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Practice parameters

Practice parameters for allergen immunotherapy

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Immunity has been defined as a freedom from or protection against certain diseases. The initial immunotherapeutic interventions, which included the development of preventive vaccines and xenogeneic

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antisera by Jenner, Pasteur, Koch, and von Behring, were effective for disease prevention. These initial efforts at immune modulation served as the model for later developments in allergen immunotherapy.

One of the initial investigations of immunization for allergic diseases was described by Noon in 1911. He administered grass pollen extract to patients with allergy, with resulting reductions in their symptoms.¹ Recent advances in allergen immunotherapy have depended on the improved understanding of IgE-mediated immunologic mechanisms, the characterization of specific antigens, and the standardization of allergenic extracts.

Allergen immunotherapy is the repeated administration of specific allergens to patients with IgE-mediated conditions for the purpose of providing protection against the allergic symptoms and inflammatory reactions associated with natural exposure to these allergens. The details of allergen immunotherapy are explained in this document.

The technique of allergen immunotherapy should be differentiated from unproven techniques such as sublingual treatment and neutralization-provocation therapy. Allergen immunotherapy should also be differentiated from the process of desensitization, which usually applies to the rapid progressive administration of an allergenic substance to render effector cells less reactive.

SUMMARY STATEMENTS

- Allergen immunotherapy is defined as the repeated administration of specific allergens to patients with IgE-mediated conditions, for the purpose of providing protection against the allergic symptoms and inflammatory reactions associated with natural exposure to these allergens.
- Despite the varied immunologic changes occurring after allergen immunotherapy, the precise mechanism or mechanisms responsible for clinical effectiveness have not been determined. Postulated immunomodulatory mechanisms include: decrease in cellular responsiveness, production of blocking antibody, induction of tolerance (B-cell, T-cell, or both), presence of anti-idiotypic antibodies, and activation of T-cell suppressor mechanism.
- Controlled studies have shown that allergen immunotherapy is effective for patients with allergic rhinitis or conjunctivitis, allergic asthma, and stinging insect hypersensitivity.
- Allergen immunotherapy is indicated in patients who have demonstrable evidence of specific IgE

antibodies to clinically relevant allergens and whose allergic symptoms warrant the time and risk of allergen immunotherapy. The necessity for initiating allergen immunotherapy may also depend on the degree to which symptoms can be reduced by medication, the amount and type of medication required to control symptoms, and whether appropriate avoidance is possible.

- In choosing the components for a clinically relevant extract, the physician should know the local and regional aerobiology of pollens, fungi, and dust mites and should be aware of potential allergens in the patient's environment.
- The potency and stability of allergenic extracts is crucial for diagnostic skin testing and allergen immunotherapy.
- The major risk of allergen immunotherapy is anaphylaxis. Therefore allergen immunotherapy should be administered under the supervision of an appropriately trained physician who can recognize early symptoms and signs of anaphylaxis and administer emergency medications if necessary. Every effort should be made to prevent anaphylactic reactions caused by allergen immunotherapy.
- Alternatives to allergen immunotherapy should be considered in patients whose medical condition reduces their ability to survive a systemic allergic reaction.
- Patients who are receiving β -adrenergic-blocking agents generally should not receive allergen immunotherapy.
- Allergen immunotherapy ordinarily should not be initiated during pregnancy, although it can and probably should be maintained during pregnancy, provided the patient is tolerating the therapy well and has reached a dose of extract sufficient to provide symptomatic relief. There are no data to indicate that immunotherapy is harmful to the fetus. Every effort should be made to control the patient's condition with appropriate environmental control and pharmacologic therapy.
- The duration of aeroallergen immunotherapy after maximum clinical efficacy has been achieved is not certain. For those patients who respond, many clinicians advise 4 to 5 years of therapy. However, withdrawal of therapy at this time may exacerbate symptoms, and aeroallergen immunotherapy may have to be continued for a much longer time. A decision about when to discontinue

aeroallergen immunotherapy must be individualized.

- Several studies suggest that venom immunotherapy may be discontinued after 5 years. The decision to discontinue venom immunotherapy must be individualized.
- Immunologic changes associated with allergen immunotherapy include changes in levels of allergen-specific IgG and IgE immunoglobulins and effects on lymphocytes, cytokines, and eosinophils.

TYPES OF IMMUNOTHERAPY

The majority of clinicians in the United States use a weekly injection schedule that begins with one to two treatments per week, with gradual tapering of the frequency of injections when maintenance levels are achieved. Administration of high doses of allergen (e.g., 1:100 to 1:30 wt/vol or the highest dose tolerated) is the ultimate goal for this type of schedule. However, the weekly schedule often requires 6 to 12 months of increasing concentrations before maximum or maintenance dosage is attained.

Shortly after the weekly injection schedules were introduced by Noon, an intensive daily buildup regimen was developed. This was soon followed by a rush buildup schedule in which the allergen was administered subcutaneously every 1½ to 2 hours.² In the last decade, this early rush method was modified by a number of investigators who used injection schedules ranging from 10 to 30 minutes.^{3,4} The latter schedules should be more properly termed *rapid/rush* and are similar to allergy desensitization schedules used for small molecular mass biologicals and drugs. Rapid/rush protocols for insect venoms and seminal plasma have been determined to be as efficacious and safe as injection schedules for buildup to maintenance doses.⁵⁻⁷ However, an increased frequency of local and systemic reactions is encountered during rapid/rush desensitization to pollens and house dust mites.⁸

DURATION OF IMMUNOTHERAPY

It is uncertain how long aeroallergen immunotherapy should be continued after maximum clinical efficacy has been achieved. For those patients who respond, most clinicians advise at least 4 to 5 years of therapy.^{9,10} (Note: If the clinical response has not been adequate after 2 years of treatment, aeroallergen immunotherapy should be reassessed.) However, exacerbation of symptoms often occurs after withdrawal at these specified times,

and aeroallergen immunotherapy may have to be continued for much longer periods. Discontinuation must be decided on a case-by-case basis. In this regard, factors that could be considered are the degree of symptomatic improvement and the history of response when aeroallergen immunotherapy was discontinued. In contrast to aeroallergen immunotherapy, as several studies have shown, venom immunotherapy may be safely discontinued after 5 years for many but not all patients.¹¹

ALTERNATIVE APPROACHES TO AQUEOUS IMMUNOTHERAPY

Vehicles such as vegetable and mineral oils have been used to produce slow release of the allergen at the site of injection.^{12,13} These are no longer recommended because of potentially serious side effects. Allergens adsorbed to alum will also retard local allergen release.¹⁴ Adjuvant and modification effects for a protective immune response have been sought with the use of alum, alginates, polyethylene glycol, polyvinyl alcohol, dextrorotary dipeptides (glutamic acid-lysine), tyrosine, allergoids, and more recently, glutaraldehyde.¹⁵ Except for alum-precipitated extracts, none of these agents has been approved for clinical use in the United States.

Local application of allergen to effector organs has been attempted for the treatment of allergic rhinitis and asthma with the rationale of inducing local "desensitization."¹⁶ Thus far, these treatments have had limited success, although a recent report concerning the use of a lyophilized "micronized" allergen extract for nasal immunotherapy demonstrated objective clinical improvement.¹⁷ Some recent reports claim that oral administration of either un-denatured or enzymatically cleaved allergens may be effective in the treatment of allergic rhinitis.¹⁶ However, oral or topical administration of allergen in any form must still be considered experimental.¹⁸

Subcutaneous injection of preformed antibody complexes has been used for the treatment of house dust mite allergy.¹⁹ Investigations of nonimmunogenic, synthetic peptides having epitopes homologous to those present in natural allergens suggest that this immunomodulatory approach may be useful in the treatment of human allergy.^{20,21}

Other immunomodulatory approaches for the treatment of allergic diseases may eventually be included in the general category of immunotherapy. These include the use of high-dose intrave-

nous γ -globulin, interferon- γ , IL-2, "humanized" monoclonal antibodies against IgE, IL-4, IL-13, intercellular adhesion molecule-1, and solubilized fragments of Fc ϵ I and II receptors.

MECHANISMS

Immunologic changes associated with allergen immunotherapy include an increase in IgG (blocking) antibodies, blunting of the expected rise in postseasonal allergen-specific IgE antibodies, a decline in allergen-specific IgE antibodies, rise of allergen-specific IgA and IgG antibodies in nasal secretions, development of allergen-specific suppressor T cells, decline in lymphocyte responsiveness to specific allergens, and in some patients reduction of *in vitro* histamine release from peripheral blood basophils when specific allergen is added.¹⁶ In addition, other findings consistent with possible immunologic changes include suppression of immediate and late nasal reactions and late bronchial reactions after allergen challenge; reduction in conjunctival sensitivity; suppression of eosinophil migration into nasal secretions after intranasal allergen challenge; and reduction of eosinophils, eosinophilic chemotactic factor, and neutrophil chemotactic factor in bronchoalveolar lavage fluid after seasonal exposure to birch pollen in patients with asthma.^{22, 23}

The rise in IgG (blocking) antibodies associated with allergen immunotherapy is dose-dependent and has been shown to occur when about 6 to 12 μ g of Amb a 1, the major allergen in short ragweed, has been administered.²² Comparable doses capable of causing a significant rise in IgG antibodies are 5000 to 25,000 protein nitrogen units or a comparable number of bioequivalent allergy units (BAU) (see Parameter on Diagnostic Testing for definition and discussion of the relevance of protein nitrogen units and BAU). With continued allergen immunotherapy, allergen-specific IgG levels continue to rise and then plateau.²³ Decline in allergen-specific IgE occurs after long-term allergen immunotherapy, but not, in most patients, to a level that results in the disappearance of immediate cutaneous reactivity.¹⁶

Considering the complexity of both cognate (specific antigen recognition) and noncognate (amplification molecules, e.g., IL-4) factors in IgE production and the role of proinflammatory cytokines and adhesion molecules in the total allergic response, clinical efficacy of allergen immunotherapy cannot yet be attributed to a

single mechanism. Recent experience with rapid/rush forms of desensitization, both for insect venom and seminal plasma immunotherapy, have demonstrated that true desensitization may be demonstrated in about 25% to 30% of treated patients (immediately after the 2-hour immunization schedule).^{4, 24} This state of decreased cell responsiveness persists as long as the injections are continued on a regular schedule.

Although the amount of specific IgG (blocking antibody) is a good indication of the total allergen dose delivered to the patient, overall correlation of this modality with clinical efficacy is modest in most clinical situations, except perhaps for insect venom immunotherapy.¹¹ Anti-idiotypic antibodies have also been demonstrated in patients receiving allergen immunotherapy, but there is as yet no good correlation with these regulatory antibodies and clinical results.²⁵⁻²⁷

Induction of peripheral T-cell tolerance appears to be another of the attractive hypotheses.^{20, 21} High dose tolerance could cause a decrease in specific B-lymphocyte cell populations. Antigen-antibody complexes would most likely induce this type of tolerance. This hypothesis is consistent with the recent demonstration that preformed antibody complexes (in antibody excess) may be effective in the treatment of some allergic diseases.²¹ However, for this hypothesis to be credible, it would be necessary to demonstrate that B-cell memory cells are completely deleted. Low dose-tolerance could involve T-helper lymphocyte subpopulations, T-suppressor lymphocyte subpopulations, and/or antigen-presenting cells, which include follicular dendritic cells, macrophages, and B cells. T-cell tolerance affecting either T-helper or T-suppressor cell populations could induce a state of anergy by affecting the T-cell receptor complex and several other costimulatory antigens in T-cell membranes. Many of the current hypotheses concerning allergenic peptide vaccines suggest that peripheral T-cell tolerance occurs in this manner.^{20, 21} Although it has been demonstrated that suppressor T-cell subpopulations are increased after allergen immunotherapy, the correlation with clinical efficacy is modest.²⁸ Recently, however, Schon et al.²⁹ have demonstrated that soluble T-cell suppressor factors are homologous with the T-cell receptor α - β heterodimer, thereby implying that these soluble factors could downregulate T-cell receptor activation by specific allergen.²⁹

CONDITIONS FOR WHICH EFFECTIVENESS OF ALLERGEN IMMUNOTHERAPY HAS BEEN DEMONSTRATED

Allergic rhinitis

Well-controlled clinical studies have demonstrated that allergen immunotherapy is beneficial in the treatment of seasonal pollinosis caused by trees (e.g., birch, mountain cedar), grasses (e.g., timothy, rye), weeds (e.g., ragweed) and in the treatment of mold-induced rhinitis (e.g., *Alternaria*, *Cladosporium* spp.).³⁰⁻³⁴ Clinical studies have also demonstrated the efficacy of allergen immunotherapy in allergic rhinitis caused by dust mites (e.g., *Dermatophagoides farinae*, *D. pteronyssinus*) and animal sensitivity (e.g., cat, dog).³⁵⁻³⁸

Asthma

Well-controlled studies have demonstrated the efficacy of allergen immunotherapy in the treatment of asthma.³⁹⁻⁴⁰ Early controlled studies relied heavily on subjective data to demonstrate that clinical improvement could occur.^{41, 42} More recently, significant clinical improvement based on symptom scores, medication use, emergency room visits, and/or pulmonary function tests has been demonstrated in patients with pollen-induced and mold-induced asthma.^{23, 43-45} Studies have also demonstrated the efficacy of allergen immunotherapy in some patients with perennial allergic asthma caused by animals (e.g., cat, dog) and dust mites.^{35, 37, 38, 46, 47} With regard to the latter, some challenge studies show that both specific and non-specific airway responsiveness can be attenuated after allergen immunotherapy.^{48, 49} The clinical relevance of these findings in regard to dust mites and animals needs to be clarified in patients with continued exposure allergen.

Insect hypersensitivity

Allergen immunotherapy should be considered for patients who have experienced insect-induced hypersensitivity reactions after exposure to insect allergens introduced through various routes (e.g., inhalation, injection). The efficacy of venom immunotherapy in the treatment of stinging insect sensitivity to honeybees, yellow jackets, hornets, and wasps has been well demonstrated.^{11, 50} In addition, several studies have demonstrated the clinical effectiveness of immunotherapy with whole-body extracts of imported fire ant in patients who have had systemic reactions after imported fire ant stings.^{51, 52} Allergen immunotherapy may be effective in preventing reactions to some types of biting

insects as well. For example, patients with a history of anaphylaxis after bites from the blood-sucking arthropod, *Triatoma protracta*, have been protected against reactions from subsequent bites after reaching maintenance levels of *Triatoma* extract⁵³ (see Anaphylaxis Parameter). Patients who have experienced symptoms after exposure to inhaled insect allergens (e.g., cockroach, caddis fly, whole-body bee allergens) may also benefit from immunotherapy.⁵⁴

CONDITIONS FOR WHICH EFFECTIVENESS OF ALLERGEN IMMUNOTHERAPY HAS NOT BEEN PROVEN

There are no well-controlled studies that support the use of allergen immunotherapy for food hypersensitivity.

Although allergen immunotherapy could, theoretically, be useful for treatment of life-threatening food-induced anaphylaxis, the use of allergen immunotherapy for this condition should be considered investigational at this time.

Data on the effectiveness of allergen immunotherapy in the management of skin and mucous membrane disease such as atopic dermatitis, urticaria, and *Candida* vulvovaginitis are conflicting.^{54a,55, 56}

CONSIDERATIONS FOR ALLERGEN 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 proper identification and selection of component allergens on the basis of the patient's history and diagnostic test results.³²

Aeroallergen immunotherapy should be considered for patients who have symptoms of allergic rhinitis and/or asthma after natural exposure to allergens and who demonstrate specific IgE antibodies to relevant allergens.^{9, 16, 32} The severity and duration of symptoms should also be considered in assessing the need for specific allergen immunotherapy. Severity of symptoms can be defined by subjective, as well as objective, parameters. Time lost from work, emergency department or physician office visits, and response to conventional medications are important objective indicators of severity. Patients with allergic rhinitis who are unable to sleep because of symptoms or whose daytime symptoms interfere with their work or school performance should be considered candi-

dates for specific allergen immunotherapy. The impact of the patient's symptoms on quality of life and responsiveness to other forms of therapy, such as allergen avoidance or medication, should also be considered. Unacceptable adverse effects of medications may also favor one's decision to initiate allergen immunotherapy. Coexisting medical conditions should also be considered in the evaluation a patient who may be a candidate for allergen immunotherapy. Patients with moderate or severe asthma and/or allergic rhinitis require a combined aggressive regimen of allergen avoidance, pharmacotherapy, and allergen immunotherapy (see Asthma Parameters).

Hymenoptera venom immunotherapy should be considered in patients who have a systemic anaphylactic reaction after an insect sting and have documented IgE sensitivity to specific insect venom.¹¹

Patients who have completed a course of allergen immunotherapy and who are again having significant symptoms may require reevaluation with consideration of an additional course of specific allergen immunotherapy.

There are insufficient data addressing the use of aeroallergen immunotherapy in preschool children. Although there is some disagreement about the role of allergen immunotherapy in children under the age of 5 years, there have been reports of effectiveness of allergen immunotherapy in this age group.⁴¹ Therefore each case should be considered individually by weighing the risks and the benefits. For example, there is concern about the difficulty of communicating with young children with regard to risks associated with immunotherapy.⁵⁷ On the other hand, for children who have had a history of anaphylaxis to stinging insects or have severe allergic disease, the benefits of allergen immunotherapy may outweigh the risks.

CONTROVERSIAL OR UNCLEAR INDICATIONS

There are no data to support allergen immunotherapy as a treatment for non-IgE-mediated symptoms of rhinitis or asthma. Data generally do not support the efficacy of allergen immunotherapy with bacterial vaccines or the efficacy and safety of urine injections. The need for continued allergen immunotherapy should be reevaluated if it was initiated on the basis of inconclusive or inadequate testing for allergen-specific IgE antibodies or if a beneficial response has not occurred.

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

Immunotherapy in patients with major humoral or cellular immune defects must be considered with regard to the benefits and risks in the individual patient. It must be remembered that concern about immunotherapy in such patients is largely theoretical and that immunotherapy may provide some relief from allergy symptoms in such individuals. It should also be remembered that administration of immunotherapy to patients who may harbor bloodborne pathogens increases the risk of needle-stick injuries to the persons administering the injections. Although concern about the safety of allergen immunotherapy in patients with autoimmune disease or connective tissue disease has been raised in the past, there is no substantive evidence that such treatment is harmful in these diseases.^{58,59} Therefore the risks and benefits of allergen immunotherapy in patients with autoimmune or connective tissue disease must be assessed on an individual basis.

SELECTION OF RELEVANT ALLERGENS

In choosing the components for a clinically relevant extract, the physician should know local and regional aerobiology with regard to pollens, fungi, and indoor allergens (e.g., dust mites) and be aware of potential allergens in the patient's own environment. A knowledge of the allergenic burden facing a patient is useful in determining whether allergen immunotherapy should be initiated in addition to pharmacologic and environmental intervention. On the one hand, the omission of clinically relevant allergens from an allergenic extract may contribute to decreased effectiveness of allergen immunotherapy. On the other hand, inclusion of all allergens to which IgE antibodies are present without establishing possible clinical relevance can dilute the individual allergen content of the extract so that immunotherapy will be ineffective. A patient's lifestyle may produce exposure to a wide variety of aeroallergens from different regions.

The most commonly used allergenic extracts are pollens of trees, grasses, and weeds, as well as mold spores, dust mites, animal allergens, and Hymenoptera venoms. House dust extract is generally an

inappropriate substitution for the house dust mite preparation.³⁶

In addition to recognizing the important allergens in a patient's environment, it is essential for the allergist to be updated continually on new environmental antigens. This includes an awareness of newly introduced flora, which may have increased in number because of changes in soil, weather, or other factors; changes in or newly recognized insect (or mite) populations; changes in animal allergen exposure; and the potential for symptoms caused by other as yet undiscovered allergens or their byproducts.

Standardized allergenic extracts should be used whenever possible. These allergens have a defined potency and are labeled with a common unit, the BAU,⁶⁰ which is based on an official Food and Drug Administration protocol of skin test titration. Extracts that produce an identical skin response at a 1:5 million dilution are bioequivalent and assigned a unitage of 100,000 BAU. Nonstandardized allergens are labeled by protein nitrogen units or weight by volume, but this does not reflect the potency of the product, and therefore a safe and effective dose of a single lot of nonstandardized allergen cannot be generalized to another lot of the same nonstandardized product. Thus there is increased danger of systemic reactions when transferring immunotherapy from one medical facility to another without reassessing the patient's sensitivity to allergenic materials that will be used for future immunotherapy in the new treatment center. Standardized allergens are generally available at a comparatively higher concentration. They are prepared as aqueous, glycerinated, and freeze-dried formulations and are compatible for mixing with nonstandardized products. Theoretically, there is less risk of adverse reactions with standardized allergens because of greater predictability about their potency.

ALLERGEN POTENCY AND STABILITY

Commercial extracts are obtained by allergists in concentrated forms (1:10 to 1:30 wt/vol). Once received in the office, the potency of the extract is affected by a number of factors. These include: (1) the passage of time, (2) storage temperature, (3) concentration, (4) relative volume of the storage vial, (5) the presence of proteolytic enzymes, and (6) the presence of stabilizers and antibacterials. The rate of potency loss over time is influenced strongly by these factors separately and collectively.^{61, 62}

To minimize the rate of potency loss, aqueous

extracts should be refrigerated at 4° C. Potency of concentrated extracts (1:10 to 1:100) under this storage condition is assumed to be constant and maintained to the expiration date of the stock material. If such extracts are removed from the refrigerator for short periods at frequent intervals, as would occur with allergen immunotherapy, comparative loss of potency over 1 year's span is minimal. On the other hand, if such extracts are kept at room temperature for extended periods, loss of potency is accelerated. Less concentrated extracts (1:1000 or more dilute) lose potency much more rapidly, especially when stored at room temperature, and should be replaced accordingly.

The more concentrated extracts lose their potency less quickly. Lyophilization is used to maintain the strength of the dry powder, but once extracts are reconstituted, stabilizing agents such as human serum albumin (0.03%) are needed to maintain potency. Stabilizers (human serum albumin and glycerol) counteract the loss of potency within storage vials by preventing adsorption of allergen on the inner surface of the glass vial. Stability of extracts is enhanced by lyophilization and/or dilution of stock allergens (1:10 or 1:20) in 50% glycerol. At this concentration, glycerol is irritating and therefore should be diluted further before immunotherapy administration. All diluents should contain an antibacterial such as phenol.

At present, data to support or reject the practice of combining allergens in one extract (e.g., combining pollen and mold allergens) are lacking.⁶³ In addition, pollen, mold, and mite allergens have enzymatic activity, including both protease and sugar-cleaving enzymes. Mold and house dust extracts may have greater proteolytic activity than pollens. The relevance of these studies in terms of mixing antigens in an allergenic extract has yet to be proven.

PRECAUTIONS REGARDING ALLERGEN IMMUNOTHERAPY

Patients who are receiving β -adrenergic-blocking agents should generally not receive allergen immunotherapy.⁶⁴ However, when the patient receiving a β -blocker is at risk of a life-threatening reaction if allergen immunotherapy is not started, as would be the case in a patient with stinging insect hypersensitivity, allergen immunotherapy might be indicated. This assumes that there is no acceptable medication that can be substituted for the β -blocker.

Alternatives to allergen immunotherapy should be considered in patients with any medical condition that reduces the ability to survive a systemic allergic reaction: patients who have markedly compromised lung function (either acute or chronic); patients with poorly controlled asthma; patients with unstable angina, recent myocardial infarction, or significant arrhythmias; patients with uncontrolled hypertension; and patients with failure of a major organ system, such as renal failure.

There may be extenuating circumstances in which immunotherapy may be indicated for a high-risk patient, but the relative risks and benefits must be carefully considered. An example of such a situation would be 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 the β -blocker is not in the patient's best interest, it may still be necessary to initiate immunotherapy with the appropriate venom extract.

Allergen immunotherapy ordinarily should not be initiated during pregnancy, although it can and probably should be maintained during pregnancy, provided the patient is tolerating the therapy well and has reached a dose of extract sufficient to provide symptomatic relief.⁶⁵ There is the potential that a systemic reaction to an injection of allergenic extract could produce severe fetal hypoxia.⁶⁵ It is also possible that a systemic reaction could cause uterine contractions, leading to spontaneous abortion or premature labor.⁵⁸ However, immunotherapy for life-threatening disease, such as anaphylactic reaction to insect stings, may warrant initiation of immunotherapy during pregnancy.

RISKS ASSOCIATED WITH ALLERGEN IMMUNOTHERAPY

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 under the supervision of an appropriately trained physician. The health care provider who administers immunotherapy injections should be able to recognize early symptoms and signs of anaphylaxis and administer emergency medications if necessary.⁶⁶ In addition, every effort should be made to prevent anaphylactic reactions caused by allergen immunotherapy. This includes: (1) adjustment of extract dosage of allergen immunotherapy if symptoms of anaphylaxis occur and allergen immuno-

therapy is continued; (2) possible adjustment of extract dosage if large local reactions occur; (3) use of more dilute initial extracts in selected patients who appear to have increased sensitivity on the basis of history and/or results of tests for specific IgE antibodies; (4) instruction for patients to wait in the physicians's office for at least 20 minutes after an immunotherapy injection and inspection of the injection site before patients leave; (5) evaluation of patients before the next immunotherapy injection with regard to local reactions or systemic symptoms occurring later than 20 to 30 minutes after the injection (in order to do this effectively, education of the patient is essential); (6) assessment of the general medical condition of the patient at the time of the injection (e.g., presence of an upper respiratory tract infection or asthma exacerbation); (7) procedures to avoid clerical or nursing errors; and (8) recognition that dosage adjustments may be necessary with newly prepared extracts, if the patient has had a significant interruption in the immunotherapy schedule, or if there are marked changes in allergen exposure (e.g., during the allergen season).

Before allergen immunotherapy is chosen as a treatment, it is incumbent on the physician to educate patients with regard to the risks and benefits of immunotherapy and methods for minimizing these risks. The patient should also be informed that despite proper attention to all these risks, reactions may occur without preceding warning signs or symptoms.

Monitoring of patients receiving allergen immunotherapy is important to maximize the efficacy and safety of this form of therapy. Safety monitoring should be designed to reduce the risk of reactions from allergen immunotherapy. Such monitoring includes assessment of the patient's condition, as well as local and systemic reactions from immunotherapy.

Local reactions, including subcutaneous nodules, are defined as reactions occurring in the immediate vicinity of the injection site. Local reactions can be subdivided into those that occur within 20 to 30 minutes after the injection (during the period of time that the patient is being observed in a clinical setting) and those that occur later than 30 minutes after the injection but before the next injection. If the patient experiences large local reactions, adjustment of extract dosage should be considered.

Systemic reactions are defined as focal or generalized symptoms and/or signs occurring distant

from the injection site. Systemic reactions may begin within 20 to 30 minutes after the injection or later. If a systemic reaction occurs, reevaluation of the patient's immunotherapy program is indicated.

In exceptional cases in which allergen immunotherapy cannot be administered in a medical facility, very careful consideration of potential benefits and risks of at-home administration of allergenic extract therapy must be made on an individual patient basis. It should be noted, however, that the Food and Drug Administration's package insert that accompanies all allergenic extracts implies that allergy injections should be given in a clinical setting under the supervision of a physician with the patient waiting at least 20 minutes after the injection. Patients who are at greater risk of reactions from immunotherapy may need to wait longer.

MONITORING OF CLINICAL EFFICACY

The only criterion for assessment of clinical efficacy of aeroallergen immunotherapy is clinical evaluation. Clinical evaluation could include subjective parameters (e.g., global assessment, symptoms) or objective parameters (e.g., results of pulmonary function tests, medication use).

During the initial treatment phase of incremental increases in dosage, patients may need to be seen at frequent intervals. Once the patient without complications has reached a "maintenance" dosage level, follow-up visits with the specialist every 6 to 12 months may be adequate.

The immediate and late skin test reactions to aeroallergens may decrease, but only after a long period of immunotherapy. Moreover, the skin test response to aeroallergens after a period of immunotherapy is variable and does not necessarily correlate with clinical response. Therefore skin testing alone may not be valuable in assessing the efficacy of immunotherapy in individual patients. As a result, frequent skin testing should not be encouraged, although a repetition of skin testing at 3- to 5-year intervals may help to assess the patient's clinical status.

The criteria for monitoring stinging insect immunotherapy are not well established. In the absence of a response from a natural sting, recent data suggest that after a 5-year period of venom immunotherapy, the patient is at no greater risk than the general population.¹⁰ While awaiting confirmation of these data, it may be appropriate to evaluate the patient with testing for specific IgE antibodies. Three criteria (two immunologic and one dependent on the duration of therapy) have been

proposed as guidelines for cessation of venom immunotherapy. These are loss of skin test reactivity, a decrease in titers of serum venom-specific IgE antibodies to undetectable levels, and a finite period of treatment (i.e., 3 to 5 years). This latter criterion is not influenced by skin test reactivity or serum antibody titer.

ALLERGEN IMMUNOTHERAPY IN REMOTE HEALTH FACILITIES

Because of convenience and logistic factors, allergy extracts are often prepared by specialists for administration in the offices of primary care physicians or specialists or other health service facilities, which can ensure that a physician will be able to respond within 2 to 3 minutes if needed. When this service is undertaken by the allergy specialist, special attention by the allergy specialist should be given to: (1) proper identification of each vial or container of extract, including name of patient, allergen content and proportions, strengths (dilutions), and dates of expiration of each ingredient (in most cases the expiration date should not exceed 1 year but more dilute extracts expire more rapidly); (2) precise instructions regarding the schedule of allergy injections; (3) emphasis on the absolute requirement of an office observation period of at least 20 minutes after each injection (patients who do not heed this advice should be referred back to the allergy specialist); (4) adequate description of immediate and late local and systemic reactions; (5) special instruction on how to modify the dosage schedule if a reaction occurs or if the patient does not adhere to the recommended schedule; and (6) provision of a list of precautions for immunotherapy including recent heavy allergen exposure, concomitant use of β -blocking drugs, acute clinical flares of asthma, upper respiratory tract infections with fever, or serious concurrent illnesses. In most cases the allergy specialist will prefer to administer the first injection of a new extract vial in his or her facility. The allergy specialist should be contacted if the patient becomes pregnant before starting or while receiving immunotherapy.

In addition to these precautions, the physician responsible for administering the allergenic extract should be informed by the allergy specialist about the type of emergency treatment that may be necessary in the event that a life-threatening, anaphylactic reaction occurs. Epinephrine (1:1000) should be available for immediate administration, and dosing instructions for its use should be given. Provisions for maintaining an open airway should be in place.

Medical equipment and supplies for treatment of shock should be in the office. Finally, the physician, with the aid of medical staff, should be competent in the technique of cardiopulmonary resuscitation.

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