

Clinical Management Review

Advances, Practical Implementation, and Unmet Needs Regarding Oral Immunotherapy for Food Allergy

Kirsten P. Perrett, MBBS, PhD^{a,b}, Sayantani B. Sindher, MD^{c,d}, Philippe Begin, MD, PhD^e, Josiah Shanks, MD^{a,b}, and Arnon Elizur, MD^{f,g} VIC, Australia; Stanford, Calif; Montréal, Canada; and Be'er Ya'akov and Tel Aviv, Israel

Treatment of food allergy is a rapidly changing landscape, with arguably, the most significant advancement in recent years, the transition of oral immunotherapy (OIT) to clinical practice. As an innovation, OIT is a phase of rapidly increasing demand, particularly for some allergens such as peanut, egg, and milk, which have substantial evidence of efficacy. However, significant questions remain about how to best treat multiple food allergies and less common food allergies and how to optimize long-term safety and efficacy. This review summarizes the currently available resources for integrating food allergy OIT into clinical practice and focuses on the multiple remaining unmet needs such as providing an approach for OIT to food allergens for which there is no or limited evidence; practical issues related to food allergy treatment particularly when it is not going well; long-term outcomes and follow-up after OIT; and strategies to help meet the impending increase in demand. © 2021

American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;■:■-■)

Key words: Oral immunotherapy; Food allergy treatment; Desensitization; Sustained unresponsiveness; Oral food challenge

INTRODUCTION

IgE-mediated food allergies affect up to 6% to 8% of children and 3% to 4% of adults and have a major impact on quality of life (QOL). Until recently, the only management option available outside a research setting consisted of allergen avoidance, along with patient training on the proper use of epinephrine and periodic testing to follow the natural evolution of the allergy. This left a great unmet need for active therapies that could either temporarily decrease reactivity (desensitization, DS) or abate the allergic immune response in a sustained manner (sustained unresponsiveness, SU). Various experimental approaches have been researched to this end, including allergen immunotherapy with native or modified allergens (either through the oral, sublingual, or epicutaneous routes, with or without adjuvants), as well as nonspecific approaches with biologics (either as monotherapy or as adjunctive therapy with oral immunotherapy [OIT]).

Arguably, the most significant advancement in food allergy treatment has been the transition of OIT to clinical practice. As an innovation, OIT could be said to be entering its disruptive phase. In economic theory, disruptive innovation is the process by which a new technology sees a more rapid improvement than the incumbent in its quality.¹ When the new technology (OIT) finally catches up with the incumbent (avoidance), there is a sudden shift in demand for the former, which disrupts the market (food allergy practice) (Figure 1). This is reflected in the OIT literature, which has recently shifted from asking whether OIT was ready to asking how it should be offered in clinical practice.

As such, it is expected that allergists will come under intense pressure to rapidly integrate OIT into their practice and meet this inevitable increase in demand. The training curriculum of most practicing allergists did not include OIT, and there is a limit to the practical knowledge that can be gathered from randomized controlled trials. A number of guidelines and review articles were recently published to help support clinicians in this transition, covering various aspects of the treatment (Table I). This review summarizes the currently available resources for integrating food allergy OIT into clinical practice and then specifically focuses on the multiple remaining unmet needs such as providing an approach for OIT to food allergens for which there is no or limited evidence; practical issues related to food allergy treatment particularly when it is not going well; long-term outcomes and follow-up after OIT; and strategies to help meet the impending increase in demand.

^aPopulation Allergy, Murdoch Children's Research Institute, Royal Children's Hospital Melbourne, Parkville, VIC, Australia

^bDepartment of Paediatrics, University of Melbourne, Parkville, VIC, Australia

^cSean N. Parker Center for Allergy and Asthma Research at Stanford University, Stanford, California

^dDivision of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Stanford, California

^eDivision of Allergy, Immunology and Rheumatology, CHU Sainte-Justine, Montréal, Canada

^fInstitute of Allergy, Immunology and Pediatric Pulmonology, Yitzhak Shamir Medical Center, Be'er Ya'akov, Israel

^gDepartment of Pediatrics, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Conflicts of interest: K. P. Perrett is Chair of the Scientific Advisory Board for AllergyPal; her institution has received research grants from the National Health and Medical Research Council, Immune Tolerance Network, DBV Technologies, and GlaxoSmithKline and consultant fees from Aravax, outside the submitted work. S.B. Sindher reports grants from the National Institutes of Health, Regeneron, AIMMUNE, DBV Therapeutics, Novartis, Food Allergy Research and Education (FARE) and Consortium of Food Allergy Research (CoFAR), grants and Advisory Committee fees from DBV Technologies, grants and personal fees from Food Allergy Research & Education, and grants and Advisory Committee fees from Astra Zeneca, grants and personal fees from Genentech outside the submitted work. P. Begin reports personal fees from Novartis, Pfizer, Sanofi, ALK, and Aralez Pharmaceuticals, as well as grants from DBV Technologies, Regeneron, and Sanofi outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication June 21, 2021; revised October 7, 2021; accepted for publication October 25, 2021.

Available online ■■

Corresponding author: Kirsten P. Perrett, MBBS, PhD, Population Allergy, Murdoch Children's Research Institute, Royal Children's Hospital Melbourne, 50 Flemington Rd, Parkville 3052, VIC, Australia. E-mail: Kirsten.perrett@mcri.edu.au. 2213-2198

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<https://doi.org/10.1016/j.jaip.2021.10.070>

Abbreviations used

<i>BAT</i> - basophil activation test
<i>CSACI</i> - Spanish and Canadian Society of Allergy and Clinical Immunology
<i>DS</i> - desensitization
<i>EAACI</i> - European Academy of Allergy and Clinical Immunology
<i>EoE</i> - eosinophilic esophagitis
<i>FDA</i> - Food and Drug Administration
<i>GI</i> - gastrointestinal
<i>OFC</i> - oral food challenge
<i>OIT</i> - oral immunotherapy
<i>OITIGER</i> - oral immunotherapy-induced gastrointestinal symptoms and peripheral blood eosinophil responses
<i>QOL</i> - quality of life
<i>SU</i> - sustained unresponsiveness
<i>WP</i> - wheat protein

CURRENT OIT RESOURCES FOR INTEGRATING OIT INTO CLINICAL PRACTICE

Five scientific societies have made recommendations for OIT in formal clinical practice guidelines (Table I). All agree that OIT is a therapeutic option to induce DS in children with food allergy. Guidelines highlight the importance of shared decision making, establishing an accurate diagnosis before initiating treatment, and ensuring safety of OIT visits with appropriate supplies and personnel. They all recognize that OIT can be performed with normal food from the grocery (eg, peanut butter or cow's milk). There is also a consensus on contraindications, which generally include uncontrolled asthma, pregnancy, eosinophilic gastrointestinal disease, disproportionate anxiety, or inability to cope with instructions.

There are also some minor differences between the guidelines, mostly for sections based on expert opinion. The European Academy of Allergy and Clinical Immunology (EAACI) guidelines suggest delaying OIT until the age of 4 or 5 years to monitor natural resolution, whereas the Spanish and Canadian Society of Allergy and Clinical Immunology (CSACI) guidelines suggest starting early in toddler years because it is best tolerated. The CSACI used multicriteria decision analysis to account for patient perspective and ethical concepts in addition to clinical evidence in its recommendations. This approach led it to generalize its recommendation to all food allergies and to suggest OIT as an option to induce DS in adult patients.

After getting familiar with clinical practice guidelines, allergists new to OIT may want to consider a number of review articles that have been published to guide implementation of OIT in practice (Table I). Although the content of guidelines is mostly used to present evidence in support of their specific recommendations, these review articles focus more on how to apply these in practice and generally center around the same themes.

The first theme is implementation. These reviews present a global overview of the various aspects when considering OIT, including patient selection, environment, food products, dosing protocols, and other logistic matters. These are especially useful for those allergists who have little experience with OIT.

The second theme is shared decision making. Shared decision making is particularly important in OIT, because its success is directly framed by patient's objectives and expectations. Several studies have examined patient expectations toward treatment

using methodologies relying on open-ended questions to avoid the risk of orienting answers. These help appreciate the diversity in patient perspectives. Various articles also describe the process and tools for shared decision making in the context of OIT.

The third theme is personalization. Although standard protocols are useful to guide novice OIT allergists at first, a one-size-fits-all approach has a certain limit in OIT. Food allergy is a highly heterogeneous disease, and patients have different health preferences and tolerance to risk. The key to successful OIT is to adapt to patient reality. These articles are intended for more experienced OIT allergists who are ready to start adapting their practice to less conventional patients (eg, severe or multiple allergies, uncommon allergens).

UNMET NEED #1: APPROACH TO FOODS WITH NO OR LIMITED PREVIOUS LITERATURE

Over the past 20 years, OIT to milk, egg, and peanut has been widely studied, including in randomized controlled prospective studies.²¹⁻²³ These led to the official EAACI recommendation on OIT as a potential treatment for milk, egg, and peanut allergy,⁶ and subsequently to the approval of a peanut product for OIT by the Food and Drug Administration (FDA)²⁴ in January 2020. It is important to note, however, that the development of OIT to food allergy has differed markedly from the usual path a new treatment typically takes. A new drug typically requires FDA or European Medicines Agency approval, necessitating several steps of clinical trials on safety and efficacy during its development. In contrast, the initial clinical trials performed in food OIT used fresh foods rather than a standardized drug product.²¹⁻²³ Moreover, because foods rather than drugs were used for OIT, official regulatory approvals were not required, and food (primarily milk, egg, and peanut) OIT was offered to the public in many countries before any official guidelines were published, and many years before a single product was approved by the FDA. These clinical OIT treatment programs have provided significant experience on safety and efficacy of milk, egg, and peanut OIT, and have been extensively reviewed. Given that commercial products for OIT are not yet available for most foods, anyone wishing to perform OIT for foods other than peanut would have to rely on fresh foods. Reports on clinical experience with OIT to foods other than milk, egg, and peanut will be briefly reviewed here and are summarized in Table II, based on the number of studies available for each food.

Wheat

Wheat OIT has been recently extensively reviewed.³⁷ Several open-label wheat OIT studies, using boiled udon or spaghetti, showed desensitization rates ranging from 37.5% to 88.9%^{26,30} (Table II). One multicenter, randomized, double-blind placebo-controlled trial, in 46 patients with wheat allergy randomized 1:1 to low-dose vital wheat gluten (1445 mg of wheat protein [WP]) OIT or placebo, was published.²⁷ At year 1, 12 (52.2%) of 23 OIT-treated subjects successfully consumed a WP dose of greater than or equal to 4443 mg, and at year 2, 7 (30.4%) were desensitized to 7443 mg WP. Placebo-treated subjects crossed over to high-dose vital wheat gluten OIT (maximum, 2748 mg of WP) in year 2. Twelve (57.1%) of 21 were desensitized after 1 year (median, 7443 mg of WP). In year 1, 15.4% of low-dose vital wheat gluten OIT doses were associated with adverse

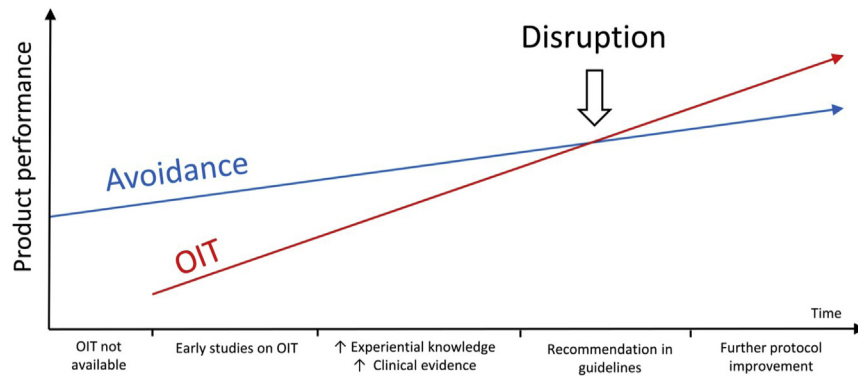


FIGURE 1. OIT as a disruptive innovation. As scientific and experiential knowledge is gained, the practice of oral immunotherapy becomes safer, more effective and more accessible, making it a rapidly evolving technology. Strict avoidance, on the other hand, follows a trajectory of slow but sustained innovation (educational programs, food labelling, etc). Market disruption will occur when the perceived value of oral immunotherapy surpasses that of strict avoidance, assuming generalized uptake is feasible.

reactions and 0.04% were severe. Five (21.7%) of the OIT-treated patients had reactions treated with epinephrine, 4 of them to home doses. It appears that wheat OIT results in successful DS in most patients. Higher doses are associated with more adverse reactions but with higher DS rates as well.

Fish

The results of OIT to fish are largely based on a few reports with small sample sizes (Table II).^{31,32} Martorell-Calatayud et al³³ performed an open, uncontrolled hake fish OIT study in 8 children aged 4 to 14 years, using a lyophilized hake extract, with a target dose of 225 mg lyophilized hake extract (equivalent to 112.5 mg hake protein or 75 g of hake). All patients passed an oral food challenge (OFC) with 150 g of hake with no symptoms. Adverse reactions, mostly mild, were experienced in response to 1.7% of doses taken. Multifood OIT studies have also reported successful treatments that included fish and shellfish.

Tree nuts

Allergies to tree nuts are among the most prevalent food allergies, and tree nut allergy is associated with a significant risk for severe anaphylactic reactions, and with low resolution rates (~9%).³⁸ Patients allergic to tree nuts are often allergic to multiple nuts and are likely to require multiple OIT treatments, potentially reducing patients' and physicians' motivation for OIT. Because patients with tree nut allergy are often advised to eliminate multiple nuts from their diet based on sensitization only, the first step in tree nut OIT requires determination of true allergy versus sensitization only.³⁹ This might necessitate several OFCs before starting OIT. A potential way to reduce the burden of food challenges would be to refer to walnut and pecan as a single group and to cashew and pistachio as a single group, given the high degree of cross-reactivity between these nut pairs.³⁹

Tree nut OIT might rely on cross-reactivity between pairs of nuts by using a single tree nut OIT to DS not only for the treated but also for untreated nuts. Alternatively, multiple tree nuts can be used simultaneously in the OIT protocol. Two single tree nut OIT studies have been described so far. One, a

retrospective single-center study of hazelnut OIT (target dose, 1635 mg hazelnut protein = 8 hazelnuts). The proportion of hazelnut-desensitized patients after 6 months was 34%.³⁵ Adverse reactions occurred in 30% of patients; none severe. DS to other nuts was not examined. Another single-center prospective controlled study of walnut OIT (target dose, 4000 mg protein) demonstrated successful walnut DS in 89% of 55 walnut-allergic patients (Table II).³⁴ In this study, full cross-desensitization to pecan, the most closely related nut to walnut, was achieved in all patients who were additionally pecan-allergic ($n = 46$) following walnut DS. In patients with allergy to hazelnut, a nut less closely related to walnut, cross-desensitization to hazelnut was still high, with 14 of 15 (93.3%) either fully desensitized or had an increase in reaction dose of greater than or equal to 10-fold or to a dose greater than or equal to 1000 mg but less than 4000 mg protein to hazelnut following walnut DS. For cashew, cross-desensitization was documented as well, but in only a few patients, reflecting its low relatedness to walnut. This potential for cross-desensitization greatly enhances the attractiveness of tree nut OIT. Although most adverse reactions during up dosing were mild in this study, 9 patients (16.4%) required intramuscular epinephrine for home doses.³⁴ One multifoods OIT study involved tree nut as well. This study also compared OIT with and without omalizumab and demonstrated successful walnut, cashew, and hazelnut DS primarily in patients who were concurrently treated with omalizumab.⁴⁰

Sesame

Sesame has become a prevalent ingredient in Western diet in recent years due to its nutritional benefits.⁴¹ Its increased availability and consumption make sesame more difficult to avoid, increases the risk of accidental exposure-induced anaphylactic reactions, and further impairs QOL in patients with allergy. Recently, the FDA advanced a new effort for the consideration of allergy labeling for sesame.⁴² So far, a single study on sesame OIT, using a prospective controlled design, has been published.³⁶ All patients reacted to sesame on an open OFC before starting OIT. Treatment efficacy was high, with 88.4% of OIT-

TABLE I. Clinical resources for integrating OIT into clinical practice

Author, year	Title
Clinical practice guidelines	
Matorell et al, ^{2,3} 2017	Oral immunotherapy for food allergy: a Spanish guideline. Immunotherapy egg and milk Spanish guide. Two-part CPG focusing on OIT for milk and egg allergy. Written in a Q&A format with a strong focus on practical content
Pajno et al, ⁴ 2017	Clinical practice recommendations for allergen-specific immunotherapy in children: the Italian consensus report Subsection on OIT that recommends OIT should be performed in specialized centers
Ebisawa et al, ⁵ 2020	Japanese guidelines for food allergy 2020 Subsection on OIT that establishes definitions and minimal requirements for OIT
Pajno et al, ⁶ 2020	EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy Traditional CPG assessing OIT, SLIT, and EPIT for IgE-mediated food allergy. Recommends OIT as a treatment option to induce desensitization and identifies gaps of knowledge for future research
Begin et al, ⁷ 2020	CSACI guidelines for the ethical, evidence-based and patient-oriented clinical practice of oral immunotherapy in IgE-mediated food allergy CPG using a multicriteria decision analysis methodology to make recommendations on the clinical practice of OIT but also on the way it is developed and integrated into the current clinical offer
Implementation in practice	
Abrams et al, ⁸ 2021	How to incorporate oral immunotherapy into your clinical practice Provides practical tips, protocol, and teaching material for starting OIT in practice, with a focus on the toddler population
Leonard et al, ⁹ 2021	Integrating oral immunotherapy into clinical practice Mainly covers various aspects of office preparedness and describes OIT procedures
Wasserman et al, ¹⁰ 2021	An approach to the office-based practice of food oral immunotherapy Covers how to orient the office for OIT, describes the OIT process and management of reactions, shared decision making, and adjunctive therapies
Sabouraud et al, ¹¹ 2021	Oral immunotherapy in food allergies: a practical update for pediatricians A combination of explanations on OIT and description of procedures and dose management aimed at pediatricians
Shared decision making	
Anagnostou et al, ¹² 2020	The role of shared decision making in pediatric food allergy management Review of shared decision-making theory and a case discussion applied to OIT
Anagnostou et al, ¹³ 2021	A practical, stepwise approach to peanut oral immunotherapy in clinical practice: benefits and risks 6 case-based scenarios addressing OIT-related questions with a family using shared decision-making approach
Mack et al, ¹⁴ 2020	A counseling video with pre- and post-testing and checklist for oral immunotherapy consent improves participant knowledge Describes potential tools to help inform patients and facilitate shared decision making
Patient and caregiver's perspective	
Greenhawt et al, ¹⁵ 2018	Understanding caregiver goals, benefits, and acceptable risks of peanut allergy therapies Semi-structured interviews with participants in trials
Blackman and Anagnostou, ¹⁶ 2019	Identification of goals and barriers to treatment from 92 consecutive consultations with families considering peanut OIT Semi-structured interviews with families referred for peanut OIT in real-life
Le Blanc et al, ¹⁷ 2021	Treatment expectations in food-allergic patients referred for oral immunotherapy Semantic analysis of expectations of 1107 patients referred to an academic OIT clinic using content analysis software
Treatment personalization	
Mori et al, ¹⁸ 2019	Oral immunotherapy (OIT): a personalized medicine Narrative review on the need for personalization in OIT
Graham et al, ¹⁹ 2021	Practical challenges in oral immunotherapy resolved through patient-centered care 8 case-based scenarios on ways protocol can be adapted to solve common practical problems with shared decision making
Mack et al, ²⁰ 2020	Novel approaches to food allergy management during COVID-19 inspire long-term change Series of possible protocol adaptations to reduce the need for in-person visits

CPG, Clinical practice guideline; EPIT, epicutaneous immunotherapy; Q&A, question and answer; SLIT, sublingual immunotherapy.

treated patients desensitized to 4000 mg sesame protein (17 g of tahini). Adverse reactions occurred in 4.7% of hospital doses and 1.9% of home doses. Epinephrine was administered to 16.7% of

patients in clinic and 8.3% of patients at home.³⁶ Sesame was also successfully included in multifood OIT treatments (Table II).

TABLE II. Selected studies on sesame, fish, wheat, and tree nut OIT

	Food/Study	Study type	Food used	Sample size	Target dose (mg protein)	Desensitization rate	AE (of doses)	Epinephrine (of patients treated)
Wheat	Sato et al, ²⁵ 2015	Open-label, historical control	Boiled udon noodle	OIT, n = 18 Control, n = 11	5200 mg	88.9%	6.8%	5.6%
	Kulmala et al, ²⁶ 2018	Open-label, uncontrolled	Wheat spaghetti	n = 100	2000 mg	77%	70% of patients	12%
	Nowak-Wegrzyn, ²⁷ 2019	Double-blind placebo-controlled	Vital wheat gluten	OIT, n = 23 Control, n = 23	HD, 2748 mg LD, 1445 mg	HD, 57.1%* LD year 1, 52.2% LD year 2, 30.4%	15.5%	Clinic, 4.3% Home, 17.4%
	Nagakura et al, ²⁸ 2020	Open-label, LD, historical control	Boiled udon noodle	OIT, n = 16 Control, n = 11	53 mg (2 g noodle)	88%	Clinic, 32.1% Home, 4.1%	None
	Sugiura et al, ²⁹ 2020	Open-label, LD, controlled	Boiled udon noodle	OIT, n = 35 Control, n = 10	53 mg (2 g noodle)	37.5%	0.64%	None
	Ogura et al, ³⁰ 2020	Open-label, LD/HD, uncontrolled	Boiled udon noodle	HD, n = 12 LD, n = 12	HD, 2600 mg LD, 650 mg	58% for both	HD, 8.82% LD, 4.76%	HD, none LD, 8.3%
Fish	Patriarca et al, ³¹ 2003	Open-label, uncontrolled	Boiled cod	n = 11	160 g fish	72.7%	Not specified	Not specified
	Patriarca et al, ³² 2007	Open-label, uncontrolled	Boiled cod	n = 9	100 g fish	100%	Not specified	Not specified
	Martorell-Calatayud et al, ³³ 2019	Open-label, uncontrolled	Lyophilized hake extract	n = 8	112.5 mg (75 g fish)	100%	1.7%	None
Tree nuts	Elizur et al, ³⁴ 2019—walnut	Prospective cohort, open-label with observational control	Walnut flour, walnut	OIT, 55 Control, 18	4000 mg	89%	Clinic, 4% Home, 2%	Clinic, 20% Home, 15%
	Moraly et al, ³⁵ 2020—hazelnut	Open-label, uncontrolled	Ground hazelnut	n = 100	1635 mg	34%	30% of patients	None
Sesame	Nachshon et al, ³⁶ 2019	Cohort, open-label with observational control	Sesame flour/tahini	OIT, n = 60 Control, n = 15	4000 mg	88.4%	Clinic, 4.7% Home, 2%	Clinic, 16.7% Home, 8.3%

AE, Adverse event; HD, high dose; LD, low dose.

*HD groups were challenged to 7443 mg; LD groups were challenged to 4443 mg (year 1) and 7443 mg (year 2).

TABLE III. Practical approach for anaphylactic reactions during OIT

1.	Provide patients with medications for the treatment of adverse reactions at home (2 up-to-date epinephrine autoinjectors, bronchodilators, antihistamines)
2.	Be aware that patients undergoing OIT to milk are at a significantly higher risk for severe reactions during treatment, compared with other foods
3.	Identify additional potential risk factors—asthma, previous severe reactions (particularly to minute doses of protein), and a lower threshold (if known)
4.	Monitor asthma control on every visit. <i>One might also consider an objective measure of airway function (eg, spirometry or peak flow)</i>
5.	Educate patients about potential triggers for severe reactions (exercise, fatigue, menses, excitement, empty stomach, etc) particularly in proximity to the dose taken
6.	Instruct patients on how to dose during concurrent illnesses (dose reduction, antihistamines)
7.	Provide patients with a clear action plan and contact information in case of home adverse reactions
8.	In case a severe reaction occurs: - Identify a potential trigger that could account for the reaction and that could potentially be avoided in the future - Reduce dose for a few days or return to the previous “safe” dose until next up dosing. Consider predosing with antihistamines for several days - Consider prolonging interval between up dosing to enable better desensitization - Consider treatment cessation in patients with recurrent severe reactions due to noncompliance with the treatment protocol
9.	In the presence of recurrent severe reactions, attempt to achieve a minimal protective dose (typically 300 mg protein) that would not elicit additional severe reactions
10.	Discuss with patient pros and cons for continued OIT and the goal of treatment (protection vs full desensitization)

TABLE IV. Practical approach for eosinophilic reactions during OIT

1.	Obtain a baseline eosinophil count from all patients starting OIT
2.	Limit the starting dose even in patients with a high threshold. We recommend against starting at a dose >300 mg protein even if the threshold is much higher
3.	Repeat a CBC according to symptoms thereafter. A significant increase in eosinophils helps differentiate OITIGER from other GI-associated complaints Be aware that some patients develop significant eosinophilia in the absence of GI complaints. Slowing down their up dosing or staying on the same dose until it resolves might be considered
4.	Educate patients that GI symptoms, even when occurring with no temporal relation to the dose taken, could represent a form of “reaction” to the treatment
5.	In case symptoms compatible with OITIGER develop, reduce dose by 50% or more until symptoms and eosinophilia resolve
6.	If no resolution occurs, reduce dose further or stop OIT until symptoms resolve
7.	Proceed if asymptomatic, initially with smaller up dosing
8.	In patients who develop symptoms during maintenance or in patients whose symptoms persist despite treatment modifications, consider a referral for gastroscopy
9.	In the case EoE is diagnosed, discuss treatment options with patients (<i>high-dose PPI vs OIT dose reduction to 300 mg vs OIT discontinuation</i>)
10.	If EoE persists, consider OIT discontinuation

CBC, Complete blood cell count; PPI, proton-pump inhibitor.

UNMET NEED #2: HOW TO ADDRESS OIT THAT IS NOT GOING WELL

Anaphylactic reactions

As much as OIT is highly effective in desensitizing food-allergic patients, it is also associated with adverse reactions, during both in-clinic up dosing and home dosing. The peanut OIT Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults trial reported that 96.4% of patients experienced 1 or more adverse event during dose increases and 87.1% during maintenance.⁴³ It should be noted that many of the reported adverse reactions are subjective (oral paresthesia, throat irritation, and pruritus), and many others are mild (lip swelling, rhinorrhea, and sneezing). Still, systemic allergic reactions, including those treated with injectable epinephrine, occur. Epinephrine was administered for adverse reactions in 14% of patients in the PALISADE trial and in 23% of patients in a clinical peanut OIT treatment program.⁴⁴ A meta-analysis concluded that peanut OIT regimens considerably increase allergic and anaphylactic reactions over avoidance or placebo.⁴⁵ In a study by Nachshon et al,⁴⁶ on 1100 OIT

treatments for various foods (milk, egg, peanut, sesame, and tree nuts), milk OIT was associated with more epinephrine-treated reactions both in clinic (26.8% vs 11.3%) and at home (13.8% vs 5.8%) compared with non-milk OIT. Of note, unlike accidental exposures, reactions during OIT occur when patients are under supervision. Also, patients and parents are educated about the use of injectable epinephrine. Still, such reactions induce stress, and are associated with lower rates of full DS.⁴⁶ A practical approach for anaphylactic reactions is presented in Table III.

Several studies have identified risk factors for severe reactions during OIT. Active asthma is one such significant risk factor.^{46,47} Interestingly, the presence of asthma as a comorbidity, but not necessarily asthma severity (assuming it is well controlled), is associated with more severe adverse reactions during OIT.²⁵ Additional risk factors reflect the severity of the individual food allergy.⁴⁶ In addition to these inherent risk factors, certain factors such as concurrent illness, physical exertion after dosing, dosing during menses or on an empty stomach, pollen allergy, and irregular dosing might trigger systemic reactions.⁴⁸ OIT treatment

TABLE V. Follow-up of participants in peanut OIT trials after *ad libitum* ingestion

Study	nut	Primary maintenance regime							Long-term maintenance regime							Instructions after long-term outcome
		Primary study (OIT n)	Age at start of OIT (y)	Adjuvant	Build-up period (mo)	Maintenance period (mo)	Maintenance dose	Trigger for primary outcome	Primary outcome	Primary outcome success	Instructions after first-degree outcome	Long-term study n	Follow-up period	Long-term outcome	Long-term success	
PPOIT-001	Hsiao et al, ⁷² 2017— <i>peanut</i>	Tang et al, ⁶⁸ 2015	1-10	Probiotic	8	10	2000 mg/d	Time (at least 18 mo on OIT, and at least 6-mo maintenance)	DS DBPCFC 4000 mg 2-wk SU DBPCFC 4000 mg	26 of 31 (ITT*), 26 of 28 (PP) passed DS 23 of 28 passed SU	<i>Ad libitum</i> for those passing SU and avoidance for those who did not pass	10 of 12 passed 2-wk SU 24 of 28 PPOIT completers participated in survey	Mean, 4.2 ± 0.6 y	8-wk SU DBPCFC 4000 mg Survey	7 of 10 (70%) of those who had achieved 2-wk SU passed 8-wk SU 16 of 24 (67%) eating peanut 4 y after treatment cessation	Included only at the primary outcome
E-OIT, Herlihy et al, ⁷³ 2020— <i>peanut</i>	Vickery et al, ⁶⁹ 2017	9-36 mo	None	10	12-36	300 mg/d or 3000 mg/d	At least 12-mo maintenance psIgE ≤ 15 kU _A /L SPT wheal diameter ≤ 8 mm No severe AE in previous 6 mo If not, after 36-mo maintenance	DS DBPCFC 5000 mg 4-wk SU DBPCFC 5000 mg	35 of 46 (ITT*), 35 of 39 (PP*) passed DS 32 of 46 (ITT*), 32 of 34 (PP*) passed SU	<i>Ad libitum</i> peanut for those passing SU and avoidance for those who did not pass Carry AAI	29 of 39 OIT completers participated	Mean, 65 ± 12 mo	Survey	27 of 29 (93%) survey responders continuing peanut consumption	Included only at the primary outcome	
Vickery et al, ⁷⁴ 2014— <i>peanut</i>	Jones et al, ⁷⁰ 2009	1-16	None	Minimum 20 wk (~ 5)	Maintenance 1: Median, 4.7 (range, 4-22)	Maintenance 1: 300 mg/d	Time 13-22 mo on maintenance (n = 7) 4-7 mo on maintenance (n = 22) [†]	DS open OFC 3900 mg	27 of 39 (ITT*), 27 of 29 (PP) passed DS (progressed to maintenance)							
					Maintenance 2: Maximum 60 (5 y) Mean length of treatment, 1453 ± 663 d	Maintenance 2: 4000 mg/d	DS OFC Initial protocol: psIgE ≤ 2 kU _A /L Amended protocol: psIgE ≤ 15 kU _A /L SPT wheal diameter ≤ 5 mm No peanut-related reactions for 6 mo If not, after 5 y of OIT	DS DBPCFC 5000 mg 4-wk SU DBPCFC 5000 mg	24 of 29 (ITT*), 24 of 24 (PP) passed DS DBPCFC * 12/24 passed 4-week SU (designated TS)	TS: “incorporate peanut into diet <i>ad libitum</i> at least several days per week” TF: restarted on OIT	21 participated in the survey	TS median, 40 mo (range, 3-56 mo) TF median, 12 mo (range, 3-36 mo)	Survey	TS: median, 555 mg (range, 0-4000 mg) peanut protein on average 3 d/wk (range, 0-7 d) TFs: median, 895 mg (range, 330-4000 mg) peanut protein on average 7 d/wk (range, 6-7 d)	TS: regular peanut ingestion without restriction	

AE, Adverse event; *DBPCFC*, double-blind placebo-controlled food challenge; *E-OIT*, early-OIT; *ITT*, intention-to-treat analysis; *PP*, per-protocol analysis; *PPOIT*, Probiotic and Peanut Oral Immunotherapy; *psIgE*, peanut specific IgE; *SPT*, skin prick test; *TF*, treatment failure; *TS*, treatment success.

†Five participants withdrew before completion of maintenance 2: 1 allergic side effects, 2 personal reasons, 1 unrelated illness, 1 moved away.

*Calculated by the author.

†Time to OFC reduced because basophil, SPT, and OFC data indicated lack of reactivity sooner than hypothesized.

TABLE VI. Follow-up of participants in peanut or walnut OIT after prolonged allergen avoidance or continued daily dosing

Study <i>nut</i>	Primary study (OIT n)	Age at start of treatment (y)	Primary maintenance regime				Trigger for primary outcome	Primary outcome	Primary outcome success	Long-term maintenance regime		Long-term outcome	Long-term success	Published instructions following outcome
			Adjuvants	Build- up period	Maintenance period	Maintenance dose				Follow-up period	Follow-up dose			
Yee et al, ⁷⁵ 2019— <i>peanut</i>	Schneider et al, ³⁸ 2013	8-16	Omalizumab	Median, 20 wk (range, 19-24 wk)	2 mo	2000 mg/d	Time (week 32 of study)	DS DBPCFC 4000 mg	11 of 13 (ITT*), 11 of 12 (PP) passed DS	6 y	Varied from 500to 3500 mg/d	Survey	7 of 13 patients initially enrolled continuing consumption at 6 y†	None
Nut Co-Reactivity —Acquiring Knowledge for Elimination Recommendations Elizur et al, ³⁴ 2019— <i>walnut</i>	NA ¹³	4-20	None	Median, 5.9 mo (IQR, 3.8-8.9)		4000 mg/d	Reaching 4000 mg/d maintenance dose	Achieve 4000 mg maintenance dose	56 of 64 (ITT), 56 of 61 (PP*) achieved maintenance dose	6 mo	1200 mg/d	DS OFC 4000mg	45 of 45 passed‡	None
Sustained outcomes in oral immunotherapy for peanut allergy Chinthrajah et al, ⁷⁶ 2019— <i>peanut</i>	NA (95; p-0 = 60; p-300 = 35)	7-55	None	p-0§: median, 57 (IQR, 53-59) wk p-300 : median, 53 (IQR, 51-58) wk	12 mo	4000 mg/d	Time (week 104 of study)	DS DBPCFC 4000 mg	p-0: 51 of 60 (ITT), 51 of 51 (PP*) passed DS p-300: 29 of 35 (ITT), 29 of 30 (PP*) passed DS	13-52 wk	p-0: avoid p-300: 300 mg/d	DBPCFC 4000 mg	p-0 13 wk: 21 of 60 ITT (35%)¶ 52 wk: 8 of 60 ITT (13%) p-300 13 wk: 19 of 35 ITT (54%)¶ 52 wk: 13 of 35 ITT (37%)	None
IMPACT Jones et al, ⁷⁷ 2020— <i>peanut</i>	NA ⁷¹	1-3	None	7 mo	24 mo	2000 mg/d	Time (104 wk on maintenance)	DS DBPCFC 5000 mg	68 of 96 (ITT), 68 of 93 (PP*) passed DS	26 wk	Avoidance	DBPCFC 5000 mg	20 of 96 (21%) of those who started OIT achieved 26-wk SU	None
Syed et al, ⁷⁸ 2014— <i>peanut</i>	NA ⁴⁵	5-45	None	24 mo		4000 mg/d	Time (24 mo on OIT)	DS DBPCFC 4000 mg	20 of 23 (ITT), 20 of 20 (PP*) passed DS	3 mo ¹ 3 mo ²¹	Avoidance	SU DBPCFC 4000 mg SU DBPCFC 5000 mg	7 of 20 passed the first 3-mo SU¶ 3 of 7 passed the second 3-mo SU and “remained clinically nonreactive”	None

DBPCFC, Double-blind placebo-controlled food challenge; IQR, interquartile range; ITT, intention-to-treat analysis; p-0, peanut-0; p-300, peanut-300; PP, per-protocol analysis.

*Calculated by author.

†One participant did not reach maintenance dose but was surveyed in the long-term follow-up.

‡Of the 56 who reached 4000 mg/d maintenance dose, only 45 were assessed by OFC at 6 mo. All 45 passed the OFC.

§p-0: peanut-0 participants completed 2-y OIT and then switched to placebo in the third (follow-up) year.

||p-300: peanut-300 participants completed 2-y OIT and then switched to lower dose maintenance in the third (follow-up) year.

¶Only those participants who passed the challenge progressed to the subsequent challenge(s).

programs typically provide patients with home dosing instructions, including how to avoid potential triggers.⁴⁸ Interestingly, a recent Israeli study described a significant reduction in the rate of home epinephrine-treated reactions during a coronavirus disease 2019 lockdown period, when parents and children were less exposed to outdoor triggers, such as temperature and aeroallergens, and when the availability of physical activity and the burden and fatigue associated with daily chores were probably reduced. This finding suggests that avoidance of potential triggers can reduce the rate of epinephrine-treated reactions during OIT.⁴⁹ Importantly, in the study by Nachshon et al, described above, full DS was achieved by most patients treated with non-milk OIT, even those experiencing epinephrine-treated reactions, while only a minority of those experiencing severe reactions during OIT to milk were fully desensitized.⁴⁶

Given that adverse reactions are the main limiting factor of OIT, various treatment modalities are being tested in an attempt to increase treatment safety. These include other routes of administration (epicutaneous immunotherapy, sublingual immunotherapy), modified proteins with reduced allergenicity, the use of probiotics, and additional experimental treatments. These treatments are still under investigation, are not available in clinical practice, and have been reviewed elsewhere.⁵⁰ Biologics, in particular omalizumab, given in conjunction with OIT, are another potential treatment for reducing adverse reactions during OIT. Several studies, comparing OIT for single or multiple food OIT, with or without omalizumab, have demonstrated comparable efficacy and a shorter duration of treatment for reaching DS.^{40,51} However, the effect on the frequency and severity of adverse reactions is apparent in some, but not in other studies. Moreover, most patients regain reactivity and experience reactions once omalizumab is discontinued.^{40,51,52} Therefore, the dose, duration of treatment, and the characterization of patients who would benefit the most from omalizumab during OIT remain to be determined.

Eosinophilic gastrointestinal reactions

The issue of eosinophilic gastrointestinal (GI) reactions during OIT is complicated by several confounding factors. First, GI adverse events during OIT can occur for several reasons. These include immediate anaphylactic reactions, subjective complaints that might represent patient anxiety, and eosinophilic GI disease. Studies attributing all GI manifestations during OIT to eosinophilic esophagitis (EoE) likely overestimate the prevalence of OIT-associated EoE.⁵³ Second, food-allergic patients are at a particular risk to develop EoE regardless of OIT, with a prevalence of 4.7% compared with 0.04% in the general population, according to one study.⁵⁴ Because gastroscopy is not routinely performed in patients starting OIT, it is impossible to know whether EoE or esophageal eosinophilia was present before treatment was started or whether it was induced by OIT. A single-center adult peanut OIT study found that 3 of 21 (14%) patients who underwent gastroscopy before starting OIT had more than 15 eos/hpf, associated with mild endoscopic findings.⁵⁵ All were asymptomatic and would have been otherwise undiagnosed. In addition, some patients develop significant eosinophilia while remaining asymptomatic and the best way to manage these patients is not clear.

It appears that 2 different types of EoE may develop during OIT. The first, referred to as OITIGER (oral immunotherapy-induced gastrointestinal symptoms and peripheral blood

eosinophil responses⁵⁶) or eosinophilic esophagitis—like oral immunotherapy—related syndrome,⁴⁴ occurs in 8.2% to 14% of patients. It typically manifests in abdominal pain, nausea, and vomiting, which occur early in the course of OIT. Unlike classic EoE, the presentation rarely includes esophageal spasm or food impaction and it is often accompanied by peripheral eosinophilia. In contrast to anaphylactic reactions (occurring immediately and up to 2 hours after the dose) or to anxiety (occurring before or shortly after the dose), the symptoms of OITIGER are typically temporally not related to the dose taken. Patients with OITIGER experience resolution of symptoms and of eosinophilia on treatment modification (dose reduction), subsequently continue up dosing without recurrence of symptoms, and often achieve full DS.⁵⁶ Although most patients with these symptoms were not biopsied, for the few who were, pathological examination did not differentiate OITIGER from classic EoE.^{44,56} Risk factors for developing OITIGER include a higher starting dose of OIT, a higher fold increase during the early up dosing phase, and a higher baseline absolute eosinophil count.⁵⁷ The second type of EoE resembles the classic presentation of EoE. It appears late in the course of OIT, often when patients have already reached their maintenance dose, and is not necessarily accompanied by peripheral eosinophilia.⁵⁸ In a single report from Spain, 8 cases (6.25%) of eosinophilic gastrointestinal diseases were described in patients undergoing OIT to milk or egg.⁵⁸ Of these, 2 occurred early in the course of OIT and might have represented OITIGER. In 4 of the remaining 6 patients, the disease was limited to the esophagus and resolved with proton-pump inhibitor and/or topical steroids without OIT discontinuation. The 2 additional cases had eosinophilic infiltration in other parts of the GI tract (duodenum or colon) and OIT was discontinued.⁵⁸ One of the patients was diagnosed while undergoing evaluation for celiac disease and had no classic EoE symptoms. Although clinically these 2 presentations of EoE have distinct characteristics, they could very well represent a spectrum. Studying genomic, proteomic, and metabolomics of OIT-associated eosinophilic GI disease might improve our understanding of these entities, but such studies are typically hampered by the lack of baseline esophageal biopsies. New techniques in development such as the esophageal string test to noninvasively identify esophageal inflammation will be welcome. One practical approach for patients at risk of eosinophilic reactions is presented in [Table IV](#).

Compliance and QOL

One of the main goals of OIT is to improve the QOL of food-allergic patients. Although a meta-analysis of randomized controlled trials comparing OIT versus no OIT for peanut allergy found no difference in QOL between groups, other randomized controlled trials as well as real-world studies have demonstrated a significant improvement in the QOL of children with food allergy and their caregivers following OIT.^{45,59-62} However, the treatment itself is challenging, and patients experience various difficulties, including adverse reactions, food aversion, anxiety related to consuming food allergens they used to fear and avoid, and limitations surrounding home dosing. As a result, some patients perceive worsening of QOL during the initial phase of the treatment process.⁵⁹ Patients who are less bothered by their food allergy before OIT are more prone to perceive worsened QOL at the beginning of OIT.⁵⁹ This trend subsequently reverses, and QOL continues to improve as treatment progresses and patients get more DS.⁶³ However, these initial difficulties might have an

impact on patients' motivation and lead to treatment cessation. Therefore, recognizing and addressing these obstacles is important. For example, presenting to patients that mild local reactions experienced during OIT can signal DS rather than an unfortunate side effect of treatment improves OIT experience and outcomes.⁶⁴ The support of a medical clown might improve the QOL of children starting OIT,⁶⁵ and consultation with a dietician specialized in OIT can help with finding options for patients who develop food aversion.⁶⁶ Patients and families should be presented with the benefits and potential difficulties of OIT so that a joint decision can be made about starting treatment, and to enable them to prepare themselves and their children to the treatment and its challenges and that decision should be revisited periodically during treatment using shared decision-making approaches, as previously described (Table I).

UNMET NEED #3: LONG-TERM OUTCOMES AND MANAGEMENT OF OIT

Although there is well-defined evidence of the efficacy of OIT to milk, egg, and peanut to desensitize the vast majority of patients while on treatment (relative risk, 0.16; 95% CI, 0.10-0.26),⁶⁷ there is still very little evidence assessing post-discontinuation effectiveness. A meta-analysis including only 4 studies of egg and milk OIT, which investigated the longer-term effects measured by an OFC performed after 1 to 3 months after discontinuation of OIT, suggested but did not confirm the benefits of OIT (relative risk, 0.29; 95% CI, 0.08-1.13).⁶⁷ Long-term outcomes of peanut and tree nut OIT in pediatric clinical trial populations are presented in Tables V and VI. Eight OIT studies (5 peanut, 1 walnut) enrolled 407 participants and 312 of these were followed up at least 6 months after establishing DS or SU (passing an OFC after a period of allergen avoidance, typically 2-8 weeks) (Tables V and VI).^{34,72-78} These longer-term effectiveness analyses are hampered by the heterogeneity of OIT protocols (rush to slow updosing; variable maintenance doses and dose intervals; duration of treatment; trigger for and assessment of primary outcome) and post-OIT allergen ingestion regimes (from avoidance to daily dosing to *ad libitum*).

Long-term *ad libitum* allergen ingestion post-OIT

Three studies followed up with participants who had passed the primary outcome of SU, after a prolonged period of *ad libitum* peanut ingestion (Table V).⁷²⁻⁷⁴ Of note, different surveys were used to assess long-term "success" or tolerance, with 1 study examining SU OFC outcomes 4 years after OIT.⁷² Furthermore, long-term outcomes are usually favorably skewed because they are frequently completed only by those patients who complete OIT,⁷³ or only by those who pass the primary outcome SU challenge.⁷² In early-OIT, children aged 9 to 36 months underwent peanut OIT (300 mg or 3000 mg/d) for a median of 29 months. At mean 5.4 years after OIT cessation, 93% (27 of 29) were continuing peanut consumption (of the 46 original OIT participants).⁷³ In the Probiotic and Peanut Oral Immunotherapy study, children aged 1 to 10 years consumed 4000 mg/d peanut protein and probiotic OIT for 18 months, with 67% (16 of 24) continuing peanut consumption 4.2 years after OIT cessation (of the 31 original OIT participants).⁷² Further in the Probiotic and Peanut Oral Immunotherapy study, an 8-week SU challenge was passed by 70% (7 of 10) (however, only 10 of 23 potential participants who had passed

the 2-week SU challenge at the conclusion of the primary study agreed to repeated SU challenge).

Furthermore, few studies publish the instructions they provide to participants following the primary outcome of OIT, and even *ad libitum* ingestion may be accompanied with advice of frequency; for example, early-OIT advising this meant "incorporate peanut into the diet *ad libitum* at least several days per week."⁷⁴ Standardization of instructions provided is crucial for participant safety, validity of the follow-up data collected, and ongoing clinical care.

Long-term avoidance or continuous allergen ingestion post-OIT

Five studies followed up with participants at least 6 months after establishing DS or SU following a period of avoidance or continuous daily dosing (Table VI).^{2-20,25-36,68-70,72-78} There is currently no agreed consensus on the duration and frequency of ingestion of allergenic foods required to maintain DS post-OIT cessation nor how to evaluate and diagnose sustained tolerance (SU) or permanent tolerance (remission). Yee et al⁷⁵ surveyed participants every 6 months for 6 years while taking daily doses (500-3500 mg/d), with 54% (7 of 13) still consuming peanut after 6 years. The Nut Co-Reactivity—Acquiring Knowledge for Elimination Recommendations and sustained outcomes in oral immunotherapy for peanut allergy trials examined the ability to maintain DS using lower daily dosing during a long-term follow-up period after achieving the primary outcome (attaining 4000 mg/d maintenance or passing a 4000-mg DS challenge, respectively). In Nut Co-Reactivity—Acquiring Knowledge for Elimination Recommendations, 45 participants were maintained on a lower dose of walnut (1200 mg/d) for at least 6 months and all 45 passed a 4000-mg DS challenge. In addition, 11 patients were maintained on a low dose for less than 6 months at the time of publication. Of these, 9 were assessed at their 6-month follow-up and passed a 4000-mg DS challenge and 2 did not arrive for follow-up (Elizur 2021, unpublished data).³⁴ In sustained outcomes in oral immunotherapy for peanut allergy, participants were randomized to avoid peanut (p-0) or take a daily dose of 300 mg (p-300) during the follow-up year.⁷⁶ In a 4000-mg DS challenge conducted at 52-week posttreatment follow-up, 37% (13 of 35) of the p-300 group passed compared with 13% (8 of 60) of the p-0 group. Of note, the proportion of the p-300 group that passed a 4000-mg DS challenge dropped from 83% (29 of 35) at week 13 of follow-up to 37% (13 of 35) at week 52 ($P < .001$).⁷⁶ Jones et al⁷⁷ and Syed et al⁷⁸ examined the ability to maintain SU after long periods of avoidance. Only 21% (20 of 96) and 13% (3 of 23) of original participants passed an SU 5000-mg challenge after 26 weeks of peanut avoidance in Jones et al⁷⁷ and Syed et al,⁷⁸ respectively. These data together suggest that most patients undergoing OIT would require many years if not life-long regular consumption of the allergenic foods to maintain a state of DS, and although SU may be achieved by some, most patients regain their allergy with longer periods of food avoidance.^{67,76-78}

Of note, although most studies of SU have focused on complete remission (passing an OFC following a period of avoidance), more data are needed on the rate of partial remission to inform patients and physicians with regard to long-term outcomes. In the seminal egg OIT study published in 2012 by Burks et al,²¹ although only 28% of children were considered as having achieved SU on their final 10-g challenge (equivalent to 2

eggs), all were able to tolerate a significantly higher amount of egg than they could on their entry challenge, suggesting that all developed at least some form of sustained clinical response. This in itself may be a worthwhile objective for some families. In the absence of available tools to predict tolerance, continuous consumption of a fixed predetermined daily dose is probably required at least 3 to 4 times per week. The size of this dose will depend on whether the patient's goal is the ability to maintain *ad libitum* consumption or to be protected from reactions in case of accidental exposures.

Long-term compliance

Given that prolonged, if not indefinite, regular OIT treatment will be required for most, long-term compliance will be a mandatory part of OIT treatment and should be presented to patients before entering OIT. The size of the required daily dose might impact long-term compliance. Patients required to regularly consume a high peanut dose (3000 mg peanut protein, roughly equivalent to 10 peanuts) after achieving full DS were much more likely (31.4% vs 3.9%) to discontinue treatment compared with patients who were required to consume only 1200 mg (roughly equivalent to 4 peanuts).⁷⁹ Importantly, patients consuming the low dose (1200 mg) were shown to maintain full DS. In contrast, in sustained outcomes in oral immunotherapy for peanut allergy, a 300 mg daily dose failed to maintain full DS in most patients.⁷⁶ Taste aversion, difficulty incorporating the dose with daily activities, adrenaline use during the build-up phase, and recurrent reactions during follow-up additionally contribute to ongoing compliance challenges.^{36,74}

Carriage of an epinephrine autoinjector device

Severe adverse reactions including anaphylaxis requiring the use of an epinephrine autoinjector device are a well-documented part of all OIT treatment regimes (risk of 22% compared with baseline risk of 7.1% without OIT⁴⁵) and may occur in the clinic as well as during home dosing. Emerging evidence suggests they reduce with increased duration on the maintenance dose but are still largely unpredictable. Individualized action plans and emergency epinephrine autoinjector devices for management of reactions should be provided.⁷⁶ Of concern, despite follow-up studies specifically instructing participants to continue carrying an epinephrine autoinjector, this advice is regularly not followed; for example, in early-OIT, 38% (11 of 29) did not carry their epinephrine autoinjector as instructed, and of these, 18% (2 of 11) had additional persistent food allergies other than peanut.⁷³ In single food-allergic patients who are not eating their food allergen outside of their regular dosing, a reasonable compromise to improve compliance might be that an epinephrine autoinjector needs to be available during and immediately after food dosing with the allergen.

Biomarkers as an indication of treatment success

When analyzing our ability to predict OIT success, we need to first define what success is; that is, is it DS? short-term SU? or long-term SU/tolerance? There is increasing evidence that baseline biomarkers are inversely associated with successful DS or short-term SU following OIT. Smaller skin test results, lower peanut specific IgE, Ara h1, and Ara h2 levels, and a reduced peanut specific IgE/total IgE ratio at baseline occur in participants who pass DS⁷⁶ or SU OFC⁷⁴ compared with those who failed. However, further evidence is required to determine whether these biomarkers are predictors of treatment success or

natural resolution of food allergy. During the maintenance phase of OIT, food-specific decreasing IgE and increasing IgG₄ levels may be used to monitor longitudinal changes in the immune response and although further research is required to determine the interpretation and relevance of these, they are highly relevant for the patient experience.⁷

Basophil activation test (BAT) is a highly specific novel diagnostic modality that has been increasingly used in the diagnosis of allergy in general, and of food allergy in specific, particularly in patients with equivocal skin prick tests or specific IgE results.⁷¹ The utility of BAT in predicting OIT results has been reviewed elsewhere.⁸⁰ Briefly, several studies have shown a significant reduction in basophil reactivity during OIT. In addition, lower basophil reactivity at baseline was associated with DS following OIT and with short-term (13-week) SU. However, whether BAT can predict tolerance is unclear. Also, the BAT is currently limited to specialized centers, and its protocol and its best outcome measure need to be better defined.⁸⁰

UNMET NEED #4: HOW TO MEET THE DEMAND OF OIT

OIT is a time-consuming and demanding process that requires a high degree of commitment and shared decision making by the patient, family, and allergist. It may not be an optimal therapeutic option for all food-allergic individuals; however, it should be offered and available to all eligible candidates.⁸¹ With increased demand, allergists/immunologists have a substantial role and obligation in offering OIT in a safe manner in their clinical practice. Guidelines published by the EAACI in 2018 and the CSACI in 2020 provide an initial foundation of how OIT may be offered in clinical practice.^{6,7}

Identifying and addressing barriers to OIT

To increase OIT's availability, the barriers to initiating OIT must first be identified and addressed. A 2020 survey from 90 practicing Canadian allergists found that lack of ancillary staff, reimbursement, and physician training were hurdles to initiating OIT in clinics.⁸² Before the FDA approval of a peanut OIT product, a survey among 34 US-based food allergy specialists found that although some were providing OIT with various peanut materials, significant barriers included the need for FDA-approved options due to concerns for medicolegal risk.⁸³ Other surveys assessing barriers to allergy-specific procedures such as OFCs showed that lack of resources and long wait times dissuaded pediatricians from referring to allergy practices.⁸⁴ Barriers to performing OFCs included time, inadequate reimbursement, risk of an adverse event, lack of resources such as office space and staff for preparation and supervision of challenges, and training, with fewer than half the respondents having performed OFCs during allergy/immunology training.⁸⁵ Some of these barriers can be addressed by (1) increasing access to clinical guidelines, protocols, and policy statements; (2) incorporating training modules for ancillary staff and allied health clinicians; (3) providing consistent training and practical guidance in allergy fellowship programs; and (4) implementing OFC- and OIT-specific billing codes with appropriate reimbursement and coverage.

Improving access to OIT services

Because allergy practices across the country redefine their workflows and processes to accommodate OIT, another area that

can be further developed includes improving access to OIT services. For those living in rural areas with limited access to allergists, OIT-trained allergists can form partnerships with and train local physicians. Additional clinic visits that may be necessary due to illness, asthma exacerbations, and other health-related situations can be managed locally with a consistent flow of information among comanaging physicians. Access to care can be improved by establishing a local telemedicine-driven network as successfully developed by dermatology practices.⁸⁶

The American College of Allergy, Asthma and Immunology created a task force to assess digital technologies and considers telemedicine a valuable method of health care delivery, especially to patients in rural or remote areas.⁸⁷ As experience with virtual technology increases,²⁰ mobile and digital devices can be used to support and improve health services, data flow, surveillance, and disease management.⁸⁸ These advances can be leveraged in the setting of food allergy and OIT. The EAACI has also created a task force to explore mobile technology-driven solutions in allergic diseases. A position paper⁸⁸ was published in 2020 with a 2-year action plan to incorporate mobile health into allergy care. Although validation of high-quality tools is still needed, such advances can improve adherence, monitor symptoms and adverse events, improve communication with the care team, and provide real-time clinical data.

Risk stratification and personalized OIT protocols

Emerging data show that there are likely multiple phenotypes of food allergy that affect reaction severity and response to OIT.⁸⁹ This is an area of active research⁹⁰ and points to the need for more personalized management and guidance. At its present stage, OIT dose escalations are strongly advised to be performed under a clinician's supervision. Two European studies conducted by Arkwright et al⁹¹ in 2018 and Garvey et al⁹² in 2017 have shown that for select patients with a mild reaction history, home-based peanut OIT was successful. For the long-term success of OIT, there is a need for more personalization of OIT within an accepted framework.

In addition to variable reaction phenotypes, there is great variability among patients and caregivers regarding their goals for therapy.⁸¹ Some individuals seeking OIT may want protection against cross-contamination or the ability to consume foods with the "may contain" label. Others want "bite-proof" protection—or the ability to be safeguarded against severe reactions from accidental ingestions of larger amounts. Some desire the ability to "free-eat" where they can consume the allergen(s) *ad libitum*.⁸¹ Wherever possible, in accordance with the practice's infrastructure, the OIT plan and protocol should be aligned with the patient's/caregiver's goals and reaction phenotype in a shared decision model.

Interdisciplinary approach

Children and their caregivers experience increased stress and anxiety in addition to decreased QOL related to daily food allergy management practices.⁹³ In a study conducted among Food Allergy Research & Education's Centers of Excellence, most centers reported to have observed child and parent anxiety during OFCs and OIT but with limited access to mental health services.⁹⁴ To further support the needs of patients and families, OIT management should include a partnership between primary and specialty care, with professional counseling recommended for those with significant anxiety. Some centers have a specialized

mental health professional dedicated to the division with expertise in food allergy.⁹⁴

WHERE TO FROM HERE?

As we work toward greater availability of OIT for eligible patients, there are still several unmet needs.^{81,82} Effectiveness of OIT needs to be further examined across patients of diverse socioeconomic status, race, age, and ethnicity. A better understanding on how to use biomarkers such as IgE ratios and IgG₄ in real-life OIT is needed as are new assessments and instruments to better understand patient-centered outcomes.⁸¹ Additional studies exploring the effect of OIT on health care utilization linked to accidental exposures will provide additional clarity on the long-term economic outcomes.^{7,81} There is a need for additional guidelines and protocols incorporating the use of biologics in food allergy.

OIT is clearly a disruptive innovation because it destabilizes the previously accepted standard of care of food avoidance as the only option for the management of food allergy.⁷ With the advent of OIT and other therapeutic options, the traditional allergy practice will have to be restructured to provide care for food-allergic individuals. Training at fellowship programs and organizations will have to be updated and interdisciplinary care will have to be prioritized. With the advent of telemedicine and digital tools, guidelines/protocols that are customizable to the individual's specific phenotype and goals of therapy will need to be created. OIT will no longer be available only to the select few with economic means or available time to join clinical research trials, but hopefully as the new standard of care for patients of diverse socioeconomic, ethnic, and racial backgrounds as well as those in rural or remote areas.

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