

GUIDELINES FOR THE USE OF ALLERGEN IMMUNOTHERAPY

Canadian Society of Allergy and Clinical Immunology

Abstract • Résumé

Objectives: To recommend guidelines for the use of allergen immunotherapy to treat allergies in patients for whom allergen avoidance and drug therapy have not been sufficiently effective.

Options: High-dose or low-dose allergen immunotherapy for the treatment of IgE-mediated allergy to insect stings, allergic rhinoconjunctivitis and asthma.

Outcomes: Clinical evaluation of symptoms, objective measurement of reactions to nasal or bronchial allergen challenge, immunologic changes as a result of allergen immunotherapy and, among patients with anaphylactic reactions to stinging insects, clinical outcome of intentional stinging challenge.

Evidence: A search of MEDLINE was conducted to identify articles that presented results of allergen immunotherapy. Proceedings of symposia held by international subcommittees and of consensus meetings, as well as references obtained from these sources, were reviewed. The articles were grouped according to their main subject: immunologic effects, specific allergies, the results of randomized placebo-controlled clinical trials, types of allergen extract and protocols for allergen immunotherapy, adverse effects and deficiencies of allergen immunotherapy.

Values: Each member of the working group assessed the importance of such issues as basic immunologic effects, clinical efficacy, adverse effects and inappropriate use; the working group then arrived at a consensus.

Benefits, harms and costs: Implementation of these guidelines would lead to the appropriate use of allergen immunotherapy and control inappropriate treatment, which could result in adverse effects and increased costs of services for patients with allergies.

Recommendations: Allergen immunotherapy with specific, standardized allergenic materials, administered in high-dose schedules, is effective in patients with an allergy to insect stings or allergic rhinoconjunctivitis, and in some patients with asthma, who have been correctly diagnosed through a meticulous history corroborated by positive results of skin tests and for whom avoidance of the allergen and drug therapy are not sufficiently effective.

Validation: These guidelines are similar to others being developed in the United States and recommended by the Joint Council of Allergy and Immunology and the American Academy of Allergy, Asthma and Immunology.

Sponsor: These guidelines were developed by a working group of the Canadian Society of Allergy and Clinical Immunology; no funding was received from any other source.

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Objectif : Recommander des lignes directrices sur l'utilisation de l'immunothérapie aux allergènes pour traiter les allergies de patients pour lesquels l'évitement des allergènes et la pharmacothérapie n'ont pas été suffisamment efficaces.

Options : Immunothérapie aux allergènes à forte dose ou à faible dose pour le traitement d'une allergie à médiation par l'IgE aux piqûres d'insectes, de la rhinoconjonctivite allergique et de l'asthme.

Résultats : Évaluation clinique des symptômes, mesure objective des réactions à la provocation allergénique nasale ou bronchique, changements immunologiques à la suite d'une immunothérapie aux allergènes et, chez les patients qui ont présenté des réactions anaphylactiques aux piqûres d'insectes, résultats cliniques d'une provocation par piqûre intentionnelle.

Preuves : On a effectué, dans MEDLINE, une recherche afin de trouver des articles présentant des résultats d'immunothérapie aux allergènes. On a examiné les actes de symposiums tenus par des sous-comités internationaux et de réunions consensuelles, ainsi que des références tirées de ces sources. Les articles ont été regroupés selon leur sujet principal : effets immunologiques, allergies spécifiques, résultats d'essais cliniques randomisés contrôlés par placebo, types d'extraits d'allergènes et protocoles d'immunothérapie aux allergènes, effets défavorables et lacunes de l'immunothérapie aux allergènes.

Valeurs : Chaque membre du groupe de travail a évalué l'importance d'enjeux comme les effets immunologiques de base, l'efficacité clinique, les effets défavorables et la mauvaise utilisation; le groupe de travail a dégagé ensuite un consensus.

Avantages, préjudices et coûts : La mise en oeuvre de ces lignes directrices entraînerait l'utilisation appropriée de l'immunothérapie aux allergènes et le contrôle des traitements inappropriés qui pourraient entraîner des effets défavorables et augmenter les coûts des services aux patients allergiques.

Recommandations : L'immunothérapie aux allergènes à l'aide de substances allergènes et normalisées spécifiques administrées à forte dose est efficace chez les patients allergiques aux piqûres d'insectes ou qui souffrent de rhinoconjonctivite allergique et chez certains patients asthmatiques à l'égard desquels on a posé un diagnostic correct après avoir établi méticuleusement leur histoire de cas corroborée par des résultats positifs de cutiréactions et pour qui l'évitement de l'allergène et la pharmacothérapie ne sont pas suffisamment efficaces.

Validation : Ces lignes directrices sont semblables à celles qui sont en voie d'élaboration aux États-Unis et qui sont recommandées par le Joint Council of Allergy and Immunology and l'American Academy of Allergy, Asthma and Immunology.

Commanditaire : Ces lignes directrices ont été mises au point par un groupe de travail de la Société canadienne d'allergie et d'immunologie clinique. On n'a reçu aucun financement d'ailleurs.

The treatment of allergy may involve allergen avoidance, drug therapy and allergen immunotherapy. "Desensitization," "hyposensitization" and "immunotherapy" are synonymous terms for injections of incremental doses of allergenic substances to treat atopic allergy such as allergic rhinitis and asthma.¹⁻³

Allergen immunotherapy is in common use, but it is the subject of considerable controversy, some of which is based on opinion instead of on objective evaluation of its results and of the validity of scientific study. In fact, allergen immunotherapy has withstood the scrutiny of controlled clinical investigations conducted during the past 20 years.

To conduct an unbiased review of the issue, the Canadian Society of Allergy and Clinical Immunology (CSACI) formed a working group to evaluate the literature and recommend guidelines on the clinical use of allergen immunotherapy. Members of the working group, chosen by the executive of the CSACI, represented academic and practising specialists in clinical allergy.

A search of MEDLINE was conducted to identify articles that presented results of allergen immunotherapy. Proceedings of symposia held by international subcommittees and of consensus meetings, as well as references obtained from these sources, were also reviewed. A list

of about 100 publications was chosen, including reviews of other published recommendations.¹⁻⁵ The articles were grouped according to their main subject: immunologic effects, specific allergies, the results of randomized placebo-controlled clinical trials, types of allergen extract and protocols for allergen immunotherapy, adverse effects and deficiencies of allergen immunotherapy.

Members reviewed, discussed and selected articles to be cited in the final article. Each member of the working group assessed the importance of such issues as basic immunologic effects, clinical efficacy, adverse effects and inappropriate use; the working group then arrived at a consensus.

The final guidelines addressed all areas of concern to the committee. Table 1 shows the issues felt to be important in allergen immunotherapy.

IMMUNOLOGIC EFFECTS

Immunotherapy is specific to the allergen injected.⁶⁻⁸ It results in the following immunologic changes: the generation of specific suppressor cells,⁹ decreased allergen-specific IgE, increased allergen-specific IgG,¹⁰ decreased inflammatory cells,¹¹ decreased mediators of inflammation^{12,13} and decreased histamine-releasing

factors.¹⁴ These changes result in decreased reactivity to the allergen in the target organ.¹⁵ Immunotherapy has proven to be safe in numerous long-term studies.^{1-3,7}

USE OF IMMUNOTHERAPY

Careful identification of the factors that provoke symptoms is the most important consideration in correct diagnosis and evaluation of patients with an allergy. Symptoms must be shown to be temporally related to exposure to an allergen. For immunotherapy to be considered, the allergic reaction must be IgE-mediated and caused by an antigen proven to be amenable to allergen immunotherapy.

A diagnosis of an allergy is supported by measurement of specific sensitivity (IgE) to an antigen that has been correlated with clinical symptoms. The simplest, least expensive and most specific means of determining allergen-specific IgE is epicutaneous-prick skin testing. Intradermal skin testing and radioallergosorbent tests may also be helpful.¹⁶

Immunotherapy should be considered for patients with a history of systemic reactions to Hymenoptera venom from stinging insects,¹⁷ allergic rhinitis⁶⁻⁹ or asthma^{18,19} who have environmental provoking factors producing significant allergic symptoms and who are not obtaining adequate relief through avoidance of environmental allergens and the use of optimal medication (Table 2).¹⁻³ Before recommending immunotherapy, the physician should make every attempt to educate the patient about the importance of preventive measures and the proper use of prescribed medications. In seasonal allergies, allergen immunotherapy should be instituted

only if symptoms have occurred for two or more successive allergy seasons.

TREATMENT SCHEDULE

The effectiveness of allergen immunotherapy is antigen-specific and dose-dependent.⁴ For a beneficial response, patients must be treated with high doses of the allergens responsible for the reaction, as determined on the basis of the history and positive results of skin tests.^{6,21-24} Low-dose treatment has not proven effective.²⁵⁻²⁸ Maintenance schedules and doses vary, depending on the specific allergen and the severity of the patient's allergy.^{7,24,29,30} In controlled studies, incremental doses of aqueous allergenic extracts were administered over several months.³¹⁻³³ Maintenance injection treatment is given for several years. Standardized allergens should be used if they are available.³⁴ Short-term preseasonal administration of allergens with modified allergenic extracts have been reported to be effective in some studies. However, because there are few such extracts available and their allergenic potency needs to be assessed individually, we cannot recommend their general use.³⁵ The duration of allergen-injection treatments is usually 4 to 5 years.¹⁻³ However, the criteria for discontinuing immunotherapy are not well established.

Table 1: Issues in evaluating allergen immunotherapy

High-dose v. low-dose treatment schedules
Immunologic specificity v. nonspecificity (immunologic changes resulting from immunotherapy, determined by measuring reactions to nasal challenge, in rhinitis, or bronchial challenge, in asthma)
Effect of immunotherapy on late-phase allergen inflammatory response
Availability of standardized allergenic extracts (e.g., ragweed pollen, cat dander, house dust mites and insect venom)
Recurrence of symptoms after discontinuation of allergen immunotherapy
Use of immunotherapy to treat specific types of allergy (e.g., allergic rhinitis, anaphylaxis from insect stings and asthma)
Cost and efficacy of immunotherapy v. drug therapy
Results of research studies in comparison with those of clinical practice
Results from modified-allergen preseasonal treatment schedules in comparison with those from perennial allergen-injection treatment
Symptomatic treatment v. cure

Table 2: Therapies for allergy²⁰

Order of use	Therapy	Forms available
First-line	Avoidance of allergens , such as animal dander, house dust mites, pollens, moulds	
Second-line	Drug therapy	
	Allergic rhinoconjunctivitis	
	H ₁ -receptor antagonists	Tablets taken orally, nasal spray, eyedrops
	Decongestants	Nasal spray (short-term use only), tablets taken orally
	Corticosteroids	Metered-dose aerosol or nasal spray, nasal powder
	Asthma	
	Corticosteroids	Metered-dose inhaler, tablets taken orally
	Sodium cromoglycate or nedocromil	Nasal spray, eyedrops, metered-dose inhaler
	Ipratropium bromide	Nasal spray, metered-dose inhaler
Third-line	Immunotherapy	

EFFECTIVENESS IN TREATING SPECIFIC INDICATIONS

ALLERGIC RHINITIS

Well-designed, double-blind, placebo-controlled studies have shown the efficacy of immunotherapy in treating allergic rhinitis, even in patients who do not respond to optimal drug treatment.^{29,36-38} Efficacy is determined not only by symptom diaries but by measuring reactions to nasal allergen challenge. Pollens (trees, grass and ragweed) and house dust mites were the main allergens studied in these trials. Because avoidance and drug treatment are usually effective, fewer than 10% of patients require allergen immunotherapy.

ASTHMA

It has been more difficult to obtain convincing proof of the efficacy of allergen immunotherapy in the treatment of asthma, a disorder with many potential nonimmunologic triggers, than in the treatment of allergic rhinitis.³⁹ Some studies of allergen immunotherapy to treat asthma were not performed under optimal, properly controlled conditions; nevertheless, its efficacy has been demonstrated in other well-designed, double-blind, placebo-controlled studies.^{20,40,41} Reduction of asthma symptoms after allergen immunotherapy with house dust mites, cat dander, grass pollen and *Alternaria* (a genus of fungi) has been reported.⁴²⁻⁴⁶ In most studies, allergen immunotherapy has been shown, through bronchial challenge, to decrease sensitivity of the airway to allergen-induced bronchoconstriction.⁴²⁻⁴⁵ Allergen immunotherapy has been reported to reduce the late-phase inflammatory reaction in the lungs.^{42,47,48} Avoidance of allergens and pollutants and the use of optimal medication (for example, inhaled glucocorticoids) are still the first line of treatment. These are usually effective in treating allergic asthma. However, in some patients with poorly controlled allergic asthma, immunotherapy with a standardized allergen may be considered.

ALLERGIC REACTIONS TO INSECT VENOM

Immunization treatment with the venom of insects (yellow jackets, yellow hornets, white-faced hornets, wasps and honey-bees) is reported to be 95% or more protective in patients with previous anaphylactic reactions to these insect venoms.⁴⁹ However, it is not indicated in children who experience urticaria but no other systemic symptoms after insect stings.^{50,51} Immunotherapy involving administration of 100 µg of insect venom every 4 to 6 weeks is currently recommended.^{50,51} The present recommendation is that venom immunotherapy should be continued for 5 years.^{17,52}

ADVERSE EFFECTS AND CONTRAINDICATIONS

Anaphylaxis is the only serious risk from allergen immunotherapy. Fatal anaphylactic reactions have rarely been reported.⁵³ Care must be taken to avoid errors in allergen dosage. All health care personnel involved in administering allergen immunotherapy should be trained to recognize and treat anaphylactic reactions promptly. Other shortcomings of allergen immunotherapy are summarized in Table 3.

FUTURE RESEARCH

Immunotherapy has proven to be effective when used properly. In addition, it is hoped that other recent advances in immunologic intervention will be of practical clinical significance. Specifically, recent modification of allergens used in immunotherapy promises to reduce allergenic effects, thus decreasing the likelihood of side effects, yet maintain the immunogenic value of the allergens.^{54,55} New forms of allergen immunotherapy now being studied could succeed in shutting down production of specific IgE and thus cure symptomatic allergies.⁵⁶ In contrast with drug therapy, immunotherapy could result in long-term, favourable alteration of the patient's immunologic status.

RECOMMENDATIONS

Allergen immunotherapy is used in the management of patients with atopic allergy. An appropriate history, physical examination and laboratory investigation are

Table 3: Disadvantages and adverse effects of allergen immunotherapy

Disadvantages
Therapy is inconvenient (because of frequency and duration of treatment)
Few standardized allergenic extracts are available
It is difficult to predict which patients will respond favourably and to determine clinical response objectively
There are no laboratory indicators to guide discontinuation of therapy
Therapy is not curative at present
Potential adverse effects
Anaphylaxis (urticaria, asthma, hypotension or death)
Severe and fatal anaphylaxis if the patient is taking β-adrenergic blocking agents
Local swelling at injection site
Theoretic aggravation of existing immunologic diseases (serum sickness, systemic lupus erythematosus or rheumatoid arthritis)
Sensitization to the allergen (if therapy is used inappropriately)

important in defining the specific cause of the allergy. Immunotherapy should be used only when other therapies are ineffective and should involve administration of specific standardized antigen in a treatment schedule that ensures that an adequate amount of antigen is injected according to a recognized protocol.

APPROPRIATE INDICATIONS

Allergen immunotherapy is appropriate for the following indications.^{4,5}

1. Severe, seasonal (lasting 2 or more years⁴) or perennial, IgE-dependent allergic rhinoconjunctivitis in which optimal allergen avoidance and medication have not been sufficiently effective in controlling symptoms.
2. Some cases of IgE-mediated allergic asthma, specifically, those in which there is a clear temporal association between exposure to the allergen and signs and symptoms of asthma, and those in which symptoms have occurred during two or more allergy seasons in successive years.⁴ Regular use of anti-inflammatory medications such as inhaled corticosteroids suppresses symptoms in most patients. In addition, allergen avoidance measures must be properly instituted. If medication and avoidance are ineffective, allergen immunotherapy may be considered. IgE-mediated asthma caused by house dust mites or ragweed pollen may occasionally be treated with allergen immunotherapy.
3. IgE-mediated anaphylactic reactions to insect stings. Immunotherapy with venom from yellow jackets, yellow hornets, white-faced hornets, wasps and honey-bees, and with whole-body extracts of fire-ants, is effective.

CONTRAINDICATIONS AND INAPPROPRIATE USE

Allergen immunotherapy is inappropriate in the following circumstances.

1. The history, physical examination and results of laboratory and radiologic tests do not indicate IgE-mediated allergy, despite positive results of skin tests or radioallergosorbent tests.
2. The patient's rhinitis, asthma or insect-allergy symptoms are not IgE mediated.
3. The patient has an IgE-dependent allergy to foods.
4. The patient's only symptoms are urticaria or atopic dermatitis.
5. The patient has a coexisting autoimmune disease.
6. The patient has severe, uncontrolled asthma.
7. The patient is a child of less than 5 years of age.⁵⁷
8. Previous properly administered allergen immunotherapy was unsuccessful.

9. The patient has had no reduction in symptoms after 2 years of allergen injections.
10. Allergen injections have been given longer than 5 years.

Furthermore, the use of extracts of bacteria, histamine or urine in lieu of specific allergen extracts is contraindicated.

VALIDATION

These guidelines are similar to others being developed in the United States and recommended by the Joint Council of Allergy and Immunology⁴ and the American Academy of Allergy, Asthma and Immunology.^{1,2}

These guidelines were prepared by a working group of the Canadian Society of Allergy and Clinical Immunology. No funding was obtained from any other source.

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May 31-June 2, 1995: 12th International Society for Quality in Health Care World Congress — Partnerships for Creating a Quality Health System: Users-Providers-Funders

St. John's

12th ISQua World Congress, Organizing Secretariat, Beclin Building, 1118 Topsail Rd., PO Box 8234, St. John's NF A1B 3N4; tél 709 364-7704, fax 709 364-6460

June 1-3, 1995: Canadian Physiotherapy Cardio-respiratory Society and Canadian Nurses' Respiratory Society 95th Annual National Conference — Climbing Higher: Reaching Your Peak

Calgary

Peter Vavougios, CPCRS program chair, or Rita Lisella, CNRS program chair, The Lung Association, 1900 City Park Dr., Gloucester ON K1J 1A3; tél 613 747-6776, fax 613 747-7430

Du 1^{er} au 3 juin 1995 : 95^e Congrès national annuel de la Société de physiothérapie cardio-respiratoire du Canada et de la Société canadienne des infirmières en santé respiratoire — Viser plus haut pour atteindre son sommet

Calgary

Peter Vavougios, président du programme, SPCRC, ou Rita Lisella, présidente du programme, SCISR, L'Association pulmonaire, 1900, prom. City Park, Gloucester ON K1J 1A3; tél 613 747-6776, fax 613 747-7430

June 1-3, 1995: Oral-Motor Skills Workshop: the Development of Oral-Motor Skills in Children Receiving Nonoral Feedings

London, Ont.

CPRI, 600 Sanatorium Rd., London ON N6H 3W7; tél 519 471-2540, ext 2074; fax 519 641-1922

June 5-6, 1995: 1995 Registered Practical Nursing Conference: Registered Practical Nurses — a New Bag of Tricks

Mississauga, Ont.

Humber College, Business and Industry Services, 205 Humber College Blvd., Etobicoke, Ont. M9W 5L7; tél 416 675-5077, fax 416 675-0135

Du 8 au 11 juin 1995 : 5^e Conférence annuelle de recherche sur le VIH/SIDA : Prévenir l'infection, prévenir la maladie (organisé par l'Association canadienne de recherche sur le VIH)

Winnipeg

M^{me} Randy Schwartz, présidente, Comité des inscriptions, Conférence ACRV 1995, bureau A1105, Hôpital général Saint-Boniface, 409, ave. Taché, Winnipeg MB R2H 2A6; tél 204 237-2948, fax 204 233-7125

June 8-11, 1995: 5th Annual Canadian Conference on HIV/AIDS Research: Preventing Infection, Preventing Disease (organized by the Canadian Association for HIV Research)

Winnipeg

Ms. Randy Schwartz, chair, Registration Committee, CAHR Conference 1995, Rm. A1105, St. Boniface General Hospital, 409 Taché Ave., Winnipeg MB R2H 2A6; tél 204 237-2948, fax 204 233-7125

June 9-10, 1995: Organ and Tissue Donation: Perspectives from the Humanities

Chicago

Organ Donation Conference, Bethany Spielman, Rm. 1113, Department of Medical Humanities, Southern Illinois University School of Medicine, PO Box 19230, Springfield IL 62794-9230; tél 217 782-4261, fax 217 782-9132