

Weighing the benefits and risks of oral immunotherapy in clinical practice

Aikaterini Anagnostou, M.D., Ph.D.^{1,2}

ABSTRACT

Food allergies are common and affect 6–8% of children in the United States; they pose a significant burden on the quality of life of children with allergy and their caregivers due to multiple daily restrictions. Despite the recommended dietary avoidance, reactions tend to occur due to unintentional exposure to the allergenic food trigger. Fear of accidental ingestions with potentially severe reactions, including anaphylaxis and death, creates anxiety in individuals with food allergy. Oral immunotherapy has emerged as a form of active and potentially disease-modifying treatment for common food allergies encountered in childhood. The efficacy of oral immunotherapy is high, with the majority of participants achieving desensitization and, as a result, protection from trace exposures and improved quality of life. The main risk of oral immunotherapy consists of allergic reactions to treatment. In general, rates of allergic reactions and anaphylaxis are reported to be higher in individuals pursuing therapy options, but most subjects who undergo oral immunotherapy will likely experience mild or moderate reactions during treatment. Adverse events tend to reduce in both frequency and number in the maintenance period. The use of immune modulators alongside oral immunotherapy has been suggested, with the aim to improve efficacy and safety, and to facilitate the overall process. It is evident that the landscape of food allergy management is changing and that the future looks brighter, with different options emerging over time. The process of how to choose the appropriate option becomes a discussion between the clinician and the patient, which involves a joint review of the current medical evidence but also the patient's preference for balancing particular attributes of the treatment. By working together, providers and patients will ensure achievement of the best possible outcome for children with food allergies.

(Allergy Asthma Proc 42:118–123, 2021; doi: 10.2500/aap.2021.42.200107)

Food allergies are common, affect 6–8% of children in the United States,^{1,2} and they have a significant effect on the quality of life (QoL) of children with allergy and their caregivers.³ Anxiety stems mostly from fear of accidental ingestion with potentially severe reactions, including anaphylaxis and death. Children with food allergy face various dietary, social restrictions, and psychological issues at school (e.g., bullying).^{4–7} Certain food allergies, such as cow's milk, soya, egg, and wheat, are usually outgrown after a few years of dietary exclusion. Fish, shellfish, sesame, peanut, and tree nut allergies tend to be lifelong and rarely resolve.⁸ There currently is no cure for food allergy. The traditional approach is based on patient education, strict avoidance of the offending food (elimination diet), and prompt treatment of adverse reactions when they occur. Unfortunately, accidental exposures occur, despite avoid-

ance; a recent review reported an average of 10% per year for peanut.⁹ Children and families are provided with patient-specific emergency medication (antihistamines and epinephrine autoinjectors) and a management plan on how to treat allergic reactions.

Over the past decade, oral immunotherapy (OIT) has emerged as a form of active and potentially disease-modifying treatment for common food allergies encountered in childhood. OIT involves the administration of small, gradually increasing doses of the food to which patients are allergic, with the aim to enable them to eat varying amounts of the allergenic food without reactions. Most research studies include an initial up dosing phase (with or without a “rush” escalation), which usually lasts a few weeks or months, and a long-term maintenance phase once the desired maintenance dose is reached. This latter phase lasts for years, and, currently, ongoing regular ingestion is advised as maintenance therapy.

“Desensitization” refers to a rise in the allergenic threshold of reactivity and implies regular dose ingestion (usually a daily dose) to maintain the desensitized state. “Sustained unresponsiveness” refers to the ability of subjects who have successfully completed an OIT protocol to discontinue treatment for a few weeks or months and then return to daily allergen consumption at their previous dose, without any allergic reactions. “Long-term tolerance” is defined as the ability to

From the ¹Section of Pediatric Immunology, Allergy and Rheumatology, Baylor College of Medicine, Houston, Texas, and ²Section of Immunology, Allergy and Rheumatology, Department of Pediatrics, Texas Children's Hospital, Houston, Texas. A. Anagnostou is the PI for Aimmune Therapeutics research trials and receives institutional funding.

Presented at the Eastern Allergy Conference, August 17, 2020, Palm, Beach, Florida. Funding provided by the Eastern Allergy Conference.

Address correspondence to Aikaterini Anagnostou, M.D., Department of Pediatrics, Section of Immunology, Allergy and Rheumatology, 1102 Bates Avenue Ste 330, Houston, TX 77030.

E-mail address: Aikaterini.Anagnostou@bcm.edu

Copyright © 2021, Published by OceanSide Publications, Inc., U.S.A.

eat the previously allergenic food *ad libitum* at any amount or frequency without any problems or the need for daily dosing.^{10,11}

BENEFITS OF OIT

OIT efficacy is high, with the majority of participants achieving desensitization. Skripak *et al.*¹² reported on a double-blind, placebo controlled study of OIT for cow's milk allergy in children. After OIT, the median cumulative dose that induced a reaction in the active treatment group was 5140 mg compared with only 40 mg before OIT, and there was no change in the median threshold in the placebo group.¹² Although reactions were common during the study, nearly 90% were transient and did not require treatment.¹² For egg, a double-blind, placebo controlled, randomized OIT trial¹³ of 55 children with egg allergy resulted in a 55% rate of desensitization in the active group after 10 months of therapy. In the placebo group, the desensitization rate was 0%.¹³ After another year of OIT, the desensitization rate rose to 75%, which suggests that a longer treatment duration results in more successful desensitization.¹³ A 4-year follow-up of these subjects reiterated this conclusion by reporting that sustained unresponsiveness after egg OIT was enhanced with a longer duration of therapy and increased the likelihood of tolerating unbaked egg in the diet.¹⁴

With regard to peanut OIT (POIT), U.S. investigators reported that, in a randomized controlled study¹⁵ of 28 participants with peanut allergy, 84% of the active subjects passed a final challenge of 20 peanuts (~5000 mg of peanut protein) compared with only one peanut (~280 mg of peanut protein; peanut content is variable, depending on the size of the peanut) tolerated by the placebo subjects in the final challenge, after completing a year of OIT. The study regimen was well tolerated, with clinically relevant symptoms seen after only 1.2% of build-up doses and no subject with POIT required adrenaline administration.¹⁵ The largest phase II, randomized controlled, crossover trial¹⁶ of POIT that originated from the United Kingdom investigated the role of POIT in desensitizing 99 children, ages 7–16 years, inclusive of all severities of peanut allergy. After completion of the intervention, in the active group, 84% were desensitized to 5 peanuts (~800 mg of peanut protein), whereas 62% of the participants on OIT successfully passed a 10-peanut challenge.¹⁶ The subjects who successfully completed the study protocol had a significant, 25-fold increase of their peanut threshold; the treatment, therefore, allowed them to eat large quantities of peanuts, well above the levels present in contaminated snacks and meals.¹⁶

The Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (PALISADE) trial¹⁷, the largest international POIT trial

to date, which included a total number of 551 participants (496 were children), confirmed the high efficacy of OIT; 67.2% of the active participants compared with only 4% of the placebo participants were able to ingest a single 600-mg dose of peanut (cumulative dose of >1000 mg of peanut protein content) at the exit food challenge without dose-limiting symptoms.¹⁷ All the above studies^{12–17} provide strong evidence that OIT for food allergy is a form of active therapy that has high efficacy in different geographic populations of children allergic to common foods (*e.g.*, milk, egg, and peanut). The time from the beginning of treatment to achieving maintenance is usually a few months, and treatment has high success rates.

Most research trials examined efficacy in children between the ages of 4 and 17 years old. However, OIT seems to be highly efficacious in the preschool age group as well. A study by Vickery *et al.*^{18,19} showed that 78% of 40 preschool children achieved sustained unresponsiveness after an average of 29 months of OIT; 71% tolerated 3000 mg of peanut protein. Most importantly, longer-term follow-up at 5 years after treatment showed the majority of these children continuing dietary peanut consumption, with 55% ingesting >1000 mg of peanut protein without any allergic reactions. Early age may provide a window of opportunity for treatment because young children potentially display clinical and immunologic characteristics that are more responsive to treatment interventions. Further studies are already underway to investigate this, but currently available data¹⁸ support the fact that POIT works well for younger children (1–3 years old) as well.

Protection from accidental trace exposures is a significant benefit of OIT. A rise in the threshold from <100 mg of peanut protein to 300 mg after immunotherapy has been shown to reduce the risk of experiencing an allergic reaction by > 95% for various food products with potential peanut contamination.²¹ A further increase to 1000 mg of peanut protein has an additional quantitative benefit in risk reduction.²¹ Studies^{16,22,23} showed that protection from inadvertent exposures driven by increases in the eliciting dose results in improved QoL. A randomized controlled trial of POIT in 99 children from the United Kingdom showed significant QoL improvement after successful desensitization.¹⁶ Blumchen *et al.*²² also reported significant improvement in QoL in 62 children undergoing low-dose POIT in a multicenter, double-blind, randomized, placebo controlled trial. Epstein-Rigbi *et al.*²³ showed that the QoL of 191 children with food allergy improved significantly on reaching OIT maintenance, with additional improvement 6 months later. The caregivers' QoL also improved in a trial of multiallergen food immunotherapy.^{24,25} QoL is an important patient-reported outcome, and OIT seems to have a positive effect on the daily life of patients.

RISKS OF OIT

The main risk of OIT is allergic reactions to treatment. In general, rates of adverse reactions and anaphylaxis are reported to be higher in individuals pursuing therapy options.²⁶ However, in OIT, most of the subjects will likely experience mild or moderate reactions during treatment (most of these will occur in the up dosing or early maintenance phases),¹⁷ with the frequency and number of reactions generally decreasing during the longer-term maintenance phase. Adverse events are suggested to be significantly associated with allergic rhinitis and skin-prick test wheal size.²⁷ For milk OIT, a Cochrane systematic review²⁸ reported adverse reactions in 97 of 106 patients on milk OIT, although most reactions were local and mild. For every 11 patients who received milk OIT, one required intramuscular epinephrine; one patient required it on two occasions.²⁸ For egg OIT, a systematic review, which included children between ages 4 and 15 years reported mild-to-severe adverse effects during OIT treatment in 69% of the participants; 5% required epinephrine.²⁹ The Study of Tolerance to Oral Peanut II (STOP II) trial¹⁶ reported mild adverse effects in the majority of the participants, with gastrointestinal symptoms being the most common. Intramuscular epinephrine was required for one participant only (0.01% of doses); no participant required more than one administration of epinephrine, and there were no therapy-related hospitalizations.¹⁶

In the PALISADE POIT trial,¹⁷ adverse events occurred in > 95% of participants 4–17 years of age, with mild events noted in 34.7%, moderate in 59.7%, and severe in 4.3%. Anaphylaxis was reported in 14.2% of the active participants and in 3.2% of the placebo participants in the PALISADE trial.¹⁷ Of the reactions that required epinephrine in the active arm, 92.7% were treated with one dose, 6.1% with two doses, and 1.2% with three doses of epinephrine.¹⁷ In the placebo arm, all the reactions were successfully treated with a single epinephrine dose.¹⁷ Overall, 43 participants (11.6%) in the active group and 3 (2.4%) in the placebo group withdrew from the trial because of adverse events during the intervention period.¹⁷ The impact of allergic reactions that require epinephrine use when these occur in a controlled setting (such as in-office or home dosing) as opposed to reactions “in the field,” in which epinephrine is often underused, should also be considered by physicians and families when evaluating the risk-benefit of OIT. In general, families regard reactions in a controlled setting, at home or in the office, as significantly less traumatic than accidental reactions in the field.

An additional risk of OIT involves external factors, such as viral illnesses, exercise, tiredness, and menstruation, which have the potential to lower the threshold of reactivity in patients undergoing OIT.³⁰ The recently

published Threshold Reactivity and Clinical Evaluation Study (TRACE) study³¹ provided evidence that exercise and sleep deprivation, each significantly reduces the threshold of reactivity in patients with peanut allergy, which puts them at greater risk of a reaction. The investigators performed baseline (nonintervention) challenges in adult participants with peanut allergy in addition to interventional challenges (after exercise and sleep deprivation).³¹ Educating families on this fact will improve risk management during OIT and ensure better safety while undergoing therapy.

The development of eosinophilic esophagitis (EoE) as a result of OIT is another current concern. A published meta-analysis reports that ~3% of patients with immunoglobulin E-mediated food allergies who underwent OIT developed this complication, with EoE often resolving after discontinuation of treatment.³² However, individual studies reported variable rates, and the available data are limited. Goldberg *et al.*³³ recently described OIT-induced gastrointestinal symptoms associated with peripheral eosinophilic responses in 65 patients. According to their report, these symptoms abated after dosage modifications or temporary discontinuation of treatment, half of the patients were able to achieve full desensitization; more than two-thirds were able to achieve partial desensitization.³³ A starting dose of >120 mg, a second-month dose more than fourfold over the starting dose and a baseline absolute eosinophil count of >600/ μ L were all identified as risk factors of developing transient gastrointestinal symptoms associated with peripheral eosinophilia (the participants were receiving OIT for milk, peanut, egg, or sesame).³³

It is evident from the multiple research studies^{16,17,28–33} described above that OIT has some associated risks that should be considered during the shared decision-making process. These risks mostly involve mild or moderate allergic reactions, but the risk of anaphylaxis must also be taken into account, even if this happens infrequently. Exercise limitations, comorbidities, and external factors should also be discussed with patients and families because these may have a varying effect on individuals. Finally, it should be noted that, although OIT is a highly successful form of therapy and provides significant protection from trace exposures, it is not a cure and rates of sustained unresponsiveness vary in different studies.

OIT FOR THE CHILD WITH MULTIFOOD ALLERGY

For children with multiple food allergies, 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,^{34,35} is shown to be comparable in safety to single-food immunotherapy. In a trial that included

40 participants (15 monoallergic to peanut, 25 with additional food allergies), similar rates of adverse reactions were observed in both groups (3.3% in the multi-food group versus 3.7% in the single OIT group), most of which were mild. The dosing protocol was designed to reach a daily maintenance dose of 4000 mg of 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, which confirmed high efficacy.^{34,35} This approach has the potential to minimize the number of in-office or in-hospital patient visits and the overall cost of treatment because 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, multifood OIT has the benefit of providing personalized patient treatment, in which 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. In the real-world environment, a clinical multiple-food OIT pediatric program reported on a small cohort of 45 patients who received OIT for up to 12 foods (with most receiving OIT for four or fewer foods).³⁶ The investigators showed reactions in 49% of the patients during up dosing or in the first 3 months of maintenance, but most were gastrointestinal local reactions.³⁶ Systemic reactions were rare, and the frequency of emergency department visits during OIT was not significantly different from emergency department visits due to unintentional food allergen ingestion in a cohort of patients who were awaiting OIT start.³⁶ It is encouraging that multiple-food OIT administration does not seem to carry more risk in terms of allergic reactions compared with single-food OIT. This form of treatment will likely benefit individuals with multifood allergy.

OIT AND IMMUNOMODULATORS

The use of immune modulators alongside OIT has been suggested in the research setting, with the aim to improve efficacy and safety, and to facilitate the overall OIT process. For a combination treatment of OIT with multiple food allergens and omalizumab, after pretreatment with omalizumab, the participants tolerated the initial rapid escalation day with minimum or no rescue therapy, and the majority of reactions experienced by the subjects were mild.³³ A recent trial has also confirmed that omalizumab enables safe and rapid desensitization in multiple food OIT. The study³⁷ showed a significantly lower per-participant percentage of OIT doses associated with any adverse events (27% versus 68%; $p = 0.0082$) in the omalizumab group versus the placebo group. The most common adverse events reported were gastrointestinal.³⁷ Limited data

exist on allergic reaction occurrence after omalizumab discontinuation, and there is no consensus on optimal total duration of treatment with anti-immunoglobulin E. The additional cost of immune modulators should be considered when evaluating this approach. Currently, there is no recommendation for combining OIT with immune modulators, and this area requires further study.

In children with peanut allergy, a study evaluated the effects of probiotics as an adjuvant to POIT. This double-blind placebo controlled, randomized trial³⁸ enrolled 31 children with confirmed peanut allergy who were allocated to the probiotic and POIT group, and received 2×10^{10} colony forming units of *Lactobacillus rhamnosus* CGMCC1.3724, along with POIT once daily up to a maintenance dose of 2 g of peanut protein. In addition, 31 children received both a probiotic placebo and an OIT placebo once daily. The investigators reported that 82.1% in the probiotic and POIT group achieved sustained unresponsiveness (after ≥ 2 weeks of therapy discontinuation) compared with only 3.6% in the placebo group ($p < 0.001$).³⁸ A follow-up study 4 years after treatment cessation reported that 58% of the participants from the probiotic and POIT groups attained 8 weeks of sustained unresponsiveness, compared with 7% of the participants from the placebo group ($p = 0.012$).³⁹ It is important to note that the above studies^{38,39} that compared POIT and probiotic with placebo OIT and probiotic placebo unfortunately failed to answer the crucial question: does probiotic use improve the outcome of POIT. A study that compares subjects, all of whom receive POIT and split between receiving probiotic or placebo probiotic would be more on target. Therefore, we are unable to recommend probiotic use as an adjuvant to POIT therapy, based on current evidence.

Practical Steps

How do we approach the consultation with a patient who is considering undergoing OIT for his or her food allergy? In practical terms, the first step is to confirm the food allergy diagnosis (this may require a food challenge if in doubt). After this, it is important to ensure that the patient is eligible for this type of therapy and does not have comorbidities that may preclude them from participating (such as active EoE or uncontrolled asthma). Next, risks and benefits of the procedure should be clearly outlined and discussed at length with the patient and the family. This will likely be an ongoing discussion, and shared decision-making is crucial (as outlined below). Finally, it is worth considering the family setup and dynamics; this therapy requires dedication and a motivated individual and/or family. If there are concerns about treatment

compliance, it would be best to defer OIT initiation until these are fully addressed and resolved.

SHARED DECISION-MAKING IN OIT

Recently, in the United States, the first drug for POIT was approved by the U.S. Food and Drug Administration. The landscape of food allergies is changing, and the future looks much brighter for patients and their families. In addition to traditional avoidance strategies, new options for active therapy are emerging over time, posing the question of appropriate decision-making. In food allergy and food immunotherapy, decisions are unlikely to be straightforward.

The patient and his or her family will be faced with a variety of potential management paths, each having trade-offs.⁴⁰ The process of how to choose a particular option becomes a discussion in which 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.⁴⁰ The involvement of children in the decision-making process is also crucial; both parents and health care providers should support young patients as they learn to make decisions on their own.⁴¹ This process can be facilitated by the physician during an office visit by examining the child's opinions, concerns, and preferences, and by checking for their understanding on what has been said.⁴² 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.⁴²

Decision-support tools, such as decision aids, may assist patients in understanding and choosing between new treatments and available options, and by balancing decisions with personal values.⁴³ These tools should also help address caregiver goals, expectations, and psychological barriers as well as identify facilitators for treatment strategies.⁴⁴ A recent publication highlighted a four-page decision aid for commercial peanut allergy therapies, which is a welcome addition to the current literature.⁴⁵

CONCLUSION

There is no doubt that patients with food allergies carry a significant multifaceted daily burden, which includes dietary, social, and psychological effects. For a long time, the only available option for the management of their disease has been avoidance of the food trigger and treatment of accidental exposures when these occurred. Recently, the emergence of OIT as an active therapy has changed the traditional approach to food allergy management and expanded the offerings for children with food allergies. Making the right decision for treatment is not easy and differs for each patient and his or her family. Balancing risks and

benefits of OIT versus no therapy requires review of the current evidence by both the provider and the patient as well as significant personal input on the patient's preferences. It is expected that shared decision-making and decision aids will become widely available over time and assist caregivers and patients in making the decision that best fits their treatment goals and personal values.

REFERENCES

1. Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011; 128:e9–17.
2. Bird J, Lack G, Perry T. Clinical management of food allergy. *The J Allergy Clin Immunol Pract* 2015; 3:1–11.
3. Avery NJ, King RM, Knight S, et al. Assessment of quality of life in children with peanut allergy. *Pediatr Allergy Immunol* 2003; 14:378–382.
4. Stensgaard A, Bindslev-Jensen C, Nielsen D, et al. Quality of life in childhood, adolescence and adult food allergy: patient and parent perspectives. *Clin Exp Allergy* 2017; 47:530–539. doi:10.1111/cea.12849
5. Greenhawt M. Food allergy quality of life. *Ann Allergy Asthma Immunol* 2014; 113:506–512.
6. Herbert L, Shemesh E, Bender B. Clinical management of psychosocial concerns related to food allergy. *J Allergy Clin Immunol Pract* 2016; 4:205–213.
7. Annunziato RA, Rubes M, Ambrose MA, et al. Longitudinal evaluation of food allergy-related bullying. *J Allergy Clin Immunol Pract* 2014; 2:639–641.
8. Burks AW, Tang M, Sicherer S, et al. ICON: food allergy. *J Allergy Clin Immunol* 2012; 129:906–920.
9. Capucilli P, Wang KY, Spergel JM. Food reactions during avoidance: focus on peanut. *Ann Allergy Asthma Immunol* 2020; 124:459–465.
10. Anagnostou K, Clark A. What do we mean by oral tolerance? *Clin Exp Allergy* 2016; 46:782–784.
11. Anvari S, Anagnostou K. The nuts and bolts of food immunotherapy: the future of food allergy. *Children (Basel)* 2018; 5:47. doi: 10.3390/children5040047
12. Skripak JM, Nash SD, Rowley H, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol* 2008; 122:1154–1160.
13. Burks AW, Jones SM, Wood RA, et al. Oral immunotherapy for treatment of egg allergy in children. *N Engl J Med* 2012; 367:233–243.
14. Jones SM, Burks AW, Keet C, et al. Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. *J Allergy Clin Immunol* 2016; 137:1117–1127.e10.
15. Varshney P, Jones SM, Scurlock AM, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol* 2011; 127:654–660.
16. Anagnostou K, Islam S, King Y, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. *Lancet* 2014; 383:1297–1304.
17. PALISADE Group of Clinical Investigators; Vickery BP, Vereda A, et al. AR101 oral immunotherapy for peanut allergy. *N Engl J Med* 2018; 379:1991–2001.
18. Vickery BP, Berglund JP, Burk CM, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol* 2017; 139:173–181.e8.

19. Lauren H, Edwin HK, Wesley B, et al. Five-year follow-up of early intervention peanut oral immunotherapy. *J Allergy Clin Immunol Pract* 2021; 9:514–517.
20. Shelley D, Monica R-G, Simon B, et al. Effect of sleep deprivation and exercise on reaction threshold in adults with peanut allergy: A randomized controlled study. *J Allergy Clin Immunol* 2019; 144:1584–1594.e2.
21. Baumert JL, Taylor SL, Koppelman SJ. Quantitative assessment of the safety benefits associated with increasing clinical peanut thresholds through immunotherapy. *J Allergy Clin Immunol Pract* 2018; 6:457–465.e4. doi:10.1016/j.jaip.2017.05.006
22. Blumchen K, Trendelenburg V, Ahrens F, et al. Efficacy, safety, and quality of life in a multicenter, randomized, placebo-controlled trial of low-dose peanut oral immunotherapy in children with peanut allergy. *J Allergy Clin Immunol Pract* 2019; 7:479–491.e10.
23. Epstein-Rigbi N, Goldberg MR, Levy MB, et al. Quality of life of food-allergic patients before, during, and after oral immunotherapy. *J Allergy Clin Immunol Pract* 2019; 7:429–436.e2.
24. Arasi S, Otani IM, Klingbeil E, et al. Two year effects of food allergen immunotherapy on quality of life in caregivers of children with food allergies. *Allergy Asthma Clin Immunol* 2014; 10:57.
25. Otani IM, Bégin P, Kearney C, et al. Multiple-allergen oral immunotherapy improves quality of life in caregivers of food-allergic pediatric subjects. *Allergy Asthma Clin Immunol* 2014; 10:25.
26. Chu DK, Wood RA, French S, et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. *Lancet* 2019; 393:2222–2232.
27. Virkud YV, Burks AW, Steele PH, et al. Novel baseline predictors of adverse events during oral immunotherapy in children with peanut allergy. *J Allergy Clin Immunol* 2017; 139: 882–888.e5.
28. Yeung JP, Kloda LA, McDevitt J, et al. Oral immunotherapy for milk allergy. *Cochrane Database Syst Rev* 2012; 11:CD009542.
29. Romantsik O, Bruschettini M, Tosca MA, et al. Oral and sublingual immunotherapy for egg allergy. *Cochrane Database Syst Rev* 2014; (11):CD010638. doi: 10.1002/14651858.CD010638.pub2
30. Anagnostou K, Clark A, King Y, et al. Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. *Clin Exp Allergy* 2011; 41:1273–1281.
31. Dua S, Ruiz-García M, Bond S, et al. Effect of sleep deprivation and exercise on reaction threshold in adults with peanut allergy: a randomized controlled study. *J Allergy Clin Immunol* 2019; 144:1584–1594.e2. doi: 10.1016/j.jaci.2019.06.038
32. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2014; 113:624–629.
33. Goldberg MR, Nachshon L, Levy MB, et al. Risk factors and treatment outcomes for Oral Immunotherapy–Induced Gastrointestinal Symptoms and Eosinophilic Responses (OITIGER). *J Allergy Clin Immunol Pract* 2020; 8:125–131.
34. Bégin P, Dominguez T, Wilson SP, et al. Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using omalizumab. *Allergy Asthma Clin Immunol* 2014; 10:7.
35. Bégin P, Winterroth LC, Dominguez T, et al. Safety and feasibility of oral immunotherapy to multiple allergens for food allergy. *Allergy Asthma Clin Immunol* 2014; 10:1.
36. Eapen AA, Lavery WJ, Siddiqui JS, et al. Oral immunotherapy for multiple foods in a pediatric allergy clinic setting. *Ann Allergy Asthma Immunol* 2019; 123:573–581.e3.
37. Andorf S, Purington N, Block WM, et al. Anti-IgE treatment with oral immunotherapy in multifood allergic participants: a double-blind, randomised, controlled trial. *Lancet Gastroenterol Hepatol* 2018; 3:85–94.
38. Tang M, Ponsonby A-L, Orsini F. Administration of a probiotic with peanut oral immunotherapy: a randomized trial. *J Allergy Clin Immunol* 2015; 135:737–744.e8.
39. Hsiao K-C, Ponsonby A-L, Axelrad C, et al. Long-term clinical and immunological effects of probiotic and peanut oral immunotherapy after treatment cessation: 4-year follow-up of a randomised, double-blind, placebo-controlled trial. *Lancet Child Adolesc Health* 2017; 1:97–105. doi: 10.1016/S2352-4642(17)30041-X
40. Anagnostou A, Hourihane JO, Greenhawt M. The role of shared decision making in pediatric food allergy management. *J Allergy Clin Immunol Pract* 2020; 8:46–51.
41. Kon AA, Morrison W. Shared decision-making in pediatric practice: a broad view. *Pediatrics* 2018; 142(suppl 3):S129–S132.
42. Miller VA. Involving youth with a chronic illness in decision-making: highlighting the role of providers. *Pediatrics* 2018; 142 (suppl 3):S142–S148.
43. Greenhawt M. Shared decision-making in the care of a patient with food allergy. *Ann Allergy Asthma Immunol* 2020; 125:262–267.
44. Chan ES, Dinakar C, Gonzales-Reyes E, et al. Unmet needs of children with peanut allergy: aligning the risks and the evidence. *Ann Allergy Asthma Immunol* 2020; 124:479–486.
45. Greenhawt M, Shaker M, Winders T, et al. Development and acceptability of a shared decision-making tool for commercial peanut allergy therapies. *Ann Allergy Asthma Immunol* 2020; 125:90–96. doi:10.1016/j.anai.2020.01.030 □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.