

An overview of current clinical practice and international oral immunotherapy guidelines: A focus on Spanish, European, and Canadian guidelines

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ABSTRACT

Oral immunotherapy (OIT) is a recent and evolving therapeutic option for the treatment of immunoglobulin E (IgE) mediated food allergies. Clinical practice guidelines are starting to emerge to establish the parameters of this new clinical offer. A comparative analysis reveals several areas of consensus, such as the need for an accurate diagnosis with immunoglobulin E testing and, if necessary, open food challenge before initiating therapy; a list of specific contraindications; the importance of performing OIT in an adequate setting with appropriate level of expertise; the possibility to use grocery products to perform OIT; and the need to adapt protocols to patient needs. Certain discrepancies among the guidelines also underscore various areas of uncertainty, which makes it important that decisions to pursue the treatment be reached by using a shared decision-making approach that involves patients and caregivers. Gaps of knowledge remain with regard to treatment of adolescents and adults, and optimal performance measures in practice. These guidelines are expected to evolve in the coming years as new scientific and experiential knowledge is gained.

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To date, various allergy organizations have made specific recommendations on the use of oral immunotherapy (OIT) for the treatment of immunoglobulin E (IgE) mediated food allergy. In 2017, both the European Academy of Allergy and Clinical Immunology (EAACI) and the Spanish Society of Allergology and Clinical Immunology (SEACI) published their first guidelines on the topic.^{1–3} The EAACI guidelines were based on a systematic review of the literature with meta-analysis, whereas the Spanish guidelines were based on a narrative review of the literature and expert consensus;^{1–3} these guidelines followed the Oxford Center for Evidence-Based

Medicine and the Scottish Intercollegiate Guidelines Network standards to grade the level of evidence and strength of each recommendation, respectively.

In 2020, the Canadian Society of Allergy and Clinical Immunology (CSACI) published Canadian guidelines for the evidence-based, patient-centered, and ethical clinical practice of OIT.⁴ These were based on a systematic review of the scientific literature as well as of Canadian written media, stakeholder consultations with patients, other health care professionals, allergists, and general practitioners, and an ethics review by ethicists. The guidelines followed a multicriteria decision analysis approach, which took into consideration sociopolitical, population, economic, and organizational dimensions, in addition to clinical evidence when making recommendations.

Although the American Academy of Allergy, Asthma and Immunology (AAAAI) and American College of Allergy, Asthma and Immunology (ACAAI) have not yet produced official guidelines on OIT, their affiliated journals have published a number of reviews on implementation of OIT.^{5–7} The Japanese Society of Pediatric Allergy and Clinical Immunology and the Italian Society of Pediatric Allergy and Immunology both included a section on food OIT in their guidelines on food allergy and allergen immunotherapy, respectively.^{8,9} Their recommendations mainly consist in limiting the practice of OIT to specialized centers with the expertise and proper setting to perform it safely.

In fact, all the guidelines underline the importance of having a trained medical and experienced team in the diagnosis of food allergy and in the recognition and treatment of allergic reactions. Adrenaline (epinephrine), antihistamine (oral and parenteral), inhaled β 2-agonist,

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Table 1 Major recommendations common to all three guidelines*

| Item | Recommendation |
|--------------------------------|---|
| Indication | OIT is indicated for the treatment of IgE-mediated food allergy to achieve desensitization, defined as an increase of reaction threshold while on treatment |
| Accurate diagnosis | Before initiating the treatment, an accurate diagnosis is essential; it is generally based on a history of acute reaction(s) after supposed allergen consumption, and confirmed by skin-prick test and/or serum specific IgE; when the diagnosis is not clear, an oral food challenge is required |
| Absolute contraindications | The lack of proper diagnosis, uncontrolled asthma, and pregnancy are absolute contraindications; the lack of understanding of the treatment, its risks and challenges, and the possibility of compliance are also contraindications to treatment |
| Relative contraindications | Active severe atopic dermatitis, preexisting EoE, heart disease, patients who require the use of β -blockers or angiotensin-converting enzyme inhibitors are relative contraindications |
| Protocol | The response to OIT is heterogeneous, and treatment must be adapted if it is not well tolerated |
| OIT product | The use of grocery products is recommended; there is no evidence that the efficacy and safety are affected by the type and nature of the food allergen |
| Food allergen | OIT can be completed with a variety of food allergen products (all types and natures) and preparation techniques, initial dose escalation schedules, buildup starting, final target dose, up dosing frequency, length of buildup phase, and maintenance dose and frequency |
| Shared decision-making process | A full explanation of the protocol, its expected duration, expected benefits, possible risks, the different therapeutic choices, and the variability of the objectives must be clearly discussed between the patient and the caregiver; a consent form should be signed; it helps to improve adherence to the care protocol |

OIT = Oral immunotherapy; IgE = immunoglobulin E; EoE = eosinophilic esophagitis.

*Adapted from Refs. 1-4.

corticosteroids (oral and parenteral) must be available. The EAACI guidelines more specifically indicate that personnel should be able to provide at least 12 hours of observation in case of adverse reactions and that an anesthesiology or intensive care or equivalent team member particularly trained in resuscitation be on call and should be available within 5 minutes.¹ Table 1 and Table 2.

RECOMMENDATIONS ON INDICATIONS AND FACTORS THAT INFLUENCE EFFICACY AND SAFETY OF OIT (PATIENT, ALLERGEN, AND/OR FOOD)

Based on their assessment of the literature, the EAACI, SEAIC and CSACI guidelines all conclude [that OIT is indicated] for the treatment of IgE-mediated food allergy to achieve desensitization, defined as an increase of reaction threshold while on treatment.¹⁻⁴ All three guidelines highlight the need for an accurate diagnosis before initiating treatment.¹⁻⁴ The diagnosis is generally based on a history of acute reaction(s) after consumption of the triggering food and is confirmed by skin-prick test and/or serum specific IgE. When the diagnosis is not clear, then oral food challenge is required. Both the EAACI and CSACI guidelines

mention that the intervention is justified by limitations in food allergy-related quality of life, which can improve with treatment.^{1,4} However, this does not yet translate into specific recommendations with regard to patient selection.

With regard to specific patient groups, most OIT studies included children and adolescents across a wide age range, with reports that suggest that the treatment is particularly efficacious and well tolerated in toddlers and preschoolers.¹⁰⁻¹³ Although the EAACI guidelines make no recommendation for adults, the CSACI guidelines suggest that OIT could be offered as an option in this age group based on the small but consistent evidence in this group and the principle of equity of access.^{1,4} Because of the small number of studies to support the efficacy of OIT at achieving sustained unresponsiveness at the time, the EAACI guidelines did not make any recommendation to that effect.¹ Three years later, the Canadian guidelines mention that, given the existing, albeit limited, favorable evidence, which was consistent with data from consultations, OIT could be recommended to promote sustained unresponsiveness in toddlers and preschool children.¹

Table 2 Major recommendations that differ among the guidelines*

| Item | Recommendations |
|---------------------------------|--|
| Adults | The CSACI guidelines suggest that OIT could be offered as an option in this age group; other guidelines make no recommendation |
| Toddlers and preschool children | The CSACI guidelines recommend OIT, regardless of age or allergen(s) to promote sustained unresponsiveness to the allergen(s); EAACI and SPEAIC guidelines suggest to wait until 2 to 5 years of age before starting OIT, because the patient has a high likelihood of developing spontaneous tolerance, particularly to milk, egg, wheat, and soy; the SPEAIC guidelines specify that the lower age limit can be waived in children with severe allergies with a high risk of persistence |
| Contraindications | A history of eosinophilic esophagitis represents an absolute contraindication for the EAACI and SEAIC guidelines but just a relative contraindication for the CSACI guidelines |
| Protocol | The EAACI guidelines recommend a standardized protocol with specific dosing schedules; the CSACI guidelines recommend a personalized protocol adapted according to each patients' need |

CSACI = Canadian Society of Allergy and Clinical Immunology; OIT = oral immunotherapy; EAACI = European Academy of Allergy and Clinical Immunology; SPEAIC = Spanish Society of Allergology and Clinical Immunology.

*Adapted from Refs. 1-4.

This, however, contrasts with the position of the EAACI and SPEAIC guidelines for young children, in whom it is suggested to wait until 2 to 5 years of age before starting OIT because they have a high likelihood of developing spontaneous tolerance, particularly to milk, egg, wheat, and soy.¹⁻³ All in all, this needs to be balanced with the risk of missing a window of opportunity for a more-effective treatment or a sustained effect. The Spanish guidelines specifically mention that the lower age limit can be waived in children with severe allergies with a high risk of persistence.^{2,3}

RECOMMENDATIONS ON OIT CONTRAINDICATIONS

The three guidelines are consistent with regard to contraindications.¹⁻⁴ The lack of a proper diagnosis, uncontrolled asthma, and pregnancy are absolute contraindications. Active severe atopic dermatitis, preexisting eosinophilic esophagitis (EoE), and heart disease, and those patients who require the use of β -blockers or angiotensin-converting enzyme inhibitors are relative contraindications. There is a discrepancy among the guidelines as to whether a history of EoE represents an absolute (EAACI and SEAIC guidelines) or relative (CSACI guidelines) contraindication.¹⁻⁴ The decision to pursue OIT or not in these patients should be based on clinical judgment, provider expertise, and shared decision-making.

There is no evidence that the severity of previous anaphylactic reactions to the targeted food allergen, the number of food allergies, and the presence of controlled asthma or eczema affect the outcome of treatment. Although food-specific IgE, either absolute or

relative to total IgE, is associated with treatment outcomes, there is no absolute value above at which a patient would not be amenable to desensitization.¹⁴⁻¹⁶ Therefore, these are not contraindications to OIT. Apart from biologic considerations, the guidelines stress that OIT requires patients and their caregivers to attend visits regularly,¹⁻⁴ understand the risks and benefits of the procedure, and are able to understand and follow instructions with regard to how to administer the treatment at home. Patients must also be able to recognize and treat adverse events. All the guidelines agree that, if these conditions are not respected, then OIT should not be initiated.

RECOMMENDATIONS ON PERSONALIZED VERSUS STANDARDIZED PROTOCOL

The Canadian guidelines make specific recommendations for a personalized approach to OIT treatment.⁴ Rather than recommending to follow specific dosing schedules, they recommend that the protocol be adapted according to each patient's need. In contrast, the EAACI guidelines mention the need for more standardization in the discussion.¹ Although the two positions may seem opposed, they are, in fact, not incompatible. When mentioning the need for standardization, the EAACI guidelines do not oppose treatment personalization but rather stress the need to standardize definitions and outcome measures to improve comparability between practices and to create minimal quality standards.¹ Standardized outcome measures would also facilitate research and knowledge translation. All three guidelines specifically recognize the heterogeneity in patient response to OIT and the need to adapt treatment if it not well tolerated.¹⁻⁴

RECOMMENDATIONS ON OIT PRODUCT

All three guidelines recommend the use of grocery products to perform OIT.¹⁻⁴ Despite a theoretical concern for the variability of nonstandardized food products, there is no evidence that pharmaceuticals offer any additional benefit over products that can be purchased in grocery stores. The CSACI guidelines specifically mention that, although pharmaceutical-based approaches have not been shown to be superior to the use of food products from the grocery store, they carry the risk of limiting access due to their high cost.⁴ Thus, unless the superiority of certain food products is demonstrated over other forms of the same allergen, the choice of product used should be guided by availability, cost, and practical considerations.

All the guidelines recognize that OIT can be completed with a variety of food allergen products and preparation techniques, initial dose escalation schedules, buildup starting and final target dose, updoing frequency, length of buildup phase, and maintenance dose and frequency.¹⁻⁴ The CSACI guidelines specifically indicate that their recommendations apply to all food allergens, and the EAACI guidelines stresses that there is no evidence that the efficacy and safety of OIT is affected by the type and nature of the food allergen used in OIT.^{1,4} However, when using a different food source for OIT, the patients must be informed of the equivalent protein content among products, and it is good practice to try new products at the clinic when in doubt.

RECOMMENDATIONS FOR SHARED DECISION-MAKING

All three guidelines and numerous review papers agree that all patients with food allergy and caregivers do not share the same values and perspectives, and that the decision to pursue the treatment should be made through a shared decision-making process.^{1-4,13} The need for shared decision-making is made even more important by the uncertainty about the outcome of OIT. Shared decision-making has also been shown to improve adherence to the care protocol.¹² Before starting OIT, a full explanation of the protocol, its expected duration, expected benefits, possible risks, and the necessary regular involvement are needed. The different therapeutic choices and the variability of the objectives must be clearly discussed. At the end of this explanation, if the patient adheres to the protocol (and his or her guardians), he or she should have to sign a consent form.

Recommendations in formal guidelines mark a critical step in the transfer of OIT from research to the bedside. However, all the guidelines identified several gaps of knowledge and these will likely change with the progress of scientific and experiential knowledge on OIT in the coming years.¹⁻⁴

CLINICAL PEARLS

- Although there is no current standardized outcome measure for OIT in practice, clinical practice guidelines agree that success is mainly measured in improvement of quality of life. This should be kept in mind when discussing the option with patients.
- All the guidelines recognize the need to adapt to the individual patient. Clinicians should not hesitate to deviate from established dosing schedules to better meet the specific needs of their patients.
- OIT can be performed with many different products. However, if patients are going to use various food products, then the OIT providers must ensure that they have appropriate knowledge of dose equivalents to do it safely. This is best achieved through a multidisciplinary approach, including intervention by an OIT-specialized nutritionist.

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