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FOOD ALLERGY

Clinical Principles & Practical Pathways

An Evidence-based Guide to Modern Allergy Care

Under the Academic Aegis of

INITIATIVE FOR SLEEP, ASTHMA AND ALLERGY SCIENCES

ISAAS



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CHAPTER 17

Food Allergy Immunotherapy in Clinical Practice: Global Perspectives, Resource-limited Settings and Future Directions

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INTRODUCTION

Food allergy has traditionally been managed through allergen avoidance, emergency preparedness, and treatment of accidental reactions. Over the past decade, however, food allergy immunotherapy and biologic therapies have shifted the therapeutic landscape toward active disease modification and increased protection against accidental exposure. Oral immunotherapy (OIT) currently has the largest evidence base, while biologics, epicutaneous immunotherapy (EPIT), sublingual immunotherapy (SLIT), lower-dose approaches, and combination strategies continue to evolve. Translation of these therapies into routine practice requires careful patient selection, shared decision-making, realistic treatment goals, structured monitoring, and appropriate emergency preparedness. This chapter focuses on the practical implementation of food allergy immunotherapy, current international recommendations, challenges in resource-limited settings, and emerging strategies that may shape future personalized care.

CURRENT GLOBAL LANDSCAPE OF FOOD ALLERGY IMMUNOTHERAPY

The therapeutic landscape of food allergy (FA) has undergone a rapid shift with options such as immunotherapy and biologics, providing allergists with tools that can be used to treat FA as opposed to being limited to life-long avoidance. Immunotherapy is the most well studied therapy for FA, which involves long-term exposure of controlled amounts of the allergen to promote a tolerogenic immune response. While immunotherapy often refers to subcutaneous immunotherapy (SCIT) in allergic rhinitis where the allergen is delivered via an injection, SCIT has not been effective for FA, where oral immunotherapy (OIT) is most common. More recent studies have highlighted the potential of directly targeting the underlying allergic pathway with therapies such as biologics, which have opened up exciting new therapeutic opportunities. The principles, protocols, efficacy, and safety of OIT and other emerging therapies are discussed in detail in Chapter 16. The present chapter builds upon these concepts, with a particular emphasis on their translation into routine clinical practice, global recommendations, resource-limited settings, and future therapeutic directions.

Introduction to the Basics of Oral Immunotherapy

Oral immunotherapy emerged as the first well-accepted FA therapy aside from life-long allergen avoidance. In comparison to other therapeutic approaches, OIT can provide a high degree of protection with the potential for lasting protection after cessation of therapy. During OIT, the patient consumes gradually increasing amounts of allergen under medical supervision, up to a predefined maintenance dose, which the patient will continue to consume for at least several months. The landmark PALISADE study investigated the potential of the peanut OIT product AR101 (also known as Palforzia®). After 24 weeks of peanut OIT, 67.2% of participants receiving AR101 were able to ingest a dose of 600 mg peanut protein (cumulative dose of 1,044 mg) without dose-limiting symptoms in comparison to only 4% in the placebo group. In the POISED peanut OIT study, 104 weeks of peanut OIT showed similar efficacy, with over 80% of participants receiving maintenance doses of 4 grams of peanut protein therapy successfully passing a 4 gram double-blind, placebo-controlled food challenge (DBPCFC). The most common adverse event (AE) was gastrointestinal (GI), followed by skin, with AEs decreasing over time.

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Oral immunotherapy can be difficult for patients due to the high frequency of GI symptoms (although mostly mild), risk of food aversion, long-treatment duration, and timing restrictions for OIT dosing. In PALISADE, nearly all participants experienced at least one AE during the study (98.7%), with 52.2% experiencing abdominal pain. 24.5% of the participants receiving AR101 discontinued the study with AEs being the most commonly indicated reason (50%). As a result, OIT is best suited for highly motivated patients that are heavily impacted by their FA.

Initiating Oral Immunotherapy in Early Childhood

Increasing evidence supports greater efficacy of OIT when started in early childhood rather than later in childhood or adolescence. Some of the earliest evidence of this came from the PALISADE study, which found that 24 weeks of peanut OIT in 4–17 year old children had a higher chance of being able to tolerate a dose of 600 mg (cumulative dose of 1,043 mg) of peanut protein than 18–55 year old adults (67.2 vs. 41.5%). Supporting this, other age-stratified findings have also been reported in peanut probiotic OIT (PPOIT-003), where desensitization and sustained unresponsiveness (SU) were more frequent in children 1–5 years (83% and 58%, respectively) than in those 6–10 years (67% and 37%, respectively). SU is defined as clinical remission of FA over a certain period of time after discontinuation of OIT. In IMPACT, remission in the per-protocol population declined progressively with increasing age at enrollment—remission was most common in children screened at 12–23.9 months and decreased in those enrolled at 24–35.9 months and 36–47.9 months. Collectively, these data suggest that earlier initiation of OIT may improve outcomes, while also raising the practical question of how early treatment can be started. The POSEIDON study found that approximately 1 year of peanut OIT desensitized 73.5% of 1–4 year olds to 1,043 mg cumulative peanut protein. In the IMPACT study, peanut OIT for 134 weeks desensitized 71% of 1–3 year old children to 5,005 mg of peanut protein and 21% achieved SU after 26 weeks of treatment discontinuation. The DEVIL study looked at peanut OIT in 9–36 months old children and found that 81% of participants were desensitized to 5,000 mg of peanut protein after up to 3 years on maintenance with 78% achieving SU after 4 weeks of avoidance. Together these studies suggest that OIT as early as 9 months of age is feasible and may allow for a greater degree of desensitization.

Position of Oral Immunotherapy in Contemporary Allergy Practice

Food allergy has become an increasing concern over the past few decades, which affects approximately 8% of children and 10% of adults worldwide, and has been increasing over time. Additionally, many children are allergic to multiple foods. Food allergen avoidance has long been the standard treatment of FA, which requires daily vigilance, and may lead to accidental exposure. OIT has been practiced for a very long time, with cases reported in the early 1900s. Not until the early 2000s were large, multicenter OIT studies conducted, showing very promising results. This led to the approval of AR101 (Palforzia®), the first approved OIT product in the United States (US).

Currently, OIT is being used by allergists all around the globe; however, FA prevalence varies from country to country. This therapy is often used as an option by specialized allergists with proper training and safety management protocols, as anaphylaxis is an inherent risk in treatment. OIT is prioritized in younger populations, showing greater efficacy. Choosing OIT needs to involve a shared decision-making approach (SDM) and candidates often need to be highly motivated for treatment to be successful. Goals need to be discussed, with some wishing to mitigate the risk of accidental exposure, while others may wish to incorporate offending foods into their diet. With increasing knowledge and studies on OIT, along with increased provider training and safety management workflows, this treatment option will likely expand in accessibility. Biologics are also being studied to use alongside OIT, with hopes to decrease AEs as well as the time it takes to reach a maintenance dose.

CURRENT INTERNATIONAL RECOMMENDATIONS

European Academy of Allergy and Clinical Immunology

The European Academy of Allergy and Clinical Immunology (EAACI) has produced the most comprehensive recommendations on immunotherapy to date, officially published in a 2025 guideline on the management of immunoglobulin E (IgE)-mediated FA. Based on a 2024

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systematic review and meta-analysis of 121 studies, the publication provides graded recommendations according to the type of immunotherapy, the specific FA, and the age of the allergic individual. OIT can be recommended as a therapeutic option for IgE-mediated peanut allergy to help achieve desensitization in children and adolescents of all ages. With IgE-mediated cow's milk or egg allergy, this recommendation is limited to children over the age of 4 years old and adolescents, mostly due to the fact that these allergies are often outgrown. There is insufficient evidence on sustained tolerance to allergens in the long-term after discontinuing OIT, suggesting patients will require ongoing maintenance dosing, while other food allergies are yet to have any EAACI-specific guidance. Benefits of OIT are also thoroughly discussed, including OIT's potential in increasing allergen reaction thresholds and therefore decreasing the risks of accidental exposure. Limitations include the need for careful monitoring of patients for adverse reactions or new symptoms of eosinophilic esophagitis (EoE), especially when increasing doses.

The EAACI guidelines are also the first to conditionally recommend sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT) for IgE-mediated peanut allergy with moderate-to-high certainty. However, neither are currently available for clinical use in Europe, limiting the practicality of this recommendation. Biologics such as omalizumab are supported for the purpose of desensitization in adults and children with any confirmed IgE-mediated FA. Despite omalizumab being Food and Drug Administration (FDA) approved for treatment of IgE-mediated FA in the US, no biologics are currently licensed for this purpose outside of the US.

British Society for Allergy and Clinical Immunology

The British Society for Allergy and Clinical Immunology (BSACI) does not have published guidelines on FA immunotherapy such as EAACI. Their allergen-specific guidelines on cow's milk, peanut and tree nut, and egg were published between 2014 and 2021, with limited scope on immunotherapy. However, the BSACI does have generalized recommendations incorporated into their website's FA resources. Mostly agreeing with the main points of the EAACI guidelines, they place a greater emphasis on the accessibility and delivery of OIT, recommending that only experienced allergists and specialist allergy centers should deliver OIT. However, access to OIT in the United Kingdom remains limited as it's mostly only available to patients through private practice or clinical research trials. Following European approval of Palforzia® for the treatment of confirmed peanut allergy in children 4–17 years in 2022, the BSACI published a Delphi consensus on the use of this commercial peanut OIT product. It summarizes guidance on patient selection, dose escalation, maintenance therapy, and safety monitoring, as well as considerations for how it should be implemented across the National Health Service (NHS). Despite the subsequent withdrawal of Palforzia® in January 2026 for commercial reasons, the document guidance reflects the BSACI's focus on practical implementation of immunotherapy within the context of the United Kingdom's healthcare context rather than broad recommendations regarding immunotherapy.

World Allergy Organization

The World Allergy Organization (WAO), like the BSACI, has food-allergen specific guidelines. Most notably, the Diagnosis and Rationale for Action against Cow's Milk Allergy guideline update in 2022 specifically evaluates the evidence surrounding OIT for IgE-mediated cow's milk allergy. Compared to EAACI, WAO is more cautious when recommending cow's milk OIT, underlining the need for SDM as well as a patient population who value the potential benefits of increased tolerance over the risks of treatment-related adverse effects. Other forms of immunotherapy, such as EPIT, remain investigational and are not recommended for cow's milk allergy outside of research settings. The 2025 WAO manifesto on biologics therapies for food allergies expands beyond cow's milk allergy. It acknowledges the growing evidence supporting OIT while highlighting limitations including treatment burden, AEs, and the need for long-term maintenance. The manifesto mainly advocates for wider global approval and access to biologics such as omalizumab for food allergies, especially as an adjunct or alternative to OIT in selected patients.

American Academy of Allergy Asthma and Immunology

The American Academy of Allergy Asthma and Immunology (AAAAI) does not have a formal clinical practice guideline, but has recommendations spread out across its website's educational resources, like the BSACI. "The Current State of Oral Immunotherapy" was

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last updated in May 2026, and echoes similar nuances regarding OIT in FA, taking specific care to explain what OIT involves while hinting at the growing research around its utility. Despite OIT not necessarily being the standard FA therapy, it is an accepted therapeutic option that should be delivered by experienced allergists. EPIT and SLIT are recognized as investigational, with limited evidence in comparison to OIT, and not currently recommended as routine alternatives. Consensus-based guidance from 2025 by AAAAI agrees with most other international bodies that biologics such as omalizumab are a promising therapy for FA, either in combination or alternatively to OIT.

Japanese Society of Pediatric Allergy and Clinical Immunology

The Japanese Society of Pediatric Allergy and Clinical Immunology (JSPACI) has most recently updated their formal guidelines on IgE-mediated allergies in 2020. The Japanese Pediatric Guideline for Food Allergy (JPGFA) classifies food allergies into four types—(1) neonatal and infantile GI allergy, (2) infantile atopic dermatitis associated with FA, (3) immediate-type of FA, and (4) special forms of immediate-type of FA such as food-dependent exercise induced anaphylaxis and oral allergy syndrome. These guidelines define these four classifications and detail epidemiology in Japan and diagnostic approaches. The JPGFA states that avoiding allergenic foods during pregnancy or breastfeeding is not recommended. It also recommends against delaying consumption of allergenic foods beyond 5–6 months. Early allergen introduction is recommended under medical supervision in select populations, namely in countries with high onset of peanut allergy. However, careless early introduction of risk-associated foods is not recommended as anaphylaxis has been reported. While OIT is recognized as an investigational therapy and not standard approved treatment, its use has rapidly increased over the past decade. The JPGFA advises against careless implementation of OIT as AEs are common and any increased tolerance seen may be reversed once OIT is discontinued. They also acknowledge safety response is inadequate at some treatment facilities. The Food Allergy Committee states OIT is indicated for those with an oral food challenge (OFC) diagnosed FA in which early acquisition of tolerance is not expected naturally.

Areas of Consensus and Controversies

Multiple international organizations such as the EAACI, BSACI, WAO, and AAAAI have generally aligned their views on food allergen immunotherapy, supporting OIT as a disease-modifying treatment for certain patients with IgE-mediated FA, although not all organizations recommend it as a part of routine clinical practice **(Table 1)**. This is through increasing the threshold of allergic reactions and decreasing the risk of accidental exposure. However, the JSPACI recommends introducing OIT only with the utmost caution. The associations all concur that this therapy should be delivered by specialized allergists with the capacity and expertise to mitigate any adverse reactions associated with OIT dose initiation, escalation, and maintenance. Desensitization is most preserved through continuous maintenance dosing, and so SDM between the clinician, patient, and family is vital to ensure success.

Despite there being a broad consensus on the role of immunotherapy in FA treatment, there are still some areas of uncertainty within the field. While EAACI conditionally recommends other forms of immunotherapy for peanut allergy, other organizations regard EPIT and SLIT as promising but investigational, needing further research to show its long-term effects, safety, and role in routine clinical practice. Furthermore, accessibility and implementation of OIT currently vary considerably between countries and regions, depending on their healthcare systems, funding, and availability of expert allergists or commercial OIT options. Similarly, omalizumab has been recognized internationally as a promising adjunct or alternative to OIT for FA but has only been approved for this purpose in the US, highlighting the gap between evidence-based recommendations and execution into clinical practice.

There appears to be no agreement on the optimal age of when to initiate OIT, possibly because of how individualistic to the patient this might be, and because the evidence around this continues to evolve. Current international recommendations fail to mention the role of immunotherapy in patients with multiple FA, while WAO and AAAAI have advocated for the use of biologics in those with multiple FA, with or without OIT. Finally, there is no universally accepted definition of OIT treatment success. Relevant outcomes may include desensitization, sustained unresponsiveness after treatment interruption, reduction in accidental-reaction risk, dietary liberalization, and improvement in patient-reported quality of life.

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TABLE 1: International Society Recommendations for emerging food allergy (FA) therapies.

- International Society Recommendations for Emerging food allergy (FA) therapies.
- Comparative guidance across major allergy societies, by therapy and organization.

	EAACI (formal IgE-mediated FA guidelines)	*BSACI (food-specific guidelines + general recommendations)*	*WAO (food-specific guidelines + biologic manifesto)*	*AAAAI (general resources)*	*JSPACI (formal FA guidelines)*
Peanut OIT	Recommended, children all ages and adolescents	Promising results; still investigational	No guidance	Investigational; shared decision-making	Investigational, increasing use; caution advised
Cow's milk OIT	Recommended, >4 years and adolescents	Not recommended for routine practice	Recommended with shared decision-making	Investigational; shared decision-making	Investigational, increasing use; caution advised
Egg OIT	Recommended, >4 years and adolescents	Not currently recommended	No guidance	Investigational; shared decision-making	Investigational, increasing use; caution advised
Other food OIT	No guidance	No guidance	No guidance	Further studies needed	Wheat OIT also in use in Japan
SLIT	Recommended for peanut allergy, children and adolescents	Not recommended; deemed ineffective	No formal recommendations	Investigational	No guidance
EPIT	Recommended for peanut allergy, children and adolescents	Not currently recommended	Investigational in milk allergy	Investigational	No guidance
Omalizumab	Use supported, children and adults	Further studies required	Advocates wider global approval	Promising therapy	No guidance
Multifood FA	No guidance	No guidance	No guidance	No guidance	No guidance

Recommended | Investigational/Promising | Not recommended | No guidance

(AAAAI: American Academy of Allergy Asthma and Immunology; BSACI: British Society for Allergy and Clinical Immunology; EAACI: European Academy of Allergy and Clinical Immunology; EPIT: epicutaneous immunotherapy; FA: food allergy; JSPACI: Japanese Society of Pediatric Allergy and Clinical Immunology; SLIT: sublingual immunotherapy; OIT: oral immunotherapy; WAO: World Allergy Organization)

EMERGING THERAPIES FROM A PRACTICAL PERSPECTIVE

Building on the international consensus, particularly WAO and AAAAI's advocacy for biologics in patients with multiple FA, this section reviews the practical evidence behind the field's most active emerging strategies—omalizumab, dupilumab, lower-dose immunotherapy approaches, and the use of real-world foods to make these therapies more accessible.

Omalizumab-facilitated Multiallergen OIT

Most allergic reactions to food are IgE-mediated, making IgE an important therapeutic target in FA. Omalizumab, a recombinant humanized IgG1 monoclonal antibody, binds free circulating IgE and blocks its interaction with the high-affinity receptor Fc epsilon RI (FcεRI) on mast cells and basophils, reducing free IgE and receptor expression on effector cells and raising the threshold needed to trigger a reaction. In February 2024, omalizumab became the first biologic approved by the US FDA for reduction of allergic reactions, including anaphylaxis, following accidental exposure to one or more foods in patients with IgE-mediated food allergy. The FDA approval was based on OUtMATCH Stage 1, in which 16 weeks of omalizumab monotherapy allowed a majority of multifood allergic participants as young as 1 year of age to tolerate clinically meaningful doses of peanut and other trigger foods without dose-limiting symptoms.

Omalizumab has been studied both as a treatment for protection against accidental exposure and as an adjunct to facilitate updosing during mOIT. Exploratory analyses from OUtMATCH have begun to identify predictors of response, including baseline IgE, allergen-specific IgE,

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and other biomarkers, that may eventually support individualized selection for omalizumab therapy. This omalizumab-facilitated approach has been independently developed and replicated by groups across North America and Europe, summarized below.

Foundational Trials in Omalizumab

Early evidence for targeting IgE in FA came from a 2003 dose-ranging trial of TNX-901, an anti-IgE antibody related to omalizumab. Treatment in the trial increased the peanut threshold from approximately half a peanut (178 mg) to nine peanuts (2,805 mg) during OFCs. The first trial of omalizumab itself in peanut allergy was conducted in 2011 but was halted early after two participants experienced anaphylactic reactions during baseline food challenges, prior to receiving the study drug. Out of the 150 planned participants, only 26 enrolled, and although results suggested potential benefits, the study was underpowered to confirm it. It was not until nearly a decade later that the rationale for combining omalizumab with mOIT was established, in two trials from Andorf, Chinthrajah, and Nadeau.

In the MAP-X phase 2 trial, 4- to 15-year-old children allergic to two to five foods received omalizumab or placebo alongside mOIT. Omalizumab increased the proportion of participants able to pass an OFC to at least 2 g of food protein for 2 or more foods by week 36. It also decreased the time to maintenance dosing, while also improving safety, reducing the proportion of doses associated with AEs from 68 to 27%. Because MAP-X left open the question of durability, the same group ran M-TAX, a multisite follow-on trial enrolling 70 participants aged 5–22 years. After an identical open-label omalizumab with an mOIT induction phase, eligible participants at maintenance were randomized to continued dosing at 1 g or 300 mg per allergen, or to discontinuation (0 mg), before rechallenge at week 36. Sustained desensitization was significantly more likely with continued maintenance dosing than with discontinuation, indicating that some ongoing allergen intake is needed to preserve the gains achieved during omalizumab-facilitated induction.

The MAP-X showed that omalizumab could improve the tolerability and speed of mOIT updosing, while M-TAX showed that continued maintenance dosing was important for maintaining desensitization after omalizumab-facilitated induction. Together these studies provide practical evidence for omalizumab-facilitated mOIT by demonstrating that omalizumab can improve the tolerability and speed of updosing, while continued allergen dosing remains to maintain desensitization.

Independent Confirmation in North America

The MAP-X and M-TAX were not isolated findings. Bégin et al. independently demonstrated feasibility in a Canadian phase 1 rush mOIT protocol, in which 25 participants allergic to up to five foods received omalizumab for 8 weeks before and after initiating a rush updosing schedule. 19 of 25 participants tolerated all steps of the initial escalation day, reaching up to 1,250 mg of combined food protein with minimal or no rescue therapy, and the group reached maintenance dosing of 4,000 mg protein per allergen at a median of 18 weeks. In an analysis of 181 patients treated across three academic centers as part of a government-funded public OIT pilot program, Azzano et al. found that omalizumab dosing should be adjusted for body weight alone, independent of total IgE level, and that a higher ratio of allergen-specific to total IgE at baseline predicted greater risk of reactions after omalizumab was weaned. The omalizumab dose for FA in the US is currently calculated based upon both body weight and serum IgE, with investigations of optimal dose still underway.

The combination approach has also been validated for single-allergen OIT outside the multifood setting. In a randomized, double-blind, placebo-controlled CoFAR trial, Wood et al. studied omalizumab as an addition to milk OIT in children with cow's milk allergy. Omalizumab helped shorten the updosing phase and reduced dosing symptoms during the early build-up period, a phase where reactions were most frequent. These studies provide evidence for the use of omalizumab with both single and mOIT.

European Evidence: Italy and Denmark

Omalizumab-facilitated FA treatment has been independently replicated in Europe as well. In Italy, a real-life observational study was conducted with 15 children with severe asthma and multiple food allergies, finding that 4 months of omalizumab raised the mean allergen threshold for milk, egg, wheat, and hazelnut from 1,012.6 mg to 8,727 mg protein, with 70.4% of participants tolerating the complete challenge dose after treatment. The Omalizumab in Severe Asthmatics with Food Allergy (OSAFA) observational study by Arasi et al. evaluated

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the dose-related efficacy of omalizumab in children with severe FA and further supported weight-based dosing strategies.

In Denmark, Mortz et al. ran a single-center, randomized, double-blind, placebo-controlled trial of omalizumab in food-allergic children with a cumulative reaction threshold of 443 mg or less. Omalizumab significantly increased food allergen threshold compared with placebo, with the last tolerated dose after 3 months of treatment rising from a baseline range of 13–443 mg to as much as 44,000 mg of food protein in responders, while only two children in the placebo group showed any improvement. These findings provide additional support that omalizumab can increase food allergen thresholds across European patients with FA.

Head-to-head: Omalizumab Monotherapy versus Omalizumab-facilitated mOIT

OUtMATCH Stage 2 directly compared omalizumab monotherapy with omalizumab-facilitated mOIT for the first time. Participants who completed Stage 1 were randomized to mOIT plus placebo omalizumab, or omalizumab plus placebo OIT, following a 16-week open-label omalizumab lead-in. In the intention-to-treat analysis, omalizumab monotherapy was superior to mOIT, driven largely by a markedly higher discontinuation and adverse-event rate in the mOIT arm. Serious AEs occurred in 0% of the omalizumab group versus approximately 30% of the mOIT group. AEs requiring epinephrine were also more frequent with OIT. In the perprotocol analysis excluding dropouts, the two approaches performed similarly, indicating that much of omalizumab's apparent advantage reflects superior tolerability rather than a ceiling on what OIT can achieve in patients who complete it. Omalizumab monotherapy is the safer default for many multifood-allergic patients, while omalizumab-facilitated mOIT remains reasonable for families who prioritize dietary liberalization and can tolerate a higher rate of reactions and discontinuation, or for those who prefer to not use an injectable medication.

Practical Implementation

In a phase 2, randomized, multiallergen omalizumab-facilitated OIT "real-life" study, participants received a fixed course of omalizumab before initiating OIT to two to five allergens, with maintenance doses of either 1,200 mg or 300 mg total protein. After 18 weeks, participants who reached a minimum of 60 mg per allergen transitioned from pharmaceutical-grade allergen powder to real-food equivalents dosed at home with household measuring tools. The transition to real-food equivalents may reduce the cost and practical burden of treatment outside of clinical trials. The OUtMATCH investigators have also published literature regarding the considerations for dosing, monitoring, and patient selection when implementing omalizumab-facilitated OIT in clinical practice. A related analysis has characterized how food reintroduction can be sequenced after a course of omalizumab. Together, this body of work is making omalizumab-facilitated mOIT an increasingly well-mapped pathway for routine practice rather than a purely investigational strategy.

Dupilumab

Allergic inflammation in FA is driven substantially by interleukin 4 (IL-4) and IL-13 signaling through the IL-4 receptor alpha subunit (IL-4Rα), making IL-4Rα a promising therapeutic target upstream of IgE itself. Dupilumab, a fully human monoclonal antibody against IL-4Rα, is already FDA-approved for moderate-to-severe atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyps, and EoE. Its current use has sparked considerable interest in its application to FA, particularly given the overlap between FA, atopic comorbidity, and OIT-associated EoE risk.

As monotherapy, a multicenter, open-label phase 2 study evaluated dupilumab in children with peanut allergy and found an acceptable safety profile with only modest effects on peanut threshold, suggesting dupilumab alone is unlikely to be desensitizing in the way omalizumab or OIT can be. As an adjunct to OIT, a pediatric peanut OIT study found that dupilumab improved GI tolerability during up-dosing without clearly accelerating desensitization on its own. A dedicated trial combining dupilumab with milk OIT for cow's milk allergy is underway to test whether these findings generalize beyond peanut.

Another approach, currently under research investigation, is the combination of dupilumab with omalizumab-facilitated mOIT. The COMBINE trial, a phase 2 randomized controlled study, was designed specifically to test whether adding dupilumab to omalizumab-facilitated mOIT increases the likelihood of SU and reduces mOIT-related AEs relative to omalizumab-facilitated mOIT alone. Preliminary results presented at AAAAI 2026 reported that adding dupilumab enhanced desensitization and reduced GI symptoms in omalizumab-facilitated mOIT. Further

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published data will help strengthen and clarify the role of this combination in routine clinical practice.

MICRODOSING STRATEGIES

Newer immunotherapy approaches have also explored whether lower doses of the allergen can provide meaningful protection while reducing treatment burden. These approaches include epicutaneous and SLIT, as well as OIT protocols that generally allow for the use of lower oral maintenance doses. Most of the clinical benefit of immunotherapy, raising the threshold needed to trigger a reaction, appears to plateau well below traditional gram-level OIT maintenance doses, while AEs and dropouts scale with dose, making dose-minimization an increasingly attractive strategy for routine practice.

Epicutaneous Immunotherapy

Epicutaneous immunotherapy delivers microgram quantities of allergen to intact skin via an adhesive patch, engaging epidermal Langerhans cells rather than the GI immune system and largely avoiding the systemic and GI exposure that drives OIT reactions. In the EPITOPE phase 3 trial, the Viaskin Peanut patch (DBV712) was evaluated in peanut-allergic toddlers 1–3 years of age. A meaningfully higher proportion of patch-treated toddlers achieved successful desensitization at month 12 compared with placebo. An open-label extension of EPITOPE showed sustained efficacy and safety with longer exposure, and the REALISE study specifically characterized long-term EPIT safety in an open-label active-treatment cohort. A Viaskin Milk patch has similarly been studied at varying doses in children with cow's milk allergy, with lower doses associated with better tolerability than higher doses.

The EPIT's appeal is safety and simplicity. It is a once-daily patch applied at home, with a comparatively low rate of systemic reactions, at the cost of a smaller absolute increase in tolerated dose than OIT typically achieves. These characteristics make EPIT an attractive investigational or emerging option for young children and families prioritizing a favorable safety profile and protection against accidental exposure, although availability and regulatory approval vary by jurisdiction.

Sublingual Immunotherapy

Sublingual immunotherapy uses microgram- to low-milligram-level doses of allergen, typically as a glycerinated extract held under the tongue and then swallowed, engaging oral mucosal dendritic cells. In the first randomized, double-blind, placebo-controlled multicenter trial of peanut SLIT, 70% of actively treated participants were responders at 44 weeks, compared with 15% of those receiving placebo. Responders were defined as participants able to tolerate at least a 10-fold increase in threshold, or 5 grams of peanut powder, despite receiving a maintenance dose of only 1,386 μg/day. Long-term follow-up of this cohort out to 3 years confirmed a favorable safety profile but showed desensitization was modest relative to OIT. Discontinuation was common, and only about 11% of participants achieved SU. More recent SLIT protocols have moved toward commercially available, grocery-store-sourced liquids and powders rather than pharmaceutical-grade extracts, materially lowering cost and improving accessibility, a shift discussed further in the real-world foods subsection below.

The smaller absolute thresholds of SLIT relative to OIT need to be weighed against its favorable safety and low day-to-day burden. SLIT may be considered in selected settings for patients whose primary goal is protection against trace or accidental exposure rather than unrestricted dietary inclusion, recognizing that availability and regulatory status remain limited.

Low-dose and Very-low-dose Oral Immunotherapy

A parallel strategy keeps the oral route but deliberately targets a maintenance dose well below the traditional benchmark. In one of the first trials to directly compare maintenance doses, preschool children undergoing early peanut OIT were randomized to a 300-mg or 3,000-mg daily maintenance target. SU at 4 weeks off therapy was achieved in a similar proportion of children in both arms (78% overall; 85% at 300 mg vs. 71% at 3,000 mg), suggesting the higher dose conferred no clear additional benefit in this age group. A subsequent multicenter, blinded study compared even lower 30-mg and standard 300-mg peanut protein maintenance doses head-to-head and found the 30-mg dose, roughly one-eighth of a peanut, produced desensitization gains and favorable immunologic changes similar to the 300-mg dose, with an improved safety profile. For patients with multiple food allergies, a very-low-dose multinut OIT protocol built to a maintenance dose of only 30 mg protein per nut across two to five nuts simultaneously and produced a significant increase in tolerated dose with a favorable safety profile in an open-label, single-arm study.

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These studies suggest that higher maintenance doses may not always be better, and that lower-dose regimens may also help reduce treatment burden and improve adherence. For many patients, particularly younger children, those with multiple food allergies, or those prioritizing safety and adherence over maximal threshold, a lower maintenance target can achieve clinically meaningful protection with fewer reactions, fewer escalation visits, and better long-term adherence, making dose-minimization an appealing direction for the field. Despite this, appropriate maintenance dose may vary between patients.

Personalizing Food Allergy Therapy for the Patient

Biological therapies, OIT, EPIT, and SLIT are all pathways in treating patients with food allergies. They each have different dosing requirements, benefits, and limitations. Treatment selection should take into account factors such as a patient's age, comorbidities, risk tolerance, and treatment goals, with emphasis on adhering to treatment regimen. Patients may also have the ability to transition from one therapy to another as their needs change.

Epicutaneous Immunotherapy-to-oral Immunotherapy and Sublingual Immunotherapy-to-oral Immunotherapy Transitions

Because EPIT and SLIT both deliver substantially lower allergen exposure than OIT, they are increasingly used as lower-risk induction strategies with a planned transition to OIT once a patient has demonstrated tolerance and the family is ready for a more intensive protocol. A review addressing the practicalities of transitioning peanut-allergic patients from epicutaneous to OIT outlines dosing considerations and safety monitoring for this handoff. SLIT-to-OIT transitions have also been studied, though the approach is less well studied than EPIT-to-OIT transitions.

Biomarkers Guiding Individualized Selection

A more mechanistic layer of personalization is emerging from biomarker work aimed at predicting which patients are likely to succeed with, or safely tolerate, a given therapy. In the POISED trial cohort, baseline epitope-specific IgE profiles were predictive of which patients would go on to achieve SU or a high threshold 1 year after peanut OIT. Separately, HLA-DR+ regulatory T cells and IL-10 have been associated with successful versus unsuccessful desensitization outcomes. Neither biomarker has been used prospectively to select therapy in routine practice, but both point toward a near-term future in which pretreatment immune profiling could help clinicians recommend OIT versus a lower-intensity modality, or anticipate which patients may need adjunct biologic support.

In practice today, personalization is largely driven by factors such as age, presence of EoE or other GI comorbidity, and the number of coexisting food allergies. Family goals and risk tolerance are also important, including whether the goal is protection against accidental exposure or free dietary inclusion of the allergen.

Using Real-world Foods for Therapy

A challenge with traditional immunotherapies such as SLIT or OIT can often be the cost. Pharmaceutical grade food powders are available for OIT and glycerinated food extracts for SLIT and while these are convenient for dosing and standardization, they can be prohibitively expensive. Therefore, more accessible and affordable options such as powders or liquids found in grocery stores have been used in a variety of studies. Examples of real-world foods, sometimes referred to as retail food equivalents, could include peanut puffs or peanut flour. Using real-world foods can be a more practical treatment option. Furthermore, Palforzia® was a prescription OIT product used for peanut desensitization in the US. However, this FDA approved therapy was recently discontinued. Since this was the only FDA approved OIT treatment, exploring real-world alternatives for OIT is necessary for FA patients seeking treatment.

The CAFETERIA study was one such trial where commercially available peanut products were used for food challenges and OIT. In the screening DBPCFC for the study, instead of using pharmaceutical grade peanut flour, commercially available peanut flour was used to evaluate the patients' threshold. Following the DBPCFC, participants who reacted at certain dosages were randomized to either peanut avoidance or ingestion. Participants in the ingestion group were able to use easily purchased peanut butter from the store and measure doses at home. Once participants in the peanut OIT group could tolerate at least one-half teaspoon of peanut butter, they could switch to other dose-equivalent peanut products such as peanut butter candy. At the end of the

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study, researchers found that all of the ingestion group participants who did the DBPCFC could tolerate 9,043 mg of protein while only 10% could tolerate the 9,043 mg of protein in the avoidance group.

Another example using real-world foods for OIT is a phase 2, randomized mOIT with omalizumab "real-life" study conducted by Sindher et al. In this study, participants were first treated with fixed-dose omalizumab before initiating OIT for two to five allergens. Total maintenance doses for participants were either 1,200 mg or 300 mg. After 18 weeks of treatment, participants transitioned to real-food protein equivalents as long as they had reached a minimum of 60 mg of each allergen. Participants then dosed at home using readily accessible real-world foods with measurement utilizing household tools. This may include having one-quarter of a peanut for the 60 mg dose. The study outlines the measurements of the doses participants were to use for maintenance if they met the requirement to switch to real foods. This demonstrates the ability to begin OIT with pharmaceutical grade allergen protein powder and eventually transition to easily accessible and cost-effective foods.

The OUtMATCH trial evaluated whether omalizumab injections with mOIT or omalizumab injections alone would allow participants with multiple food allergies to consume food in a DBPCFC without dose-limiting symptoms. Stage 3 of the study investigated post-treatment safety with daily dietary consumption of up to three allergens. Findings demonstrated that after a year of treatment with omalizumab alone or omalizumab facilitated mOIT, >60% were regularly eating their allergic foods, with no significant difference between the groups. Groetch et al. focused on estimation of protein content of allergens such as peanut or wheat in retail food equivalents. A systematic approach was created and what they referred to as "retail food equivalents" were identified for the seven OUtMATCH allergens. The paper also includes a sample education handout for the participants which highlights real-world food equivalents and measurements to use. The figure includes real-world foods such as peanut flour, Reese's Pieces Candies, peanut butter, and more.

Sublingual immunotherapy is another option in which real-world foods are being utilized. In clinical trials, SLIT generally includes providing a patient with a glycerinated allergen underneath the tongue every day for desensitization. Many SLIT trials have used real-world foods and have conducted OFCs, measured adherence, and more. Williams et al. considered practical aspects of using readily available food beverages and powders within their paper. Sample protocols for real-food SLIT dosing were created, including outlines of specific equations for both liquid-based allergens and powder-based allergens to measure out the doses. Peanut in powder form is an example of a powder-based allergen, while cow's milk is a liquid-based example. The protein dose the protocols used for maintenance was 2–4 mg of allergen protein daily. Furthermore, these sample protocols are based on food available in Canada from retailers. They also include adherence and OFC data from their site which has patients who have completed or are undergoing SLIT with real-world foods. Their study site had 305 real-food SLIT patients from 2020 to 2024 and 82% of survey respondents took the dose on a consistent basis.

A trial conducted by Soller et al. also used real-world foods for the SLIT doses and outlined the preparation process. The researchers describe how the doses were prepared fresh daily by mixing water with powder/flour or milk that are commercially available. This differs from other studies in which the peanut SLIT is instead composed of glycerol-saline with the peanut protein inside which is at a stock concentration from a pharmaceutical laboratory. Another study received their SLIT treatment through the same laboratory with a treatment consisting of sodium chloride, sodium bicarbonate, and nonroasted peanut. In this study, peanut powder and oat flour (placebo) were used in the DBPCFC. The SLIT treatment used in these studies which came from the laboratory demonstrate the difference between nonreal-world food SLIT treatments and using real-world food for SLIT.

Real-world foods have been used in many immunotherapy trials including both OIT and SLIT. The variety of uses for real-world foods in these allergy trials demonstrates the many possibilities for incorporation of real-world foods that are accessible for participants into allergy treatment.

IMPLEMENTING ORAL IMMUNOTHERAPY IN ROUTINE CLINICAL PRACTICE

Oral immunotherapy has become a popular and well-accepted clinical treatment option for patients with IgE-mediated FA. Treatment involves following a strict dosing regimen, which includes determined participation from patients and their caregivers, as well as follow-up visits with a clinical team. Before starting OIT, clinicians should

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consider the patient's clinical characteristics, treatment goals, and whether the dosing schedule is practical for the patient and family.

Patient Selection

Patient selection is an important first step in implementing OIT in routine clinical practice. Currently, there is no single "ideal" OIT candidate. However, OIT should be considered for patients with a confirmed diagnosis of IgE-mediated FA and for whom the potential benefits of increasing the threshold for their allergy outweigh the risks and treatment burden. Clinical factors such as age, allergen, severity of allergy, comorbid atopic disease, and likelihood of benefit should also be considered. A critical component to OIT implementation is also understanding the patient and family's lifestyle and whether they have the practical capacity to start OIT.

Oral immunotherapy involves regular dosing over an extended period, and patients and caregivers need to be able to follow the dosing regimen and associated safety precautions. Patient and family readiness, adherence, safety, and quality of life should be considered when determining whether OIT is appropriate, particularly given the treatment burden and potential adverse effects associated with treatment. The practical demands of OIT, including daily dosing and required clinic visits, should also be discussed with the patient and family before treatment is started as these factors can affect the maintenance dose and the degree of desensitization that is pursued.

Shared Decision-making

The decision to start OIT should be made through SDM between the clinician, patient, and family. Greenhawt et al. describe OIT as preference-sensitive care, where the decision to pursue treatment should take into account the potential benefits and risks, alternatives to OIT, and the practical demands of treatment, as well as what the patient and family hope to achieve. For example, a patient who is primarily concerned about accidental exposure may have different treatment goals from a patient who wants to expand their diet. These goals can influence the degree to which desensitization is pursued, and what maintenance strategy is selected. Laubach et al. stress that SDM should identify patient and family values that guide the selected OIT protocol and the subsequent maintenance strategy.

The discussion to start OIT should include the potential benefit of increasing the amount of allergen required to trigger a reaction, as well as the risks and burdens associated with treatment. Patients also need to understand that OIT is not a cure for food allergies and that any desensitization requires long-term allergen exposure via immunotherapy. It is important for clinicians to explain that protection may not continue after OIT is stopped. Continued food avoidance remains an alternative to OIT and should be discussed as part of the decision-making process. Anagnostou et al. created a decision aid to help families during their OIT discussions where they can compare OIT with continued food avoidance. Based on the literature, the decision aid helped provide potential benefits, risks, and practicality of OIT and was found to be well accepted by families.

When making a decision, both the potential benefits of OIT and treatment burden, including regular dosing, clinic visits, safety precautions, and the possibility of treatment-related reactions, should be discussed. For some patients, reducing their anxiety around allergenic foods and reactions could be a priority, whereas for others, the daily commitment of OIT is not worthwhile.

Counseling and Expectation Setting

When deciding whether OIT is the right individual treatment for food allergies, patients and their families should be given the time to talk through their thoughts surrounding the treatment. This means working with the clinical team to understand what they can expect during treatment, including home dosing, clinic visits, and precautions around dosing. It is important that families understand what OIT entails and feel confident about pursuing the treatment. As part of this discussion, the effects of treatment on daily routine should also be discussed as well as any common misunderstandings patients have regarding OIT. As research has increased around OIT, structured counseling has become a useful approach that help address these misconceptions and give families a consistent understanding of the treatment. In one study, a checklist-based counseling process improved patient and caregiver knowledge and helped ensure that key OIT topics were covered.

Treatment success should also be considered beyond achieving a predetermined dose or challenge threshold. Prior to treatment, clinicians should approach OIT discussions with transparency and provide realistic expectations, as treatment response and the time needed to reach a desired outcome may vary between patients. The international Delphi consensus recommends assessing

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patient and family-specific factors before and during OIT, including the ability to adhere, understanding risks of treatment, treatment expectations, as well as practical barriers. Since these factors are likely to change over time, it is important that they are consistently assessed during any clinical visit and revised as needed.

Monitoring and Follow-up

Oral immunotherapy requires regular follow-up beyond the initial period. Since OIT is primarily done at home, follow-up visits in clinic intermittently are recommended to review and revise treatment plan. Adherence is an important factor when translating OIT efficacy demonstrated in clinical trials into routine practice, where treatment demands may be more difficult to sustain at home.

In the follow-up clinic visits, missed doses and changes in dosing circumstances should also be addressed. Management of missed doses varies between OIT programs, especially when treatment has been interrupted for several days. Programs should have clear guidelines for when families should contact the clinical team regarding missed doses, and whether the missed dosing requires a dose reduction or supervised redosing in clinic. This is especially important during dose escalation, when patients have not yet reached a stable maintenance dose and should not proceed with changes in dosing without consulting their care team. Additionally, if a patient has an illness, the care team should be consulted regarding how to proceed with dosing, as allergen threshold may be temporarily diminished.

During the maintenance phase, clinicians should work with patients to assess tolerance of current dose and how well the dosing schedule is working for the patient and family. Changes in the patient's routine or treatment goals may affect adherence and could require adjustments to the treatment plan.

Long-term Maintenance Strategies

Reaching the maintenance dose does not necessarily mean that OIT is complete. Continued allergen exposure is usually recommended to maintain desensitization. The maintenance regimen should take into account the patient's goals, tolerability, ability to adhere, and treatment burden. For example, some patients prefer lower daily dosing schedules to maintain the consistency of dosing, whereas some patients prefer higher dosing but more infrequently. Given the variability, maintenance regimens need to be revisited over time as the patient's goals, tolerance, or ability to follow treatment change.

Eosinophilic Esophagitis

Eosinophilic esophagitis and other food-driven eosinophilic GI disorders are discussed comprehensively in Chapter 12; the present section focuses specifically on their relevance to patients undergoing OIT. While OIT has been extensively studied and shown to be highly efficacious, AEs during therapy are common, with most patients experiencing at least one dose related AE during the course of immunotherapy. The most frequently reported symptoms are skin, GI, and respiratory AEs, and are generally classified as mild or moderate in severity. Most reactions to treatment occur during the updosing phase of OIT, where the individual is gradually increasing the amount of allergen they are consuming. During the maintenance phase, where the daily OIT dose is consistent, these reactions generally are much less frequent and tend to decrease over time.

While many AEs are manageable, some patients may develop OIT-induced GI symptoms and eosinophilic responses during treatment. One potentially severe response, EoE is a chronic type 2 inflammatory disorder of the esophagus characterized by symptoms of esophageal dysfunction and eosinophil-predominant mucosal inflammation. This can occur in both children and adults and has rapidly increased in prevalence and recognition over the past several decades. The disease is defined by esophageal mucosal eosinophilia of ≥15 eosinophils per high-power field, along with esophageal dysfunction symptoms. In children, symptoms often include reflux, vomiting, and abdominal pain, often presenting by refusal to feed. Adults and adolescents generally present with dysphagia and food impaction. Heartburn and chest discomfort may also be present. It can be a challenge to diagnose EoE, as several biopsies are generally needed, and other conditions associated with esophageal eosinophilia need to be ruled out, including but not limited to gastroesophageal reflux disease (GERD), Crohn's disease, and infection. Additionally, the presentation of EoE is similar to common GI AEs associated with OIT. While many symptoms are possibly EoE related, most patients with these symptoms do not undergo endoscopy, so the actual rate of EoE is unclear. Furthermore, it is not known how many patients may have had EoE prior to OIT initiation.

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Current understanding is that allergenic foods and certain inhaled antigens cause the esophageal mucosa to be infiltrated with eosinophils, mast cells, and basophils, damaging the mucosa. This chronic, allergen-triggered inflammation can lead to esophageal remodeling and stricture formation. It was found in a meta-analysis that EoE affects approximately 34.4/100,000 people in Europe and North America. This analysis also showed the incidence of EoE to be 7.7/100,000 person-years in adults and 6.6/100,000 in children. While the pathophysiology of EoE is not fully understood, EoE is substantially more common among patients with IgE-mediated food allergy than in the general population (4.7% vs. 0.04% prevalence). A 2017 meta-analysis looked at the incidence of EoE or symptoms possibly related to EoE in patients undergoing milk, egg, or peanut OIT. The overall discontinuation rate of OIT was 14.1%, and of the studies that reported a reason for discontinuing OIT, 4.7% indicated symptoms possibly related to EoE. Of the studies that used biopsy to confirm the EoE diagnosis, EoE was shown in 5.3% of patients receiving OIT. Symptoms of EoE can occur at any time point during OIT.

It is important to note that patients who have an esophageal mucosal eosinophilia count of ≥15 eosinophils per high-power field but lack any EoE symptoms would not be diagnosed with EoE, but with asymptomatic esophageal eosinophilia (aEE). These patients often have similar endoscopic findings to those with EoE, such as furrows and rings. However, there is not currently strong data to suggest that aEE will progress to EoE or lead to fibrosis. Because of this, empiric treatment is generally not started. These patients should be monitored for new or worsening fibrosis, or progression to EoE. Dysphagia can often be missed as a symptom due to patients developing ways to overcome this difficulty, and some patients may have atypical symptoms. Because of this, a thorough medical history is important to distinguish aEE and EoE.

As soon as EoE is confirmed, treatment needs to be started to control symptoms and prevent irreversible fibrosis. The three treatment strategies are proton pump inhibitors (PPIs), corticosteroid treatment, and dietary elimination of the contributing allergen. SDM between the clinician and patient and/or their caregivers is needed to decide whether to treat the EoE with medication, to modify the OIT dose, or to discontinue OIT altogether. Currently, most clinicians discontinue the immunotherapy, yet some may modify treatment in mild cases.

Gastrointestinal Symptom Management in Oral Immunotherapy

While there are no standard clinical guidelines for managing AEs during OIT, algorithms for managing GI symptoms have been developed for both the outpatient setting and clinical trials. The outpatient algorithm classifies GI symptoms into three separate categories. The categories are immediate IgE-mediated reactions occurring <2 hours after an OIT dose, delayed GI reactions occurring >2 hours postdose, and symptoms unrelated to OIT. For IgE-mediated symptoms, options for resolving the issues are ensuring the dose is taken on a full stomach, identifying other cofactors, predosing with a second-generation antihistamine, or decreasing the OIT dose. Other cofactors that can lower allergen tolerance threshold include exercising <1 hour before or 2 hours after dosing and consuming alcohol while undergoing immunotherapy. These steps can be taken one by one, or concurrently. Considering smaller percentage dose increases moving forward and doubling the previous dose interval may be prudent in patients with these IgE-mediated symptoms. In patients with non-IgE-mediated symptoms, a duration of <7 days could be related to an illness, and it is recommended to hold OIT until symptoms resolve. If the symptoms last over a week, one must consider non-OIT-related issues, including constipation, functional abdominal pain, GERD, and celiac disease. If these diagnoses are ruled out, gastroenterology assessment is recommended to consider eosinophilic gastrointestinal disorders (EGID), including EoE. While many experts will discontinue OIT in the presence of EoE, Chua et al. recommend a SDM approach with the patient in mild cases. The two options they present are to persist or to pause. Persisting includes holding doses until asymptomatic, then reducing the dose and/or adding PPIs for 8–12 weeks, doubling the previous dose interval if successful. Pausing includes discontinuing dosing for 8–12 weeks and considering PPIs for 8–12 weeks as well. If successful, OIT is restarted at a lower dose, also doubling the previous dose interval here. Patients may transition from persisting to pausing, or discontinue treatment if difficulties persist, highlighting the importance of the SDM approach.

The clinical trial algorithm for persistent GI AEs drafted by the OUtMATCH Consortium of Food Allergy Research has many similarities to the outpatient algorithm, however, due to strict protocols and visit windows, interrupting

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dosing for 8–12 weeks is often not feasible. They also use a top-down approach, offering more standardization across study sites. After ruling out cofactors, participants were instructed to predose with H1 and/or H2 blockers, decreasing the dose if symptoms persist. If symptoms continue after an additional 2 weeks, OIT is paused and investigators had the option to prescribe PPIs for 1–2 months while resuming OIT at a previously tolerated dose. If the AEs continue for another 2 weeks, investigators discussed with protocol chairs about either pausing dosing once more or further decreasing the dose. If symptoms continue for another 3 days, participants were referred to gastroenterology for consideration for EGID with biopsies. While this algorithm is suited well for clinical trials, one could also use this approach in the real-world setting. Both algorithms will likely go through changes as understanding of EGID and EoE is increased.

FOOD ALLERGY IMMUNOTHERAPY IN RESOURCE-LIMITED SETTINGS

Translating FA immunotherapy from clinical trials and highly specialized centers into routine care requires adaptation to local healthcare systems, available resources, food practices, and economic realities. These considerations are particularly important in low- and middle-income countries (LMICs), where the burden of allergic disease is increasingly recognized but access to trained allergy specialists, standardized products, diagnostic facilities, and emergency medications may remain limited.

Most FA immunotherapy evidence comes from high-income countries, yet sensitization and probable allergy are increasingly documented across LMICs. Community data from Karnataka, India estimate probable FA at roughly 0.14% of children and 1.2% of adults, against a strikingly high any-food sensitization rate of 26.5% in adults by specific IgE. Such sensitization means detectable food-specific IgE to at least one tested food, not clinical allergy. This marked discrepancy highlights a critical diagnostic issue in that sensitization alone does not establish clinical FA and may substantially overestimate disease burden in populations where confirmatory OFCs are not widely available. Even conservative prevalence estimates, however, translate into a substantial absolute burden in countries such as India, given its population of approximately 1.4 billion people. This burden is compounded by limited access to allergy specialists, standardized allergen products, diagnostic testing, and epinephrine autoinjectors.

In LMICs, a major barrier to FA immunotherapy implementation is the lack of standardization on three fronts. First, there are no standardized immunotherapy products. Clinical trials have generally used characterized food preparations, including Good Manufacturing Practice (GMP)-grade allergen flour or fixed-dose sublingual extracts, whereas clinical programs in many LMICs would need to improvise with locally sourced whole foods. Second, definitions of treatment success vary substantially across studies. Trials adopt widely varying tolerated-dose thresholds as their endpoint, so reported success is not directly comparable. Third, OFC protocols are not standardized, with differing dosing steps and stopping criteria, further limiting cross-study comparison. These methodological differences complicate interpretation of the literature and translation of research protocols into routine practice.

In most LMICs, licensed products (e.g., defatted GMP peanut powder) are inaccessible or unaffordable, so protocols must use locally sourced whole foods. Nonproprietary, food-based OIT has been delivered safely for single and multiple allergens in supervised clinical settings with trained staff, and economic modeling suggests it can be cost-effective. However, clinical trial outcomes can be highly variable under resource-rich, standardized conditions and real-world delivery without standardized product will present an even bigger challenge.

Regardless of the product used, OIT programs require prerequisites. Staff must be trained to recognize and treat anaphylaxis, with a physician on hand during initial dosing and any dose increases. A supervised area for observed dosing and OFCs, if applicable, must be available, with on-site resuscitation capacity, immediate access to epinephrine, a written emergency action plan, and a clear escalation and referral pathway **(Fig. 1)**. Furthermore, structured patient selection and counseling, including reliable epinephrine access at home, capacity for longitudinal follow-up and adherence support are needed. In settings such as India, where access to trained allergy specialists and dedicated allergy services remains limited relative to population needs, and epinephrine autoinjector access is constrained, scalable OIT programs should initially be anchored in experienced tertiary or referral centers with appropriate emergency infrastructure.

Beyond these operational prerequisites, cost and training shape feasibility. Commercial allergen OIT is cost-effective only under favorable assumptions, with product cost and durability of response as dominant

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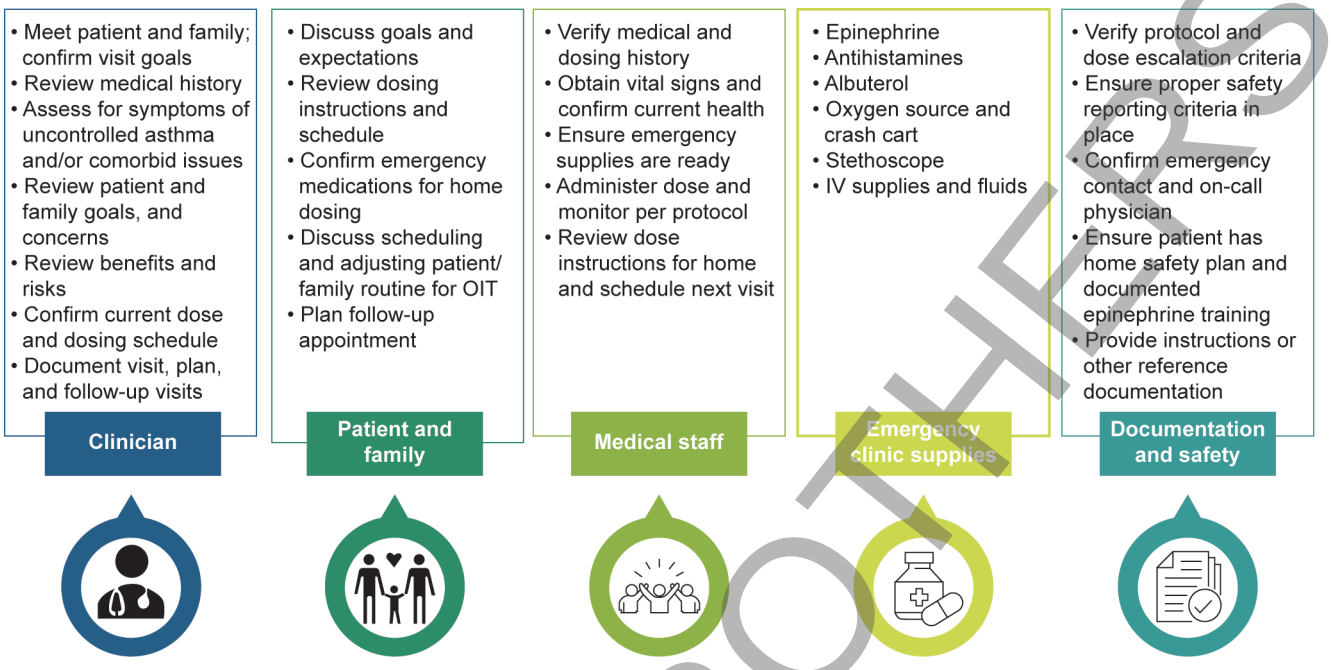

Fig. 1: Oral immunotherapy (OIT) visit checklist: Items for a successful oral immunotherapy visit in clinic.

levers. Food-based protocols remove the product-cost lever altogether by replacing the pharmaceutical grade product with store-bought foods. For example, peanut OIT delivered this way (peanut flour, peanut butter, Bambas, etc.) has been shown safe and effective in practice and modeled as cost-saving relative to no treatment, with residual expense shifting from product to clinician time and monitoring. Direct cost data on nonpropriety, multiallergen whole-food OIT in LMIC settings, however, are lacking. Food-based and real-world OIT can even be cost-saving, though expense then shifts from product to clinician time and monitoring. Data from real-world implementation highlights the importance of clinician preparation, patient selection, and structured counseling in driving outcomes.

In addition to the above prerequisites, safety remains the central implementation concern. GI symptoms, dosing reactions, and anaphylaxis are the principal AEs associated with OIT, particularly during updosing. These can be mitigated by counseling, action plans, and epinephrine access. Where epinephrine and emergency infrastructure are limited, patient selection must be more conservative.

Countries such as India may nonetheless have a plausible pathway toward scalable, food-based immunotherapy. Rising demand, lower personnel costs, familiarity with whole-food dosing, and the potential to use locally available foods could support carefully designed programs. Initial implementation should focus on tertiary centers with structured protocols, clinician training, excellent patient education, and referral networks. Key challenges and practical considerations for implementing FA immunotherapy in resource-limited settings are summarized in **Table 2**. Further research is needed to establish feasible low-cost protocols and assess long-term adherence and safety.

FUTURE DIRECTIONS

Advances in biomarkers, artificial intelligence (AI), digital tools, and precision medicine are discussed more broadly in Chapter 25. Here, these developments are considered specifically in the context of their potential to personalize and improve FA immunotherapy.

The field of FA has made tremendous strides over the past decade, and there is much promise regarding the future of FA treatment. Increased knowledge in the field, along with emerging technologies, may allow for highly personalized treatment moving forward, along with potential alternatives to OFCs for definitive allergy diagnosis.

Precision medicine is a model aimed to shift treatment from a one size fits all approach to customized healthcare. In order to proceed with this patient-specific treatment approach, identifying predictive biomarkers is critical. Discovering predictive biomarkers can allow for improved

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TABLE 2: Practical considerations for food allergy immunotherapy in resource-limited settings.

Challenge	*Practical consideration*
Limited availability of standardized immunotherapy products	Consider carefully characterized, locally available food-based approaches within structured clinical protocols
Limited specialist workforce	Initial programs should be concentrated in experienced tertiary or referral centers
Limited access to epinephrine autoinjectors	Careful patient selection, emergency preparedness, patient education, and clear referral pathways are essential
Variable diagnostic resources	Confirm clinical food allergy carefully and avoid initiating immunotherapy based on sensitization alone
Cost of commercial products	Locally available food-based approaches may improve affordability, although standardization and safety remain essential
Limited emergency infrastructure	Initial dosing and dose escalation should occur only where anaphylaxis can be promptly recognized and treated
Long travel distances and follow-up difficulties	Structured counseling, clear home-dosing instructions, and planned longitudinal follow-up are important
Limited local evidence	Prospective studies evaluating locally appropriate protocols, safety, adherence, and cost-effectiveness are needed

clinical outcomes, reduced AEs, and increased quality of life. For example, a subset of food allergic individuals do not experience a significantly increased threshold when undergoing treatment with omalizumab. Researchers are working to discover which, if any, traits or biomarkers predict treatment success or failure, which would allow for reduced healthcare spending and improved patient outcomes. Another example is related to diagnosing FA. The gold standard, especially in clinical trials, of confirming FA diagnosis is to perform DBPCFCs, which carry inherent medical risk. If biomarkers are identified that can confirm diagnosis, eliminating the need for DBPCFCs, patient safety, and accessibility to care can be improved. Biomarkers being studied include but are not limited to immunoglobulins, basophil activation, allergen specific T cells, and the microbiome.

One method of developing and refining precision medicine in FA will be to use AI and machine learning algorithms to analyze complex data to identify patterns yet to be discovered. Using AI may have the ability to improve clinical trial design, enhance biomarker discovery, and optimize dosing schedules. AI may be used in the future to predict the likelihood of FA development and optimize the timing of allergenic food introduction in infants. As more tools are discovered to enhance FA immunotherapy, diagnosis and treatment will become more personalized. Epigenetic profiling may be used to identify which treatment, or combination of treatments, has the highest probability of successful therapy.

SUMMARY

Food allergy immunotherapy is rapidly transitioning from a predominantly research-based intervention toward an increasingly personalized component of clinical allergy practice. OIT currently has the largest evidence base, while biologics, EPIT, SLIT, lower-dose approaches, and combination strategies continue to expand the therapeutic landscape. Successful implementation requires careful patient selection, SDM, realistic treatment goals, structured monitoring, and appropriate emergency preparedness. Importantly, treatment models developed in resource-rich settings cannot always be directly transferred to LMICs, where locally adapted, affordable, and safe approaches are needed. Future advances in biomarkers, precision medicine, and emerging technologies may allow clinicians to better match individual patients with the treatment strategy most likely to provide meaningful benefit with an acceptable treatment burden.

Key Learning Points

- FA immunotherapy should be individualized according to the patient's age, clinical phenotype, comorbidities, treatment goals, risk tolerance, and ability to adhere to therapy.
- OIT can increase the threshold for allergic reactions but should not be presented as a cure; continued allergen exposure is generally required to maintain desensitization.
- SDM and realistic expectation setting are central to successful implementation.
- Appropriate clinical infrastructure, trained personnel, access to epinephrine, and clear emergency pathways are essential prerequisites for safe OIT.
- Lower-dose, real-food, and other resource-adapted approaches may improve accessibility, but require careful standardization and clinical supervision.
- Future FA therapy is likely to become increasingly personalized through biomarkers, biologics, combination approaches, and precision medicine.

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