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Title: Food Immunotherapy: Choosing Wisely

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Food allergies are common ^{1,2} and as practicing physicians, we regularly see food-allergy sufferers in our clinics. We also find them in schools and classrooms, sometimes within our close family and friends' environment. The effect that food allergies have on the individual and their family is significant. All aspects of daily life can be affected, including physical, psychological and social interactions, ultimately impacting on quality of life ^{3 4 5}. It is hard to imagine a world without food allergies, but many researchers are aiming for exactly this. Over the last 5-10 years there have been tremendous progress and impressive breakthroughs in both preventative measures ⁶ and treatment options for patients with food allergy ⁷.

In terms of active treatment, food immunotherapy (oral, sublingual or epicutaneous) is at the forefront of the research and clinical landscape. Oral immunotherapy (OIT) consists of the administration of small (usually a few milligrams), gradually increasing doses of the food that the patient is allergic to, with the goal to provide protection from accidental exposures and potentially, over time, enable the patient to eat varying amounts of the allergenic food without reactions. Most research protocols include an initial up dosing phase (with or without a 'rush escalation'), which usually lasts a few weeks or months followed by a long-term maintenance phase once the desired maintenance dose (usually from 300 mg to multiple grams of protein) is reached. The maintenance phase lasts for years and currently, ongoing regular ingestion is advised as long-term therapy. Sublingual Immunotherapy (SLIT) is administered in a liquid form, held under the tongue for a few minutes and then swallowed or spat out. The typical starting dose for SLIT is lower than OIT (begins in micrograms), thus gradually elevating the food threshold of reactivity. Doses are escalated in a similar fashion to OIT, but the maintenance dose reaches only approximately 10 mg of food protein ^{8 9 10 11 12}. It usually takes longer to reach maintenance than in OIT and long-term treatment is also needed to maintain desensitization. Epicutaneous immunotherapy (EPIT) provides an alternative route of desensitization to a food allergen via the skin. In EPIT, an adhesive patch (for peanut, containing 250 µg of protein) is applied daily to the back or inner arm, usually for a total period of 3-

5 years¹³ (see table 1). Subcutaneous immunotherapy (SCIT) has been used for over 100 years to successfully treat allergic rhinitis, but does not hold a popular place currently for foods. The main reason for this is that SCIT has been associated with a significant rate of systemic reactions (13.3–39%), in two separate trials for peanut-allergic adults^{14 15}. Both studies showed good efficacy but, unfortunately, the high rate of systemic reactions made this form of treatment unacceptable for routine use in subjects with peanut allergy.

The availability of different food immunotherapy options in the research or clinical setting present many challenges for both the patient and the healthcare provider. There are multiple decisions and choices to be made since different benefits and risks are associated with the various routes of administration.

The safety profiles in food immunotherapy vary. For OIT, most patients report mild or moderate allergic reactions, but anaphylaxis is also reported in approximately 14% of subjects^{9 16 17 18 19}. It is important to note that OIT increases the risk of anaphylaxis albeit in a supervised hospital or clinic setting as opposed to doing nothing, which leaves the patient at a lower risk of anaphylaxis, but in an unsupervised community setting (without direct medical support). Frequency and number of reactions generally decrease during the maintenance phase, but it has been identified that viral illnesses and other factors (such as exercise, tiredness, menstruation) may lower the threshold of reactivity in patients undergoing OIT²⁰. Additionally, a published meta-analysis reports up to 2.7% of patients with IgE-mediated food allergies undergoing food OIT developing eosinophilic esophagitis (EoE). This condition however, often resolves following discontinuation of OIT treatment²¹. The role of biologics, such as anti-IgE, as an adjuvant alongside oral immunotherapy is shown to be effective in facilitating rapid oral desensitization and having a significantly lower rate of adverse events^{22 23 24 25}. This area, largely unexplored, has the potential to improve the OIT safety profile and is currently in development with multiple biologics in play (omalizumab, dupilumab and others). For SLIT, the safety profile is quite different with systemic reactions being rather uncommon (reported in up to 2.3% of doses)^{9,10,12,26}. SLIT has generally fewer side effects when compared to OIT and symptoms

are typically mild and localized to the oropharyngeal region ²⁷. EoE has not been observed with food allergen SLIT, but has been reported in aeroallergen SLIT ²⁸. For EPIT, the safety profile has so far been favorable. The epidermis is not vascularized and as a result, systemic effects are much less likely to occur. Mild local reactions at the patch site have been observed in over 90% of patients receiving the active treatment and mild, non-local reactions were observed in less than 20% of subjects ^{13 29 30–32}. EoE has not been reported with EPIT.

In terms of efficacy, it is generally accepted that OIT is highly successful in achieving desensitization, usually within a period of a few months. 'Successful desensitization' in most studies is defined as no dose-limiting symptoms to 300mg (or more) of peanut protein. Studies on food immunotherapy for milk, egg and peanut have shown promise in desensitizing food-allergic children with the majority achieving this goal ^{33,34,35,19}. Systematic reviews have reported that when compared to an elimination diet alone, oral food immunotherapy increased the likelihood of achieving clinical tolerance to milk, egg and peanut ^{36 9 37}. In addition to raising the threshold of reactivity, OIT has demonstrated a significant effect on improving the quality of life of children and their caregivers, following successful desensitization ^{8 19 39}. For EPIT, patients treated successfully with the peanut patch for 12 months showed a 35.3% response rate for desensitization ¹³. Additionally, they demonstrated a relative risk reduction of 73.2% to 78.4% when consuming peanut-contaminated packaged food products ⁴⁰. A recently published follow up report of longer-term EPIT (involving an additional two years of treatment after reaching maintenance) in peanut-allergic children demonstrated sustained clinical benefit with high compliance and low discontinuation rates due to adverse events ⁴¹.

For the multi-allergic child, the simultaneous oral administration of a combination of food allergens compared with the administration of a single allergen has been studied. Multifood OIT in small phase I trials, is shown to be comparable in safety to single-food immunotherapy. Similar rates of adverse reactions (3.3 and 3.7%), were observed in both groups, most of which were mild ^{42 43}. The

dosing protocol was designed to reach a daily maintenance dose of 4,000 mg protein of each allergen (up to a 20,000 mg cumulative dose for those on five allergens), which was achieved by the majority of study participants confirming high efficacy. This approach has the potential to minimize the number of hospital patient visits and the overall cost of treatment, as OIT to more than one food allergen can be time-consuming and expensive if the allergens are to be administered sequentially, one at a time. Most importantly, multi-food OIT has the benefit of providing personalized patient treatment, where a combination of different food allergens, depending on the patient's unique food-allergic profile, may be used to match the intervention to individual requirements and preferences. Multi-food immunotherapy has not been studied for any other routes.

Food immunotherapy is not a cure, but it does provide benefits, especially in terms of protection from accidental exposures. There is no doubt that successful desensitization increases the threshold of reactivity to the relevant food, as demonstrated by food challenges and the ability to consume varying amounts of the allergenic food. A rise in threshold from less than 100 mg of peanut protein to 300 mg post immunotherapy, has been shown to reduce the risk of experiencing an allergic reaction by more than 95% for various food products with potential peanut contamination (cookies, ice cream, doughnuts/snack cakes and snack chip mixes) ⁴⁴. These advantages have to be balanced against long-term commitment to dosing and ongoing restrictions (such as the 2-hour exercise restriction in OIT).

Ultimately, it comes down to patient choice. But how can the patient choose? And most importantly, how can the patient know they have made the right choice? This is where decision making comes into play. We live in an era that has seen a significant shift in medical decision making, from a previously 'paternalistic approach' to a 'patient-guided process' ⁴⁵, with the term 'patient centered care' coined in 1988 ⁴⁶. A report by the Institute of Medicine in 2001 promoted patient-centered care, defined as 'providing care that is respectful of and responsive to individual patient preferences, needs and values' and 'ensuring that patient values guide all clinical decisions'. It is now expected

that medical decisions are based on current scientific knowledge, while communication between patients and healthcare providers is effective, with information and knowledge shared freely both ways ⁴⁷. The American Academy of Pediatrics also issued a revised policy statement in 2016, stating that 'shared decision-making is a central tenet of the family-centered medical home' ⁴⁸. Additionally, the 'Choosing Wisely' initiative (<https://www.choosingwisely.org/>), embraced by the American Board of Internal Medicine Foundation, has a mission to promote conversations between clinicians and patients by helping patients 'choose care that is supported by evidence, not duplicative of other tests or procedures already received, free from harm and truly necessary'. This initiative provides a structure for shared decision-making with focus on the discussion of benefits, risks, alternatives or doing nothing. (see Figure 1).

In food immunotherapy decisions are not straightforward. Usually the patient is faced with a variety of treatment options with no absolute guarantee of any desired outcome and no clear indication of the 'best choice'. Food Immunotherapy therefore, is an ideal area where shared decision-making is of key value; there are many potential management paths, each having trade-offs, and parents (and patients) often have very particular preferences for care ⁴⁹. The process of how to choose a particular option becomes a discussion where the clinician and the patient have to jointly review the medical evidence, but also the patient's preference for balancing particular attributes of the treatment (both positive and negative) ⁴⁹. Each encounter is a building block in an ongoing partnership between patients and physicians. Both contribute equally to the discussion by bringing important, albeit different perspectives to the decision-making process. By working together, they ensure achievement of the best possible outcome.

Children should also be involved in decision-making and both parents and healthcare providers play a crucial role in supporting young patients as they learn to make decisions on their own. In pediatrics, shared decision making often includes the parent or legal guardian, since minors lack legal authority to provide informed consent for treatment, although older and mature children may be primary decision makers in their own care and in some cases overrule the parents' choices ⁵⁰. This

process can be facilitated by the physician during an office visit by asking for the child's opinions, concerns and preferences and checking for their understanding on what has been said ⁵¹. Parents may also engage their children in specific decisions, involve them in the management of their condition and prepare them for the transition to greater independence when they reach adulthood ⁵¹.

Decision-making tools are needed to assist patients in understanding and choosing between new treatments and available options. The lack of support tools in food allergy has been identified as an unmet need; these tools should help address caregiver goals, expectations, and psychological barriers as well as identify facilitators for treatment strategies ⁵². A recent publication highlighted a 4-page decision-aid for commercial peanut allergy therapies ⁵³. This decision-aid is a welcome addition to the current landscape; it describes the upcoming available therapies, outlines key risks and benefits of the different treatment options and also includes a self-check assessment regarding adequacy of information and next steps ⁵³. It is expected that more such tools will become available over time and enable caregivers and patients to successfully navigate the complex decision-making relevant to food allergy treatments. The goal is to allow families to make the decision that best fits their treatment goals.

Decisions have to be made not only at the patient level, but more widely, at individual country and government level as well. As expected, practices vary in different countries and geographical areas with regards to food immunotherapy. Some countries have already developed specific guidelines ⁵⁴ whereas others are in the process of forming consensus documents for novel treatments, as these emerge. In the US, important differences in the practice of OIT have been noted between academic and non-academic providers, with academics obtaining institutional review board and Investigational New Drug approval more often than non-academic clinicians ⁵⁵. Recently, the first commercial product for POIT became available in the United States. Food immunotherapy also comes with an important warning: it should never be initiated at home, nor should any up dose ever

occur outside a supervised, medical environment with healthcare professionals trained in this procedure.

Another area that merits further exploration relates to health economics ⁵⁶. For peanut OIT, an economic analysis was performed with the aim to characterize the cost-effectiveness of this intervention. This work revealed that peanut OIT may be cost effective in a long-term economic model when compared with strict avoidance. Rates of accidental reactions, therapy-associated adverse events and likelihood of therapy-induced tolerance were all taken into account in the analysis ⁵⁶. More studies are needed in this area, ideally examining different food allergens, for a better understanding of the cost-effectiveness of novel treatment options for food-allergic patients.

There is no doubt that we are living in exciting times for food allergy and navigating new areas of treatment, which present novel challenges for both patients and healthcare providers. In our role as patient advocates, we should make the process of decision-making as smooth as possible, allowing families to reach the decision that is the 'best fit' for their individual circumstances, preferences and needs.

Table 1: Comparison of different food immunotherapy routes

Differences in administration, age group, daily dosing, restrictions, treatment duration, efficacy, adverse events, sustained unresponsiveness and available commercial drugs are shown.

	OIT	EPIT	SLIT
<i>Route of administration</i>	Oral	Epicutaneous	Sublingual
<i>Age group</i>	Children: 1-17 years	Children: 4-11 years	Children: 4-17 years
<i>Daily dose protein amount</i>	300-4000 mg	50-500 µg	2-7 mg
<i>Most commonly used daily dose</i>	300 mg	250 µg	-
<i>Dose adjustment required</i>	Likely, if adverse event occurs* or external factors are present (illness, tiredness, menstruation, alcohol consumption)	Likely, if adverse event occurs*	Likely, if adverse event occurs*
<i>Daily restrictions</i>	2- hour exercise restriction after dose	None	No food or drink for 30 minutes after dosing

<i>Duration of treatment until maintenance achieved</i>	Months	Years	Years
<i>Desensitization Efficacy</i>	High	Small to moderate	Small to moderate
<i>Adverse events</i>	Local: frequent Anaphylaxis: infrequent EoE: cases reported	Local: frequent Anaphylaxis: rare EoE: No reported cases	Local: frequent Anaphylaxis: rare EoE: No reported cases
<i>Sustained unresponsiveness</i>	Variable	Not evaluated	Not evaluated
<i>Availability of commercial drug</i>	Yes, currently in the USA only	Not available currently	Not available currently

***dose adjustment will depend on the severity and/or frequency of adverse event(s)EoE:
Eosinophilic esophagitis**

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