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IMMUNOTHERAPY AND IMMUNOMODULATORS (B VICKERY, SECTION EDITOR)

How to Incorporate Oral Immunotherapy into Your Clinical Practice

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Abstract

Purpose of Review The purpose of this review is to discuss how to best incorporate oral immunotherapy into your clinical practice based on recent evidence and guidelines, and address controversies.

Recent Findings Oral immunotherapy is the food immunotherapy treatment with the most literature supporting its use. Recent data from both randomized clinical trials and real-world studies show OIT is especially safe and effective in preschoolers, while avoidance may be less safe than previously thought. OIT guidelines support its use outside of research.

Summary Oral immunotherapy can be safely and effectively incorporated into your clinical practice, with careful planning and consideration of scenarios where benefits outweigh risks. Baseline oral food challenges are necessary in clinical trials, but in clinical practice, these are best done when the history is unclear due to resource limitations. There is a role for both regular food and FDA-approved products. Future research should focus on optimizing safety and adherence in the real-world setting.

Keywords Peanut allergy · Food allergy · Tertiary prevention · Oral immunotherapy · Immunotherapy

Introduction

Food allergy affects approximately 6% of the population and has increased in prevalence over the past few decades [1–3]. In the past, the only option with a diagnosis of food allergy was strict avoidance of the implicated allergen. However, many food allergies such as peanut allergy are rarely outgrown [4] and food allergy has a significant ongoing impact on quality of life [5–7]. As a result, focus has shifted to therapies that have the potential to alleviate this burden among children and their families.

Immunotherapy involves administering increasing doses of allergen over time with the goal of allowing either protection from accidental exposures, or increasing the safety margin with ongoing ingestion of allergens [6, 8]. The goals of this article are to review the benefits and risks of immunotherapy, in particular oral immunotherapy, and to discuss in-depth how this could be incorporated into a clinical practice.

Definition and Types of Immunotherapy

There are mainly three types of food immunotherapy that are being studied: oral immunotherapy (OIT), epicutaneous immunotherapy (EPIT), and sublingual immunotherapy (SLIT) [9]. The initial goal of any type of immunotherapy is to provide clinical desensitization (an increase in the threshold of allergen required to cause an allergic reaction which is dependent on ongoing exposure to the allergen over time) [9,10]. However, a longer term goal is sustained unresponsiveness (SU), which refers to the persistence of desensitization even in the absence of ongoing exposure to the allergen [9,10]. Each type of immunotherapy involves increasing doses leading to a maintenance dose for a period of time [10].

However, they differ in the route of exposure to the allergen, dose of allergen exposure, and duration of maintenance therapy. Epicutaneous immunotherapy refers to placing a patch on the surface of the skin of a very small concentration of allergen (e.g., maintenance dose of approximately 250-μg protein) which remains on the skin 24 h a day [10]. Sublingual immunotherapy refers to placing a small amount of allergen

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(e.g., maintenance dose of approximately 2-mg protein) under the surface of the tongue once a day, followed by swallowing the solution after 2 min [10]. In oral immunotherapy, the allergen is ingested typically starting with a buildup phase until maintenance dosing is reached, at which point the allergen is ingested once a day on an ongoing basis [9].

Of the three types of immunotherapy, the one that is used most commonly outside of research is OIT, and its use is increasing over time. A recent survey of American allergists found that 47.5% (48/101) had used OIT in the past year, a significant increase from 13.8% in 2013 [11]. As a result, the focus of this article will be on OIT.

Benefits of Oral Immunotherapy

Studies to date have shown desensitization rates of between 67 and 92% [12••, 13••, 14–16]. In Vickery et al.'s study of 40 peanut-allergic toddlers aged 9–36 months who were randomized to receive low-dose (300 mg) or high-dose (3000 mg) peanut OIT over a median of 29 months (including a 10.5-month buildup), there was an 85% desensitization rate in the low-dose group and 76% desensitization rate in the high-dose group [13••]. A multicenter double-blind randomized controlled trial of low-dose peanut OIT (median buildup: 13 months, median maintenance: 2.4 months, median maintenance dose: 125-mg peanut protein) in 62 children aged 3 to 17 years with peanut allergy by Blumchen et al. noted desensitization rates of 74.2% in the active group (compared to 16.1% in the placebo) [17]. In the largest randomized controlled trial of peanut OIT to date, PALISADE, of 551 patients aged 4–55 years (of which 496 were children), desensitization rates of 67.2% (compared to 4.0% on placebo) after 6 months of maintenance of 300-mg protein (total duration of trial 12 months) were noted [18, 19, 20••]. In the Probiotic and Peanut Oral Immunotherapy (PP-OIT) study, a randomized placebo-controlled trial of peanut OIT in children aged 1 to 10 years of age with median buildup of 8.9 months and median maintenance of 9.9 months (maintenance dose 2000mg protein), there were desensitization rates of 89.7% (compared to 7.1% in the placebo group) [21]. The authors' real-world study of preschool peanut oral immunotherapy, CPP-OIT, found that of 117 patients who successfully completed peanut OIT and underwent a cumulative 4000-mg follow-up challenge, 78.6% had a negative challenge and 98.3% tolerated a cumulative dose of $\geq$ 1000 mg [22••]. Of those who reacted, their threshold increased by 3376 mg (95%CI: 2884–2868 mg) from baseline to follow-up.

Sustained unresponsiveness rates have been less frequently studied and have ranged between 58 and 78% [13••, 14]. Vickery et al.'s study of preschoolers found that 78% in the intention-to-treat analysis achieved a 4-week SU over a median of 29 months [12••]. PP-OIT noted 2- to 5-week SU in 82.1% of patients after 18 months; at a 4-year follow-up, an 8-week SU rate of 58% was found [14]. Sustained unresponsiveness outcomes in peanut OIT studies have been at 2 [14], 4 [13••], and 8 weeks [14] after completion of OIT. A recent meta-analysis and systematic review of the use of food allergen immunotherapy including both pediatric and adult studies noted efficacy with desensitization but an unclear benefit on sustained unresponsiveness (although SU is a less commonly studied outcome) [23].

A recent meta-analysis and systematic review of peanut OIT (12 trials; n = 1041; median age 8.7 years) by Chu et al. found that OIT (versus no OIT) did not improve quality of life (combined parents and self-report RR 1.21; 95%CI: 0.87–1.69) [24]. However, quality of life outcomes were only available for a minority of subjects included in the meta-analysis which makes it difficult to derive any firm conclusions. This is in stark contrast to positive effects demonstrated on quality of life during OIT, illustrated in studies which had a better depth/higher rate/were more focused on quality of life data. Most convincingly, in a prospective cohort study of parents of 191 food-allergic children aged 4 to 12 years of age undergoing OIT, quality of life was assessed comprehensively at multiple time points. It improved significantly upon reaching OIT maintenance in multiple dimensions including emotional impact (P = .001), food anxiety (P < .001), social and dietary limitation (P < .001), and global score (P < .001), whereas changes were not seen in matched controls [25]. Additional improvements in quality of life were seen in those who remained on OIT 6 months later.

Safety of Oral Immunotherapy

There can be anaphylaxis with OIT, although this rate tends to be much lower in preschool-aged children than in children of school age or older [13••, 18, 19, 20••]. Reactions are more common with co-factors such as viral infection, lack of snack with the dose, or exercise. However, they are difficult to predict and can occur even once at maintenance dosing [19, 20••]. In the PP-OIT study, severe adverse events occurred in 45.2% of participants (although also occurring in 32.3% of placebo patients) [21]. In the PALISADE study, adverse events occurred in 95% of OIT participants; 4.3% had severe adverse events, 14.2% had systemic allergic reactions, and 14% required epinephrine [12••]. The Chu et al. meta-analysis found that OIT (versus no OIT) increased anaphylaxis risk (risk ratio [RR] 3.12; 95%CI: 1.76–5.55), anaphylaxis frequency (incidence rate ratio [IRR] 2.72; 95%CI: 1.57–4.72), and epinephrine use (RR 2.21; 95%CI: 1.27–2.83) [24]. However, this meta-analysis did not include preschool-aged children, in whom a much more favorable safety profile has been noted [13••, 20••]. In our CPP-OIT safety analysis, only 0.4% of 270 preschoolers undergoing peanut OIT experienced a severe reaction during buildup [20••].

It also should be noted that while anaphylaxis can occur, most adverse events with OIT are mild cutaneous or gastrointestinal symptoms, especially in the younger age groups such as toddlers [23]. There is also a risk of eosinophilic esophagitis (EoE), estimated at approximately 2.7% (although it appears to be lower in toddlers), which tends to resolve with discontinuation of OIT [19,26]. It is possible that the risk of EoE is an associated, rather than a causative, risk, as IgE-mediated food allergy is a risk factor for EoE in general [27]. Finally, adverse events may be reduced in low-dose OIT. The randomized controlled study of 62 children aged 3 to 17 years with peanut allergy described above noted no difference in adverse events between the peanut OIT or placebo groups with a low-dose (125 mg) peanut OIT protocol [17].

Anaphylaxis from Food Accidents Is Underappreciated, and Food Avoidance Is Not "Risk Free"

Observational studies have noted that there is a significant risk of accidental allergic reactions with strict avoidance. A study of 429 children with confirmed peanut allergy noted an annual incident rate of 12.4% accidental exposures (95%CI: 11.4–13.4%); of the 66% (377/567) that were moderate to severe only, 28.9% sought medical attention, and of those that did, only 36.7% received epinephrine [28].

More recently, a 3-year follow-up study of 83 peanut-allergic children in the Netherlands noted an accidental allergic reaction rate of 41%, with 29% of those reacting experiencing severe symptoms (i.e., a 9.8% annual risk of anaphylaxis) [29]. One of the strengths of this study was that all children had DBPCFC-confirmed peanut allergy, to avoid any underestimates of anaphylaxis. Of most concern, none of the children with severe symptoms received epinephrine, despite clear instructions on when/how to use it. These rates of anaphylaxis are much higher than the 2.7% reported by Chu et al. [24]. This discrepancy may be largely explained by the populations analyzed, with Chu et al analyzing data mostly from clinical trials in which patients are very closely monitored and adherence tracked, while the Netherland studies are largely observational data collected in the "real world." Observational data provides a higher level of external validity and suggests that the risk of moderate-to-severe accidental reactions, and more concerningly lack of use of epinephrine if that occurs, is very high, as it is made out to be. Especially in preschoolers, the risk of oral immunotherapy is similar to that of food avoidance. OIT in this age group we predict will soon become the standard of care.

OIT Guidelines

Several international allergy organizations have released guidelines on the use of oral immunotherapy. Recently, the Canadian Society of Allergy and Clinical Immunology (CSACI) published an evidence-based and patient-oriented clinical practice guideline for OIT [30••]. This guideline was unique in its patient-oriented focus and multidisciplinary approach, involving experts from a diversity of fields including not just only healthcare providers but also ethicists and patients in the process. This guideline advocates for patient empowerment and education with respect to OIT, and a personalized approach in evaluating the risks and benefits of OIT for any patient, in addition to economic considerations. Similar to previous guidelines, such as those published by the European Academy of Allergy and Clinical Immunology (EAACI), the CSACI guideline recommends that OIT is an effective therapy for desensitization, and while it can be recommended for sustained unresponsiveness, data remains limited and variable [30••, 31]. In keeping with previous guidelines, it recommends that uncontrolled asthma is an absolute contraindication to OIT; relative contraindications include pre-existing eosinophilic esophagitis, use of beta-blockers or ACE inhibitors, or active severe eczema. The CSACI guideline also stresses the importance of having safety equipment available in the office and notes that any allergist offering OIT must be comfortable performing oral food challenges routinely.

Practical Tips to Starting OIT Outside of Research

The Canadian Preschool Peanut OIT (CPP-OIT) national collaboration established some key principles, and practical tips, that may be useful when considering starting OIT outside of a research protocol in the "real-world" setting. This protocol was used initially only for toddlers starting peanut OIT but is now being used in slightly older children, and for foods other than peanut, as well. Our protocol has a number of documents, provided as appendices, that may assist the allergist considering starting OIT in their practice for the first time. Our enrollment criteria was initially children aged 9 to 71 months (preschool aged) with either a history of an allergic reaction to peanut and positive skin prick test ≥ 3 mm or peanut-specific IgE ≥ .35 kU/L or no peanut ingestion and a peanut-specific IgE ≥ 5 kU/L. Exclusion criteria were a previous life-threatening reaction to peanut, allergy to the vehicle used in peanut capsules, severe eczema requiring systemic therapy, or asthma on more than moderate dose inhaled corticosteroid therapy. Factors that were considered to require extra caution included language barriers, a previous asthma exacerbation requiring an emergency room visit or hospitalization, or oral steroid therapy in the past 6 months.

Our protocol included a consent form that listed the benefits and risks of OIT, contraindications to OIT, and the process of OIT (scheduling, observation period after a dose) as well as reasons to notify the allergy clinic (such as changes in medications or an asthma exacerbation). Our protocol also allowed the use of different peanut products: Bamba® peanut butter

puffs, peanut flour/powdered peanut butter compounded into capsules, or a hybrid of the previous two. We found it useful to use shared decision-making, describing the benefits and risks of each protocol and then asking families to provide input in deciding which protocol to use. All 3 options had an initial buildup leading to a daily maintenance dose of 300 mg, with dose escalations occurring every 2 weeks. Our protocol had a flow sheet for parents that reviewed symptom severity and reasons for protocol disruption (such as fever, gastroenteritis, or asthma exacerbations).

Please see Tables 1, 2, and 3 and Figs. 1 and 2 for a variety of resources with practical tips for starting OIT outside of research.

Case Example A 3-year-old boy, previously well, is referred to the pediatric allergy clinic with a history of generalized urticaria, vomiting, and sneezing 10 min after consuming peanut for the first time, in the form of one teaspoon of peanut butter. The family presented to the emergency department where he was given intramuscular epinephrine with prompt symptom resolution. He has been avoiding peanut since, and parents are afraid to introduce tree nuts.

Skin prick testing (SPT) is performed to peanut and tree nuts, and is positive to peanut (14 mm), cashew (20 mm), and pistachio (18 mm). SPT is negative for walnut, pecan, hazelnut, almond, and brazil nut, with appropriately positive and negative controls. Serum-specific IgE testing for peanut is 80 kU/L, and for cashew is > 100 kU/L.

The family is extremely interested in oral immunotherapy (OIT) and was initially considering flying out of country for treatment from a specialist their relatives recommended, but did not think they could afford this option. They were very excited to learn that their local pediatric allergist was starting to offer this treatment option.

Based on the convincing history of peanut allergy with sensitization on SPT, you decide that OIT should be started to peanut without a baseline oral food challenge (OFC). Given the strong sensitization to cashew and pistachio, you determined that the safest option would be to also start OIT to cashew, without a baseline OFC, describing to parents that at > 100 kU/L, the risk of reaction upon OFC to cashew would be high despite a lack of history of ingestion.

You review the consent form (Fig. 2) in detail with the family and review the sick day management and symptom management (Fig. 1). You order capsules for PB2 flour and cashew flour from your compounding pharmacy (Table 2). After discussion with the family, you decide to start initially with peanut OIT using the hybrid protocol (Table 2), and to add in cashew OIT at visit 3, once they are more comfortable with OIT.

The family returns with capsules for peanut OIT initiation. You open the first PB2 capsule (28.8 mg PB2; 12 mg PP) and show parents how to mix it with a small amount of apple sauce, which is the patient's favorite food. The patient is observed for 30 min after ingestion. He complains that the food is "spicy" and develops two small perioral urticaria, which you reassure parents are considered mild symptoms (Fig. 1), which are common with OIT, and not a contraindication for continuing therapy.

The patient continues to have the same dose at home daily for 2 weeks, and parents notice that his mild symptoms decrease over time. They return to the clinic 2 weeks later, where the patient is given the next buildup dose, and observed for 30 min, again with only mild symptom development. Two weeks later, the patient returns to the clinic. He is once again giving the next peanut buildup dose and observed for 30 min. After 30 min, he is given his first dose of cashew OIT, and observed for 30 min. He complains of mild abdominal pain, which you again reassure parents is considered having a mild symptom (Fig. 1).

The family continues OIT with both peanut and cashew at home, given at the same time daily. They continue with the buildup schedule (Table 2), coming to clinic for buildup of both foods every 2 weeks. They follow the peanut hybrid protocol (Table 2), and at week six, they switch to Bamba, which the patient enjoys.

During week eight, parents call you because the patient has fever (39 °C), and they are unsure what to do. You refer them to the sick day flow sheet (Fig. 1) and inform them to hold the OIT dose on days of fever > 38.5 °C. The fever continues for 2 days, after which, based on the flow sheet, they restart OIT at home, at the same dose, which is tolerated without adverse reaction. At week 14 of cashew buildup, parents purchase a food scale, to weigh out whole cashews instead, which they crush and mix with apple sauce.

The patient reaches the maintenance dose (~ 300-mg food protein) for both peanut and cashew, in the form of Bamba and weighed, crushed cashews. The patient continues to tolerate this maintenance dose daily for 2 years, after which you arrange for food challenges to both peanut and cashew to assess the extent of desensitization.

Ongoing Controversies

Should Peanut OIT Be Offered Preferentially to Preschoolers?

While limited to two large studies (combined $N = 310$), available data indicates that severe adverse events are much less common in the toddler age group than in older children, perhaps due to immune plasticity in younger children [32]. In the Vickery et al. study of 40 toddlers aged 9 to 36 months with suspected or known peanut allergy randomized 1:1 to receive peanut OIT or placebo, no severe adverse events occurred in the peanut OIT group [13••]. The authors' recent real-world study of 270 preschool-aged children with median age of 23 months, CPP-OIT, found very low rates of severe adverse

Table 1 Practical tips for starting OIT, based on key recommendations in CSACI guidelines on OIT [29]

Recommendation area	Practical tips/recommendations
Eligible food allergens and types of clinical outcomes that can be achieved by OIT	1. Any food allergen can be used. There is no convincing evidence of a clinically significant difference between food allergens in terms of safety and efficacy outcomes in OIT for treatment of IgE-mediated food allergies. 2. OIT is recommended as a treatment to achieve desensitization. 3. OIT may be recommended to achieve sustained unresponsiveness, but data is limited and variable.
Who could benefit from OIT (indications)	1. An accurate diagnosis of IgE-mediated food allergy is essential before proceeding with OIT. 2. OIT is indicated for children of all ages, although, severe adverse events are much less common in the toddler age group. 3. OIT may be indicated for adults.
Contraindications	1. Previous history of anaphylaxis to the targeted food is not a contraindication for OIT. 2. Multiple food allergies are not a contraindication to OIT. 3. Uncontrolled asthma is an absolute contraindication to OIT. Asthma must be controlled before beginning OIT and pro-actively managed during OIT. 4. Pregnancy is an absolute contraindication for initiating OIT. 5. Conditions such as active severe atopic dermatitis, pre-existing eosinophilic esophagitis, and heart disease, and those requiring the use of beta-blockers or ACE inhibitors are relative contraindications for OIT. 6. Patient- or caregiver-specific contexts that may impair safe administration of therapy may constitute contraindications (ex., unreliable adherence to protocol, reluctance to use epinephrine, language barrier, and severe anxiety).
Safe provision of OIT	1. OIT providers and patients should be prepared to recognize and treat allergic reactions, including anaphylaxis during OIT. Food escalation should only be performed in a clinic with appropriate equipment and infrastructure available to treat anaphylaxis (Table 3). 2. A personalized action plan should be provided to patients to guide management of reactions occurring at home (Fig. 1). 3. Providers should only offer OIT in age groups in which they have training or experience in treating anaphylaxis. 4 Patients should be observed in clinic for 1 h following dose escalation. The observation period can be decreased as appropriate to a minimum of 30 min, based on various factors that include patients who are reliable, confident, and comfortable with the management of allergic reactions. 5. Surveillance for the emergence of EoE or EGID should be based on monitoring for the emergence of clinical symptoms (e.g., dysphagia, esophageal spasm, vomiting, diarrhea). Endoscopy and biopsy should be used to confirm the diagnosis in suspected cases not responding to dose adjustments or medication.
Personalized OIT protocols	1. OIT can be performed with many different food products. 2. The goals of OIT can be achieved with many different protocols. There is little evidence that specific dosing schedules are superior to others. Reference protocols can be useful to guide therapy, but need to be selected and adapted based on the patient's specific situation. 3. When performing OIT in patients with multiple food allergies, the preferred approach is to treat multiple foods simultaneously. 4. Short-term concomitant use of omalizumab can be considered in challenging cases.
Patient-centered care	1. The ultimate goal of food allergy care should be the empowerment of patients and their caregivers to manage the risk of food allergy reactions, reduce food-related anxiety, and achieve a sense of control over their condition. Tactful and empathic shared decision-making with patients, their caregivers, and the OIT providers is necessary before making a decision to proceed with OIT. 2. Informed consent must be obtained before initiating OIT (Fig. 2). This should include clear discussion of potential outcomes, risks, and benefits, as well as the patients' and their caregivers' concerns, expectations, and goals. Patients should be informed on how to recognize and mange reactions during therapy. 3. Throughout treatment, patients' goals and perceived benefits should be reassessed periodically to ensure that clinical decisions continue to reflect their personal objectives.
Promotion of optimized organization of care	1. A multidisciplinary approach adapted to patient needs should be promoted and should include nurses, registered dieticians, psychologists, and peer supporters, when possible. 2. In areas with limited or no access to allergists, pediatricians and family physicians could provide certain OIT services after receiving adequate training and under close supervision by an allergist.
Sustainable provision of OIT	1. Extreme care should be taken to avoid creating unnecessary financial barriers that could limit access to treatment based on ability to pay.

events to peanut OIT in this population, with only 0.4% of children experiencing a severe reaction and 4.07% receiving epinephrine during buildup phase [20••]. These rates of severe reactions are much lower than those noted in the Chu et al. meta-analysis, which only included children over the age of 5 years (16.5% anaphylaxis; 8.2% epinephrine use) [24]. Another benefit to OIT in the preschool-aged group is lower rates of food aversion and fear related to food ingestion, which

can hinder the success of OIT and rates of subjective reactions in older age groups [19,33,34].

As a result, in the authors' opinion, there is an argument to be made that peanut OIT should be offered preferentially in the toddler aged group [19]. This would be an especially poignant argument in centers or locations where wait lists are long and there is no capacity to offer OIT broadly [19]. However, as with OIT in general, if offered to preschoolers, practitioners must be comfortable performing oral food challenges in this age group and assessing and managing anaphylaxis [30••] (Table 4).

Should Peanut OIT Be Offered Outside of Research?

In the authors' opinion, OIT is a safe and effective therapy that should be offered outside of research, in particular to toddlers [19]. One group even went as far as to say that it is time to stop doing placebo-controlled trials and start focusing on real-life studies [35]. Additionally, there are an increasing number of allergists who are practicing OIT in the USA, up from 13.8 to 50% from 2013 to 2016 [36,37].

Arguments against the use of OIT outside of a research setting include the risk of anaphylaxis, and insufficient information about dosing, sustained unresponsiveness, mechanism of action, and comparative effectiveness [26,38–42]. In addition, although the use of OIT outside of research is not uniformly supported by national guidelines published approximately 10 years ago [43,44], more recent international guidelines including the EAACI OIT guideline and the CSACI guideline have supported it [30••, 31]. CPP-OIT provided recent real-world national data that this therapy is safe and effective [20••, 22••].

However, this must be balanced against the "hidden costs" of food allergy, including not just only accidental ingestion but also lifelong persistence of peanut allergy and its significant impact on quality of life for both the child and their family [1, 43, 45, 46]. Peanut OIT has been shown in multiple studies to improve quality of life [47–49] and has been shown to be safe and effective in "real-world" community practices [16, 20••, 45, 50]. OIT has been offered outside of research for several years [36, 51], and allergists have noted it to be "the most impactful thing that they have done in medicine" [19,52].

Any decision to proceed with OIT outside of a research center should be done in a patient-centered way and incorporate patient preference and patient-centered outcomes [19, 30••]. When surveyed, parents report that their primary goal with OIT is to reduce the risk of a fatal food reaction, a patient-

Table 2 CPP-OIT protocol options for peanut OIT. Reproduced with permission from Soller et al. [19]. OIT dosing table

Week no.	Hybrid (PB2* then Bamba+)	PB2* only	Bamba+ only
0	28.8 mg PB2 (12 mg PP)	First-day escalation (every 15–30 min) 0.24 mg PB2 (0.1 mg PP) 0.48 mg PB2 (0.2 mg PP) 0.96 mg PB2 (0.4 mg PP) 1.92 mg PB2 (0.8 mg PP) 3.6 mg PB2 (1.5 mg PP) 7.2 mg PB2 (3 mg PP) 14.4 mg PB2 (6 mg PP)	1/8 Bamba stick (~ 10mg PP)
2	60 mg PB2 (25 mg PP)	28.8 mg PB2 (12 mg PP)	¼ Bamba stick (~ 20 mg PP)
4	120 mg PB2 (50 mg PP)	60 mg PB2 (25 mg PP)	½ Bamba stick (~ 40m g PP)
6	1 Bamba stick (~ 80 mg PP)	120 mg PB2 (50 mg PP)	1 Bamba stick (~ 80 mg PP)
8	1.5 Bamba stick (~ 120 mg PP)	180 mg PB2 (75 mg PP)	1.5 Bamba sticks (~ 120 mg PP)
10	2 Bamba sticks (~ 160 mg PP)	240 mg PB2 (100 mg PP)	2 Bamba sticks (~ 160 mg PP)
12	3 Bamba sticks (~ 240 mg PP)	300 mg PB2 (125 mg PP)	3 Bamba sticks (~ 240 mg PP)
14	4 Bamba sticks (~ 320 mg PP = maintenance dosing)	374.4 mg PB2 (156 mg PP)	4 Bamba sticks (~ 320 mg PP = maintenance dosing)
16	Maintenance dosing	468 mg PB2 (195 mg PP)	Maintenance dosing
18	Maintenance dosing	588 mg PB2 (245 mg PP)	Maintenance dosing
20	Maintenance dosing	720 mg PB2 (300 mg PP = maintenance dosing)	Maintenance dosing

PB2, powdered peanut butter; *PP*, peanut protein

*Allergists who chose to use peanut flour instead of PB2 adjusted for protein content

+ There are different types of Bamba packages with different protein content. The calculations in this table for the number of Bamba sticks are based on the package with 5-g protein/28-g Bamba

Table 3 Equipment required. The following tables on the minimal and additional safety requirements for the management of emergencies in allergy office are from the CSACI position paper on safety standards for the management of office emergencies (in redaction)

Minimal safety medications, equipment, and supplies	
Category	
Vital sign assessment	- Stethoscope - Sphygmomanometer and blood pressure cuffs - Oxygen saturation monitor - Personal protective equipment (gloves, mask, eye shield) - Watch or clock
Medications	- Intramuscular epinephrine (3 doses) - Glucagon or vasopressin for adults on beta blocker - Salbutamol (with MDI and spacer or nebulizer) - Second generation antihistamine
Airway	- Oropharyngeal airway (adult and pediatric)
Breathing	- Self inflating bag-valve-mask (adult and pediatric) - Disposable face masks (adult and pediatric) - Oxygen tank - Oxygen extension tubing - Oxygen nasal cannula - Non-rebreather mask (adult and pediatric)
Circulation	- Tourniquet - Tape - Alcohol swabs - Drip chamber - Syringe with needles - T-connector - Extension tubing - Intravenous 0.9 normal saline (two 1-L bags) A method to establish parenteral access which could include any of: - Intravenous butterfly needles - Indwelling catheters -Intraosseous devices
Other	- Written anaphylaxis management protocol - Flow chart for recording times and events -911 script for office staff to use
Additional equipment and medications to consider, depending on provider experience, skill, and location	
Category	
Vital sign assessment	- Automated BP cuff, HR, and O2 sat monitor - 5-min timer
Airway	- Portable suction - Nasal airway - Laryngeal airway masks (LMA) with lubrication - Laryngoscope with blades, ET tubes, stylet and CO2 detector, tape and suction, and Magill forceps - Alternative airway devices (e.g., King Airway)
Breathing	- Nebulizer mask
Circulation	- Pediatric armboard - Set up for 3 way stopcock for pediatric fluid bolus - Intraosseous devices - AED
Medications for treatment of allergic conditions	- Ipatropium bromide (spacer with MDI or nebulizer) - Diphenhydramine IV - Corticosteroid for injection
Medications for treatment of non-allergic conditions	- Nitroglycerine spray - ASA - Naloxone - Lorazepam or diazepam - Glucose gel

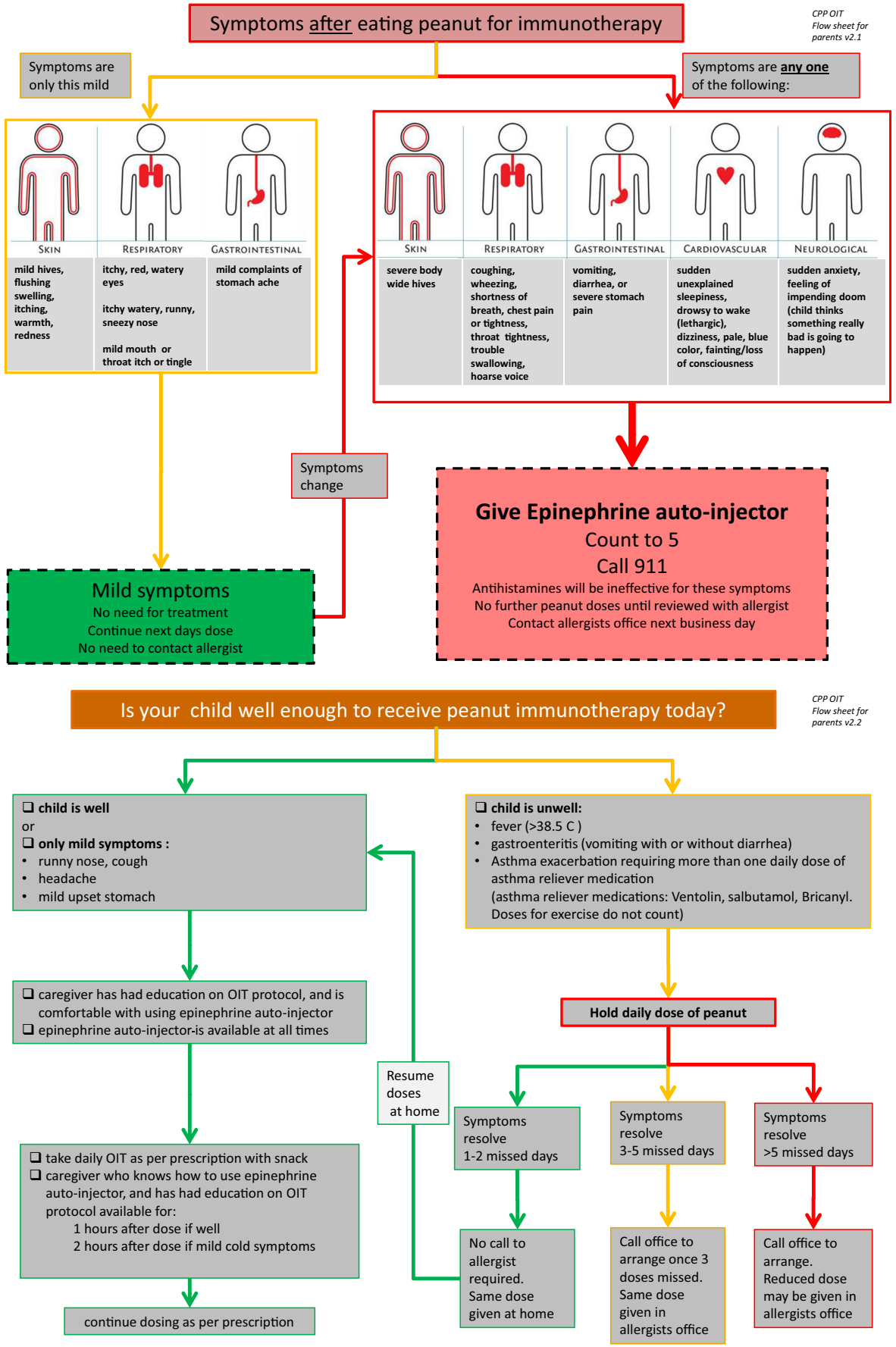

Fig. 1 CPP-OIT flow sheet for parents—daily dose instructions and side effect management. Reproduced with permission from Soller et al. [19]

centered outcome that has been successful in multiple OIT studies to date [53]. The goal of long-term sustained unresponsiveness is less important from a patient perspective, yet is often viewed by allergists as the only worthwhile primary outcome. The lower rate of achieving this physician centered outcome unfortunately results in allergists hesitating to offer a therapy that families still perceive high value in.

Some argue that OIT should not be performed outside research because in clinical trials, it has become mandatory to perform baseline OFCs to confirm the presence of food allergy. In the real world, however, it is neither practical (given long waiting lists for OFCs for example) nor safe (e.g., unnecessary to do a baseline OFC if recent convincing history of immediate reaction or anaphylaxis) to do baseline OFCs on every patient before initiation of OIT. Therefore, in the authors' opinion, in the real world where resources are inherently limited, baseline OFCs should be done when the diagnosis of food allergy is not anchored in a recent, convincing history, but is not necessary for patients with a high pre-test probability of food allergy.

Should Allergists Who Offer OIT Be On Call "24/7" for Their Patients?

In the authors' opinion, requiring 24/7 on call availability for all patients who wish to participate in OIT would be a significant barrier to physician acceptability and feasibility of implementing this therapy. In particular, for toddlers, where the real-world safety data is robust, the authors' opinion on on call availability is not required, nor was it required in the CPP-OIT protocol. The recommendation in the CPP-OIT protocol was to contact the physician/allied healthcare provider for issues related to OIT during the weekday. If there was a severe reaction, irrespective of time of day, the recommendation was to use the epinephrine autoinjector and proceed to the emergency room. Some physicians within our protocol elected to provide email availability after hours, which is an option that could be considered. In particular as demand for OIT increases and use of OIT outside of research becomes more mainstream, providing 24/7 availability is likely not sustainable. In the authors' experience, providing a patient algorithm that provides guidance around commonly encountered situations (such as illness or missed doses) reduces the need for on call availability as well. The higher risk of anaphylaxis with OIT in older children, adolescents, and adults, however, may require consideration of on call availability if offering OIT for those age groups.

Should Commercial/Licensed Products Be Used for Peanut OIT?

The CSACI guideline does not require the use of commercial OIT products for peanut OIT [30••]. This recommendation is based on several factors including the price of commercial peanut OIT products (approximately 100 times higher than a non-pharmaceutical-based approach) that results in a "significant additional and long-term expense without reducing base costs," as well as the assumption with commercial products that the treatment is lifelong (in contrast to a non-pharmaceutical approach that allows non-medicalization and ingestion of "regular food"). While commercial products, such as Palforzia (AR101), have been recently approved by the Food and Drug Administration (FDA) as a commercial peanut OIT product for use in the USA [54], no such commercial therapy is available in other countries such as Canada, and no commercial therapies are available for other common food allergens such as milk, egg, tree nuts, or sesame.

One rationale in favor of commercial products is the concern that "grocery store allergen variability" with non-pharmaceutical OIT might affect clinical outcomes. However, this was not found to be a factor that changed expected effectiveness with CPP-OIT. The CPP-OIT protocol allowed participating allergists to select from three different protocol options: Bamba® peanut butter puffs, peanut flour/powdered peanut butter compounded into capsules, or a hybrid of the previous two [20••]. While it was noted that there could be up to a 25% difference in peanut protein content between different Bamba packages (4 g/oz versus 5 g/oz), systemic reactivity to Bamba was very low [20••]. There is no data from CPP-OIT to suggest that grocery store allergen variability increases the risk of reactions in toddlers.

Should Biologics or Probiotics Be Used in Conjunction with OIT?

Studies have examined the use of omalizumab (anti-IgE) in conjunction with OIT, noting a short course of omalizumab with an accelerated 8-week buildup protocol to improve desensitization rates ($P < .01$) and reduce the rate of systemic reactions (if factoring in the higher dose of peanut that those randomized to omalizumab received) in school-aged peanut-allergic children [55]. Preliminary data also suggests that the anti-IgE mechanism of action can induce a Th1 and regulatory T cell response, potentially reversing established peanut allergy [56,57]. However, use of omalizumab is less feasible for some families due to cost, and may not be an acceptable intervention for all families [30••]. The CSACI guideline recommends that "recourse to omalizumab should occur responsibly and judiciously, as widespread use could jeopardize treatment sustainability" [30••]. Omalizumab could be considered in "challenging" cases, especially for short-term use in older children [30••]. Its use in the toddler age group is largely unnecessary due to the favorable safety profile of OIT in this age group and likely poor patient tolerability of this intervention [30••]. Other biologics in conjunction with OIT, such as

Oral Food Immunotherapy (OIT) Informed Consent Form

The following information is for families who may be considering oral food immunotherapy (OIT) as part of their food allergy treatment plan. The goal of OIT is to increase your child's ability to tolerate the food of concern (e.g. protection from accidental exposures). Treatment involves eating small amounts of the food on a daily basis. The amount of food eaten starts at a low dosage and then is gradually increased over a period of months until your child reaches the highest amount of food that has been prescribed by your doctor. Each dosage increase will be done in your allergist's office.

The benefit of OIT is the possibility of your child being able to eat the food without a reaction, e.g. being protected from reaction due to accidental exposures. Research suggests that quality of life improves during OIT. Very convincing preschool data came from a small U.S. research study that looked at 40 children aged 9-36 months with confirmed peanut allergy who were provided early peanut OIT. Almost 80% tolerated full servings of peanut after an average OIT period of 29 months [Vickery et al]. More recently, our "Canadian Preschool Peanut Oral Immunotherapy" study published safety outcomes in 270 preschoolers across the country [Soller et al]. We found that 243 children (90 per cent) reached the maintenance stage successfully. Only 0.4 per cent of children experienced a severe allergic reaction and 4% received epinephrine. Out of over 40,000 peanut doses, only 12 went on to receive epinephrine (0.03 per cent). Besides reporting on safety, we are currently analyzing effectiveness.

In the above studies on preschool peanut OIT, side effects were very common, but the majority were mild or moderate. Symptoms are generally more common when increasing the amount of food the child is ingesting (build-up phase) than once the child reaches the maintenance phase. Abdominal pain is very common, as are skin symptoms such as hives and rash, and other abdominal symptoms (nausea, vomiting). A recent study from Stanford University showed that adopting the mindset of mild or moderate symptoms as "expected" and a "signal of desensitization" actually improves OIT experience and outcomes, i.e.) overcoming mild symptoms are not something to be discouraged by, but rather a sign of progress.

The risk of a severe anaphylactic reaction appears to be very dependent on the age of your child. Our preschool peanut OIT data (average child 23 months of age) showed only 0.4% had a severe reaction and 4% received epinephrine, whereas a systematic review of older children (average 9 years old) showed 16.5% had a severe reaction and 8% received epinephrine. Despite this, for some older children the benefits of OIT may still outweigh the risks (e.g. older child experiencing recurrent anaphylaxis despite diligence with avoidance.) All severe reactions would require use of an epinephrine autoinjector as prescribed by your child's pediatric allergist and outlined in your child's anaphylaxis action plan. These reactions would then require you to call 911 or go to the nearest Emergency room immediately. Mild reactions may be treated with a non-sedating antihistamine such as Reactine or Aerius liquid if desired. If a severe reaction occurs, the dose of food will be adjusted. All severe reactions must be communicated with your pediatric allergist on the next business day.

There is a small risk of eosinophilic esophagitis (EoE) (2.7%), or inflammation in the esophagus. This has been seen in some studies on food OIT, but it is unclear if those same individuals would have developed EoE even without using food OIT. The EoE has not always resolved when the trigger food was removed from the diet.

If during OIT you decide to switch from one food product to a different product, it is recommended that the first dose of the new product be given in your allergist's office.

All children receiving OIT must wait in their allergist's office for 30-60 minutes after each dosage increase. If there is a reaction, a longer wait time may be required for medical treatment. Children receiving OIT will have repeat skin prick testing and blood testing done, likely about once a year, to monitor changes while on OIT. Oral food challenges to the food of concern will also be done at various time points while on OIT, to see if the treatment has worked and whether your child will be able to eat a full serving of the food. At this point in time, it is important to eat the food on a regular basis even after passing an oral food challenge, as there is a risk of the food allergy coming back if the food is no longer eaten regularly.

Fig. 2 Sample informed consent

There are some suggested contraindications to OIT, such as a previous very severe life-threatening anaphylactic reaction to the food (involving such things as low oxygen levels, low blood pressure, altered level of consciousness), an allergy to an ingredient in the food, severe atopic dermatitis, poorly controlled asthma, or asthma that requires higher doses of inhaled steroid medications for control. In addition, your allergist may consider other contraindications such as difficulty in communicating in English, chaotic households, or inability of parents to previously administer an epinephrine injector when indicated.

Please notify the allergy office if your child starts any new medications or has any health changes over the period of OIT. Changes to health such as an asthma exacerbation may increase risk of a reaction to OIT and should be communicated with your allergist. Please notify the allergy office if your child misses a dose of the food at home. Your child will need to have their epinephrine autoinjector available to them at all times.

Your child's medical information may be used in the future to examine the results of OIT, as part of quality improvement. No identifying information will be used at any time. All personal information will be kept strictly confidential.

If you have concerns about anything in this consent, please discuss them with your pediatric allergist. Otherwise, please sign below.

I have read the consent form and understand the information it contains. I have had the opportunity to ask questions regarding the risks and benefits of OIT, and my questions have been answered. I hereby give consent for the patient designated below to be given OIT over a period of time. I also give authorization and consent for treatment for my allergist and staff to treat any reactions that may occur.

Name of OIT patient:

Legal Guardian signature:

Date:

Witness:

Date:

References:

Vickery BP, Berglund JP, Burk CM et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol* 2017;139:173-81.

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Fig. 2 (continued)

dupilumab (anti-IL4 receptor alpha) are being studied and may provide some benefit such as treating more than one atopic condition at once (including atopic dermatitis) [6].

Another therapy that is under investigation is the use of probiotics in combination with OIT. Preliminary studies have suggested possible increased likelihood of inducing sustained

Table 4 Generic sample protocol for buildup of any food OIT allergen to ~ 300-mg maintenance dose. Eight to 11 visit buildup schedule

Dose number	Protein (mg)	Actual weight or volume of food	Interval (weeks)
Optional	1		2–4
Optional	2.5		2–4
Optional	5		2–4
1	10		2–4
2	20		2–4
3	40		2–4
4	80		2–4
5	120		2–4
6	160		2–4
7	240		2–4
8	300		2–4

unresponsiveness [8]. The aforementioned PP-OIT double-blind randomized controlled trial of *Lactobacillus rhamnosus* in combination with peanut OIT in children with peanut allergy noted significantly higher rates of SU in those in the probiotic group than in those in the placebo group (82.1% versus 3.6%, respectively; $P < .001$), with high rates of SU at a mean of 4 years after completing treatment (58% versus 7%; $P = .012$) [14]. However, a limitation of PP-OIT to date is lack of a direct comparison between peanut OIT, and peanut OIT in combination with probiotics, making it difficult to assess whether there is a true additive effect from probiotics [8]. Additionally, Vickery et al.'s outcome in preschoolers of 78% in the intention-to-treat analysis achieving 4-week SU over a median of 29 months appeared to be equally impressive [12••].

What We Still Need

There are limitations to the current clinical outcomes that have been used in OIT studies to date [6]. In particular, while randomized controlled trials provide internal validity, this is done at the extent of external validity and real-world applicability. CPP-OIT has provided a measure of real-world safety and effectiveness for peanut OIT [22••], but other real-world studies are required. Moving forward, the validation and incorporation of patient-centered outcomes into studies would help solidify patient goals, and their attainment, with OIT [6]. Pragmatic observational studies can provide a measure of "real-world" adherence, and assist in developing and measuring implementation outcomes such as acceptability, feasibility, and tolerability. The association between OIT and EoE also requires further investigation, including whether EoE should be an absolute contraindication to offering OIT. In selected cases (especially if IgE-mediated food allergy develops as an iatrogenic complication of dietary elimination to treat EoE) such as the case we published recently, it may be reasonable for patients to choose the outcome of worsened EoE (and possible need for swallowed topical corticosteroids) over the risk of untreated anaphylactic food allergy by choosing OIT [27]. The time has come for all allergists to accept that OIT outside research is here to stay, given the increasing number of allergists offering OIT in clinical practice [18]. Instead of hoping for OIT to revert back to a research-only phase, our focus should be on ensuring that the safest and most effective evidence-based protocols are used in clinical practice. Additionally, there needs to be recognition among allergists that there is no one-size-fits-all when it comes to regular food products versus FDA-approved commercial products, with both approaches having merit depending on the clinical context. If our specialty can finally get past these controversies, patients will be able to move beyond all the mixed messages on whether OIT is "right or wrong," and recognize that OIT outside research is indicated when the benefits outweigh the risks for a particular patient.

Top 10 List of How to Incorporate OIT into Your Clinical Practice

1. Ensure you are comfortable performing oral food challenges (OFCs) before starting OIT, as OFCs may be needed at baseline to confirm diagnosis, and are necessary at follow-up to assess extent of desensitization or tolerance.
2. Ensure you have the proper safety equipment required (same safety equipment needed for OFCs and OIT) (Table 3).
3. Make sure those with asthma are well controlled before starting OIT.
4. Have pre-existing informed consent, protocol, and adverse event sheets that can be used with each family.
5. At each follow-up visit, it is important to consider co-factors of anaphylaxis and risk factors for eosinophilic esophagitis.
6. On call availability is not required if offering OIT to preschoolers, but may be necessary when offering OIT to older children, adolescents, and adults.
7. There is a role for both regular food products and FDA-approved commercial products for OIT, depending on variables such as cost, the family's financial situation, and which allergens the patient is allergic to.
8. A past history of anaphylaxis is not a contraindication to offering OIT, and offering it should be based on a careful assessment of benefits versus risks, plus shared decision-making with patient and family.
9. Consider offering patient information sessions on OIT, to more efficiently provide patient counseling and instruction

10. Start small, to build OIT into your practice in a sustainable way.

Conclusion

Oral immunotherapy has accumulated evidence as a safe and effective therapy with high rates of desensitization and sustained unresponsiveness. Its safety profile is especially favorable in preschoolers, such that in the authors' opinion, it should be considered standard of care. In contrast, newer evidence suggests the risk of anaphylaxis from allergen avoidance is higher than previously thought, and epinephrine appears to be rarely used in the real world by patients practicing avoidance. The newly published CSACI OIT guidelines provide North America with is first OIT guideline, which not only provide recommendations for offering OIT outside research but also focus on ethical considerations. Baseline oral challenges have been mandatory for clinical trials, but for real-world studies and clinical practice, outside research baseline oral challenges should be based on true clinical need for establishing diagnosis where there is unclear history, due to resource limitations. Protocols, sample forms, and safety measures such as the ones included in this article provide a practical guide for the clinician aiming to incorporate OIT into their clinical practices. Future studies should continue to provide pragmatic observational data to facilitate successful implementation, especially in terms of safety and adherence. While ongoing controversies about offering OIT will remain, the combination of data from randomized controlled trials and real-world studies demonstrate there is a role for both FDA-approved and regular food products in the provision of OIT care, especially when shared decision-making is needed to account for variables such as healthcare system resource limitations and family socioeconomic status. With increased options for OIT treatment and greater uniformity in practice over time, the future is bright for implementing OIT safely to patients where benefits outweigh risks.

Declaration

Conflict of Interest EMA received an unrestricted educational grant from Novartis and is a member of the scientific advisory board for Food Allergy Canada. SCE and SBC have nothing to declare. LS participates in research sponsored by DBV technology. ESC has received research support from DBV Technologies; has been a member of advisory boards for Pfizer, Pediapharm, Leo Pharma, Kaleo, DBV, AllerGenis, and Sanofi Genzyme; is a member of the healthcare advisory board for Food Allergy Canada; was an expert panel and coordinating committee member of the National Institute of Allergy and Infectious Diseases (NIAID)–sponsored Guidelines for Peanut Allergy Prevention; was co-lead of the CSACI oral immunotherapy guidelines; and was a member of the committee for the American Gastroenterological Association & AAAAI/ACAAI Joint Task Force guidelines on the management of eosinophilic esophagitis.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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