

Current management and use of oral immunotherapy in the United States for patients with peanut allergy

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ABSTRACT

Background: Peanut allergy is a major health burden in the United States. Treatment is limited to avoidance and acute reaction management. No drug or medical product is approved for use as a peanut oral immunotherapy (POIT) agent.

Objective: To examine peanut allergy diagnosis and treatment, peanut challenge protocols, nonpublished POIT approaches, POIT practice requirements and logistical considerations, and barriers to providing POIT.

Methods: Qualitative in-depth telephonic interviews were conducted with 34 allergists and nurse food allergy specialists across the United States between April and June 2016. Interviewed clinicians managed > 100 patients with peanut allergy per year; 50% of the interviewed allergists offered POIT in clinical studies or used self-developed approaches.

Results: The physicians consistently reported conducting food challenges in 5–10% of patients to confirm a peanut allergy diagnosis. The allergists who offered POIT described using a variety of approaches. Areas of divergence included patient selection (ages, 4–7 years), peanut material (crushed peanuts, peanut flour, peanut protein, peanut butter, peanut extract), starting and ending doses, and updosing intervals (1 to 2 weeks). Generally, POIT administration and observation occupied an examination room for up to 2 hours; some practices reported accommodating 2 to 5 patients who received POIT simultaneously. Among physicians who did not offer POIT, barriers included medicolegal risks and the lack of a U.S. Food and Drug Administration (FDA) approved therapy.

Conclusion: Although POIT is currently not supported in treatment guidelines, some allergists have developed experimental POIT approaches to support patient needs. In the absence of a product that has approval by the FDA, European Medicines Agency (EMA) or other national competent authority, substantial variability in POIT approaches exists. Although logistical factors are not major obstacles to adoption, POIT dose preparation can be perceived as burdensome, and observation requires a dedicated staff. All the physicians interviewed suggested a need for effective, FDA-approved, disease-modifying treatments.

(Allergy Asthma Proc 40:214–220, 2019; doi: 10.2500/aap.2019.40.4228)

Food allergies are a significant and growing health problem in the United States. Among children, food allergy prevalence estimates range between 6.5%

and 8.0%.¹ Of those who have food allergies, between 17.7% and 25.2% have a peanut allergy.^{1–3} The U.S. Centers for Disease Control noted that food allergy hospitalizations in children increased 3.6-fold between 2000 and 2006 in the United States.⁴ Furthermore, the overall economic burden associated with food allergies is estimated to be \$24.8 billion. Although direct medical costs, including physician office visits, emergency department visits, rescue medications, and hospitalizations, account for \$4.3 billion annually, patients and their families bear most costs associated with lost time from work, out-of-pocket expenses, and lost opportunity costs because of the need to change jobs or leave employment.⁵

Although food allergies present a significant risk to health and well-being, and inflict a substantive cost burden on families, there are no approved therapies for treatment.⁶ Results of studies indicate that peanut allergy contributes to stress and anxiety among patients and their families.^{7,8} Given the significant impact that such stress and anxiety has on the quality of life of the patients with peanut allergy and their family,^{8,9} the

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Funding was provided by Aimmune Therapeutics

M.S. Blaiss has consultant associations with DBV Technologies, Sanofi/Regeneron, Pfizer, Stallergenes, JDP Therapeutics, PMD Healthcare, ALK-Abelló A/S. S. Tilles has an employment association with Aimmune Therapeutics. E. Zigmont had an employment association with Aimmune Therapeutics. M. Cassese has a consultant association with Aimmune Therapeutics. B. Kwak has a consultant association with Aimmune Therapeutics. N. Georgitseas has a consultant association with Aimmune Therapeutics. J. Liebermann has consultant associations with Aimmune Therapeutics, DBV Technologies, and Aquestive Therapeutics, and an employment association with Annals of Allergy, Asthma and Immunology. The remaining author has no conflicts of interest pertaining to this article

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Published online May 23, 2019

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need for a more active treatment approach has led to investigation and debate about the use of peanut oral immunotherapy (POIT).^{10–12} A recent report that described 8.5 years of real-world POIT experience with 270 patients in a practice setting indicated that it is possible to offer POIT on a large scale in a community setting.^{13,14}

The Guidelines for the Diagnosis and Management of Food Allergy in the United States¹² do not recommend allergen-specific immunotherapy to treat any food allergy, including peanut allergy. POIT use remains limited and experimental. Access to a U.S. Food and Drug Administration (FDA) approved product and a standardized protocol that defines patients best suited for treatment, dosing regimen, and strategies to maintain desensitization could allow for greater POIT adoption. This research was conducted to better understand the current use of peanut allergy challenge protocols, describe the characteristics of practices that choose to offer POIT, compare the attributes of non-published POIT approaches used, and investigate obstacles that limit POIT use in U.S. allergy practices.

METHODS

Practitioner interviews were used to evaluate the current state of POIT in U.S. allergy practices. Thirty-four in-depth, 1-hour telephonic interviews were conducted with community and university-based allergists and nurse food allergy specialists across the United States between April and June 2016. Study participants were recruited *via* e-mail from a panel of allergy practices; interested respondents answered screener questions to gauge participation eligibility. Eligibility criteria included managing > 100 unique patients with peanut allergy per year and previous experience with offering subcutaneous or sublingual immunotherapy to patients with environmental allergy, and/or oral immunotherapy (OIT) to patients with food allergy. To examine the qualitative differences between practitioners who were food OIT experienced versus those who were food OIT naive, selection was enriched to ensure that half of the participants had OIT experience. Eligible respondents were interviewed on a first-qualified basis for 1 hour by trained interviewers (MC, BK) using a questionnaire. The allergists and nurses received an honorarium for participating in this research. In total, 28 allergists and 6 nurses were interviewed with 14 of 28 interviewed physicians reporting experience with POIT. Nearly two-thirds of the physicians interviewed practiced in the community setting. Twenty-one of 28 physicians treated pediatric patients with peanut allergy, and, across all interviewed practices, 75% of the patients with peanut allergy were described as pediatric.

RESULTS

Diagnosis and Food Challenge

All interviewed physicians confirmed a peanut allergy diagnosis through a combination of clinical history and skin-prick test. Food challenges were reserved for patients whose clinical history in combination with serologic and/or skin test results were inconclusive or low. The physicians estimated that 5–10% of patients required diagnostic food challenges. Ninety-four percent of practices interviewed performed peanut food challenges; the exceptions were two solo private practices that referred patients to university-based or larger group practices better resourced to safely handle anaphylactic reactions.

Peanut food challenge protocols were not standardized. Protocols varied in terms of dosing quantities, observation periods, and approach, with half raising doses gradually and then exponentially according to a set schedule, whereas the remaining reported adjusting the dose based on the patient's ability to tolerate the dose. Peanuts, peanut protein (*i.e.*, purchased peanut protein mix), or peanut butter were commonly used, and doses were prepared by the practice nurses. Observation periods between doses lasted 15 to 30 minutes, and the overall process required 3 to 6 hours, depending on doses tolerated by the patient and the practice protocol used. All practices that offered POIT conducted food challenges in candidates for POIT.

Treatment

Although all the participants offered immunotherapy for patients with environmental allergy, POIT was uncommon. The physicians found it easy and safe to administer current standard of care, guideline-validated, and/or FDA-approved environmental desensitization therapies. Whereas all the participants agreed that studies^{6,9,11,13,14} imply that POIT holds promise as a desensitization option, most of the physicians believed that OIT for food allergies, especially peanuts, was riskier compared with environmental allergies because of the perceived increased potential to trigger anaphylaxis. Without access to a protocol validated in a large double-blind study, the physicians stated that many questions remain about which patients are best suited for POIT and if rapid induction or slow, steady increases by using a home self-administered dose buildup phase is the best approach. These uncertainties contributed to interviewees' hesitancy to offer non-FDA-approved POIT.

POIT allergy practices offered POIT to a select subset of patients with the intent to protect them from accidental exposure and the goal of increasing the amount of food needed to trigger an allergic reaction. Fifty-five percent of interviewed POIT practices were multipractitioner practices with greater resources. In compari-

Table 1 Profile of POIT-experienced vs POIT-naive practices in the United States

Practice Attributes*	POIT Experienced	POIT Naive
Institution type	The decision to offer POIT is a function of practice size and capability and is less related to university vs community setting; although many practices that offer POIT are affiliated with or located near a hospital	The decision to offer POIT is a function of practice size and capability and is less related to university vs community setting
Practice type and size	Are typically multipractitioner or multispecialty, with access to more trained support resources, such as nurses, physician assistants, and examination room space	Tend to be solo or 2-physician practices with limited space and trained support staff; approximately one-third noted that staffing concerns were a primary reason for not offering POIT
University affiliation	Physicians either practice at a university-affiliated institution or are in private practice with an academic appointment and commonly cited scientific literature as the basis of support for designing the practice POIT approach and offering it as an experimental treatment	Are more likely to be community-based physicians who do not have an appointment with an academic institution
Severe reactions	Secure that existing food challenge infrastructure and capability can be leveraged to handle a potential severe reaction during POIT	Express concerns over treating extreme reactions, which poses a barrier to adoption of OIT
Practice setting	Are mostly located in urban areas (70%), with a minority in rural settings (30%)	Are largely located in urban areas (64%), with slightly more POIT naive practices in rural settings (36%)

POIT = Peanut oral immunotherapy.

* Not all practices that are POIT experienced or POIT naive have all characteristics described.

son, 20% of participants in POIT-naive practices who were interviewed were part of a multipractitioner practice. Frequently mentioned differences between POIT-experienced and POIT-naive practices are described in Table 1.

All POIT-naive practices contemplated offering non-FDA-approved POIT but cited concerns about the medicolegal liability associated with administering a nonstandardized, non-FDA-approved therapy as the main reason for postponing POIT use. Physicians also described reluctance to dedicate staff to a resource-intensive treatment when they were uncertain that insurers would pay without an approved POIT product and reimbursement codes. Occasionally, the physicians mentioned lack of trained staff and space.

POIT practices reported patients' desire for a more active choice beyond avoidance to alleviate the anxiety caused by the fear of accidental exposure was the

motivating factor to initiate POIT. Most POIT practices reviewed POIT published literature and discussed the pros and cons of use with trusted experts and colleagues experienced with POIT. The physicians addressed legal risks by using informed consent forms that clearly outlined a confirmed peanut allergy diagnosis, the experimental nature of POIT, all possible associated safety risks, and patient instructions regarding symptoms to observe and report, and emergency care. Patient and family education also included advice regarding the possibility of POIT reactions during times of illness (e.g., viral upper respiratory infection). Common questions raised by patients and families centered around the time commitment to undergo desensitization and potential risks.

Patient selection for POIT varied and was not well defined. However, all the physicians described using clinical and social criteria when selecting candidates.

Commonly cited clinical criteria included patient age, typically >4 to 7 years to ensure that the child could communicate adverse symptoms, and the absence of a history of systemic reactions or anaphylaxis. Approximately 40% of the allergists interviewed excluded patients with comorbidities or multiple allergies as candidates and cited that these patients were more prone to experience an adverse reaction. Conditions mentioned varied and included cardiovascular disease, asthma and/or allergic asthma, and atopic dermatitis. Most of the physicians also factored in their personal estimation of the patient's peanut allergy severity and described the ideal candidate for POIT as one who experienced moderate peanut allergy reactions.

Commonly mentioned symptoms used to describe moderately severe peanut allergies included diarrhea, stomach cramps, nausea, vomiting, a sensation of tightness in the throat, or wheezing after an accidental exposure. Generally, physicians believed that patients who had a history of anaphylaxis with restricted airway and lower blood pressure were poor candidates for POIT. Only a few of the physicians (2 of 14) who had multiple years of POIT experience offered POIT to patients with a history of life-threatening anaphylaxis, citing that these patients would benefit the most from treatment. Social factors also weighed heavily in selection and included the level of risk of accidental exposure and a clear sense that the patient or family was committed and motivated to follow the desensitization approach. Physicians emphasized the importance of a supportive family environment to safeguard long-term treatment adherence. As part of a shared decision-making process, physicians described dedicating 30–60 minutes to discussion of risks and benefits, and commitment requirements for undertaking POIT with caregivers to enable them to make an informed choice.

Practice-developed POIT approaches were based on published studies, university hospital–developed, and colleague-adopted approaches that described POIT methods. Still, many differences existed in terms of the peanut material, start and end doses, up dosing intervals, and maintenance dose (Table 2). Although the use of a 2-week up dosing interval is common, several of these allergists stressed that dosing amounts and intervals must be patient tailored. All warned that the overall time frame for up dosing is determined by the patient's ability to tolerate up dosing levels.

OIT Preparation

OIT peanut product sourcing and preparation varied greatly across practices, but all of the physicians and nurses agreed that in-house preparation was time and labor intensive. Some practices crushed whole peanuts, whereas others used peanut flour; all weighed out the desired dose with a highly sensitive scale. Several prac-

tices reported using low-dose measuring spoons that can measure out 1/32 tablespoon of peanut butter. Peanut product for up dosing as well as the maintenance doses to be administered at home were prepared by the nurse before each appointment or on the patient's arrival; home doses were prepackaged for storage. Only one physician used a compounding pharmacy. Generally, the physicians preferred to control all aspects of product handling to ensure safe accurate preparation.

Practice and Personnel Logistics

The allergists typically administered the initial POIT dose, and the nurses monitored the patient. Dedicated nurses managed POIT administration of up doses; observation required 1–2 hours of use of an examination room or food challenge area. Typically, POIT-experienced practices managed two to five patients for POIT simultaneously, based on the size of the practice and staff availability. Some of the physicians preferred to schedule all patients on POIT dedicated days or time slots to optimize resources and workflow efficiency. Mornings or early afternoon appointments were preferred to easily manage potential reactions, and patients were generally instructed to take maintenance doses earlier in the day.

Nearly all the practices followed a missed-dose procedure based on experience or colleague recommendations. If a patient missed a single dose, then most of the physicians allowed the patient to continue at the same dosing level. If a patient missed multiple doses, then most of the allergists titrated down to the previously tolerated dose. Alternative approaches described included dropping the dose to one-half of the dose after missing 1 week or to one-fourth of the dose after missing 2 weeks. The allergists also considered how far along the patient was in the up dosing process. If a patient repeatedly missed doses, then some of the physicians discontinued treatment. However, most of the physicians and nurses found that patients on POIT were highly motivated and that nonadherence was uncommon. The allergists and the practice nurses managed after-hours support for patients on POIT; after-hours calls were uncommon and generally attributed to mild symptom management.

DISCUSSION

Here we reported descriptive results from the structured interviews of physicians who choose to offer or not offer POIT to share their perspective on various attitudes and practice behaviors reported. These findings discerned similarities and differences in peanut allergy diagnostic approaches as well as factors that motivated and restrained allergy practices from introducing non-FDA-approved POIT to patients. Food

Table 2 Select peanut OIT approaches in the United States

Practice Type	OIT Material	Start Dose	End Dose	Time Interval Between Updoses	Total Time of Updosing	Maintenance Dose (per day)
University based	Peanut protein	0.1 mg	3 Peanuts (~750 mg peanut protein)	2 wk	Varies	3 Peanuts (~750 mg peanut protein)
University based	Crushed peanuts	0.1 mg	400–500 mg	2 wk	4–6 mo	400–500 mg crushed peanuts
Community	Peanut flour	0.1 mg	4 Peanuts (~1 g peanut protein)	1 wk	3 mo	4 Peanuts (~1 g peanut protein)
Community	Peanut butter	1/32 Tbsp	2 Tbsp	2 wk	Varies	~2 Tbsp peanut butter
Community	Liquid peanut extract	2 Drops of 1:1000 or 1:10000 dilution	8 Drops of 1:1 Dilution	2 wk (8 drops are the maximum dilution)	6 mo	8 Drops of 1:1 dilution (final challenge: 2 tbsp of peanut butter/25 peanuts)
Community	Peanut protein	25 μ g	2.5–10 g	2 wk	~34 wk	Up to 10 g peanut protein
Community	Crushed peanuts	1/1000 mg	250–300 mg (~1 peanut) up to 4 peanuts	2 wk	~6 mo to reach 4 peanuts	1–4 Peanuts (~250 mg to 1 g peanut protein)
Community	Crushed peanuts	Varies (0.01–0.2 mg)	5 g	Varies, usually 2 wk	Varies	Varies, typically 5 g crushed peanuts

OIT = Oral immunotherapy.

challenges as a method of confirming a peanut allergy diagnosis is reserved for those few patients whose serologic or skin test results are inconclusive. Although the allergists accepted the scientific principles associated with immunotherapy and routinely administered standard of care, guideline-validated, and/or FDA-approved immunotherapy to desensitize patients with environmental allergy, many of the physicians hesitated to incorporate POIT into their clinical practice without an FDA-approved product that offers standardized guidance on initiation, up dosing, and maintenance dosing.

POIT-naïve practices commonly cited the risk of reaction as a chief concern. Although initial open-label studies indicate that POIT can be safely administered, reported data indicate that a risk of reaction can occur during the initial escalation day (93%), buildup phase (46%), and home dosing (3.5%).¹⁵ The most commonly cited reactions were mild-to-moderate upper respiratory tract and abdominal symptoms. Even though the physicians who were POIT naïve perceived these risks to be low, their reservations stemmed from the fact that most published data are primarily from small studies or case reports and did not evaluate long-term outcomes. Naïve practices perceived that the medicolegal jeopardy associated with POIT outweighed the benefits, whereas POIT proponents advocated reducing the stress and fear of anaphylactic reactions from accidental exposure and the burden of hypervigilance outweighed the risk. Although accurate anaphylaxis-related data are sparse, fatal food-triggered anaphylaxis rarely occurs, with a reported incidence of 1.35 to 2.71 per million person-years.¹⁶ Still, in children and young adults, food remains the most common cause of severe anaphylaxis^{16,17} which prompts POIT practices to offer a proactive approach to peanut allergy management to address patients' needs.

The absence of treatment guidelines and the lack of an FDA-approved standardized product contribute to the substantial variability in POIT approaches. Although some of the physicians advocated that patients with severe peanut allergy may receive the greatest benefit from desensitization, most of the allergists with POIT experience who were interviewed offered POIT to patients with a history of moderate reactions to reduce the risk of anaphylaxis to immunotherapy. Most of the allergists (12/14) did not offer POIT to patients with a history of anaphylaxis, whereas two practitioners from academic centers who had more POIT experience did offer it to these patients. All the practitioners agreed that selection of patients for POIT requires motivated and adherent patients and families. Undertaking POIT requires that practices accommodate extended patient and caregiver consultative visits to provide adequate time for interactive discussion about the benefits, potential risks,

and POIT treatment requirements for an informed choice.

The physicians were less uniform about other criteria related to the existence of multiple allergies and/or the presence of various comorbid conditions. This highlighted a need for a more uniform POIT practice. All interviewed physicians who administered POIT preferred a gradual steady buildup approach in which the patient undergoes a series of incremental dose increases in the office under observation and self-administers that daily dose at home in between visits. Yet, the peanut material, amount administered, duration of buildup, and ending dose tended to be tailored based on individual practice procedures. Key logistical barriers described included labor-intensive, time-consuming POIT dose preparation and educational material development. However, scheduling logistics and patient volume management did not seem to constitute significant challenges for practices.

There were a few limitations to consider in this descriptive study. The sample of interviewed physicians was small, and the mix of practices was enriched to include individuals with experience in administering POIT in a variety of clinical settings as well as POIT-naïve practices. Thus, individuals who participated may not have been representative of practice views and POIT approaches in the broader allergist medical community. This study was also conducted before the availability of large-scale safety and efficacy data from the Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (PALISADE) NCT02635776, a phase III study. Because the PALISADE study enrolled more subjects than the combined total of all other published OIT treatment trials and included patients with a high comorbidity burden, it is possible that data from this study will alter allergists' perception of POIT. Nevertheless, this study was intended to be descriptive and to raise awareness of the POIT approaches being used in the clinical setting in a nontrial environment.

CONCLUSION

All interviewed physicians suggested a strong need for effective, standardized, FDA-approved, disease-modifying POIT treatments with proven long-term outcomes.

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