Considerations for a shared decision-making conversation when initiating food oral immunotherapy

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ABSTRACT

Oral immunotherapy (OIT) is an office-based procedure that offers potential treatment of immunoglobulin E mediated food allergy. OIT has multiple benefits, e.g., the ability to desensitize the individual with food allergy, which shifts the eliciting dose threshold required in that individual to trigger an allergic reaction, and also potentially to decrease the severity of any resulting reactions. However, OIT is not a cure and has distinct risks, including the risk of allergic reactions (including anaphylaxis) from the therapy itself, the potential risk of developing eosinophilic esophagitis (or similar clinical symptoms without a formal biopsy), and logistical issues in coordinating when to give the daily dose, and there are still uncertain intermediate–to–long-term outcomes with regard to OIT. The decision to start OIT is complex and potentially nuanced. Shared decision-making is a process that allows the patient and family and the clinician to undergo a mutual discussion of the risks, benefits, alternatives, and other considerations with regard to a medical decision (such as starting OIT) whereby there is an exchange of information that allows the patient and family to formally clarify and express their values and preferences with regard to facets of the decision in this particular context. The goal is for the patient to be able to make a fully informed decision that is reflective of his or her goals, values, preferences, and desires. This article outlined some of the key considerations to discuss with parents and patients before enrolling in an OIT program with regard to the risks and benefits, to assist in engaging in shared decision-making and obtaining informed consent.

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Oral immunotherapy (OIT) is an office-based procedure for treating immunoglobulin E mediated food allergy.[1–3] Although OIT has been available for many years in some clinical practices, there is now a standardized U.S. Food and Drug Administration approved peanut OIT product.[4,5] OIT offers multiple potential benefits, including allergen desensitization, increasing the allergen quantity needed to trigger an allergic reaction, and potentially decreasing reaction severity.[1–3] However, OIT is not a cure. Few patients will become tolerant to their allergen (*e.g.*, achieve sustained unresponsiveness, which allows for *ad libitum* ingestion), and not all patients undergoing OIT will achieve desensitization.[1] Moreover, OIT has distinct risks, including allergic reactions (including anaphylaxis) from the therapy itself, eosinophilic esophagitis (EoE) (or similar clinical symptoms without a formal biopsy), logistical constraints with regard to daily dosing, and uncertainty with regard to intermediate-to-long-term outcomes.[1,6] The decision to start OIT affects the entire family and requires careful consideration.[7] This article outlines key considerations for prescribing clinicians to discuss with families before starting office-based OIT, to engage in shared decision-making (SDM) with regard to therapy risks and benefits before obtaining informed consent. (Table 1)

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WHY SDM?

SDM and SDM principles are detailed elsewhere.[8–10] Briefly, in SDM, the patient and/or family and the clinician have a mutual discussion of the risks, benefits, alternatives, and other considerations with regard to a medical decision (*e.g.*, starting OIT), whereby information is exchanged, which allows the family members to clarify and express their values and preferences with regard to facets of the decision in this particular context. This involves both a firm understanding of the evidence and/or outcomes related to the decision, the potential choices and/or alternatives involved in the decision, and a way for the patient and/or family to identify what aspects of the choices they identify with and do or do not prefer. The goal is for the patient

Table 1 **Checklist for a shared decision-making conversation with regard to oral immunotherapy**

Topic	Rationale
Goals of therapy, from both for the patient's and the allergist's perspective	Provide a clear understanding of what oral immunotherapy can and cannot accomplish as a therapeutic option, verify that the patient and the family have realistic goals that would be well served through oral immunotherapy
Benefits of therapy	Provide a clear and evidence-based explanation of the evidence for the efficacy of oral immunotherapy to the particular allergen and in the particular age group; include both short- and longer-term outcomes
Risks of therapy	Provide a clear and evidence-based explanation of the evidence for the risks of oral immunotherapy to the particular allergen and in the particular age group; include both short- and longer-term outcomes; key outcomes to emphasize are the risk of allergic reactions, including therapy-associated anaphylaxis, eosinophilic esophagitis, or eosinophilic esophagitis–like symptoms, and it is strongly recommended that the possible although unlikely risk of fatality does exist
Timing and logistics of therapy	Provide a clear understanding of the day-to-day routine and rigor that is associated with daily home dosing and in-office updosing; discuss dosing forms, vehicles, *etc.*; discuss postdosing observation and medication-related issues, treatment plan, contact plan to notify the prescribing allergist in the event that a reaction occurs, when to contact if there is concern about the next dose
Safe dosing rules	Provide a clear understanding of what the safe dosing rules are and why these are crucial so that they be followed as closely as possible to prevent reactions, and the consequences of what may happen if these cannot be adhered to in terms of continuing in therapy
Alternatives to therapy	Discuss age-appropriate alternatives to oral immunotherapy available as a clinical or research option and the risks and benefits of these therapies
Timeline	Discuss the approximate time course of therapy, reassure that there is no firm evidence that this has to be done in a particular time window; discuss that the published evidence to date supports this is likely to be a daily, indefinite therapy, and there are little data to suggest that this can be discontinued or spaced out and the effect maintained, although this could change in the future
Informed consent and questions	Detail the process and next steps for informed consent, when this will be obtained and why, and provide an opportunity for the patient and/or family to ask questions; consider a "cooling off" period of several days to allow for reflection before obtaining informed consent and starting therapy

to be able to make a fully informed decision, reflective of his or her goals, values, preferences, and desires. What a patient wants and/or values may vary considerably among patients and families, and may be discongruent with what the clinician may feel is best.

SDM is an optimal approach in which care is preference sensitive, which means multiple potential approaches (but no single dominant option) exist, each having distinct potential trade-offs and outcomes, in which the decision is heavily dependent on personal values and preferences.[11] Often, such choices could deviate from evidence-based guidelines, in particular, in situations with conditional or weak guideline recommendations based on the underlying evidence. Although SDM has been robustly explored elsewhere, there is minimal work in food allergy and food allergy therapy.[12] However, SDM is very important when considering food allergy therapy because this meets all criteria for preference-sensitive care. For the choice of food allergy therapy, several decisional support tools, including two decision aids and one video have been formally published to help guide clinicians and patients through this process.[7,13–15] Decision-aid development is discussed elsewhere, and these aids are used to help patients clarify values but are not primary educational material and do not

substitute for a discussion between the clinician and the patient.[16,17] When available, International Patient Decision Aid Standards (IPDAS)-compliant decision aids could be useful tools to offer patients and/or families in helping to determine goals and preferences with respect to choosing OIT.

WHAT TO DISCUSS WITH REGARD TO BENEFITS OF OIT

OIT has numerous evidence-based benefits that have been demonstrated. Most prominently, a high percentage of participants in OIT can achieve desensitization through OIT to multiple allergens (primarily peanut, tree nut, milk, sesame, and egg), between 50% and 90% in published studies, although what constitutes efficacy *vis-à-vis* level of desensitization has not been consistently defined, nor has the protocol or approach (*e.g.*, challenge for entry) used for OIT. It is important to discuss appropriate therapy goals with the patient and/or family, but clinicians should avoid discussing and/or promising lofty expectations of OIT being curative or allowing for *ad libitum* allergen ingestion, given data that indicate this is unlikely for most persons. Certain protocols aim for a high-target desensitization level (*e.g.*, ≥4 g of protein), which may allow a functional daily tolerance between a certain dose range, supported by Israeli data that a lower daily maintenance dose provides desensitization to a target three- to fourfold higher.[18] It is important to clarify that analysis of most of the data indicates that OIT is a daily, indefinite therapy, for the moment at least, which means that it is unlikely that a child can "graduate" without continuing daily dosing to maintain desensitization. There are no robust or randomized controlled data that show that OIT consistently produces allergen tolerance analogous to a cure or that desensitization can be maintained without daily dosing. This could change with future studies.

Analysis of data from a recently published trial does suggest that, for a commercialized peanut product, OIT may also decrease reaction severity among persons who reach maintenance dosing.[4] The end-of-study oral challenge data after a year of peanut showed that fewer individuals required epinephrine to treat symptoms that resulted from this challenge than at the baseline study entry challenge, although this has not necessarily been shown to occur in real-world scenarios and may or may not translate to other contexts, dose exposure levels, or allergens. Although desensitization goals and targets can approach the protein content of a typical serving size, lower targets are also possible, associated with certain OIT protocols, and are even desired by some families. For families concerned about trace and/or precautionary labeling (PAL) and proximity exposure, nearly all OIT protocols can produce a level of desensitization above the likely threshold of allergen contained in those situations.[3] Such PAL content rarely exceeds published eliciting dose 5% or eliciting dose 10% levels for allergens (generally well below 5–10 mg of protein). Even for participants unable to achieve target desensitization levels, generally, this lower PAL threshold is achievable.[19]

WHAT TO DISCUSS WITH REGARD TO RISKS OF THERAPY

No treatment is free of risk or adverse effects, or is completely safe. This has been one of the more prominent issues with regard to OIT.[1,6] Such issues are not necessarily detriments as much as they are trade-offs that require careful explanation to patients and/or families so they understand the potential risks associated with OIT and can make an informed decision if those risks outweigh the perceived benefits. There are several key risks that must be discussed with patients and/or families. Importantly, OIT implies that this is an oral therapy that involves allergen ingestion and carries the risk of an allergic reaction with each and every dose, even if recent doses were tolerated.[3]

The highest risk of a reaction is with updosing, which is why protocols clearly specify that this must only be done in-office, under an allergist's supervision, and with emergency medication available (similar to oral food challenge [OFC]). However, there are also risks with daily home dosing, which requires the patient's emergency medicines and anaphylaxis management plan be available and that the patient be observed by someone familiar with how to use self-injectable epinephrine.[20] "Safe dosing rules," covered elsewhere in this compendium, must be clearly explained and followed. A lack of adherence to safe-dosing rules may result in symptoms associated with the dose, and, although some patients may not tolerate a particular dose, this is rare, and most symptoms result from relaxed safe-dosing rules.[3,20] It should be clearly disclosed and explained that OIT carries a risk of anaphylaxis (or severe reactions and/or systemic hypersensitivity) from the therapy itself, and that, in some studies, up to 15% of patients had reactions that required epinephrine treatment.[4,6] Epinephrine use has been noted with all allergens studied for OIT but is best defined for peanut.

A recent meta-analysis of peanut OIT showed that, compared with peanut avoidance, peanut OIT had increased odds of anaphylaxis (odds ratio 3.12 [95% confidence interval, 1.76–5.55]; number needed to harm, 7) and had high odds of adverse events that led to OIT discontinuation (odds ratio 2.55 [95% confidence interval, 1.2–5.42]). In the Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization (PALISADE) trial, 98% of the participants had at least one adverse event (96% in buildup, 87.8% in maintenance).[4,6] Events that occurred in the course of OIT may be more tolerable to the patient and/or family than naturally occurring reactions, given

they are not related to a random exposure. Dose-related allergic symptoms of varying severity are highly likely to occur and underscore that patients and/or families who enter into OIT must be made aware of these risks and be willing to accept these trade-offs for the benefits of OIT. Overall, although dose-related adverse events are common to all allergens, the published experience may suggest that these occur more with milk OIT than other allergens.[1,21–23]

OIT-related fatality is exceptionally rare. There is believed to be one fatality related to induction of OIT dosing, which occurred in the OFC–rapid updosing phase in a Spanish adolescent with poorly controlled asthma.[24,25] There are confirmed reports of a second event that involved milk OIT, although documentation and reporting are sparse. This event occurred in 2017, in a young Japanese male enrolled in a clinical trial of milk OIT at month 3 of maintenance dosing, who, after taking his dosing despite 48 hours of mild asthma symptoms, developed acute respiratory arrest while in the backseat of his family car and experienced anoxic brain injury, which required life support. (Author's note–it is unclear what the child's ultimate disposition is. This event occurred at the Kanagawa Children's Medical Center in 2017, and was presented at the Japanese Society for Pediatric Allergy and Clinical Immunology 2017 conference).[26–28]

The other major complication to discuss is the potential development of EoE or a clinical symptom of EoE-like symptoms without a biopsy-proven diagnosis.[28–32] OIT-related gastrointestinal (GI) symptoms, such as abdominal pain, choking and/or gagging on foods, dysphagia and/or odynophagia, and nausea and/or vomiting can be indicative of EoE.[34] The biopsy-proven rate of OIT-associated EoE is low, ~2.7%, and generally prompts OIT discontinuation in most studies and real-world settings.[29] However, because patients are rarely referred for diagnostic biopsy when these symptoms arise, the true incidence of OIT-associated EoE is likely higher.[30,31] A recent review suggests that GI symptoms suspicious for EoE have occurred in 34% of patients across 110 OIT studies, with 4.7% discontinuing OIT, and only 18 studies reported performing a biopsy in 35 cases (5.3%).[31] In the PALISADE study,[4] 52% of the subjects developed GI symptoms and ~32% discontinued OIT because of these, although only three patients underwent biopsy, with one case of EoE diagnosed.

Furthermore, when examining all 1217 participants treated with peanut OIT across all phase II and III trials (including the PALISADE study), only 28 of 62 who withdrew due to GI symptoms were referred for evaluation, and 17 underwent an esophagogastroduodenoscopy, with a total of 12 diagnosed with EoE. Although this is reported as a ~1% incidence, it shows that ~20% with GI symptoms had EoE, with not all such patients undergoing a biopsy.[35] A separate entity that describes EoE-like symptoms in the absence of obtaining a biopsy specimen has been described in both the United States and Israel, called either OITIGER (oral immunotherapy induced gastrointestinal symptoms and eosinophilic responses) or ELORS (eosinophilic esophagitis–like oral immunotherapy–related syndrome). This has occurred in ~8%–11% of patients across large case series, with 50%–75% still able to successfully reach their target maintenance dose.[31,32] Although the risk of developing EoE or ELORS and/or OITIGER is poorly specified, families and/or patients should also be counseled that many patients can be successfully managed without discontinuing OIT.[32,33]

OTHER CONSIDERATIONS

Logistical issues should be emphasized and are detailed in Table 2. Following safe-dosing rules can be potential barriers to adherence, although motivated families can accommodate therapy into their lifestyle. Families with children active in after-school athletics and/or activities may struggle to accommodate therapy, in particular, finding a time when the child is not either scheduled to be going to or immediately coming from a sporting event or practice, has food in his or her stomach, and is not about to go to bed or off to school.[3,20] Some patients cannot reach their target maintenance dose due to developing dose-limiting symptoms.[20,22] Other patients may develop taste aversions that limit dose advancement or that prompt OIT disocntinuation.[18] Therapy is not curative.[1,20] Therefore, patients still need to avoid deliberately ingesting non-OIT allergen sources, although they are generally protected against some degree of accidental exposure in excess of their daily dose, and still must carry self-injectable epinephrine despite being desensitized.[3,20] Intermediate–to–long-term goals are difficult to specify in terms of 5–10-year outcomes.[22]

Although OIT to multiple foods simultaneously is a published approach,[22] many allergists may not offer this, which forces patients with multiple food allergies and/or families considering OIT to prioritize treating one allergen over another, which may be a difficult choice. There has to be acceptance and willingness that the patient will have to ingest his or her allergen daily, which may not fit certain patient preferences and values. Comorbid allergic conditions (*e.g.*, asthma, allergic rhinitis) require careful management and optimized treatment because poor control is associated with a risk for dose-related adverse events.[3] Quality of life (QoL) has been shown to generally improve in OIT, but this has been limited mainly to the parent-proxy reports of their impression of the child's life as opposed to the child directly reporting QoL improvement.[3,36–38]

Table 2 **Common logistical issues that face patients and/or families initiating oral immunotherapy**

Logistical Issue	Potential Impact on Therapy Outcome
Involvement in before or after school activities	Difficulty arranging or prioritizing the schedule to allow the dose to be timed to the safe dosing rule recommendations with regard to avoiding exercise, hot shower or bath, bedtime
Parent or caregiver schedule	Difficulty in finding a time when one or both of the primary caretakers are able to administer and observe dosing, to avoid someone with less experience or familiarity with the allergy and treatment plan from the burden of having to administer and supervise therapy; consider if the child shares the time between different households or if both caregivers frequently travel for their jobs
Other children	With multiple children who have activities or their own medical and/or social concerns, this may present difficulty in being able to commit to a rigorous therapy program for food allergy that has many particular rules that require diligent adherence; in particular, if there is another child with a food allergy at home, this may raise additional concerns
Travel schedule	Families who travel a lot, in particular, with long drives, frequent flights, or who travel to more remote places without close access to medical care may find that this could pose a potential for frequent interruption of the dosing schedule and make progress more difficult
Other medical comorbidities	If the person receiving therapy has other medical issues, the potential for interference with therapy should be considered; this includes potentially prioritizing the choice of one allergen if the patient has multiple food allergies
Availability for updosing	Families who live a distance from the primary location where updosing occurs could have difficulty in consistently being able to travel long distances to make these visits

CONSIDERING ALTERNATIVES

OIT is not necessarily the right choice for all patients. It requires a motivated patient and family, willing to accept the trade-offs of adverse events, allergen ingestion, and daily and/or indefinite therapy duration. There are multiple other therapies in the developmental pipeline, including epicutaneous immunotherapy and multiple biologic options, which may be available in the near future and should be discussed as alternatives.[21] Avoidance should be emphasized as a perfectly reasonable alternative and not to be viewed as a default choice. Although avoidance carries a risk of accidental reactions and poor QoL, these trade-offs may be preferred for some families, and, as clinicians, we must remain nonjudgmental of such choices.[3] Alternatives to each decision must be presented in the SDM process so that a patient and/or family is not leveraged into making a decision without full consideration of other potential choices.[9,10]

OBTAINING INFORMED CONSENT

It is highly recommended to obtain formal written consent from the patient and/or family before initiating OIT.[3,20] This is a strong recommendation for any OFC-related procedure, which includes OIT.[39] The SDM discussion is only a preamble to written informed consent and does not suffice as written consent, it only supplements it. It is strongly advised that every practice that offers OIT has a written consent form, which, at minimum, incorporates the basic risks and/or benefits, and documents that the patient and/or family formally consents to undergo OIT. Risks should clearly state that OIT is not curative, that patients are still considered allergic and need both an active food allergy action plan and to carry self-injectable epinephrine at all times, and that, with each dose, there is a risk of an allergic reaction, including a severe allergic reaction and fatality. More detailed forms may elect to document the patient and/or family acknowledging the potential need for care to escalate in rare circumstances, in either the emergency department or hospital, and that admission to the hospital from OIT-related sequelae is also a possibility.[3,20] This may be associated with unanticipated charges apart from the cost of OIT. We recommend that the SDM session is separate, precedes obtaining informed consent, and allows time for the family to reflect and process the information. When possible, information sheets that explain OIT, as well as providing contact information

for families to ask questions while considering their options, may be helpful.

CONCLUSION

OIT has multiple potentially benefits. However, these are balanced by significant risks, some great enough to potentially dissuade participating in the therapy. OIT is not a universal option for all patients, and clinicians need to have a keen understanding that this is not a "one size fits all therapy." The decision to start OIT can be difficult and requires significant investment on behalf of the prescribing clinician to engage in SDM and to detail the risks, benefits, and alternatives so that the patient and/or family can make an informed decision. Written consent is a key last step before starting therapy.

CLINICAL PEARLS

- The goal of shared decision-making in OIT is for the families to understand the risks and benefits of OIT, as well as be aware of the alternative food allergy management approaches
- Anaphylaxis and Eosinophilic Esophagitis are the two most important medical risks to discuss as possible consequences of OIT
- Reduced risk of severe reactions and an increased threshold to trigger a reaction are the two most important medical benefits to discuss
- It is important to emphasize the logistical constraints of therapy, including safe dosing rules, and the anticipated duration of therapy, given families may be simultaneously managing multiple priorities with their children

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