

Oral Food Challenges in Infants and Toddlers



Justin Greiwe, MD^{a,b,*}

KEYWORDS

• Food allergy • Oral food challenge • Anaphylaxis • Infants • Epinephrine

KEY POINTS

- Oral food challenges are a critical procedure to identify patients with IgE-mediated food allergy when the history and testing are not specific enough to confirm a diagnosis.
- Food challenges in infants and toddlers are both safe and practical in a clinical setting.
- Comprehensive past medical history is critical in the diagnosis of food allergy and should be used to determine subsequent testing and interpretation of results.
- Food allergies are associated with significant social and psychological consequences that often are overlooked by health care professionals.
- More emphasis needs to be placed on food challenge education and hands-on experience during fellowship training.

INTRODUCTION

Oral food challenges (OFCs) remain the gold standard for diagnosis of food allergy. Although double-blind placebo-controlled OFCs are the criteria standard, they are time consuming and unrealistic in a clinical setting and, therefore, reserved mainly for research purposes. Open (nonblinded) challenges are the method of choice, with ingestion of meal-sized portions of the concerning food prepared in its usual state. OFCs often are recommended when there is an approximately 50% likelihood that the food challenged will be tolerated based on available data and clinical history.

SAFETY

OFCs are an indispensable tool for accurately diagnosing clinically relevant food allergy; however, their use in clinical practice is not widespread due in part to supposed safety concerns. Infants especially are perceived as high-risk because they are

Disclosure: Dr J. Greiwe is a speaker for Regeneron and Sanofi Genzyme and on advisory boards for AstraZeneca and Genentech.

^a Bernstein Allergy Group Inc, 8444 Winton Road, Cincinnati, OH 45231, USA; ^b Division of Immunology/Allergy Section, Department of Internal Medicine, The University of Cincinnati College of Medicine, Cincinnati, OH, USA

* 8444 Winton Road, Cincinnati, OH 45231.

E-mail address: jcgreiwe@gmail.com

Immunol Allergy Clin N Am 39 (2019) 481–493

<https://doi.org/10.1016/j.iac.2019.07.003>

0889-8561/19/© 2019 Elsevier Inc. All rights reserved.

immunology.theclinics.com

smaller, nonverbal, and more difficult to objectively monitor. Allergic reactions in this age group present diagnostic challenges that can dissuade caregivers from providing OFCs for their patients. Infants, for example, are unable to describe certain symptoms, such as pruritus or throat tightness, and can develop behavioral changes and increased irritability that can be difficult to interpret because they may occur in healthy infants as well. Objective pulmonary function testing is also not feasible in this age group, so an accurate assessment of lung function is not available. With time and experience, recognizing subtle, nonverbal infant cues of a reaction becomes easier and can include signs like ear picking, tongue rubbing, neck scratching, putting a hand in the mouth, and a change in general demeanor (ie, quiet, withdrawn, clingy, or fussy).¹ Differentiating between normal, immunoglobulin E (IgE)-mediated, and non-IgE-mediated symptoms is where physician experience comes into play.

Despite perceived concerns, the data suggest OFCs, including infant OFCs, are both safe and practical in a clinical setting.^{2–5} Akuete and colleagues,⁶ for example, analyzed 6377 OFCs from 2008 to 2013 and a large majority (86%) were challenged without a reaction. Only 2% required epinephrine, leaving 98% of OFCs completed without symptoms of anaphylaxis, demonstrating OFCs are much safer than previously thought. This is in stark contrast to previous studies where epinephrine usage during OFCs was closer to 6% to 33%.^{7–11} Late-phase and biphasic reactions after OFCs are rare, with an estimated occurrence of approximately 1.5% to 4% in previously published studies.^{12–14} One known fatality has been documented (2017) since the description of modern OFCs published in 1976.¹⁵ Additional data demonstrate safety and efficacy in children less than 18 months old as well, with most reactions being mild in presentation and limited to the skin. Infants seem to have a low rate of anaphylaxis with infrequent use of epinephrine and intensive care unit admissions.^{2–4,16–18}

ACCURACY OF TESTING

Accurately interpreting serum and skin testing for food allergies has been an ongoing issue in the field of allergy and immunology, often leading to mislabeling of the food allergy diagnosis. This discrepancy is due in part to both the poor sensitivity and specificity of current testing available as well as the impressive differences in user interpretation. Practice approaches involving testing administration and interpretation vary greatly within the subspecialty, which has likely led to a misrepresentation of true IgE-mediated food allergy versus sensitization. Both skin prick testing (SPT) and food-serum-specific IgE (slgE) testing are relied on heavily to screen patients for sensitivity to specific foods and to determine if OFCs should be considered. SPT to foods has a high negative predictive value (NPV) but poor positive predictive value (PPV) of only 50%.¹⁸ Negative SPT effectively confirms the absence of an IgE-mediated process (NPV >95%).¹⁹ Skin testing protocols, extracts, and testing devices may vary, which can affect reliability of testing. ImmunoCAP is the most common serologic method used to test for food allergies; however, alternative assays are not identical.

Past medical history, therefore, is critical in the diagnosis of food allergy and should be used to determine subsequent testing and interpretation of results. Many patients come to an office with positive testing but no history of ingestion or reaction. The most common example is an infant with moderate/severe eczema who underwent broad-panel slgE food testing. Age, clinical history, and history of sensitivity but no exposure also may affect accuracy of testing. To make matters more confusing, a large proportion of patients have intermediate values on skin and/or serum testing.

Criteria indicating high or low probability of passing vary among studies but there are certain trends that improve the accuracy of testing. Larger SPT wheal size (>8 mm) and higher food-sIgE levels are associated with persistent food allergy and higher rates of failed challenges. Rate of change of these levels can help predict likelihood that food allergy has resolved.^{20,21} There have been multiple attempts to provide guidance based on sIgE levels associated with a 50% PPV and 95% PPV for clinical allergy.^{22,23} Guidelines suggest using the 50% PPV to guide the timing of an OFC. The Standardized Clinical Assessment and Management Plan for food challenges is another tool that has been published that attempts to improve sIgE and SPT thresholds and triage patients safely into either a low-intensity or high-intensity care setting for OFC.²⁴ Although these values can act as a guide, serum testing should always be interpreted on a case-by-case basis. Factors such as an absence of history of a clinical reaction to the food, a prior history tolerance to a food, African American race, concomitant inhalant allergies, atopic dermatitis (AD), older age, and high total IgE can all lower the probability of a true clinical food allergy. Fleischer et al. examined a cohort of 125 AD patients and reported that no patient with a sIgE level below the 95% predictive decision point for milk, egg, or peanut failed an OFC suggesting that reliance on serum food-specific IgE testing to determine the need for food elimination diets in children, especially those with AD, is not sufficient.⁶ In addition, Frischmeyer-Guerrero et al. estimated that AD subjects with a milk IgE of 43 kUA/L, egg IgE of 28 kUA/L, and peanut IgE of 34 kUA/L had at least a 50% chance of not being allergic to the food.²⁵ Relying solely on these predictive values to make clinical decisions can lead to misdiagnosis, as demonstrated in the clinical scenario outlined in **Table 1**.

According to the available data, the 3-year-old boy described in **Table 1** should not have been challenged to any of these foods. Instead of condemning this patient to years of restrictive eating and social isolation, an honest conversation was started with the parents on the risks and benefits of attempting OFCs under observation in a supervised setting. Although this conversation is often difficult for all parties involved, it is necessary to provide the best possible care for patients. Although the example provided in **Table 1** is an extreme case, there are millions of children in the United States avoiding foods that they might not be allergic to, subjecting families to increased financial burdens (clinician visits, specialty foods and diets, and lost

Table 1
Exception to the rule, a recurring theme with oral food challenges

A 3-year-old boy with a history of multiple food allergies and severe eczema as an infant comes to your office for further evaluation. At 12 months old the patient had broad-panel food sIgE completed which showed the following:

Total IgE 3873 IU/mL	Sesame 87.6 kU/L	Almond 64.1 kU/L
Egg white 75.3 kU/L	Wheat >100 kU/L	Cashew >100 kU/L
Cow's milk >100 kU/L	Chickpea >100 kU/L	Pistachio 97.5 kU/L
Pea >100 kU/L	Lentils 96.1 kU/L	Walnut 30.8 kU/L
Hazelnut 68.6 kU/L	Pecan 10.2 kU/L	

- SPT: wheals anywhere from 6 mm to 9 mm; some skin tests were negative.
- Told to avoid all these foods despite never ingesting leading to a very restrictive diet, poor growth, and poor nutrition.
- Eczema has significantly improved over the last 2 years and recent SPT demonstrate wheals anywhere from 6 mm to 9 mm; some skin tests were negative.
- Passed OFC: baked then uncooked eggs, baked milk, all tree nuts except cashew/pistachio, chickpea, pea, lentils, and sesame.
- Failed OFC: wheat (with final dose) and cashew/pistachio.

productivity due to time off work/school), nutritional deficiencies/lifetime of picky eating, sibling effects (entire family often practices avoidance even if they do not have a food allergy), and social/psychological consequences. To avoid accidental exposures, some parents try to control all situations, leading to isolation and fear. Hypervigilance can instill excessive amounts of anxiety in food-allergic children, which sometimes spills over into other areas of life, leading some parents to home-school, forbid normal social interaction like sleepovers and birthday parties, and even avoid traveling on airplanes or sporting events.

To save parents and patients from going down this rabbit hole of fear and anxiety, physicians must take it upon themselves to properly educate families of food allergic children on the real risks of accidental exposure and challenge those whose history and evaluation might not be consistent with an IgE-mediated response. The example discussed previously suggests that current testing modalities are inaccurate and should be approached with more skepticism rather than thought of as absolute truth. Good old-fashioned comprehensive food allergy history and clinical judgment are still important when diagnosing food allergy, and blind reliance on testing has led to a lot of misdiagnosis.

Food testing that is not validated includes food-specific IgG and IgG4 tests, which typically yield multiple positive results, leading to unnecessary avoidance and restrictive diets. Positive results with these tests likely represent normal immune responses to foods and should not be used to diagnose food allergy or food intolerance. Other tests that should be avoided include sublingual or intracutaneous provocation tests, tests of lymphocyte activation, kinesiology, cytotoxic tests, and electrodermal testing.

Food allergy diagnosis and testing are still as much art as science and remain an area of medicine where experience and clinical judgment still matter. To help improve the accuracy of food testing, several additional methods are being investigated to aid in diagnosis and monitoring for tolerance. These include IgE epitope specificity, component-resolved diagnostics, IgE/IgG4 ratio, cellular-based assays, basophil activation test, and specific IgA and IgA2 levels.^{22,26–32} Ultimately, current modalities are inadequate, and both skin and serum testing have limited predictive power to determine which patients are likely to pass an OFC.^{33–35} More sensitive and specific biomarkers are needed that provide better correlation with clinical reactivity to both specific IgE-mediated and non-IgE-mediated food reactions.

THE NUTS AND BOLTS OF FOOD CHALLENGES

The approach to OFCs should be straightforward and handled with the same attention to detail as with other risky procedures done in the office setting like subcutaneous allergen immunotherapy or drug challenges. All OFCs should be standardized and follow these simple steps:

1. Initial assessment, including physical examination
2. Monitoring of vital signs before, during, and after challenge
3. Administration of food in a standardized manner: starting low and gradually increasing until a cumulative dose equivalent to a standard portion for age is consumed
4. Symptoms (if present) treated

This pattern should be repeated in a similar manner for all patients, mirroring an assembly line to maximize efficiency and minimize errors. There should be predetermined protocols that include both high-risk and low-risk protocols depending on the clinical history of reaction as well as results of serum and/or skin testing (Table 2).³⁶

Table 2 Risk assessment for oral food challenges	
Low risk of reaction	1. Recent accidental ingestion to small amount of food without clinical symptoms 2. Favorable test results^b
High risk of reaction	1. Recent reaction to the food in the past 6–12 mo 2. Diagnostic or high-positive test results
Low risk of severe reaction ^a	1. No past severe reactions 2. Food not usually implicated in severe food-induced anaphylaxis (eg, meat, fruit, and vegetable^c) 3. No asthma
High risk of severe reaction	1. Past severe reaction 2. Severe reaction to trace amounts of food 3. Food frequently implicated in fatal and near-fatal food-induced anaphylaxis (eg, peanut, tree nuts, fish, shellfish, and seeds) 4. Asthma (regardless of severity) 5. Conditions that may affect the resuscitation: cardiovascular disease, difficult vascular access or intubation, β-blocker medication

^a Severe reaction is defined as any lower respiratory or cardiovascular symptoms or any 4 organ systems involved.

^b Laboratory cutpoints for deferring OFC were defined for a few foods in children. These cutpoints have not been evaluated in adults with food allergy.

^c A food is capable of inducing a severe anaphylactic reaction, including fruits and vegetables. The patient's previous reactions should be a guide for assessing the risk of a potential reaction during an OFC.

Adapted from Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, et al. Work Group report: oral food challenge testing. *J Allergy Clin Immunol* 2009;123(6 Suppl):S367; with permission.

For food challenges in a clinical setting to be successful, the office needs to be set up for success. This includes maximizing efficiency of the physical layout of the office as well as the supporting staff. Key components to performing successful food challenges are outlined in [Fig. 1](#).

Although not everyone is able to change the layout of an office due to space limitations and/or cost, there are certain office setups that are better suited for providing multiple food challenges at once. A large common dosing area that is clearly visible from the nursing station offers many advantages, including

1. Quick, easy dosing administration
2. The ability to clearly observe clinical reactions
3. More nurses available to administer doses and check vital signs/peak flow
4. Allowing multiple challenges to be performed at once

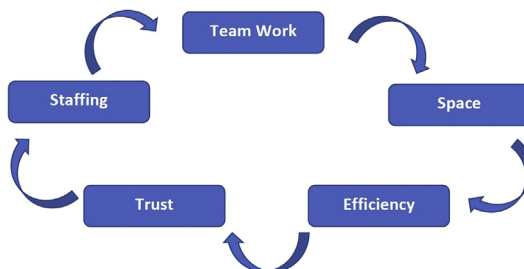


Fig. 1. Key components to performing successful food challenges in clinical practice.

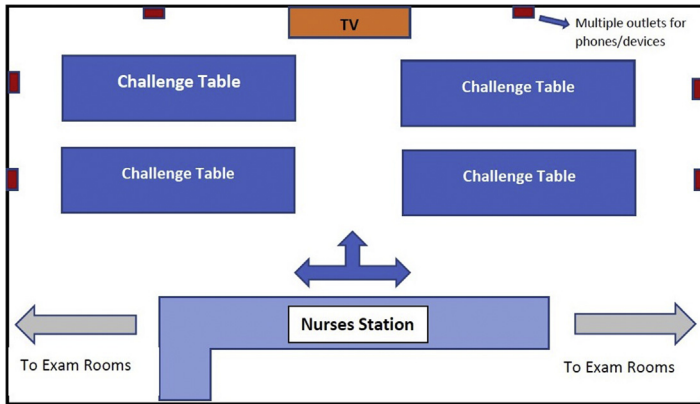


Fig. 2. Example of an office space amenable to OFCs.

5. Not monopolizing examination rooms; providing a community feel, fostering healthy patient-patient and parent-parent interactions
6. Added benefit of increasing distractions for kids undergoing challenges

An example of an ideal setup is included in [Fig. 2](#). In this setup, there is a clear line of vision from the nurses station to the challenge tables, with a room large enough to perform multiple challenges and skin tests at the same time. Patients experiencing more severe reactions can be removed from the communal area, examined, and administered treatment accordingly. Challenge tables should be cleaned and wiped down thoroughly between patients to limited risk for accidental exposure. The nurses station should be an area removed from patient access to reduce the risk of allergen cross-contamination and have space where food may be heated and measured. It also should be equipped with a small food scale, which may be necessary for graduated challenges, and be well stocked with clean, disposable plates, cups, and utensils.

AVOID DELAYS/FAILURES

Food allergies are associated with significant social and psychological consequences that often are overlooked by health care professionals. Anxiety and fear are so pervasive with this condition that many OFCs are cut short due to the inability of a patient or parent to proceed, often with no indication of a clinical reaction. Children and their parents report a range of psychosocial concerns that include parenting stress, fear of reaction, chronic anxiety around mealtime, depression, and worries about bullying. To avoid accidental exposures, some caregivers attempt to control their child's environment by limiting social interaction by home-schooling, forbidding sleepovers and birthday parties, avoiding traveling on airplanes, and not attending certain sporting events, all of which can be isolating for their food-allergic children. This hypervigilance can instill excessive amounts of anxiety and fear, which can affect all members of the family, food allergic or not.^{37–39} For most families, the primary question that must be addressed is how to balance the vigilance and preparedness required of a potentially life-threatening chronic illness with anxiety management and engagement in developmentally appropriate activities.⁴⁰

Addressing the psychological impact of food allergy for both patients and parents is an unmet need that needs to be addressed prior to any OFC in the office. Tackling these concerns early on will save valuable time in the future and help foster trust by

normalizing parent and patient feelings. If symptoms are concerning enough, referral to a mental health professional for consultation is indicated to improve coping strategies and improve quality of life. Cognitive behavioral therapy is a well-validated, collaborative treatment that focuses on the relationships of thoughts, feelings, and behaviors. Cognitive behavioral therapy helps patients and parents identify patterns of thinking and behavior that contribute to distress and learn ways to change these patterns in a positive direction.^{37,41}

To avoid OFC delays or failures related to increased anxiety and stress, an attempt must be made to create a relaxing, child-friendly environment. Tablets, toys, books, and other activities should be encouraged to aid in distracting patients during challenges and help avoid subjective complaints, which can often derail a challenge before it has the chance to get started. Parents should bring their child's favorite cups, plates, and utensils from home to create a sense of familiarity. There should be lots of food challenge options available in both liquid and solid forms along with tasty mixers and condiments to mask bad tastes, including ketchup, chocolate sauce, ice cream, applesauce, candy, and so forth. Infant challenges require additional preparation secondary to unique issues that arise due to their age and size (**Box 1**).⁴²

PREPARE AND CONSENT

Preparing for a successful OFC in the office does not start the day of the challenge but instead starts at the initial consultation. Most of the time and effort should be spent at the initial visit beginning with a comprehensive medical history, including a detailed timeline of previous food reactions, amount of suspected food that was ingested, the form of food ingested (baked, raw, or canned), timing from ingestion to onset of symptoms, and whether the suspected food was tolerated without symptoms either before or since the reaction occurred. Reviewing changes of previous sIgE and/or skin tests over time provides more insight into disease progression and can help determine if a patient is a candidate for challenge. The final and most important

Box 1

Issues unique to infant oral food challenges

- Appropriate portion sizes for age
 - Portion size is more important than protein content.
 - Infant may not eat entire portion but may eat enough to rule out diagnosis.
- Appropriate vehicles/food forms
 - Soft/pureed
 - Avoid choking hazards (ie, peanut and tree nut kernels).
 - Have alternative food options available (ie, butters, puffs, and liquids).
- Provide mixing vehicles/condiments infant has previously tolerated.
- Allow ample time to feed.
 - Infants often dictate visit length so reserve plenty of time.
- Appropriate weight-based doses of emergency meds should be available.
- Familiarity with age-appropriate vital signs
 - Appropriately sized blood pressure cuffs
- OFC planned for a time of day when the infant is normally awake and alert
 - Avoid appointments during nap time.

Data from Greenhawt M. Pearls and pitfalls of food challenges in infants. *Allergy Asthma Proc* 2019;40(1):62-69.

step is educating the family on the nuances of a food allergy diagnosis, including everything from developing a food allergy and anaphylaxis emergency care plan, to how to read food labels, to ordering safe foods in restaurants and while traveling, to managing food allergy in school and daycare settings, and to knowing what cross-contamination exposures are worrisome and which are not. After determining that an in-office food challenge is indicated, specific questions should be addressed before the actual OFC appointment. Standard questions include:

1. What is an OFC?
2. What are the reasons to perform an OFC in the office versus at home?
3. What are the benefits?
4. What are the risks?
5. What needs to be done in preparation for an OFC?
 - a. Medications that need to be stopped, including antihistamines
6. Who provides the food?
 - a. Standardized recipes of baked milk and baked egg
 - b. Bringing nut butters from sources where foods are not cross-contaminated
7. What happens the day of the challenge?
 - a. Timing, sequence of events
 - b. How long do I have to stay after challenge is completed?
 - c. Make sure parents are aware of timeline; allocate approximately 4 hours to 6 hours.
8. What is the usual treatment in case of an allergic reaction?
9. If challenge is passed, how much and how often does food need to be ingested?

A phone call 1 day to 2 days prior to the OFC is important to confirm that the patient is well with no health issues that could affect interpretation of the challenge.⁴² This is especially important in nonverbal infants where a concurrent illness during OFC could lower the threshold to react or increase the risk of a more severe reaction. Challenges should be scheduled in the morning or early afternoon so that patients have extra time in office for observation in case a reaction occurs. In preparation for the challenge, patients should not eat for at least 4 hours prior because fasting has been shown to enhance absorption of the challenged food.³⁶ For infants and toddlers, a light meal can be administered at approximately 2 hours before the challenge. It is important to time challenges to coincide with mealtimes, specifically breakfast or lunch. The concerning food served alongside chosen mixers or condiments can serve as a meal and improve chances of completing the challenge. Any food residue left on lips, face, and hands should be wiped off immediately to avoid contact irritation.

On the day of the challenge, baseline vital signs should be obtained, including respiratory rate, heart rate, blood pressure and peak flow if able. If the peak flow is low or there are concerns for asthma, a spirometry should be performed to exclude asthma. Patients with previously confirmed asthma should have a baseline spirometry prior to any challenges to confirm lung function is stable. Good asthma control prior to OFCs is essential for the safety of the patient. Optimizing control of other allergic conditions like allergic rhinitis and AD cannot be overlooked as well. Better control of atopy in general can minimize the risk of a severe reaction and limit variables that could affect interpretation of the challenge outcome. Physical examination findings should be documented as well to serve as a reference in case there are any changes during the challenge. Emergency medications should be readily accessible (high-risk challenges may have epinephrine drawn up and ready to go). Before proceeding, a standardized informed consent should be reviewed with the parents in detail and signed before any challenge takes place. It is the opinion of the author that written informed

consent should be mandatory for any possible life-threatening procedure and should be standard practice in any office offering OFCs.

In addition to documentation of consent, OFC flow sheets/procedural forms should be meticulously maintained during the challenge. Detailed recordings of time, doses, vital signs, symptoms, and intervening treatments improve safety and accuracy of the challenge and provide a historical record that can be referred to in the future if needed. Timers can be used to keep challenges on track, especially in busy practices where multiple food challenges are taking place at the same time.

PREASSIGNED ROLES

To streamline efficiency and improve safety of OFCs, there needs to be clear, defined roles for the entire treatment team. In busy offices, preassigned roles limit errors and

Box 2

Proposed stopping criteria infant peanut oral food challenge for early peanut introduction

Adverse Reactions to Foods Committee of the AAAAI proposed food challenge stopping criteria^a

The OFC should be stopped if any one of the following symptoms are present during the OFC:

Skin

- ≥ 3 urticarial lesions
- Angioedema
- Confluent erythematous, pruritic rash

Respiratory

- Wheezing
- Repetitive cough
- Difficulty breathing/increased work of breathing
- Stridor
- Dysphonia
- Aponia

Gastrointestinal

- Vomiting alone not associated with gag reflex
- Severe abdominal pain (such as abnormal stillness, inconsolable crying, or drawing legs up to abdomen) that persists for ≥ 3 minutes

Cardiovascular

- Hypotension for age not associated with vasovagal episode

If 2 or more of the following are present, the OFC should be stopped:

Skin

- Persistent scratching for ≥ 3 minutes

Respiratory

- Persistent rubbing of the nose or eye for ≥ 3 minutes
- Persistent rhinorrhea for ≥ 3 minutes

Gastrointestinal

- Diarrhea

Can be generalized to any infant challenge.

Suggested food challenge stopping criteria from the Adverse Reactions to Foods Committee of the AAAAI.

^a It is important to note that the physician is encouraged to use discretion and clinical judgment when assessing the challenge outcome. Whenever observed signs or symptoms are inconclusive, it may be appropriate for the clinician performing the challenge to decide if a challenge dose should be repeated, the next dose should be delayed, or if the challenge should be stopped and repeated on another day. If clinically indicated, dosing is stopped. Objective symptoms that recur on 3 doses or persist (eg, 40 minutes) are more likely indicative of a reaction than when such symptoms are transient and not reproducible.

From Bird JA, Groetch M, Allen KJ, et al. Conducting an Oral Food Challenge to Peanut in an Infant. *J Allergy Clin Immunol Pract* 2017;5(2):309; with permission.

allow clinics to accommodate multiple food challenges at once. Specific roles can include determining who prepares and divides up the food for challenge, who performs vital signs and assesses symptoms, who administers doses, and who administers treatments should a reaction occur. The patient should be closely monitored throughout the duration of OFC, with re-examination at regular intervals by experienced observers trained in OFCs. At the first sign/symptom of an allergic reaction, a physical examination should be performed and include auscultation of the chest, inspection of the skin and oropharynx, and repeat vital signs and peak flow. Subjective complaints are common, especially with the first few doses. Classic symptoms include nausea and throat, mouth, and skin itch as well as a sensation of throat tightness or globus sensation (usually with no other findings). For mild symptoms, a period of observation should be allowed before giving the next dose. Administering epinephrine at the first sign of a reaction should be avoided if criteria have not been met for anaphylaxis. There also should be clearly determined stopping criteria and a standardized treatment approach for all patients, with a plan on how to transfer patients to the emergency room in refractory cases (Box 2).⁴³ In group practices, assessing providers should agree with these criteria to avoid confusion among ancillary staff. OFCs are not always clear-cut, so questionable reactions can be treated at the discretion of the physician. The supervising physician should always be onsite for OFCs and perform the prechallenge examination as well as be available for any reactions should they occur. In a busy practice, limiting disruptions to patient flow is important, but staff should feel free to interrupt the treating physician if any concerns arise during a challenge. Every effort should be made to standardize and streamline OFC procedures to limit confusion, provide continuity among providers, and maximize safety. Standardized approaches should be used when administering food using premeasured doses as well as standardized protocols for stopping and treating any reactions should they occur. Clear, well-understood, prespecified stopping criteria is a key safety feature in published clinical trials and likely contributed to the low rates of anaphylaxis reported.

If the OFC is successful, clear postchallenge instructions should be provided to the parents encouraging regular consumption at home. This is especially true if baked challenges are completed, so parents know what foods are safe and what foods still need to be avoided. There are few data regarding the appropriate amount of the allergenic food that needs to be ingested after a successful OFC. Based on available evidence and consensus opinion, regular consumption at least 3 days a week is recommended.⁴³ In rare situations, there can be relapse in children who pass a challenge but fail to consistently incorporate concerning foods into their diet, so follow-up in 3 months to 6 months is recommended to reinforce the importance of regular ingestion.^{16,43,44}

FUTURE CONSIDERATIONS

Although the need for OFCs continues to increase, there seems to be an increasing reluctance to offer them in clinical practices. This trend was demonstrated in a work-group report from the American Academy of Allergy, Asthma & Immunology (AAAAI) Adverse Reactions to Foods Committee (ARFC).⁴⁵ A survey was provided to both AAAAI and American College of Allergy, Asthma & Immunology (ACAAI) members looking at OFC practices among allergists in the United States. It was based on a food allergy survey administered by Pongracic and colleagues in 2009 that was updated to reflect recent advances in food allergy and knowledge gaps that were not addressed in previous survey, such as OFCs in very young children.⁴⁶ Compared to 2009, while more providers offer OFCs, multiple perceived barriers to performing OFCs have worsened over time including lack of time, experience, staff, and office

space. These concerns were heightened in the infant patient population with an emerging pattern of hesitancy to challenge infants despite nearly all respondents reporting seeing patients <12 months of age in their practice. The demand for OFCs in infants and toddlers will likely continue to increase, and existing guidelines (as defined in the National Institutes of Allergy and Infectious Diseases addendum guidelines) are predicated on both access and willingness to perform OFCs in this age group. Additional follow-up surveys related to hesitancy for performing infant OFCs will likely be pursued in order to further clarify barriers and other safety concerns in this age group.

SUMMARY

Food challenges in infants and toddlers seem to be safe when looking at the available data for both high-risk patients with prior history of reactions and infants with no known exposure to the food being challenged. The benefits of OFCs are far reaching and impactful for both patients and their parents. Improvement in quality of life, clarifying unnecessary dietary restrictions, increased social interactions, and reduction in fear and anxiety are just a few of the many advantages of providing this service. Demand for OFCs in infants and toddlers will continue to increase in the coming years. Board-certified allergists will need to meet these demands by providing this service in a safe and welcoming environment. The barriers discussed in the recent ARFC survey need to be addressed, including more comprehensive food challenge education and hands-on experience during fellowship training, so patients can receive the care they deserve.

REFERENCES

1. Simons FE, Sampson HA. Anaphylaxis: Unique aspects of clinical diagnosis and management in infants (birth to age 2 years). *J Allergy Clin Immunol* 2015;135:1125–31.
2. Palmer DJ, Sullivan TR, Gold MS, et al. Randomized controlled trial of early regular egg intake to prevent egg allergy. *J Allergy Clin Immunol* 2017;139:1600–7.e2.
3. Wei-Liang Tan J, Valerio C, Barnes EH, et al. A randomized trial of egg introduction from 4 months of age in infants at risk for egg allergy. *J Allergy Clin Immunol* 2017;139:1621–8.e8.
4. Bellach J, Schwarz V, Ahrens B, et al. Randomized placebo-controlled trial of hen's egg consumption for primary prevention in infants. *J Allergy Clin Immunol* 2017;139:1591–9.e2.
5. Mankad VS, Williams LW, Lee LA, et al. Safety of open food challenges in the office setting. *Ann Allergy Asthma Immunol* 2008;100:469–74.
6. Akuete K, Guffey D, Israelsen RB, et al. Multicenter prevalence of anaphylaxis in clinic-based oral food challenges. *Ann Allergy Asthma Immunol* 2017;119(4):339–48.e1.
7. Fleischer DM, Bock SA, Spears GC, et al. Oral food challenges in children with a diagnosis of food allergy. *J Pediatr* 2011;158:578–83.
8. Noone S, Ross J, Sampson HA, et al. Epinephrine use in positive oral food challenges performed as a screening test for food allergy therapy trials. *J Allergy Clin Immunol Pract* 2015;3:424–8.
9. Lieberman JA, Cox AL, Vitale M, et al. Outcomes of office-based, open food challenges in the management of food allergy. *J Allergy Clin Immunol* 2011;128:1120–2.

10. Perry TT, Matsui EC, Conover-Walker MK, et al. Risk of oral food challenges. *J Allergy Clin Immunol* 2004;114:1164–8.
11. Ram G, Cianferoni A, Spergel JM. Food allergy to uncommonly challenged foods is rare based on oral food challenge. *J Allergy Clin Immunol Pract* 2016;4: 156–7.e5.
12. Järvinen KM, Amalanayagam S, Shreffler WG, et al. Epinephrine treatment is infrequent and biphasic reactions are rare in food-induced reactions during oral food challenges in children. *J Allergy Clin Immunol* 2009;124:1267–72.
13. Lee J, Garrett JP, Brown-Whitehorn T, et al. Biphasic reactions in children undergoing oral food challenges. *Allergy Asthma Proc* 2013;34:220–6.
14. Osborne NJ, Koplin JJ, Martin PE, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol* 2011;127:668–76.e1-2.
15. Clopton, J. (2017, August 8). Alabama Boy's Death Worries Food Allergy Parents. WebMD Health News. Retrieved from <https://www.webmd.com/allergies/news/20170807/alabama-boys-death-worries-food-allergy-parents>.
16. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372:803–13.
17. Perkin MR, Logan K, Tseng A, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med* 2016;374:1733–43.
18. Perry TT, Matsui EC, Kay Conover-Walker M, et al. The relationship of allergen-specific IgE levels and oral food challenge outcome. *J Allergy Clin Immunol* 2004;114:144–9.
19. Sampson HA. Food allergy. Part 2: diagnosis and management. *J Allergy Clin Immunol* 1999;103:981–99.
20. Shek LPC, Soderstrom L, Ahlstedt S, et al. Determination of food specific IgE levels over time can predict the development of tolerance in cow's milk and hen's egg allergy. *J Allergy Clin Immunol* 2004;114:387–91.
21. Ho MH, Wong WH, Heine RG, et al. Early clinical predictors of remission of peanut allergy in children. *J Allergy Clin Immunol* 2008;121:731–6.
22. Savage J, Sicherer S, Wood R. The natural history of food allergy. *J Allergy Clin Immunol Pract* 2016;4:196–203.
23. Santos AF, Brough HA. Making the most of in vitro tests to diagnose food allergy. *J Allergy Clin Immunol Pract* 2017;5(2):237–48.
24. Simberloff T, Parambi R, Bartnikas LM, et al. Implementation of a standardized clinical assessment and management plan (SCAMP) for food challenges. *J Allergy Clin Immunol Pract* 2017;5(2):335–44.
25. Frischmeyer-Guerrero PA, Rasooly M, Gu W, et al. IgE testing can predict food allergy status in patients with moderate to severe atopic dermatitis. *Ann Allergy Asthma Immunol* 2019;122(4):393–400.
26. Urisu A, Yamada K, Tokuda R, et al. Clinical significance of IgE-binding activity to enzymatic digests of ovomucoid in the diagnosis and the prediction of the outgrowing of egg white hypersensitivity. *Int Arch Allergy Immunol* 1999;120: 192–8.
27. Nicolaou N, Murray C, Belgrave D, et al. Quantification of specific IgE to whole peanut extract and peanut components in prediction of peanut allergy. *J Allergy Clin Immunol* 2011;127:684–5.
28. Tuano KS, Davis CM. Utility of component-resolved diagnostics in food allergy. *Curr Allergy Asthma Rep* 2015;15:32.

29. Caubet JC, Bencharitiwong R, Moshier E, et al. Significance of ovomucoid- and ovalbumin-specific IgE/IgG(4) ratios in egg allergy. *J Allergy Clin Immunol* 2012; 129:739–47.
30. Santos AF, Douiri A, Becares N, et al. Basophil activation test discriminates between allergy and tolerance in peanut sensitized children. *J Allergy Clin Immunol* 2014;134:645–52.
31. Santos AF, Du Toit G, Douiri A, et al. Distinct parameters of the basophil activation test reflect the severity and threshold of allergic reactions to peanut. *J Allergy Clin Immunol* 2015;135:179–86.
32. Konstantinou GN, Nowak-Węgrzyn A, Bencharitiwong R, et al. Egg-white-specific IgA and IgA2 antibodies in egg allergic children: is there a role in tolerance induction? *Pediatr Allergy Immunol* 2014;25:64–70.
33. Rolinck-Werninghaus C, Niggemann B, Grabenhenrich L, et al. Outcome of oral food challenges in children in relation to symptom-eliciting allergen dose and allergen-specific IgE. *Allergy* 2012;67:951–7.
34. DunnGalvin A, Daly D, Cullinane C, et al. Highly accurate prediction of food challenge outcome using routinely available clinical data. *J Allergy Clin Immunol* 2011;127:633–9.e1-3.
35. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;100:444–51.
36. Nowak-Węgrzyn A, Assa'ad AH, Bahna SL, et al. Work Group report: oral food challenge testing. *J Allergy Clin Immunol* 2009;123:S365–83.
37. Cummings AJ, Knibb RC, King RM, et al. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents, and their families: a review. *Allergy* 2010;65:933–45.
38. Ravid NL, Annunziato RA, Ambrose MA, et al. Mental health and quality-of-life concerns related to the burden of food allergy. *Immunol Allergy Clin North Am* 2012;32:83–95.
39. Lieberman JA, Sicherer SH. Quality of life in food allergy. *Curr Opin Allergy Clin Immunol* 2011;11:236–42.
40. Herbert L, Shemesh E, Bender B. Clinical management of psychosocial concerns related to food allergy. *J Allergy Clin Immunol Pract* 2016;4(2):205–13.
41. Knibb RC. Effectiveness of cognitive behaviour therapy for mothers of children with food allergy: a case series. *Healthcare (Basel)* 2015;3(4):1194–211.
42. Greenhawt M. Pearls and pitfalls of food challenges in infants. *Allergy Asthma Proc* 2019;40(1):62–9.
43. Bird JA, Groetch M, Allen KJ, et al. Conducting an oral food challenge to peanut in an infant. *J Allergy Clin Immunol Pract* 2017;5(2):301–11.
44. Fleischer DM, Conover-Walker MK, Christie L, et al. The natural progression of peanut allergy: resolution and the possibility of recurrence. *J Allergy Clin Immunol* 2003;112:183–9.
45. Greiwe J, Oppenheimer J, Fleischer DM, et al. AAAAI AFRC workgroup report: oral food challenge practices among allergists in the United States. Manuscript in preparation.
46. Pongracic JA, Bock SA, Sicherer SH. Oral food challenge practices among allergists in the United States. *J Allergy Clin Immunol* 2012;129:564–6.