000 BAU/mL | 0.4 mL | HS xxxxx | 1-1-03 |
| 2 | White ash (tree) | 4,000 PNU/mL | 40,000 PNU/mL | 0.5 mL | Ctr xxxxx | 8-15-02 |
| 3 | Short ragweed | 4,000 PNU/mL | 40,000 PNU/mL | 0.5 mL | Gr xxxxx | 10-13-02 |
| 4 | | AgE 12.5 U/mL | AgE 125 U/mL | | | |
| 5 | | | | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | | | | | | |
| 9 | | | | | | |
| 10 | | | | | | |
| Diluent | Saline/alb/phenol | | | 3.6 mL | | |
| Total Volume | | | | 5 mL | | |

**Specific Instructions**:

$$\text{Volume to add} = \frac{\text{Projected Effective Concentration}}{\text{Conc. of Manufacturer's Extract}} \times \text{total volume}$$

_____ Signature

_____/_____/_____ Date

| Allergen | Projected Effective Concentration 0.5mL injected | 1.0mL injected |
|---|---|---|
| Dust mite (*D. pteronyssinus*) | 1200 AU/mL | 600 AU/mL |
| Dust mite (*D. farinae*) | 4,000 AU/mL | 2,000 AU/mL |
| Dust mite (equal mix) | 1,500-2,000 AU/mL | 750-1,000 AU/mL |
| Cat | 4,000-6,000 BAU/mL | 2,000-3,000 BAU/mL |
| Grass | 8,000 BAU/mL | 4,000 BAU/mL |
| Short ragweed | 1:100 – 1:30 (w/v) | 1:200 – 1:60 (w/v) |
| Other pollen | 1:100 – 1:30 | 1:200 – 1:60 |
| Molds | 1:100 – 1:50 | 1:200 – 1:100 |

Appendix 4. Immunotherapy Injection Techniques

Immunotherapy should be given with a 26- or 27-gauge syringe with a ⅜- or ½-inch nonremovable needle. Syringes designed specifically for immunotherapy are available from medical supply companies. The use of safety-engineered syringes with retractable needles is becoming more common.

There should be no air in the hub of the syringe. Air can be expelled by flicking the syringe with a finger while holding the syringe with the needle end up.

The immunotherapy injection usually is 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. Before the injection is given, the skin should be wiped with an alcohol swab. This does not sterilize the area, but it does remove gross contamination from the skin surface.

Immunotherapy injections should be given subcutaneously. Subcutaneous injections result in the formation of a reservoir of vaccine that is slowly absorbed. Absorption that is too rapid, such as that 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.

Before injection, the syringe should be aspirated to check for blood return. If blood is present in the syringe, the needle should be removed and the syringe discarded in an appropriate container (e.g., a sharps box). A fresh syringe and needle are necessary to determine whether a blood vessel has been entered. Another dose of vaccine 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. After use, the syringe and needle should be discarded appropriately.

The plunger should be depressed at a rate that does not result in wheal formation or excessive pain. Immediately after removal of the needle, mild pressure should be applied to the injection site for approximately 1 minute. This reduces the chance of leakage of the vaccine, which could result in a local reaction.