American Academy of Allergy Asthma & Immunology

Conducting an Oral Food Challenge: An Update to the 2009 Adverse Reactions to Foods Committee Work Group Report

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Oral food challenges are an integral part of an allergist's practice and are used to evaluate the presence or absence of allergic reactivity to foods. A work group within the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma & Immunology was formed to update a previously published oral food challenge report. The intention of this document was to supplement the previous publication with additional focus on safety, treatment of IgE-mediated allergic reactions, guidance for challenges in infants and adults, psychosocial considerations for children and families participating in an oral food challenge, specific guidance for baked milk or baked egg challenges, masking agents and validated blinding recipes for common food allergens, and recommendations for conducting and interpreting challenges in

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Abbreviations used
AD- atopic dermatitis
BE- baked egg
BM- baked milk
DBPCFC- double-blind, placebo-controlled food challenge
FPIES- food protein—induced enterocolitis syndrome
IV- intravenous
OFC- oral food challenge
PFAS- pollen food allergy syndrome
PRACTALL- Practical Allergy
SPT- skin prick test
VS- vital sign

patients with suspected food protein—induced enterocolitis syndrome. Tables and figures within the report and an extensive online appendix detail age-specific portion sizes, appropriate timing for antihistamine discontinuation, serum and skin test result interpretation, written consents, and instructional handouts that may be used in clinical practice. **(J Allergy Clin Immunol Pract 2020;8:75-90)**

Key words: *Oral food challenge; Double-blind placebo-controlled food challenge; Food allergy; Baked egg; Baked milk; FPIES; Food protein—induced enterocolitis syndrome; Peanut; Milk; Egg; Wheat; Tree nut; Anaphylaxis*

INTRODUCTION

The oral food challenge (OFC) is instrumental for diagnosing food allergy and evaluating the development of tolerance. The Adverse Reactions to Foods Committee within the American Academy of Allergy, Asthma & Immunology published a Work Group Report in 2009 providing guidance for safely conducting an OFC in the office.[1] The main objective of this publication was to update the original work group report, focusing on the following areas: baked milk (BM) and baked egg (BE) OFCs; psychosocial considerations associated with the OFC; special aspects of OFCs for infants, adults, and research patients; food protein—induced enterocolitis syndrome (FPIES) OFCs; and blinding foods for single- and double-blind OFCs. In addition, the Online Repository to this article provides an abundance of supplemental information that is useful for clinical practice.

OFC INDICATIONS AND PREPARATION

Risks and benefits

The value of performing the OFC should be determined, taking into consideration the risk and benefits of undergoing the OFC. As outlined in the previous report, an OFC is useful for identifying foods causing reactions in the following situations[1]:

- Serum IgE testing and/or skin prick test (SPT) results are not consistent with the patient history.
- When the family/patient and physician agree that the risk estimated from the medical history and the test results (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) is outweighed by the benefit of possibly adding a food to the diet.
- Determining whether food allergens associated with chronic conditions such as atopic dermatitis (AD) or eosinophilic esophagitis will cause immediate reactions.
- Expanding the diet in persons with multiple dietary restrictions.
- Assessing the status of tolerance to cross-reactive foods.
- Assessing the effect of food processing on food tolerability (eg, fruits and vegetables that may be tolerated in cooked form in patients with pollen food allergy syndrome [PFAS]).

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TABLE I. Reasons to reschedule or delay an OFC

Consider postponing the OFC if the patient has any of the following:
• Concurrent illness, fever, or active respiratory symptoms (ie, wheeze or cough)
• Used a short-acting β-agonist within the preceding 48 h for cough or wheeze
• Poorly controlled asthma, AD, or allergic rhinitis
• Unstable cardiovascular disease
• Pregnancy
• Beta-blocker therapy
• Patient has not discontinued medications as outlined in Tables II and III

The decision to proceed with an OFC is also influenced by the importance of the food in the diet and whether the food will or will not be incorporated. For example, a patient allergic to cashews and pistachios may have a low likelihood of reacting to Brazil nuts based on testing; however, Brazil nuts are often processed with other tree nuts, and it may be very unlikely that Brazil nuts will be incorporated into the patient's diet. In this instance, performing a Brazil nut challenge would not likely improve the patient's quality of life nor change the associated risk of a reaction with the already existing cashew and pistachio allergies. On the contrary, if the patient's diet is significantly restricted because of multiple food allergies and the family's eating preferences restrict protein choices (eg, vegan or vegetarian), then adding additional tree nut choices may be nutritionally beneficial and improve quality of life.

It is recommended that all patients undergoing an OFC have documented verbal or a signed written consent.[1] An example of a written consent is provided in Table E2 in this article's Online Repository at www.jaci-inpractice.org. The greatest risks of an OFC are life-threatening anaphylactic reactions potentially requiring hospitalization and death.[2] In the 45-year history of performing OFCs, there has been only 1 reported fatality in the United States.[3]

SAFETY CONSIDERATIONS

Patients must be in good health on the day of the OFC to minimize the risk of a severe reaction and to not confound the interpretation of the results.[1,4] Reaction severity cannot be reliably predicted with allergen-specific IgE levels or component-resolved diagnostic testing[5]; however, when considering the importance of the OFC and the preparedness of the staff conducting the OFC, it is prudent to note factors that have been reported as associated with fatal and near-fatal food-induced reactions[6]:

- Peanut, tree nuts, fish, shellfish, and milk are commonly implicated in fatal and near-fatal food-induced anaphylaxis.
- Asthma (regardless of severity).
- Delayed use of epinephrine.
- Upright posture during assessment of the anaphylactic reaction may contribute to cardiovascular compromise.

An OFC is not recommended if the patient has concurrent illness, fever, active respiratory symptoms such as coughing or wheezing, has needed to use a short-acting β-agonist to relieve respiratory symptoms within the preceding 48 hours, or is taking a beta-blocker, because any of these factors may increase the risk of a severe reaction or interfere with the ability to effectively treat a

TABLE II. Suppressant effects of antihistamines and medications with antihistamine-like properties

Medication	Recommended last dose based on suppression of SPT wheal diameter*
Antihistamines (oral)	
First-generation H_1-blocking	
Brompheniramine	>2-4 d[7]
Chlorpheniramine	3-6 d[8]
Clemastine	5-10 d[7]
Cyproheptadine	9-11 d[8]
Diphenhydramine	2-5 d[8]
Hydroxyzine	5-8 d[8]
Promethazine	3-5 d[7]
Tripolidine	3-7 d[7]
Second-generation H_1-blocking	
Acrivastine	3 d[7]
Cetirizine	3 d[7]/3-5 d[9]
Desloratadine	7 d[7]
Fexofenadine	2 d[7]/3-5 d[9]
Levocetirizine	Unknown
Loratadine	7 d[7]/3-5 d[9]
H_2-blocking	
Cimetidine	0-2 d[9]
Famotidine	0-2 d[9]
Ranitidine	<1 d[8]
Antihistamine (nasal)	
Azelastine	2 d[8]
Levocabastine	0 d[8]
Olopatadine	Unknown
Antihistamine (ophthalmic)	
Levocabastine	0 d[8]
Olopatadine	Unknown
Atypical antidepressants/sedatives	
Bupropion	0-3 d[9]
Eszopiclone	0-3 d[9]
Mirtazapine	5-7 d[9]
Quetiapine	5-7 d[9]
Trazodone	0-3 d[9]
Zolpidem	0-3 d[9]
Benzodiazepines	
Clonazepam	5-7 d[9]
Diazepam	5-7 d[9]
Lorazepam	5-7 d[9]
Midazolam	5-7 d[9]
Tricyclic antidepressants	
Amitriptyline	5-7 d[9]
Desipramine	2 d[8]
Doxepin	6 d[8]
Imipramine	>10 d[8]
Nortriptiline	5-7 d[9]

Range = mean to maximum number of days for references 10 and 7 and minimum to maximum days for reference 8.

*PRACTALL guidelines recommend discontinuation of antihistamines 5 half-lives before the OFC[5]; however, it is the opinion of this Work Group that objective data related to suppression of the histamine response are a more reliable indicator of the effect of the antihistamine, and in cases when the suppressive effect of the antihistamine is in question it is recommended to place a histamine SPT before proceeding with the OFC. Data related to the half-life of antihistamines have been included in the Online Repository for additional reference (Table E3).

TABLE III. Medications that may interfere with OFC interpretation or reaction treatment should be discontinued 5 half-lives before the OFC unless otherwise referenced*

	Recommended last dose based on theoretical ability to either worsen reaction severity, interfere with OFC interpretation, and/or interfere with treatment of a reaction (recommendation based on 5 half-lives [$T^1/_2$ in hours of product] unless otherwise stated)	
Medication	**$T^1/_2$ (h)**	**5 half-lives (h)**
ACE inhibitors†		
Captopril	1.7-2.3	8.5-11.5 (<1 d)
Enalapril	Children: 5.1-20.8 Adults: 35	Children: 25.5-104 (1-4 d) Adults: 175 (7 d)
Lisinopril	12	70 (3 d)
Quinapril	2.3	11.5 (<1 d)
Ramipril	13-17	65-85 (3-4 d)
Beta-blockers‡		
Atenolol	Children and adolescents: 3.5-7 Adults: 6-7	Children and adolescents: 17.5-35 (~1 d) Adults: 30-35 (~1 d)
Carvedilol	Children and adolescents: 3.6 Adults: 7-10	Children and adolescents: 18 (1 d) Adults: 35-50 (1-2 d)
Labetalol	6-8	30-40 (1-2 d)
Metoprolol	3-4	15-20 (1 d)
Propranolol	3.9-6.4	19.5-32 (1 d)
Timolol	2-2.7	10-13.5 (<1 d)
Cromolyn		
Inhaled	1.3-1.5	6.5-7.5 (<1 d)
Systemic	1.3-1.5	6.5-7.5 (<1 d)
NSAIDs		
Aspirin	3 (doses of 300-600 mg)	15 (1 d)
Short-acting		
Diclofenac	2	10 (<1 d)
Ibuprofen	1.6-2	8-10 (<1 d)
Ketoprofen	2-4	10-20 (1 d)
Long-acting		
Celecoxib	Children and adolescents: 3-10 Adults: ~11	Children and adolescents: 15-50 (1-2 d) Adults: 55 (2 d)
Meloxicam	Children and adolescents: 12.7 Adults: 15-22	Children and adolescents: 63.5 (3 d) Adults: 75-110 (3-5 d)
Naproxen	Children and adolescents: 8-10 Adults: 12-17	Children and adolescents: 40-50 (2 d) Adults: 60-85 (3-4 d)
Piroxicam	Children and adolescents: 22-40 Adults: 50	Children and adolescents: 110-200 (5-8 d) Adults: 250 (10 d)
Proton pump inhibitors		
Esomeprazole	1-1.5	5-7.5 (<1d)
Lansoprazole	0.5-1.5	2.5-7.5 (<1d)
Omeprazole	0.5-1	2.5-5 (<1d)
Pantoprazole	1.27 ± 1.29	6.35 ± 6.45 (<1 d)
Rabeprazole	1-2	5-10 (<1 d)
Short-acting bronchodilator§		
Albuterol	8 h[11]	
Isoproterenol	8 h[11]	
Metaproterenol	8 h[11]	
Terbutaline	8 h[11]	
Medium-acting bronchodilator		
Ipratropium	24 h[11]	
Long-acting bronchodilator		
Salmeterol	Continue at lowest dose possible and on fixed schedule because withdrawal could result in exacerbation.[5] Discontinuation at least 8 h before the OFC has been recommended[1]	
Formoterol		

(continued)

TABLE III. *(Continued)*

	Recommended last dose based on theoretical ability to either worsen reaction severity, interfere with OFC interpretation, and/or interfere with treatment of a reaction (recommendation based on 5 half-lives [$T^1/_2$ in hours of product] unless otherwise stated)	
Medication	**$T^1/_2$ (h)**	**5 half-lives (h)**
Oral bronchodilators		
Theophylline (liquid)	12 h[11]	
Theophylline (long-acting)	48 h[11]	
Systemic steroids	7-14 d (disease rebound might confound the interpretation of the OFC result)[5]	
Prolonged high-dose steroids, omalizumab, or possibly other new drugs to control atopic disease are likely to modify challenge outcomes and should be avoided.[5]		
No need to discontinue inhaled or intranasal corticosteroids, calcineurin inhibitors, leukotriene antagonists, topical steroids, topical crisaborole, topical pimecrolimus, topical tacrolimus, selective serotonin reuptake inhibitors, or selective norepinephrine reuptake inhibitors.		

ACE, Angiotensin-converting enzyme; *NSAID*, nonsteroidal anti-inflammatory drugs.
*Concomitant use of any of these medications is not an absolute contraindication to undergoing an OFC, but their use must be considered when determining the risk vs benefit of the OFC.
†Aspirin/NSAIDs, ACE inhibitors, alcohol, and antacids can act as eliciting factors that increase reactivity in susceptible individuals.[5]
‡Beta-blockers can pose safety concerns if epinephrine is required for treatment.[5]
§If used within 48 h of challenge for cough/wheeze, consider rescheduling due to potential underlying unstable pulmonary disease that may worsen reaction severity.

reaction (Table I).[1] If allergic diseases such as asthma, AD, urticaria, and/or allergic rhinitis are active, then the OFC may be delayed because these symptoms may also affect interpretation of the OFC. The OFC may be deferred if the patient has a chronic medical condition that may pose a health threat in the event of anaphylaxis (eg, unstable underlying cardiovascular disease, angina, or severe chronic lung disease).[12] It is not recommended to perform an OFC during pregnancy because the OFC can be delayed for the duration of the pregnancy and a potential episode of anaphylaxis that may result from the OFC may harm the pregnant mother or the fetus. It is not uncommon for several of the already-mentioned variables to influence the decision regarding whether to perform an OFC. For example, performing an egg OFC with a 10% chance of reacting based on testing in a child with cystic fibrosis or asthma and low lung function carries higher overall risk than performing an egg OFC with an 80% chance of reacting in a healthy child with no asthma and a history of a mild reaction. For these reasons, clinical judgment is used when determining whether it is in the best interest of the patient to proceed with an OFC.

It is recommended that patients discontinue medications for specific time periods before the OFC that may interfere with interpretation of the OFC and/or compromise treatment of anaphylaxis (Tables II and III). Beta-blockers block the sympathomimetic effects of epinephrine, making the reaction refractory to traditional treatment.[13-17] OFCs are not recommended in patients who are unable to discontinue beta-blockers, unless the benefit of potentially expanding the diet outweighs the risk of the OFC. In that circumstance it is emphasized that written consent be obtained including documentation of the potential risk of death.[1] Glucagon (1-5 mg intravenous [IV] over 5 minutes, followed by an infusion of 5-15 mg/min titrated to achieve an adequate clinical response), may be necessary for epinephrine-unresponsive reactions, which can help to reverse the actions of beta-blockers.[18] Angiotensin-converting enzyme inhibitors may enhance or induce allergic reactions and discontinuation before the OFC may be considered if an equally effective alternative agent is available.[1,18,19] Antihistamines may interfere with OFC interpretation and should be discontinued, if possible.[1,5,18] Omalizumab may decrease skin test reactivity and increase allergen-specific IgE levels checked before an OFC.[20,21] Omalizumab may increase the threshold dose for a reaction, and therefore the OFC may not be reflective of the reaction that may occur if omalizumab had not been used.[22] This may apply to other biologic agents as well, although there are insufficient data to date. H2 blockers and proton pump inhibitors may increase severity of reactions by decreasing digestion of food proteins.[10,23,24] Concomitant use of any of these medications is not an absolute contraindication to undergoing an OFC, but their use must be considered when determining the risk versus benefit of the OFC.

PSYCHOSOCIAL CONSIDERATIONS

Asking patients to ingest a food that has previously been avoided and considered dangerous by a patient or their family may cause stress and anxiety about the possibility of an allergic reaction occurring during the procedure. Some patients may elect not to participate in OFCs, yet many patients do participate in spite of anxiety about an allergic reaction and are likely to experience worry or distress during OFCs.[25] Patients may experience symptom differentiation difficulty, because anxiety and allergic reaction symptoms can overlap (eg, stomach pain, increased heart rate, and difficulty breathing). Stress and anxiety about OFCs may be more likely for patients who vividly recall previous allergic reactions, but is not limited to these patients because fear of the unknown can be equally profound.[26,27] Research has indicated that OFCs improve quality of life for patients and reduce parental burden regardless of the outcome, but the greatest improvement in quality of life may be seen among patients who demonstrate tolerance to the food.[28-33] Therefore, it is important for medical providers to assess the patient's OFC readiness when deciding if and when to schedule an OFC. Mental health professionals, when available, can support patients as they prepare for OFCs and undergo the procedure. They may also equip patients with anxiety management strategies in advance, either through consultation or psychotherapy, and provide procedural support during OFCs.

Children pose additional unique psychosocial considerations because they have limited communication skills and may display developmentally typical food neophobia that impedes OFC

completion. Before the OFC, parents should explain the process to the child in development appropriate language to accommodate for a child's limited vocabulary and understanding of the OFC procedure, emphasizing that the goal of the OFC is to learn whether or not they are allergic to the food. Effort should be made to avoid using the terms "pass" or "fail" about the OFC so as not to appear to place blame on the child. Children should be informed that the OFC will take place in the doctor's office and a medical team will be present to ensure their safety. Children should also be given the opportunity to select which toys and activities they want to engage in during the OFC. To mitigate food neophobia, if there are multiple ingestion options for the target food (eg, yogurt, ice cream, and liquid milk for cow's milk), children should be given the opportunity to select which food they want to eat. In addition to providing procedural support, mental health professionals, when available, can help children prepare for OFCs by providing psychoeducation about OFCs, teaching children age-appropriate anxiety management strategies, and equipping parents with behavioral strategies that encourage ingestion during the OFC.

In the event that an allergic reaction occurs during an OFC, it is likely that patients will experience stress and anxiety during treatment and for a short period of time after discharge. Consultation with a mental health professional may be prudent to provide support to patients during allergic reactions and consultation/therapy services to patients who experience more long-term stress and anxiety.

OTHER PRE-OFC CONSIDERATIONS

On the day of the OFC, it is recommended that the patient refrain from eating for at least 4 hours before the challenge, because fasting enhances the absorption of the challenge food. This also ensures that the outcome of the OFC is due to the food administered and not something else previously ingested. More practically, being hungry encourages younger patients who may be reluctant to try a new food to ingest the challenge servings. In those unable to fast for at least 4 hours, such as infants or young children, a light meal of foods previously and regularly tolerated, approximately half the usual amount, may be eaten 2 hours before the challenge. Starting an OFC at the patient's normal mealtime allows the challenge food plus vehicle to serve as the meal.

Patients and their parents should be advised that an OFC is a long process. If a patient has a significant reaction, he or she may be observed for 2 to 4 hours or more after the reaction. Parents should be advised to plan to keep the child entertained during this time to help ensure the challenge progresses smoothly and to reduce any subjective complaints. If possible, other children should not be brought to the OFC visit so the parent(s) can focus attention on the child being challenged. Table E4 in this article's Online Repository at www.jaci-inpractice.org is a sample document that may be provided to families at the time an OFC is scheduled.

EMERGENCY PREPAREDNESS

Physicians considering conducting OFCs should ensure that their office is prepared to treat a potentially life-threatening allergic reaction before performing an OFC in the office. The following criteria are recommended as minimal requirements for conducting an OFC[34]:

1. Perform the OFC in a monitored setting with a physician, advanced practice provider (physician's assistant or nurse practitioner), or a nurse under a physician's supervision present throughout the OFC. Providers conducting an OFC should be experienced in the recognition and treatment of anaphylaxis. Consider access to an emergency response team or emergency medical services for transport to a medical facility.[12]
2. Medications that interfere with interpretation of the OFC and/or treatment of anaphylaxis should be discontinued if possible (Tables II and III).
3. Vital signs (VSs) should be obtained before starting the OFC, especially weight, temperature, respiratory rate, heart rate, and baseline blood pressure. Peak flow, spirometry, and pulse oximetry may be considered, especially in patients with asthma.[12] Specific attention should be paid to the examination of the patient's skin, nose, eyes, oropharynx, heart, and lungs before commencing the OFC. A focused examination and repeat VSs should be repeated at any point during the OFC if there is a perceived change in the patient's clinical status and before discharge from the clinic. Abnormal VSs by age are listed in Table E5 in this article's Online Repository at www.jaci-inpractice.org.
4. Emergency medications should be readily available and doses calculated on the basis of patient's weight before starting the OFC. Intramuscular epinephrine, H1 antihistamines, albuterol, supplemental oxygen and supplies, nebulized epinephrine, IV fluids, vasopressors, steroids, and H2 antihistamines may be needed to treat anaphylaxis. IV access may be considered before commencing the OFC, and should be placed at the discretion of the physician conducting the OFC. In general, an IV is not typically needed, especially for OFCs in which the patient has a high likelihood of passing on the basis of history and/or prechallenge testing. Medications for treatment of anaphylaxis are typically given intramuscularly, orally, or inhaled. The primary anticipated reason for needing IV access is for the administration of IV fluids. Previous trials evaluating the safety of OFCs have reported infrequent use of IV fluids, ranging from 0.008% of challenges in standard clinical OFCs[35] to 7 of 74 OFCs (10%) in a population of individuals expected to react in order to qualify for a food allergy therapy trial.[36]
5. Equipment that may be necessary to treat and manage anaphylaxis includes supplemental oxygen, a nebulizer, pulse oximeter, stethoscope, sphygmomanometer with age- and size-appropriate cuffs, nasal cannula, masks, a bag-mask ventilation kit, and an appropriate oropharyngeal airway. IV or intraosseous needles, tubing, and supplies should be available. If staff is not experienced in starting IV or intraosseous lines, then an emergency plan should be in place allowing for expedient access to emergency care. A standard protocol for anaphylaxis management is outlined in Table IV.

STOPPING THE OFC

This information has been covered extensively in the previous publication by Nowak-Wegrzyn et al,[1] and the reader is encouraged to review its contents for additional detail. The OFC should be stopped for any objective signs of an allergic reaction. Suggested stopping criteria are outlined in Table E6 in this article's Online Repository at www.jaci-inpractice.org. Signs of an allergic reaction include the following by organ system:

TABLE IV. Standard protocol for anaphylaxis management[12,18,37]

1. Initial steps
• Assess appearance, breathing, circulation, mentation
• Give epinephrine 1:1000 at a dose of 0.01 mg/kg intramuscular in the lateral thigh (maximum 0.5 mg). Appropriate epinephrine autoinjectors may alternatively be used
• Lie patient flat with legs elevated unless this causes increased respiratory distress, in which case the patient may prefer to sit up. Return the patient to the supine position if there is any deterioration in consciousness
• Airway management (according to skills and equipment) if required
• Obtain BP
• Gain IV access, if necessary
• Give oxygen for respiratory distress and/or hypotension
• If the patient is hypotensive, also give IV normal saline bolus 20 mL/kg
• Inhaled short-acting β2-agonists may be needed to relieve symptoms of bronchoconstriction
• For upper airway obstruction/stridor, also consider giving continuous nebulization of epinephrine (5 mL of 1 mg/mL)
• H1 and H2 antihistamines may be considered as supportive therapy but should not be given in lieu of epinephrine
2. If there is inadequate response, an immediate life-threatening situation, or deterioration,
• Repeat intramuscular epinephrine injection every 3-5 min as needed or start an IV epinephrine infusion as per hospital guidelines/ protocol. Monitor BP closely
• If the patient remains hypotensive, additional normal saline fluid boluses (up to 50 mL/kg in total) may be required
• When indicated at any time, prepare to initiate cardiopulmonary resuscitation including standard IV epinephrine dosing if the patient goes into cardiac arrest
• Consider calling a code team or Emergency Medical Services
3. Disposition
• Duration of observation after a reaction should be based on clinical judgment following symptom resolution with treatment. It is typical to observe 2-4 h after resolution of symptoms
• If the patient remains unstable they should be transported to a higher acuity medical facility for further care and monitoring

BP, Blood pressure.

- Respiratory: sneezing, rhinorrhea, coughing, wheezing, stridor, dysphonia, aphonia
- Cutaneous: urticaria, angioedema, flushing, scratching
- Gastrointestinal: dysphagia, vomiting, abdominal cramping, diarrhea
- Cardiovascular: pallor, hypotension, loss of consciousness
- Behavioral: change in activity/behavior (especially in young children and infants)

Consideration may be given to stopping the OFC for subjective symptoms, and the risks versus benefits of continuing the OFC should be considered. Subjective symptoms accompanied by changes in behavior in a child may be more indicative of early signs of reactivity compared with complaints without any changes in behavior. It has been suggested that an OFC may be considered positive if complaints such as throat itching/tightness, mouth itching, pruritus, nausea, or stomach pain follow 3 doses of the test food in a single-blind OFC, or if symptoms persist (eg, 40 minutes).[5,38] In practice, multiple variables, including the patient's health, may influence whether the physician decides to stop an OFC. For example, the physician may be more inclined to stop the OFC in a patient with cystic fibrosis and asthma with poor lung function complaining of an itchy mouth than in a healthy child with the same complaint. In addition, the appearance of subjective complaints from more than 1 organ system (ie, itchy mouth plus stomach pain) may influence the decision to stop or continue the OFC. In such circumstances, it may be prudent to extend the observation period before proceeding with a next dose, repeating the same dose, or discontinuing the OFC per the physician's judgment.[1]

CHALLENGE METHODS

Food options and portion sizes

In 1976, May[39] published recommendations for conducting double-blind, placebo-controlled food challenges (DBPCFCs), which led to the general adoption of DBPCFCs as the criterion standard for the diagnosis of food allergy by the allergy community. The DBPCFCs were conducted using dried food in capsules, and he reported that most patients reacted between 100 mg and 4000 mg of dry food by weight. Cumulative challenge doses of 3500 mg food protein (top dose of 875 mg) have reported false-negative rates of approximately 5%, and Practical Allergy (PRACTALL) guidelines suggest that the top dose required to avoid false-negative DBPCFC results is at least 2000 mg.[5,40] PRACTALL guidelines therefore recommend a final dose of 3000 mg of food protein (4443 mg cumulative) for DBPCFCs, with negative challenges followed up with an open challenge giving the native food in amounts usually consumed.[5] There may be some patients where larger amounts consumed over meal-size portions could trigger a reaction, or that augmentation factors might play a role (eg, fever, exercise, NSAID use, etc), where in both cases a negative OFC might still not exclude reactivity in some circumstances.

In clinical practice, it is not always practical nor necessary to measure doses with a high degree of specificity for most open OFCs, provided that results are used for individual care and not for research purposes. Nowak-Wegrzyn et al[1] recommend performing an open OFC with a cumulative dose equivalent to an age-appropriate serving of the food, and as mentioned above, PRACTALL guidelines recommend following a negative DBPCFC with an open feeding of a standard serving of the challenged food.[5] Table V provides an extensive list of foods that may be challenged and age-appropriate portion sizes for each food. Preparation of foods for the OFC should take into consideration safety issues regarding allergens (avoid cross-contact, care about label reading, etc) and general food safety (attention to expiration dates, appropriate storage).

In most circumstances, it is preferable to challenge with the least processed or cooked form of the allergenic food that will be incorporated into the patient's diet because tolerance of the most allergenic form of the food would provide a definitive answer, allowing the food to be introduced into the diet normally without restrictions. An exception to this practice includes challenging with a BM or BE item because most milk- and egg-allergic patients may tolerate the baked form while reacting to the lesser-cooked form.[44] In addition, it is not always practical to challenge to the most allergenic form of the food (eg, raw egg, raw fish, and undercooked beans). The section "Baked milk and baked egg OFCs" provides more detail regarding patient selection for baked challenges.

The starting dose will vary on the basis of patient's history.[1] For example, a patient with a history of a severe reaction and/or a higher probability of reacting should have the entire serving divided into at least 6 doses with a starting dose of approximately 1% or less of the

TABLE V. Age-appropriate portion sizes for open OFC

Allergen	Food	Protein content per serving size	Age				
			4-11 mo	1-3 y	4-8 y	9-18 y	19+ y
Egg	French toast (1 egg per 1 slice of bread)*	6 g if made with 1 large egg	1/2-1 slice	1/2-1 slice	1 slice	1-2 slices	1-2 slices
	Hard-boiled or scrambled egg	6 g/1 large egg	1/2-1 egg	1/2-1 egg	1 egg	1-2 eggs	1-2 eggs
Fish	Cooked fish†	6 g/1 oz	1/2-1 oz	1 oz	1 oz	2-3 oz	3-4 oz
Grains	Cooked cereal	5 g per 1/4 cup dry (oatmeal or Cream of Wheat)	1/4 cup	1/4 cup	1/3-1/2 cup	1/2-1 cup	1/2-1 cup
	Cooked pasta*/rice	3 g per 1/2 cup	1/4 cup	1/4 cup	1/3-1/2 cup	1/2-1 cup	1/2-1 cup
	Infant cereal	1-2 g per 1/4 cup	1/4-1/2 cup	1/4-1/2 cup			
	Muffin or roll bread*	4-6 g/muffin or roll	1/4-1/2 piece	1/2 piece	1/2-1 piece	1 piece	1 piece
	Ready-to-eat cereal	2-6 g/1 cup	1/4-1/3cup	1/4-1/3 cup	1/2-3/4 cup	3/4-1 cup	3/4-1 cup
	Slice bread	2-4 g/slice	1/4-1/2 slice	1/2 slice	1/2-1 slice	1-2 slices	2 slices
Milk	Infant formula	2-3 g/5 oz	4-8 oz				
	Milk	8 g/8 oz		4-8 oz	4-8 oz	8 oz	8 oz
	Cottage cheese	10-14 g/4 oz	1/4-1/2 cup	1/4-1/2 cup	1/2-1 cup	1/2-1 cup	1 cup
	Hard cheese	6-8 g/1 oz	1/4-1/2 oz	1/2 oz	1 oz	1 oz	1 1/2 oz
	Yogurt (NOT Greek style)	8 g/8 oz	1/4-1/2 cup	1/4-1/2 cup	1/2-1 cup	1/2-1 cup	1/2-1 cup
Peanut	Peanut (whole)	2 g/~8 peanuts			16 pieces	16 pieces	16 pieces
	Peanut butter	3 g/1 tbsp	1 rounded tbsp‡	1-2 tbsp	1-2 tbsp	2 tbsp	2 tbsp
	Peanut flour or peanut butter powder	3 g/1 tbsp original or 2.25 g/1 tbsp chocolate flavor	1 rounded tbsp‡	1-2 tbsp	1-2 tbsp	2 tbsp	2 tbsp
	Peanut/chocolate candy cups (full-size)	0.875 g/1 cup		1-2 candy cups	1-2 candy cups	2-3 candy cups	2-3 candy cups
Shellfish	Shellfish§	5 g/1 oz	1/2-1 oz	1 oz	1 oz	2-3 oz	3-4 oz
Soy/legumes	Infant formula	2-3.1 g/5 oz	4-8 oz				
	Soy beverage	7 g/8 oz		4-8 oz	4-8 oz	8 oz	8 oz
	Cooked beans (kidney, black, chickpeas, lentils)	7-9 g per 1/2 cup	1/8-1/4 cup	1/4 cup	1/3-1/2 cup	1/2-1 cup	1 cup
	Tofu	8 g/3 oz Firm tofu	1/2-1 oz	1 oz	1 oz	2-3 oz	3-4 oz
	Yogurt	5 g/6 oz	1/4-1/2 cup	1/4-1/2 cup	1/2-1 cup	1 cup	1 cup
Tree nut	Almond	3 g/11 whole nuts			11 pieces	11 pieces	11 pieces
	Almond butter (Barney butter brand)	3 g/1 tbsp	1 tbsp ‡	1-2 tbsp	1-2 tbsp	1-2 tbsp	1-2 tbsp
	Brazil nut	3 g/4.5 nuts			4 1/2 pieces	4 1/2 pieces	4 1/2 pieces
	Cashew	3 g/10 whole nuts			10 pieces	10 pieces	10 pieces
	Coconut flour	3 g/1 tbsp	1 tbsp	1-2 tbsp	1-2 tbsp	2-3 tbsp	2-3 tbsp
	Coconut milk‖	3 g/3 oz‖		3 oz	3 oz	4-8 oz	4-8 oz
	Hazelnut	3 g/3 tbsp hazelnuts or hazelnut meal			3 tbsp	3 tbsp	3 tbsp
	Pecan (halves)	3 g/25 halves			10-25 halves	25 halves	25 halves
	Pine nuts	3.5 g/3 tbsp pine nuts			3 tbsp	3-4 tbsp	4 tbsp
	Pistachio	3 g/20 whole nuts			20 pieces	20 pieces	20 pieces
	Walnut (halves)	3 g/10 halves			10 halves	10 halves	10 halves

Seeds	Seeds		10-15 g = 1-2 tsp	1-2 tbsp	10-15 g = 1-2 tsp	10-15 g = 1-2 tsp
	Sunflower seed butter (Sun butter brand)	3 g/1 tbsp	1 tbsp*	1-2 tbsp	1-2 tbsp	1-2 tbsp
	Tahini (sesame seed)	3 g/1 tbsp	1 tbsp	1 tbsp	1 tbsp	1 tbsp
Meats	Cooked lean meat or poultry	6 g/1 oz	1/2-1 oz	1 oz	1 oz	2-3 oz	3-4 oz
Fruits	Raw fruit		1/8-1/4 cup	1/4 cup	1/4-1/3 cup	1/3-1 cup	1 cup
	Small apple/banana/orange/pear		1/8-1/4 each	1/4-1/2 each	1/2-1 each	1 each	1 each
Vegetables	Raw or cooked vegetable¶	0.5-2 g per 1/2 cup	1/8-1/4 cup	1/4 cup	1/4-1/2 cup	1/2-1 cup	1/2-1 cup
	French fries (white potato)		1/8-1/4 cup	1/4 cup	1/4-1/2 cup	1/2-1 cup	1/2-1 cup
	Leafy raw vegetable	2-3 g per 1/2 cup	1/8-1/4 cup	1/4 cup	1/2-1 cup	1-2 cup	1-2 cups
	Small baked white or sweet potato	1-4 g/potato	1/8-1/4 each	1/4-1/2 each	1 each	1 each	1 each

Tbsp, Tablespoon; *tsp*, teaspoon.
Age-specific portion sizes were adapted from recommended portion sizes for age from ChooseMyPlate.gov[41] and HealthyChildren.org.[42]
*If a multi-ingredient food is used for the challenge, the patient should be tolerant to the food ingredients other than the one being challenged; for example, if French toast is used for an egg challenge, the patient should be tolerant to the bread ingredients. Alternatively, a form that is free of the other food allergens can be used, such as in a patient who has egg allergy and who is being challenged to wheat using pasta, egg-free pasta should be used. It should be noted that the OFC should be performed with the least processed/cooked versions of foods: therefore, if the OFC was done with processed/cooked food (eg, hard-boiled egg) after a negative OFC, only similarly processed/cooked versions of food may be added to the patient's diet.
†Protein in canned tuna and canned salmon is sufficiently degraded that many fish-allergic patients may tolerate the challenge and would otherwise fail a challenge with fish that has not been canned.[43]
‡Refer to the article by Bird et al[24] for specific observed peanut challenge protocol options and incremental dosing. Recipes from option 1 and option 2 from the peanut challenge protocols may be applied to almond butter and seed butter for infants.
§Average number of shrimp per 4-oz serving: extra large: 7, large: 8, medium: 12, small: 14.
‖Brands may vary in protein content—goal is 3 g of coconut protein for older children (eg, 3 oz Goya brand coconut milk = 3 g protein).
¶Raw vegetable is preferred for the OFC because of the effects of cooking on the vegetable protein.

total dose. Literature is lacking regarding the number of challenge doses necessary for open OFCs in a patient with a high likelihood of passing the OFC and without factors outlined above that may interfere with treatment of a reaction. In clinical practice, higher starting doses may be considered with as few as 3 or 4 doses administered for a low-risk OFC.[1] It should be noted, however, that high starting doses may be associated with more severe reactions during an OFC.[5] Starting doses at the low milligram level are generally safe and seem to result in fewer severe reactions.[5,45,46]

Figure 1 provides approaches to dividing the OFC portions on the basis of how many doses are to be given. Whether using the 4- or 6-dose protocol for an open OFC, doses are typically given 15 to 30 minutes apart.[1,5,47] The percentages suggested in the 6-dose protocol may be approximated and using a scale for precise measurement is not often necessary. Precise measurement of food protein is required for standardization of challenges in research studies, but a small food scale is not a routine piece of equipment in the allergist's office and is not commonly used in the authors' practices.[1]

Baked milk and baked egg OFCs

Most children with IgE-mediated allergies to cow's milk or hen's egg can tolerate milk and egg protein in extensively heated (baked) forms.[44] Incorporation of BM and BE into the diet appears well tolerated and may shorten the time to tolerance of regular (non-baked) milk and egg.[48-51] Immunologic changes reported with regular ingestion of BM and BE mirror those seen in milk and egg oral immunotherapy trials, including decreased SPT size, decreased specific IgE levels, and increased specific IgG levels.[52-54]

Baseline SPT and specific IgE levels have not been consistently predictive of BM and BE OFC outcomes. A systematic review of studies predicting BE tolerance using specific IgE and SPT noted that there was a high risk for bias, broadly different cutoffs, lack of criterion standard DBPCFC, and differences in degree of cooking or presence of food matrix.[55] No study of BM/BE was performed at a population level, a significant limitation to calculating predictive values. Predictive values are best interpreted in the context of a known prevalence in the population, which varies in the BM/BE studies. Although individual studies of BM/BE challenges have reported predictive cutoff levels, such levels best represent an explanation of a predictive level in that particular sample that underwent the OFC, and generalization to other clinical settings or the general population is limited. Positive and negative likelihood ratios may be more broadly applicable for decision making on the general population.[56] Sensitivity/specificity and positive/negative likelihood ratios have been calculated for available studies, and additional information regarding interpretation of positive and negative likelihood ratios has been provided in Table E7 in this article's Online Repository at www.jaci-inpractice.org.

The mechanism for tolerance of BM and BE is thought to be a result of denaturing of conformational epitopes, which alters the tridimensional configuration of the protein, thereby decreasing specific IgE-binding capacity.[57] It has also been proposed that the wheat matrix decreases specific IgE-binding.[58] Most products used in BM and BE studies to date were baked in a wheat matrix at 350°F/180°C for 30 minutes. The Jaffe Food Allergy Institute at Mount Sinai et al recipes (see Table E8 in this article's Online Repository at www.jaci-inpractice.org) contain 1.33 g of milk protein and 2 g egg white protein per serving.[57] Although 30 minutes was the baking time used in these studies, items of different sizes or with other ingredients may require shorter or longer baking times. For instance, a small cookie or mini muffin will require less baking time, and a large cake will require

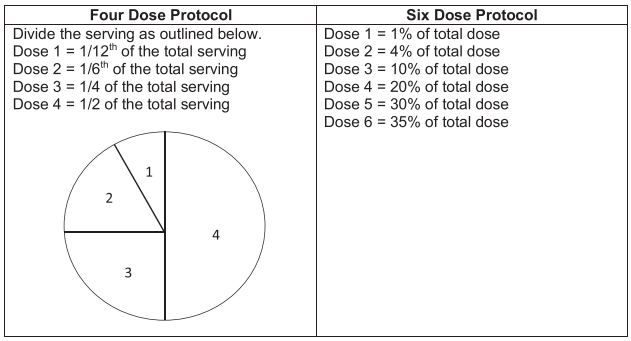

FIGURE 1. Dosing options for an in-office open OFC.[1] The clinician may choose to perform a 4-dose OFC or a 6-dose OFC depending on the prechallenge probabilty of reacting and inherent patient risk factors. Doses are typically administered 15 to 30 minutes apart.

more baking time. In general, items baked as individual servings (muffin, cupcake, bread roll) should be used, as opposed to cake or bread loaf, to ensure thorough and even baking. Items that should be avoided are those with egg and milk ingredients that are not baked (eg, milk/egg-containing frosting on a baked cake, cheese coating on a cracker or chip applied after baking, and items cooked on the stove top such as pancakes, cheese sauce, and omelets), items that are not baked all the way through (ie, are liquid or wet in the middle), and items with more milk or egg protein than the recommended challenge dose. Some studies have reported tolerance of waffles that are not baked but are cooked in a waffle iron at 500°F for 3 minutes by those who tolerated traditional BM muffins.[53]

Education and dietary counseling is essential before introduction of BM and BE in the diet. The amount of BM or BE protein allowed per serving should reflect the challenge amount and degree of cooking, as mentioned above. Nowak-Wegrzyn et al[53] and Lemon-Mule et al[54] allowed up to 3 servings of BM or BE products per day. Lee et al[59] advised BM or BE ingestion at least weekly, and in this study, 13% of subjects ingesting BM and 15% ingesting BE reported tolerating regular milk or egg after 12 months, although no OFCs were performed. The baked item being used for the challenge is typically prepared by the patient's family; however, in some circumstances, the challenge food may be prepared in a hospital kitchen. Undercooked or insufficiently baked items may result in an allergic reaction in children; therefore, guidance on how to safely prepare BM or BE items is required. Some studies report that subjects experience symptoms at home after tolerating a baked challenge, but most do not repeat challenges so it is not possible to rule out improperly home-baked products. Recipes and patient education materials are provided in Tables E8 to E10 in this article's Online Repository at www.jaci-inpractice.org.

Data are limited regarding tolerance of BM or BE proteins in non–IgE-mediated food allergy. Small case series have shown tolerance for the minority of children with eosinophilic esophagitis and some children with FPIES, but larger studies are needed before definitive recommendations may be provided.[60,61]

INFANT OFCs

The need to perform an OFC in a child younger than 1 year increased following recommendations for early introduction of peanut from the National Institute of Allergy and Infectious Diseases.[62] Detailed guidance regarding specific considerations for an infant OFC have been outlined by Bird et al.[34] Performing OFCs in infants raises important practical considerations that are detailed in Table E11 in this article's Online Repository at www.jaci-inpractice.org. Foremost among these considerations include the following:

- Infant must be tolerating other solid foods, including the food and texture to be used as a vehicle during OFC.
- Infant should be in good overall health at the time of OFC and free from viral upper respiratory tract illness symptoms.
- Infant should eat only a light meal (eg, half of the usual serving) no sooner than 2 hours before the scheduled OFC.[34]
- Staff should be familiar with unique challenges specific to medical treatment of infants (ie, IV placement and dosing of medications).

Many infants being considered for an OFC may have significant AD; therefore, it is particularly important to stress appropriate skin care before the OFC to ensure that AD is well-controlled at the time of OFC. Uncontrolled AD could lead to difficulties interpreting the OFC outcome due to normal variations in erythema, pruritus, and AD lesions.[63] In these patients, a complete skin examination before initiation of the OFC is essential.

There are excellent publications highlighting unique aspects of recognizing and treating anaphylaxis in infants.[34,64] Signs and symptoms of reactions in infants are similar to those in older children and adults but can be difficult to interpret given infants' lack of ability to verbalize sensations and emotions. For example, the "sense of impending doom" that older individuals may report with anaphylaxis will not be verbalized in an infant. Behavior changes that may be noted during a reaction may include clinginess, fussiness, or inconsolability, but it is important to note that these behaviors alone may also be present in healthy infants not experiencing an allergic reaction.[64] Infants may express symptoms in other ways, such as ear picking, tongue rubbing, putting a hand in the mouth, or neck scratching.[64] Physical examination and VS findings are thus crucial parts of the evaluation during an infant OFC. In a large chart review of children presenting to the emergency department with food-induced allergic reactions, cutaneous signs/symptoms (including urticaria) were present in 98% of reactions in children younger than 2 years, respiratory in 59%, and gastrointestinal in 56%.[65]

ADULT OFCs

Performing an OFC in an adult also presents a special set of challenges. An adult, as compared with a child, is more likely to have coexisting medical conditions that may interfere with interpretation of the OFC outcome (eg, chronic idiopathic urticaria or a psychiatric condition such as anxiety) or may be taking medications that may interfere with the ability to safely conduct the OFC (see discussion under "OFC Preparation"). An adult patient may also have underlying unstable cardiovascular disease that could affect the risk assessment when considering proceeding with an OFC. With these cofactors in mind, the necessity of the OFC must be considered, though not necessarily contraindicated.

Patients may experience upper airway symptoms such as difficulty with inspiration, stridor, dysphonia, and hoarseness

during OFC reactions. Such symptoms could be secondary to laryngeal angioedema or, alternatively, paradoxical vocal fold motion.[66] Rarely, when unaccompanied by objective signs, subjective upper airway symptoms may represent factitious stridor, but this is a diagnosis of exclusion.[67] Direct visualization of the vocal cords via laryngoscopy may be necessary to distinguish among these possibilities and determine appropriate management. Alternatively, spirometry may show flattening of the inspiratory portion of the flow volume loop in paradoxical vocal fold motion.

Patients with PFAS (also called oral allergy syndrome), a condition commonly seen in adolescents and adults, rarely experience systemic symptoms with OFC.[68] Patients with PFAS typically experience subjective oropharyngeal pruritus, and the physician may rely more on objective symptoms before stopping the OFC. The physician may also consider a second OFC with a heated or cooked food, which will often be tolerated by patients with PFAS. Foods commonly associated with PFAS may be more likely to lead to systemic reactions in patients not sensitized to the corresponding pollen.[69]

Food-dependent exercise-induced anaphylaxis is a disorder that most commonly affects young adults, but patients of all ages are reported.[70-72] The following criteria are suggested for diagnosis[72]:

- signs and symptoms consistent with anaphylaxis that occurred during (or within an hour of) exercise but only when exercise was preceded by food ingestion
- absence of another diagnosis that explains the clinical presentation

If a specific food is implicated, there should be:

- evidence of specific IgE to the implicated food, either by skin testing or by food-specific IgE testing, and
- no symptoms on ingestion of the implicated food in the absence of exertion and no symptoms if exercise occurs without ingestion of the implicated food, although there may be rare exceptions (ie, patients may report isolated incidences when symptoms occurred at rest in the presence of other augmenting factors, such as illness).

The diagnosis of food-dependent exercise-induced anaphylaxis is confirmed with a food + exercise challenge; however, a negative challenge does not exclude the diagnosis. Various protocols have been published, but the procedure is not standardized.[71,73-77] Variability exists regarding the amount of food, intensity and duration of exercise, and requirement for additional augmenting factors required to reproduce symptoms (ie, preceding use of nonsteroidal anti-inflammatory drugs). Published challenge procedures have in common the withholding of antihistamines, premedication with acetylsalicylic acid, relatively large amounts of the suspect food, and strenuous exercise.[74,78,79]

Case series have documented adults with isolated delayed gastrointestinal symptoms, typically emesis and abdominal pain similar to FPIES in children, after ingestion of fish, crustacean shellfish, mollusks, and egg.[80-82] These reactions often occur after the offending food has been previously tolerated and are generally not associated with evidence of IgE sensitization to the offending food. OFCs for such patients should be performed with an observation period of several hours to observe for delayed reactions, and gastrointestinal reactions managed in accordance with guidelines for FPIES,[60] as discussed in the following section.

FPIES OFC

FPIES is a non−IgE-mediated food allergy that often affects infants and resolves by school age for most affected children.[60] Acute FPIES reactions present with profuse repetitive vomiting that begins 1 to 4 hours after ingestion of the allergenic food. Other symptoms include pallor, lethargy, and/or limpness, and in severe cases may lead to hypotension and hypovolemic shock.[83] Diarrhea may also occur in some patients an average 5 to 10 hours after ingestion.[83] Cow's milk, soy, rice, and oat are the most common FPIES triggers in the United States and Australia, though any food may be implicated, including fruits and vegetables.[84,85] Fish is the second most common trigger reported in Italy, and egg is a commonly reported trigger in the United Kingdom (13% of cases) and Australia (10% of cases).[86-90] Chronic FPIES has only been reported in infants younger than 4 months fed with cow's milk or soy infant formula and occurs when there is regular exposure to the eliciting food. It typically presents with intermittent emesis, chronic diarrhea with blood and/or mucus, failure to thrive, and hypoalbuminemia.[60]

International FPIES guidelines[60] recommend using the medical history and OFC results to establish a diagnosis of FPIES, because there are no reliable biomarkers to diagnose FPIES or to confirm the food allergen trigger(s). A confirmatory OFC is considered unnecessary in case of a clinical history consistent with acute FPIES, especially if the patient has reacted more than once with the same food, and the patient is well once the food is eliminated from the diet.[60,91] OFCs may be considered in the initial diagnostic evaluation for cases in which the history is unclear, a food trigger is not identified, the time course of symptoms is atypical, or if symptoms persist despite removing the suspected trigger food or foods from the diet.[60,91] Given the less specific nature of chronic FPIES symptoms, a trial of food elimination followed by a supervised OFC to potential food triggers might be necessary to confirm diagnosis.[60] Furthermore, an OFC may be used to safely introduce new high-risk foods in FPIES (eg, introduction of wheat in a child who had an FPIES reaction to rice) or to evaluate whether the child has outgrown FPIES, a procedure usually considered 12 to 18 months after the most recent reaction.[60,91] It is recommended that an OFC for a previously known trigger of FPIES be undertaken in a hospital or office setting under close supervision of health personnel trained to treat an acute FPIES reaction.[60] Many experts recommend securing peripheral IV access before the OFC, because at least 15% of reactions may result in hypotension.[60] IV placement is strongly considered in patients with a history of a severe reaction (ie, a previous reaction requiring IV hydration or hospitalization) or in those with anticipated difficult emergency IV access.[60,92]

Various protocols for FPIES OFCs have been published, none validated by large studies.[1,84,93,94] Recently published guidelines suggest using a challenge dose of 0.3 g of food protein per kilogram body weight with a maximum total 3 g of protein (range, 0.06-0.6 g/kg body weight).[60] The food dose may be administered as a single dose or 3 equal doses over a 30-minute period, and the patient remains under observation for at least 4 hours from the onset of the OFC.[1,84,91] Lower starting doses (0.06 g

TABLE VI. FPIES OFC[60,95,96]

FPIES OFC protocol	
Basic requirements:	• Physician supervision
	• Secure IV access or be prepared to secure one quickly if needed
	• Calculate doses of emergency medications
	○ Normal saline (0.9% isotonic solution) or lactated ringers: 20 mL/kg/dose bolus administered over 5-10 min
	○ Ondansetron in patients >6 mo old: 0.15 mg/kg/dose IV or IM (maximum single dose IV 16 mg, maximum IM dose not established)
	○ Glucocorticoids (eg, methylprednisolone 1 mg/kg IV, maximum daily dose 80 mg)
Obtain baseline VSs	
Consider obtaining complete blood cell count with differential to determine baseline neutrophil count	
Administer food protein 0.06-0.6 g/kg body weight as a single dose (low-risk challenge) or in 3 equal doses with 15 min between each dose. Do NOT exceed 3 g of protein or 10 g of total food (100 mL of liquid) for initial feeding. (The lower dose is generally used in patients with a history of a severe reaction.) With detectable food-specific IgE to the challenge item, a more gradual administration of the challenge food according to an IgE-mediated food allergy protocol is recommended, with the postchallenge observation period longer than the typical IgE-mediated OFC protocol to account for the potential of a delayed FPIES reaction	
Refer to Tables E12 and E13 for OFC interpretation and reaction treatment	
If no reaction occurs within 2-3 h of administration of the final dose of a low-dose challenge, feed the patient an age-appropriate serving of the food followed by 2-4 h of observation. The patient is then instructed to slowly introduce the food at home over several days	

IM, Intramuscular.

protein/kg body weight), longer observation periods between doses, or both should be considered in patients with a history of severe reactions.[1,84,91] When a very low dose OFC is performed and tolerated, a second OFC with a higher dose (eg, 3 g of food protein) is to be undertaken within 2 to 3 hours of the first feeding before declaring the child is no longer reactive to the food of concern. In patients with detectable specific IgE to the challenge food, an OFC protocol for IgE-mediated food allergy with a longer postchallenge observation period is recommended to account for a possible IgE-mediated or FPIES reaction.[1,84,91] A typical FPIES challenge is outlined in Table VI.

An OFC is considered positive if typical symptoms (eg, profuse vomiting with lethargy, pallor, limpness, and/or diarrhea) develop 1 to 4 hours after the ingestion (see Table E12 in this article's Online Repository at www.jaci-inpractice.org). Reactions may require IV fluids (20 ml/kg bolus), ondansetron (0.15 mg/kg, maximum dose 16 mg IV, maximum intramuscular dose not established) in patients 6 months or older, and/or methylprednisolone (1 mg/kg, maximum dose 60 mg IV).[60] Table E13 in this article's Online Repository at www.jaci-inpractice.org provides details regarding appropriate treatment of a reaction based on its severity.[1,84,91]

OFCs FOR RESEARCH

Most clinical research studies use a DBPCFC protocol to minimize bias. OFCs performed for research studies have a 3-fold purpose. They are often used during a study's screening process to (1) establish the diagnosis, (2) document the amount of allergen that elicits symptoms for the purpose of qualifying an individual for a study and establishing a baseline threshold, and (3) determine any change in threshold that has occurred after treatment with an investigational product.

At this time, most trials perform DBPCFC according to the recommendations from the PRACTALL consensus report.[5] The PRACTALL consensus report provides guidance regarding the quantity of foods being challenged, timing between doses, and detailed stopping criteria.[5] An interval of 15 to 30 minutes between doses is typical.

It is recommended that active and placebo challenges be conducted on separate days. If they are conducted on the same day, they must be separated by at least 3 hours, which results in a very long procedure and may not be acceptable for many individuals, particularly young children.

DBPCFC results are commonly considered to be positive only when objective symptoms occur. It is important for multicenter studies to use uniform stopping criteria for standardization purposes. Subjective symptoms may not be a clear indicator of a positive challenge, but they must be documented and the next dose possibly delayed so that the subject can be closely observed for any increase in symptoms. Persistence of subjective symptoms (ie, itchy throat and/or abdominal pain) may lead to stopping a challenge if the symptoms persist for at least 45 minutes or occur with 3 doses, as per the study-specific challenge stopping criteria.[97,98] The postchallenge observation period also varies by protocol, but usually is about 2 to 4 hours from the resolution of symptoms.

DBPCFC outcomes may be reported by stating the highest successfully consumed dose (also called the single highest tolerated dose) or the eliciting dose (also called the reactive dose) where the challenge was stopped (Figure 2). Studies have also reported the cumulative tolerated dose as well as the cumulative reactive dose. For example, if the standard PRACTALL challenge guideline is followed and the subject reacts after ingesting the 100-mg dose, the result could be reported as the successfully consumed dose was 30 mg, the eliciting dose was 100 mg, the cumulative tolerated dose was 44 mg, or the cumulative reactive dose was 144 mg. These concepts are illustrated in Figure 2.

MASKING AGENTS FOR BLINDED CHALLENGES

For single-blind challenges and DBPCFCs, the challenge food should be masked in a challenge vehicle. The use of capsules with dried food is not recommended because of issues of getting sufficient amount of the allergenic food into the capsules, risk of altered allergenicity by processing (eg, dehydration), difficulty in swallowing capsules (especially for children), bypassing the oropharynx and possibly missing early signs and symptoms of an allergic reaction, and potential delayed absorption leading to subsequent delayed reactions.[1]

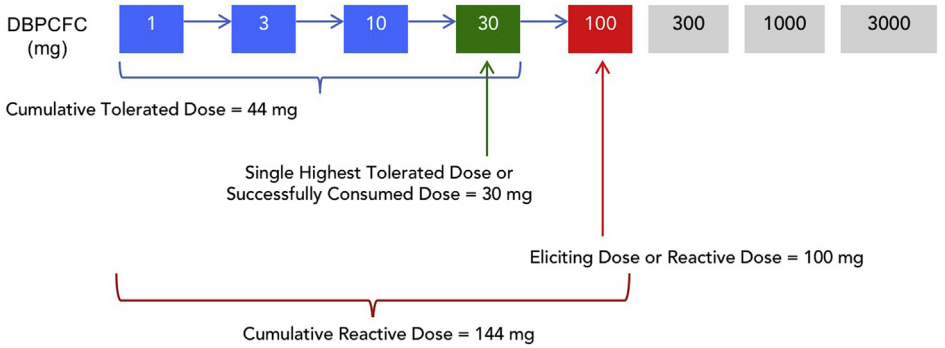

FIGURE 2. Typical PRACTALL dosing protocol and outcome definitions.[5] In this example, the subject has an objective reaction, meeting stopping criteria after ingesting the 100-mg dose. The cumulative tolerated dose is 44 mg, successfully consumed dose is 30 mg, eliciting dose is 100 mg, and cumulative reactive dose is 144 mg.

For each blinded OFC, a placebo and active test food recipe should be developed and prepared, and sensory properties of both test foods should be as similar as possible.[1,4,5,37,99] To guarantee that the challenge food has been blinded appropriately, recipes that have been validated for blinding should be used.[100] This is especially important in research settings and when the risk of placebo reactions is increased (ie, for patients with AD or anxiety).

Validating recipes is a labor-intensive procedure.[99,100] Validation by sensory testing is performed by test panels with professional tasters, volunteers, or children. Published recipes that are validated for blinding for double-blind challenge tests are available for the following allergenic foods: milk, egg, soy, hazelnut, peanut, cashew, wheat, and codfish (see Table E14 in this article's Online Repository at www.jaci-inpractice.org).

In clinical practice, when validated recipes are not available or not feasible, recipes may be developed by dietitians and/or chefs. In some countries, for example, the Netherlands, nonvalidated ready-to-use test kits for milk DBPCFCs with milk powder in hypoallergenic or elemental formulas are provided by the manufacturers.

The challenge food may be incorporated into vehicles for masking, ideally meeting the following requirements:

- Age-appropriate serving size with an acceptable volume, taste, and texture. For example, infant formulas, pudding, custards, and baby food are suitable vehicles to use when challenging an infant.[1,99,101]
- Absence of cross-contamination in challenge foods from other potential allergens (eg, avoid packaged foods with warning labels, or foods where ingredients are unknown or prepared outside the home).
- Utilization of few ingredients to minimize unknown matrix effects[37,99] and a low fat content to minimize the likelihood of a delayed reaction due to delayed absorption.[101]
- Avoidance of commonly allergenic ingredients (eg, milk, egg, and wheat) with verification that the patient has tolerated vehicle ingredients before the challenge.[37,99]
- Challenge foods may be ground or pureed and should be well homogenized in the food matrix. Granulated foods, such as grain flakes or coconut, as well as strong flavors such as peppermint, may support masking.[101,102]
- The challenge food should closely replicate the usual edible form of the food implicated in the allergic reaction, because food processing can influence the allergenicity of the food (eg, raw egg powder is more allergenic than egg baked into a cake or muffin).[37,99,101]

GUIDANCE AFTER THE OFC

Postchallenge instructional handouts, whether the patient tolerated the food or had a reaction, have been developed and may be found in Tables E15 and E16 in this article's Online Repository at www.jaci-inpractice.org. In summary, those recommendations include ensuring that all patients, regardless of the outcome of the challenge, have an emergency treatment plan and medications available at the time of discharge. Additional information regarding coding for the OFC has been included in Table E17 in this article's Online Repository at www.jaci-inpractice.org.

After a negative OFC (ie, the patient tolerated the food) the patient should be advised to avoid the food for the remainder of the day in case a rare delayed reaction to the food occurs. Patients are typically observed for at least 1 to 2 hours for an immediate-type reaction and up to 4 hours after an FPIES challenge.[1] In addition, a small percentage of individuals may react with repeat ingestion despite a negative OFC, and parents should be advised to watch for signs of reactivity as the food is reintroduced into the diet in the days and weeks after the OFC.[103,104] The patient should be encouraged to contact the office with any concerns about possible delayed reactions or reactivity with repeat ingestion.

With a negative OFC, this Work Group recommends encouraging the patient to ingest the food in a manner typical of dietary consumption, at least eating it periodically. This recommendation is based on limited data suggesting that when peanut allergy resolves (a negative food challenge after a history of reactions), lack of regular exposure may be associated with recurrence.[103,104] The recommendation is additionally based on the observation that acute allergic reactions have been noted, albeit uncommonly, in children and adults when a food to which they are sensitized but is included in the diet is removed for an extended period and then this same food triggers acute reactions on reexposure.[105,106] By at least periodically ingesting the food in a manner consistent with its usual inclusion in the diet, concerns about loss of tolerance should be reduced without a burden of any prespecified ingestion regimen. An exception regards the early introduction of peanut according to National Institute of Allergy and Infectious Diseases–sponsored expert panel guidelines where

a recommended weekly dose of exposure is provided on the basis of results of the Learning Early About Peanut study.[62,107]

Emergency treatment plans and school paperwork should be updated to document resolution of the food allergy and include any appropriate changes in school management. The patient should be assessed for concerns regarding ingestion of the challenge food at home, because it is possible that the patient will feel hesitant to eat the food, either due to distaste for the previously avoided food or anxiety about an allergic reaction. Concerns should be discussed openly. Providers are encouraged to help the patients problem solve ways to introduce the food into their diet and provide referral to a mental health professional if necessary.

After a positive OFC (ie, the patient reacted to the food), the patient is advised to continue strict avoidance of the food. There is no consensus regarding the optimal amount of observation time for a patient who has been successfully treated for anaphylaxis.[83] Duration of observation in clinic is influenced by clinical judgment after resolution of symptoms. Typically, patients are observed for 2 to 4 hours after resolution of an immediate hypersensitivity reaction and up to 6 hours after an FPIES reaction.[1] Instructions should be given on keeping activity minimal for rest of the day, monitoring for and treating the rare occurrence of a biphasic reaction, and always having an epinephrine autoinjector twin pack available. It is normal for patients who have reacted during an OFC to experience increased worry about food allergy management in the days after the OFC. Patients should be assessed for food allergy—related anxiety and providers are encouraged to normalize and validate these concerns, while also reinforcing the food allergy safety plan. Referral to a mental health professional may be considered for patients who experience significant distress regarding an allergic reaction during an OFC.

SUMMARY

At the present time a lack of reactivity cannot always be accurately predicted with currently available testing modalities, making the OFC an integral part of practice. With the current food allergy epidemic and evolving practice guidelines for early introduction of peanut and other foods, allergists can expect increased need for OFCs. Future research needs include identifying reliable biomarkers to indicate the development of tolerance in treatment-naive patients and the development of sustained unresponsiveness in patients receiving interventional therapies for food allergy. In addition, serological biomarkers are needed for diagnosis of non—IgE-mediated food allergies and efforts should be made to standardize FPIES OFCs.

This document serves to expand on previously established guidance and to provide practical information for performing OFCs in clinical practice.[1,5] OFCs can be safely performed in the allergist's office with special attention to ensuring staff is prepared to assess and treat allergic reactions and anaphylaxis, and quick and ready access to emergency medical services. It is important to review risks and benefits when considering an OFC. If the patient has concomitant illness or is symptomatic with an asthma exacerbation, allergic rhinitis, uncontrolled eczema, or AD, the OFC is best postponed. Identifying allergenic foods will allow the patient and the family to practice appropriate avoidance while expanding the food-allergic patient's diet with safe foods will improve the patient's nutrition and quality of life.

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ONLINE REPOSITORY

TABLE E1. Predictive values of diagnostic tests used to assess OFC outcomes[E1]

	Serum food-IgE (kU/L)*		SPT Wheal (mm)*	
Food	**~95% Positive OFC**	**~50% Negative OFC†**	**~95% Positive OFC**	**~50% Negative OFC†**
Cow's milk	≥15[E2]	≤2[E3]	≥8[E4]	
	≥5 if younger than 1 y[E5]			
Egg white	≥7[E2]	≤2[E3]	≥7[E4]	≤3[E6]
	≥2 if younger than 2 y[E7]			
Peanut	≥14[E2]	≤2 with and ≤5 without history of peanut reaction[E8]	≥8[E4,E9]	≤3[E9]
Fish	≥20[E2]			

A subset of patients with undetectable serum food-specific IgE antibody and negative SPT result has been reported to have objective reactions confirmed by OFC.[E10]
*Phadia ImmunoCAP; SPT with commercial food extracts.
†In the authors' experience, children with at least a predicted 50% chance of tolerating the challenge food are the optimal candidates for an office-based OFC. However, serum levels of food-specific IgE antibodies and SPT wheal sizes are not absolute indications or contraindications to performing an OFC. The physician's choice to use the cutoff may be based on individual risk assessment, which may vary according to circumstances under which the OFCs are offered. For example, if a child had an egg white IgE of 2 kU/L and SPT wheal at 3 mm, but had an anaphylactic reaction to egg in the past 6 mo, it is more prudent to defer an office OFC even though the test values are at a 50% pass rate. In contrast, a child with peanut IgE of 20 kU/L who recently tolerated an accidental ingestion of a product containing peanut butter may be a candidate for an OFC, even though the IgE level in isolation indicates a ~95% chance of reaction.

TABLE E2. Consent for OFC

PATIENT:
MR NO.:
DATE OF BIRTH:
DATE OF VISIT:
Consent for OFC
You/your child has been offered a medically supervised diagnostic feeding test (oral food challenge). This test is considered the best way to determine whether there is an allergy to the tested food. For the remainder of this consent form "you" will refer to you or your child.
The food challenge involves eating the food in gradually increasing amounts (doses) over time and a period of observation. The amounts offered and timing between the doses may vary depending on your doctor's assessment. The test may take several hours or longer. If your doctor determines that you are having an allergic reaction, feeding will stop and treatment for the allergic reaction will be given. If you have a reaction, you may be watched for additional time.
Benefits and risks of food challenges. The oral food challenge is an accepted medical test. The benefit includes finding out if you have an allergy and understanding your reaction to the food. Your doctor will explain the specific risks for a feeding test to this food. Eating a food to which there is a possible allergy can result in a reaction. Reactions can be mild or severe, including anaphylaxis, a severe, potentially life-threatening allergic reaction. Possible symptoms include throat/mouth itching, swelling, hives, worsening of eczema, nausea, vomiting, stomach pain, diarrhea, wheezing, fainting, and/or a drop in blood pressure. Death is a risk. If a reaction occurs, treatment could include an antihistamine, an injection of epinephrine, an inhaled bronchodilator, steroids, and other medications and treatments. Payment for treatment of adverse events related to this food challenge will occur in the manner you routinely pay for health care.
If an allergic reaction should occur during a food challenge, you will be required to remain under care until the physician believes it is safe for you to go home. In unusual circumstances, you may need to be transferred to an emergency room or hospital unit for further observation/treatment.
Alternatives to an oral food challenge: If you choose to not have an oral food challenge, the safest thing to do is restrict the food in question from your diet.
Signing this consent form indicates that you have read this form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this food challenge.
_____ _____
Subject or legally authorized representative Date
_____ _____
Physician/medical representative Date
_____ _____
Witness (if applicable) Date

TABLE E3. Half-lives of antihistamines and medications with antihistamine-like properties*

Medication	$T^1/_2$ (h)	5 half-lives (h)
Antihistamines (oral)		
First-generation H_1-blocking		
Brompheniramine	24.9 ± 9.3	78-171 (3-7 d)
Chlorpheniramine	27.9 ± 8.7	96-183 (4-7 d)
Clemastine	21.3 ± 11.6	48.5-164.5 (2-7 d)
Cyproheptadine	16	80 (3 d)
Diphenhydramine	9.2 ± 2.5	33.5-58.5 (1-2 d)
Hydroxyzine	20 ± 4.1	79.5-120.5 (3-5 d)
Promethazine	9-16	45-80 (2-3 d)
Tripolidine	3.2	16 (<1 d)
Second-generation H_1-blocking		
Acrivastine	1.4-3.1	7-15.5 (<1 d)
Cetirizine	7-11	35-55 (1-2 d)
Desloratadine	7.8 ± 4.2	18-60 (1-3 d)
Fexofenadine	14.4	72 (3 d)
Levocetirizine	7 ± 1.5	27.5-42.5 (1-2 d)
Loratadine	7.8 ± 4.2	18-60 (1-3 d)
H_2-blocking		
Cimetidine	1.39 ± 0.25	5.7-8.2 (<1 d)
Famotidine	2.5-3.5	12.5-17.5 (<1 d)
Ranitidine	2.5-3	12.5-15 (<1 d)
Antihistamine (nasal)		
Azelastine	25	125 (5 d)
Levocabastine	35-40	175-200 (7-8 d)
Olopatadine	8-12	40-60 (2-3 d)
Antihistamine (ophthalmic)		
Levocabastine Olopatadine	Does not achieve significant plasma concentration when administered ophthalmically	
Atypical antidepressants/sedatives		
Bupropion	12-30	60-150 (3-6 d)
Eszopiclone	6	30 (1 d)
Mirtazapine	20-40	100-200 (4-8 d)
Quetiapine	5.3-6	26.5-30 (1 d)
Trazodone	5-9	25-45 (1-2 d)
Zolpidem	2.5	12.5 (<1 d)
Benzodiazepines		
Clonazepam	Children: 22-30 Adults: 17-60	Children: 110-150 (5-6 d) Adults: 85-300 (4-13 d)
Diazepam	44-48 (oral)	220-240 (9-10 d)
Lorazepam	12 (oral)	60 (3 d)
Midazolam	3	15 (<1 d)
Tricyclic antidepressants		
Amitriptyline	13-36	65-180 (3-8 d)
Desipramine	15-24	60-120 (3-5 d)
Doxepin	15	60 (3 d)
Imipramine	8-21	40-105 (2-4 d)
Nortriptiline	14-51	70-255 (3-11 d)

*PRACTALL guidelines recommend discontinuation of antihistamines 5 half-lives before the OFC.[E11]

TABLE E4. Preparing for a food challenge—information and recommendations from your doctor

An OFC or feeding test is the most reliable method for food allergy diagnosis. A food challenge is used to evaluate whether a food allergy has been outgrown or to figure out whether someone truly has a food allergy when the history and allergy test results are unclear. Food challenge visits are very involved, so please read this handout carefully.
What is a food challenge?
An oral food challenge is a medical procedure in which a food is eaten in gradually increasing doses under medical supervision.
How long is a food challenge visit?
Plan to stay between 3 and 6 h in the office; average is about 4 h. Your stay may be longer or shorter, depending on history, type of food allergy, and what happens during the challenge. If you/your child has no symptoms, you/your child will be monitored in our office for 1-2 h after the last dose. In children with a history of FPIES, plan to stay 2-6 h after the food is fully ingested for observation. If you/your child has a reaction during the challenge, monitoring times will vary. If a reaction requires treatment with epinephrine, you/your child may be monitored for several hours after the administration of epinephrine. If a reaction is significant or severe, there is a small chance that you/your child will need to be transferred to an emergency room or be hospitalized for further monitoring or additional medications. Please have a back-up plan in place in case you need to stay the whole day.
How to prepare for a food challenge
You/your child must be well on the day of the challenge. Please call the office to discuss any symptoms of illness, asthma, or allergy. A food challenge may need to be rescheduled if
• You/your child is sick the week of the challenge, eg, fever, infection, or antibiotics.
• You/your child has poorly controlled or worsening of asthma, eczema, or nasal allergy symptoms the week of the challenge, eg, using rescue inhaler within 2-3 d before the challenge, having to blow nose constantly, or active flare of eczema.
Medication guidelines
Stop all antihistamines 3-10 d before the challenge as directed by your doctor. Other medications may be discontinued per your doctor's instructions.
Continue all asthma steroid preventative inhalers and nasal steroid sprays (fluticasone, budesonide, beclomethasone, flunisolide, mometasone, ciclesonide, triamcinolone). If your asthma preventative inhaler has salmeterol or formoterol in it, do not use this inhaler 8 h before the challenge. Do not use a rescue inhaler (albuterol, xopenex) preventively (eg, before exercise to prevent symptoms) 8 h before the challenge. Please always use a rescue inhaler if needed for symptoms and then let the office know.
Never avoid treating allergy or asthma with rescue medications because a food challenge is approaching. If you/your child needs to use a rescue inhaler, an antihistamine, or even epinephrine, please use the medicine and then call the office to discuss the symptoms in case the challenge should be postponed.
If you have a question about a specific medication, please contact the office.
Eating before the food challenge
You/your child should not have anything to eat for at least 4 h before the challenge. Infants and young children may be given a light meal 2 h before the challenge.
What to bring to the food challenge
Details will be provided by your physician about the specific food to bring; however, it is recommended that you bring at least 2 different servings of the food to be challenged.
Additional details regarding the challenge food may be provided by your physician.
Bring your/your child's epinephrine autoinjector twin pack to the visit.
Bring something to entertain yourself/your child during the visit.
Special considerations for children
Prepare your child for the food challenge by explaining the procedure to them. The language you use can give your child necessary information without overwhelming him or her. Tell your child that he or she will have an OFC to see whether he or she is allergic to the food. Tell him or her that the food will be eaten at the doctor's office and doctors and nurses will be at the challenge to keep them safe. Emphasize that your child can bring games and fun activities to the challenge.
For young children or picky eaters, it is helpful to bring several forms of the food (eg, cow's milk and cow's milk yogurt).
Bring anything that may make it easier for your child to eat a new food (favorite plates, cups, spoons, prizes, etc).
Who to call
A food challenge is an important part of a food allergy evaluation. If you have any questions or concerns about the procedure, please call _____.
Because there is a substantial waiting list for food challenges, please take care in scheduling the food challenge appointment and inform the office as soon as possible if you need to reschedule.

TABLE E5. Abnormal VSs by age[E12-E14]

	When is it hypotension?
Age	**Systolic blood pressure (mm Hg)**
Infants (1-12 mo)	<70
1-10 y	(Age × 2) + 70
>10 y	<90

	When is it tachycardia?
Age	**Heart rate (bpm)**
<2 y	>160
2-12 y	>140
>12 y	>100

	When is it tachypnea?
Age	**Respiratory rate (breaths/min)**
3-6 mo	≥65
6-9 mo	≥62
9-12 mo	≥59
12-18 mo	≥54
18-24 mo	≥47
2-3 y	≥39
3-4 y	≥34
4-6 y	≥30
6-8 y	≥28
8-12 y	≥26
12-15 y	≥24
15-18 y	≥23

bpm, Breaths per minute.

TABLE E6. Adverse reactions to Foods Committee–Suggested Stopping Criteria*[E15]

The OFC should be stopped if any **1** of the following symptoms is 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
• Aphonia
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 min
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 min
Respiratory
• Persistent rubbing of the nose or eyes for ≥3 min
• Persistent rhinorrhea for ≥3 min
Gastrointestinal
• Diarrhea

*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 whether a challenge dose should be repeated, the next dose should be delayed, or whether 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 min) are more likely indicative of a reaction than when such symptoms are transient and not reproducible.

TABLE E7. Performance of cutoff levels noted in studies of BM and BE tolerance[E16-E27]

Study	Cutoff levels	Sensitivity	Specificity	Positive LR*	Negative LR*
BM					
Nowak-Wegrzyn et al[E16]					
	CM SPT < 5 mm	1	0.13	1.14	0
	CM SPT < 10 mm	0.5	0.79	2.38	0.63
	CM sIgE > 35 kU/L	0.26	0.99	26	0.75
Bartinikas et al[E17]					
	CM SPT < 7 mm	1	0.17	1.20	0
	Casein SPT > 9 mm	0.67	0.86	4.79	0.38
	CM >13 mm	0.67	0.72	2.39	0.46
Caubet et al[E18]					
	CM sIgE > 24.5 kU/L	0.3	0.95	6	0.74
	Casein sIgE > 20.2 kU/L	0.3	0.95	6	0.74
	Casein sIgE > 4.95 kU/L	0.74	0.77	3.22	0.34
BE					
Lemon-Mule et al[E19]	*Sensitivity, specificity, and positive and negative LRs could not be calculated on the basis of data available in the article. The authors report that OM sIgE levels showed the greatest predictive value in the studied population; a level of 50 kU/L was >90% predictive of reacting, EW SPT of 15 mm was 60% predictive of reacting, and a negative EW SPT indicated a <5% chance of reacting to BE				
Ando et al[E20]					
	EW sIgE > 30.7 kU/L	0.42	0.96	10.5	0.6
	OM IgE > 10.8 kU/L	0.55	0.96	13.75	0.47
	OM sIgE > 1.16 kU/L	0.97	0.53	2.06	0.06
Lieberman et al[E21]					
	EW sIgE > 10 kU/L	0.2	0.94	3.33	0.85
Caubet et al[E22]					
	EW sIgE > 26.2 kU/L	0.12	0.95	2.4	0.93
	EW sIgE > 0.78 kU/L	0.96	0.35	1.48	0.11
	OM sIgE > 12.8 kU/L	0.28	0.95	5.6	0.76
Tan et al[E23]					
	OM SPT > 11 mm	0.18	1	—	0.82
	BE muffin SPT < 2 mm	0.96	0.17	1.16	0.24
Bartinikas et al[E24]					
	EW SPT > 3 mm	1.00	0.17	1.2	0
	EW SPT > 11 mm	0.69	0.56	1.57	0.55
	EW sIgE > 9.65 kU/L	0.37	0.95	7.4	0.66
	OM sIgE > 9.74 kU/L	0.07	0.99	7	0.94
Peters et al[E25]					
	EW PST > 11 mm	0	0.99	—	1.01
Turner et al[E26]					
	EW SPT > 12 mm	0.16	0.98	8	0.86
	Raw egg SPT > 25 mm	0.05	0.99	5	0.96
Saifi et al[E27]					
	EW SPT < 10 mm	0.72	0.78	3.27	0.36
	EW sIgE < 8 kU/L	0.6	0.75	2.40	0.53
	OM sIgE < 8 kU/L	0.31	0.81	1.63	0.85

CM, Cow's milk; *EW*, egg white; *LR*, likelihood ratio; *OM*, ovomucoid; *sIgE*, specific IgE.

The negative LR may be used to indicate when a patient is likely to pass the challenge. A negative LR of <0.1 indicates that the test result is very likely to result in tolerance (ie, passed challenge), a negative LR of 0.1-0.5 indicates a moderate probability of passing the challenge, and an LR of >0.5 indicates a small effect on decreasing disease probability. Based on the data from Bartinikas et al,[E24] an EW SPT wheal of <3 mm would be highly predictive for passing a BE challenge.

*When interpreting LR results (ie, the likelihood that a patient will react with ingestion), the higher the positive LR, the more likely the patient is to react with ingestion. A positive LR of >10 indicates that the test result has a large effect on increasing the probability of reacting, a positive LR of 5-10 indicates that the test result has a moderate effect on increasing the probability of a reaction, and a positive LR of <5 indicates a small effect on increasing the probability of reacting. For example, using the data generated from Nowak-Wegzryn et al, a CM sIgE proved to be the strongest predictor of a reaction with a baked CM challenge, and a CM sIgE of >35 is highly predictive of reacting.

TABLE E8. Muffin recipes (4 recipes)[E28]

BE muffin recipe
Yield: 6 muffins
Ingredients:
Dry ingredients
1 cup all-purpose wheat flour
1/2 cup sugar
1/4 tsp salt
1 tsp baking powder
Wet ingredients
2 tbsp canola oil (or other tolerated vegetable oil)
1/2 tsp vanilla extract
2 large eggs, beaten
1/2 cup rice milk (may use other tolerated milk or milk substitute)
1. Preheat oven to 350°F. Bake muffins only in an oven that is completely preheated to 350°F.
2. Line a muffin pan with 6 muffin liners. Use aluminum or parchment paper muffin liners or alternatively, you may grease the muffin tins with Pam or safe margarine (or butter if not allergic to milk).
3. Stir together the liquid ingredients until well combined: milk, canola oil, vanilla extract, and egg. Set aside.
4. In a separate mixing bowl, mix together the dry ingredients (flour, sugar, salt, baking powder).
5. Add liquid ingredients to dry ingredients all at once and gently stir with a large spoon (about 15-20 light strokes) until wet and dry ingredients are just combined. Do not overstir. Some small lumps may remain.
6. Divide the batter into the 6 prepared muffin liners. Depending on the size of your muffin tin, you may need to fill the muffin liners all the way to the top.
7. Bake 30-35 min or until golden brown and firm to the touch. Cool completely before serving.
If you make more than 6 muffins, please note how many muffins you made and bring at least 2 muffins with you on the day of the challenge.
Wheat-free BE muffin recipe
Yield: 6 servings
Ingredients
Dry ingredients
1 1/4 cups rice flour
1/2 cup sugar
1/4 tsp salt
1 tsp baking powder
Wet ingredients
1 cup rice milk (may use other tolerated milk or milk substitute)
2 large eggs
1/2 tsp vanilla
2 tbsp oil, such as corn oil
1. Preheat oven to 350°F. Bake muffins only in an oven that is completely preheated to 350°F.
2. Grease 6 muffin tins (wipe oil around each cup or use cooking spray).
3. Stir together dry ingredients in a large bowl (rice flour, sugar, salt, baking powder).
4. In a separate bowl, stir together the liquid ingredients until well combined (milk, egg, vanilla, oil).
5. Add the liquid to the dry ingredients stirring with a spatula or spoon. Only mix until just combined, about 20 s; batter will be thin and lumpy. Do not overmix!
6. Divide the batter into the 6 prepared muffin liners. Depending on the size of your muffin tin, you may need to fill the muffin tins all the way to the top.
7. Bake 30-35 min or until golden brown and firm to the touch. Cool completely before serving.
If you make more than 6 muffins, please note how many muffins you made and bring at least 2 muffins with you on the day of the challenge.
BM muffin recipe
Yield: 6 muffins
Ingredients:
Wet ingredients
1 cup of milk
2 tbsp canola oil
1 tsp vanilla extract
1 egg* or 1 1/2 tsp egg replacer if child is allergic to egg (Note: We use Ener-G brand egg replacer)

(continued)

TABLE E8. *(Continued)*

Dry ingredients
1 1/4 cups of all-purpose flour (wheat)
1/2 cup sugar
1/4 tsp salt
2 tsp baking powder
1. Preheat oven to 350°F. Bake muffins only in an oven that is completely preheated to 350°F.
2. Line a muffin pan with 6 muffin liners.
3. Stir together the liquid ingredients until well combined: milk, canola oil, vanilla extract, egg or egg replacer (although the egg replacer is a dry ingredient, please add at this step). Set aside.
4. In a separate mixing bowl, mix together the dry ingredients (flour, sugar, salt, baking powder).
5. Add liquids ingredients to dry ingredients all at once and gently stir with a wooden spoon (about 15-20 light strokes) until wet and dry ingredients are just combined. Do not overstir. Some small lumps may remain.
6. Divide the batter into the 6 prepared muffin liners. Depending on the size of your muffin tin, you may need to fill the muffin liners all the way to the top.
7. Bake 30-35 min or until golden brown and firm to the touch. Cool completely before serving.
If you make more than 6 muffins, please note how many muffins you made and bring at least 2 muffins with you on the day of the challenge.
Wheat-free BM muffin (contains eggs)
Yield: 6 servings
Ingredients:
Dry ingredients
1 1/4 cups rice flour (this recipe works best with rice flour rather than a gluten-free flour blend)
1/2 cup sugar
1/4 tsp salt
1 tsp baking powder
Wet ingredients
1 cup milk
2 large eggs
1/2 tsp vanilla
2 tbsp oil, such as corn oil
1. Preheat oven to 350°F. Bake muffins only in an oven that is completely preheated to 350°F.
2. Grease 6 muffin tins (wipe oil around each cup or use cooking spray).
3. Mix well all dry ingredients in a large bowl (rice flour, sugar, salt, baking powder).
4. In a separate bowl, stir together the liquid ingredients until well combined (milk, egg, vanilla, oil).
5. Add the liquid to the dry ingredients stirring with a spatula or spoon. Mix until combined, about 20 s; batter will be thin and lumpy. Do not overmix!
6. Divide the batter into the 6 prepared muffin liners. Depending on the size of your muffin tin, you may need to fill the muffin tins all the way to the top.
7. Bake 30-35 minutes or until golden brown and firm to the touch. Cool completely before serving.
Any changes to this recipe must be approved by your doctor or dietitian.
If you make more than 6 muffins, please note how many muffins you made and bring at least 2 muffins with you on the day of the challenge.

Tbsp, Tablespoon; *tsp*, teaspoon
*DO NOT use egg if your child is allergic to egg.

TABLE E9. Guidance if BE is tolerated[E28]

Instructions for introducing BE at home—after the physician-supervised oral food challenge and when approved by your doctor:
When your child has passed the BE challenge he or she will be able to eat extensively baked products with egg as an ingredient. Should your child develop an allergic reaction to the food that contains BE, please record the offending food, amount eaten, preparation technique, and symptoms, and contact our office at your earliest convenience to review the reaction.
Your child MAY NOW EAT the following:
☐ Store-bought baked products with egg/egg ingredients listed as the third ingredient or further down the list of ingredients
☐ Home-baked products that have no more than $^{1}/_{3}$ of a BE per serving. For example, a recipe that has 2 eggs/batch of a recipe that yields 6 servings*
☐ Remember to check store-bought products and ingredients based on your child's food allergies in order to avoid a reaction to other allergens
☐ All baked products must be baked throughout and not wet or soggy in the middle
Your child SHOULD CONTINUE TO AVOID unbaked egg and egg-based foods such as:
☐ Baked products with egg listed as first or second ingredient
☐ Caesar salad dressing
☐ Custard
☐ Eggs in any form such as hard or soft boiled, scrambled, or poached
☐ Egg noodles
☐ French toast/pancakes
☐ Home-made waffles
☐ Frosting-containing egg
☐ Ice cream
☐ Mayonnaise
☐ Quiche

*Serving sizes are specified in the nutrition information section of the food label or determined by the yield of the recipe.

TABLE E10. Guidance if BM is tolerated[E28]

Instructions for introducing BM at home—after the physician-supervised OFC and when approved by your doctor:
When your child has passed the BM challenge, he or she will be able to eat extensively baked products with cow's milk as an ingredient. Should your child develop an allergic reaction to the food that contains BM, please record the offending food, amount eaten, preparation technique, and symptoms, and contact our office at your earliest convenience to review the reaction.
Your child MAY NOW EAT the following:
☐ Store-bought baked products with cow's milk/cow's milk ingredient listed as the third ingredient or further down the list of ingredients
☐ Home-baked products that have no more than 1/6th cup of cow's milk per BM serving. For example, a recipe that has 1 cup cow's milk per batch of a recipe that yields 6 servings*
☐ Remember to check store-bought products and ingredients based on your child's food allergies in order to avoid a reaction to other allergens
☐ All baked products must be baked throughout and not wet or soggy in the middle
Your child SHOULD CONTINUE TO AVOID unbaked milk and cow's milk−based foods such as:
☐ Baked products with cow's milk listed as first or second ingredient
☐ Products that may have a cow's milk ingredient that has not been baked such as a cow's milk ingredient containing frosting on a cookie or cupcake or a cheese flavoring on a cracker that may not have been baked (eg, flavorings may be applied topically after the product is baked)
☐ Milk chocolate chips that will melt during baking but not "bake." Please continue to use cow's milk−free chocolate chips
☐ Regular milk or dairy in any form including whole, low-fat, nonfat, or skimmed cow's milk, lactose-free products, dry milk powder, yogurt, sour cream, butter, hard and soft cheeses, ice cream/sherbet, butter, etc
☐ Frostings with a cow's milk ingredient
☐ French toast/pancakes
☐ Home-made waffles
☐ Cooked milk products that are not baked such as puddings

*Servings are specified in the nutrition information section of the food label or determined by the yield of the recipe.

TABLE E11. Considerations and preparation for infant OFC[E15]

Before the challenge
1. Assess feeding concerns with the family, such as oral-motor skill deficits, and determine whether the infant is eating solid foods. If there are feeding concerns or the infant is not eating solid foods, it may be appropriate to wait until feeding concerns are addressed by an occupational/speech therapist or the parents have introduced other solid foods.
2. Have an open discussion with the family with particular emphasis on plans following the challenge. For instance, if the family states they will not be able to feed the child peanut products after the challenge, then reconsider the necessity of performing the challenge.
3. Optimize control of atopic dermatitis (AD) and asthma. Do not perform the challenge in a child with poorly controlled AD, wheezing, coughing, URI symptoms, or febrile illness.
4. Remind parents that the child may have a light meal (eg, $^1/_2$ of the usual serving) 2 h before the challenge.
5. Remind the family to bring entertainment, toys, music, etc during the challenge and multiple forms of the target food.
6. Structure the timing and environment of the OFC to be as similar to the home meal environment as possible (ie, avoid scheduling the challenge during the infant's nap time; have a high chair available).
Day of the challenge
1. Ensure medications have been discontinued as outlined in Tables I and II.
2. Obtain the child's weight, temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation level.
3. Perform a thorough physical examination including examination of ears (do not perform challenge if the child has evidence of an ear infection), oropharynx and nose (getting baseline visualization of uvula and tongue, rhinorrhea, congestion, etc), lungs (listen for wheezing, crackles, or coarse breath sounds), and skin (looking for any rashes, urticaria, birth marks, etc).
4. Calculate doses of emergency medications.
5. Prepare the food challenge product.
6. Administer doses. Give each dose 15-20 min apart. Perform a brief physical examination including visualization of the oropharynx, auscultation of the lungs, and visualization of the skin between each dose.
POSTCHALLENGE INSTRUCTIONS
☐ **CHILD INGESTS FULL AMOUNT AND DOES NOT HAVE A REACTION**
1. Instruct family to reintroduce the food as a normal part of the child's diet.
☐ **CHILD INGESTS MORE THAN HALF OF THE CHALLENGE BUT REFUSES THE REMAINDER.**
1. Instruct the family to give an equivalent amount at home and if tolerated, increase serving to an **age-appropriate, serving of the food**.
☐ **CHILD DOES NOT COMPLETE DOSE 3 BUT TOLERATES DOSES 1 AND 2.**
1. Results are inconclusive. Continue avoidance and return for challenge at another time (eg, in 1-2 wk or longer depending on family preference).
☐ **CHILD HAS A REACTION DURING THE CHALLENGE AND IS CONSIDERED ALLERGIC.**
1. Instruct family on allergen avoidance.
2. Provide food allergy action plan and discuss the signs and symptoms of a food-induced allergic reaction.
3. Provide a prescription for 2 autoinjectable epinephrine devices and demonstrate appropriate use with a trainer device.

TABLE E12. Diagnostic criteria for the interpretation of OFCs in patients with a history of possible or confirmed FPIES[E29]

Major criterion	Minor criteria
Vomiting in the 1-4-h period after ingestion of the suspect food and the absence of classic IgE-mediated allergic skin or respiratory symptoms	Lethargy
	Pallor
	Diarrhea in 5-10 h after food ingestion
	Hypotension
	Hypothermia
	Increased neutrophil count of at least 1500 neutrophils above the baseline count

The OFC will be considered diagnostic of FPIES, ie, positive, if the major criterion is met with at least 2 minor criteria. However, we would suggest 2 important caveats to these criteria: (1) with the rapid use of ondansetron, many of the minor criteria, such as repetitive vomiting, pallor, and lethargy may be averted; and (2) not all facilities performing challenges have the ability to perform neutrophil counts in a timely manner. Therefore, the treating physician may decide that a challenge be considered diagnostic in some instances even if only the major criterion was met. However, in challenges performed for research purposes, stringent criteria for challenge positivity should be adhered to.

TABLE E13. Management of an acute FPIES episode at the medical facility during an OFC[E29]

Presenting symptoms		
Mild	**Moderate**	**Severe**
Symptoms		
1-2 episodes of emesis No lethargy	>3 episodes of emesis and mild lethargy	>3 episodes of emesis, with severe lethargy, hypotonia, ashen or cyanotic appearance
Management		
1. Attempt oral rehydration (eg, breast-feeding or clear fluids)	1. If age 6 mo and older: administer ondansetron intramuscular 0.15 mg/kg/dose, maximum 16 mg/dose	1. Place a peripheral intravenous line and administer normal saline bolus 20 mL/kg rapidly, repeat as needed to correct hypotension
2. If age 6 mo and older: Consider ondansetron intramuscular 0.15 mg/kg/dose, maximum 16 mg/dose	2. Consider placing a peripheral intravenous line for normal saline bolus 20 mL/kg, repeat as needed	2. If age 6 mo and older: administer intravenous ondansetron 0.15 mg/kg/dose, maximum 16 mg/dose
3. Monitor for resolution about 4-6 h from the onset of a reaction	3. Transfer the patient to the emergency department or intensive care unit in case of persistent or severe hypotension, shock, extreme lethargy, or respiratory distress	3. If placement of intravenous line is delayed because of difficult access and age is 6 mo or older, administer ondansetron intramuscular 0.15 mg/kg/dose, maximum 16 mg/dose
	4. Monitor VSs	4. Consider administering intravenous methylprednisolone 1 mg/kg, maximum 60-80 mg/dose
	5. Monitor for resolution at least 4-6 h from the onset of a reaction	5. Monitor and correct acid-base and electrolyte abnormalities
	6. Discharge home if patient is able to tolerate clear liquids	6. Correct methemoglobinemia if present
		7. Monitor VSs
		8. Discharge after 4-6 h from the onset of a reaction when the patient is back to baseline and is tolerating oral fluids
		9. Transfer the patient to the emergency department or intensive care unit for further management in case of persistent or severe hypotension, shock, extreme lethargy, respiratory distress

Strong consideration should be lent in performing food challenges in children with a history of severe FPIES in the hospital or other monitored setting with immediate availability of intravenous resuscitation.

Oral challenges in the physician's office may be considered in patients with no history of a severe FPIES reaction, although caution should be urged because there are no data that can predict future severity of an FPIES reaction.

TABLE E14. Overview of published recipes for DBPCFCs validated by sensory testing (professionals or volunteers)*

Active recipe	Placebo recipe	Amount of allergenic protein; Total amount of test food; Remarks
Milk in Nutramigen[E30]		
300 mL of Nutramigen (54 g powder and 270 mL water)	400 mL of Nutramigen (54 g powder and 360 mL water)	3.5 g cow's milk protein
100 mL of pasteurized fat-free milk		Total: 400 mL
Method	*Method*	
Boil water, cool until lukewarm, mix with powder, add fat-free milk	Boil water, cool until lukewarm, mix with powder	
Milk in rice milk[E30]		
260 mL of rice milk	360 mL of rice milk	3.5 g cow's milk protein
100 mL of fat-free pasteurized milk	6 g of cow's milk–free margarine or sunflower oil	
12 g of ready-to-use rice flour	12 g of ready-to-use rice flour	Total: ~422 mL (active)/418 mL (placebo)
40 mL of fruit syrup or agave syrup	40 mL of fruit syrup or agave syrup	
Method	*Method*	
Warm rice milk (do not boil), add rice flour while stirring, add syrup and stir	Warm rice milk (do not boil), add margarine or oil and rice flour while stirring, add syrup and stir	
Soy milk in milk[E30]		
290 mL of low-fat milk (1.5% fat)	370 mL of low-fat milk (1.5%) fat	~3.5 g soy protein (depending on brand of soy milk used)
100 mL of unsweetened soy milk	—	
40 mL of whipping cream (35%; do not whip)	60 mL of whipping cream (35%; do not whip)	
30 mL of fruit syrup or agave syrup	30 mL of fruit syrup or agave syrup	Total: 460 mL recipe
Method	*Method*	Remark:
Mix all ingredients	Mix all ingredients	High fat content
Peanut recipe IV[E31]		
30 g of dark milk-free chocolate (70%)	30 g of dark milk-free chocolate (70%)	1.1 g peanut or 0.26 g peanut protein per 10 g serving
10 g of cocoa powder	10 g of cocoa powder	Total amount: 193 g (active)/194 g (placebo) recipe
40 g of icing sugar	40 g of icing sugar	Concentration peanut and fat: 11% in active and 12% in placebo
20 g of rolled roasted oats	20 g of rolled roasted oats	
20 g of oatmeal	42 g of oatmeal	
20 drops of peppermint oil	20 drops of peppermint oil	
50 g of coconut yogurt	50 g of coconut yogurt	
5 g of vanilla sugar	5 g of vanilla sugar	
22 g of molded roasted peanut	—	
1 g of salt	1 g of salt	
1 pearl of sugar (g/item)	1 pearl of sugar (g/item)	
Method	*Method*	
Preheat the oven to 345°F (175°C). Cover a baking tray with baking paper, spread out oat flakes, and roast for 15-20 min until the flakes are golden brown. Stir now and then while roasting. Cool down and mix all ingredients	Preheat the oven to 345°F (175°C). Cover a baking tray with baking paper, spread out oat flakes, and roast for 15-20 min until the flakes are golden brown. Stir now and then while roasting. Cool down and mix all ingredients	
Lupine cookies[E32]		
8.5 g of whole wheat flour	10 g of whole wheat flour	2.19 mg lupine protein
8.5 g of all-purpose wheat flour	10 g of all-purpose wheat flour	Total: 55 g (active)/59 g (placebo) recipe (weight may vary because of evaporation)
6.05 g of lupine flour (*L angusti-folius* [blue lupine] or *L albus*)	6 g of custard powder or equivalent	
15 g of cane sugar	15 g of cane sugar	

(continued)

TABLE E14. *(Continued)*

Active recipe	Placebo recipe	Amount of allergenic protein; Total amount of test food; Remarks
15 g of cow's milk–free margarine	15 g of cow's milk–free margarine	
2 g of vanilla sugar	3 g of vanilla sugar	
0.3 g of salt	8 drops of artificial sweetener	
	0.3 g of salt	
Method	*Method*	
Whisk together all ingredients and knead thoroughly. Chill for 30 min. Preheat oven to 160°C. Press dough into 2-4 cookies onto ungreased cookie sheets.	Whisk together all ingredients and knead thoroughly. Chill for 30 min. Preheat oven to 160°C. Press dough into 2-4 cookies onto ungreased cookie sheets.	
Bake for 10-15 min in the preheated oven. Remove from cookie sheets to cool on wire racks	Bake for 10-15 min in the preheated oven. Remove from cookie sheets to cool on wire racks	
Cod in spiced chicken meat, recipe III[E33]		
1 part (40 g) of cod fish	—	~9 g fish protein
1 part (40 g) of chicken breast	2 parts (80 g) of chicken breast	Total: 250 g recipe
2 parts (80 g) of potato flakes	2 parts (80 g) of potato flakes	
1/8 part (5 g) of salt	1/8 part (5 g) of salt	
1/8 part (5 g) of pepper, spearmint, dill	1/8 part (5 g) of pepper, spearmint, dill	
2 (60 g) parts of water	2 (60 g) parts of water	
0.5 part (20 mL) of vinegar	0.5 part (20 mL) of vinegar	
Method	*Method*	
Mix ingredients in a commercial blender until a homogeneous mixture is obtained. Form meat balls and fry in olive oil	Mix ingredients in a commercial blender until a homogeneous mixture is obtained. Form meat balls and fry in olive oil	
Peanut in gingerbread (muffins)[E34]††		
31 g of brown sugar	31 g of brown sugar	4.4 g peanut protein (equivalent to 17.6 g of peanuts or 1 serving of peanut butter)
6.2 g of dairy-free margarine	6.2 g of dairy-free margarine	Total: ~122 g (weight may vary because of evaporation)
43 g of self-rising wheat flour	43 g of self-rising wheat flour	
8.6 g of defatted peanut flour‡	0.09 mL of peanut flavor QL 35189§	
0.025 mL of hazelnut flavor QL§	0.025 mL of hazelnut flavor QL 13849§	
37 mL of rice milk	31 mL of rice milk	
0.12 g of salt	0.12 g of salt	
1.25 g of gingerbread spice mixture: cinnamon, coriander, nutmeg, clove, cardamom, ginger‖	1.25 g of gingerbread spice mixture: cinnamon, coriander, nutmeg, clove, cardamom, ginger‖	
7.4 mL of beet sugar syrup¶	6.4 mL of beet sugar syrup¶	
Method	*Method*	
Preheat the oven to 160°C	Preheat the oven to 160°C	
Mix and blend all ingredients	Mix and blend all ingredients	
Divide evenly between 2 and 3 muffin cases and bake for 15 min	Divide evenly between 2 and 3 muffin cases and bake for 15 min	
Peanut in minced meat[E34]		
92 g of lean fine-ground minced beef (6% fat)	92 g of lean fine-ground minced beef (6% fat)	4.4 g peanut protein (equivalent to 17.6 g of peanuts or 1 serving of peanut butter)
25 mL of rice milk	18.5 mL of rice milk	Total: ~107 g (weight may vary because of evaporation)
8.6 g of defatted peanut flour‡	0.09 mL of peanut flavor QL 35189§	
0.65 g of salt	13 g of breadcrumbs (free of egg/milk)	
0.3 g of pepper	0.56 g of salt	
	0.3 g of pepper	
Method	*Method*	
Mix ingredients in a commercial blender until a homogeneous mixture is obtained. Form meat balls and fry in olive oil	Mix ingredients in a commercial blender until a homogeneous mixture is obtained. Form meat balls and fry in olive oil	

(continued)

TABLE E14. *(Continued)*

Active recipe	Placebo recipe	Amount of allergenic protein; Total amount of test food; Remarks
Hazelnut in gingerbread# (muffins)[E34]†		
24.6 g of brown sugar	24.6 g of brown sugar	1.7 g hazelnut protein (equivalent to 12.4 g of hazelnuts or 12 hazelnuts)
4.8 g of dairy-free margarine	4.5 g of dairy-free margarine	Total: ~120 g
34.5 g of self-rising wheat flour	34.5 g of self-rising wheat flour	
12.4 g of ground blanched unroasted hazelnuts	0.06 mL of peanut flavor QL 35189§	
0.06 mL of peanut flavor QL 35189§	0.36 mL of hazelnut flavor QL13849§	
29.6 mL of rice milk	24.9 mL of rice milk	
0.12 g of salt	0.12 g of salt	
2.4 g of gingerbread spice mixture: cinnamon, coriander, nutmeg, clove, cardamom, ginger‖	1.8 g of gingerbread spice mixture: cinnamon, coriander, nutmeg, clove, cardamom, ginger‖	
6 g of desiccated coconut	6 g of desiccated coconut	
7.2 mL of beet sugar syrup¶	6 mL of beet sugar syrup¶	
Method	*Method*	
Preheat the oven to 160°C	Preheat the oven to 160°C	
Mix and blend all ingredients	Mix and blend all ingredients	
Divide evenly between 2 and 3 muffin cases and bake for 15 min	Divide evenly between 2 and 3 muffin cases and bake for 15 min	
Cashew nut in gingerbread (muffins)[E34]†		
30 g of brown sugar	30 g of brown sugar	2.9 g cashew nut protein (equivalent to 15 g or 22 cashew nuts)
6 g of dairy-free margarine	6 g of dairy-free margarine	Total: ~120 g
42 g of self-rising wheat flour	42 g of self-rising wheat flour	
15 g of ground cashew nuts	0.12 mL of peanut flavor QL 35189§	
0.12 mL of peanut flavor QL 35189§	0.36 mL of hazelnut flavor QL 13849§	
36 mL of rice milk	30 mL of rice milk	
0.12 g of salt	0.12 g of salt	
3.6 g of gingerbread spice mixture: cinnamon, coriander, nutmeg, clove, cardamom, ginger‖	2.4 g of gingerbread spice mixture: cinnamon, coriander, nutmeg, clove, cardamom, ginger‖	
7.2 g of desiccated coconut	7.2 g of desiccated coconut	
7.2 ml of beet sugar syrup¶	7.2 mL of beet sugar syrup¶	
Method	*Method*	
Preheat the oven to 160°C	Preheat the oven to 160°C	
Mix and blend all ingredients	Mix and blend all ingredients	
Divide evenly between 2 and 3 muffin cases and bake for 15 min	Divide evenly between 2 and 3 muffin cases and bake for 15 min	
Wheat muffins[E35]		
100 g of self-rising wheat flour	140 g of gluten-free flour blend	1.4 g wheat protein
30 g of cocoa	30 g of cocoa	Total: 10 g wheat flour in 1 × 50 g muffin
30 g of rice flour	—	Produced as a tray bake to be served as slice of cake or prepared as a muffin
1 tsp of baking powder	2 tsp of baking powder (gluten free)	
150 g of margarine/spread	150 g of margarine/spread	
150 g of caster sugar	150 g of caster sugar	
2 medium eggs, lightly beaten	2 medium eggs, lightly beaten	
4 tbsp of milk	4 tbsp milk	
Makes 10 chocolate muffins of 50 g each	Makes 10 chocolate muffins of 50 g each	
Method	*Method*	
Preheat the oven to 180°C/Gas 5	Preheat the oven to 180°C/Gas 5	
Cream together the margarine and sugar until light and fluffy	Cream together the margarine and sugar until light and fluffy	
Gradually add the beaten egg	Gradually add the beaten egg	

(continued)

TABLE E14. *(Continued)*

Active recipe	Placebo recipe	Amount of allergenic protein; Total amount of test food; Remarks
Fold in the sieved flours, cocoa, and baking powder, gradually adding the milk	Fold in the sieved flours, cocoa, and baking powder, gradually adding the milk	
Divide evenly between 10 muffin cases and bake for 15 min	Divide evenly between 10 muffin cases and bake for 15 min	
Egg white in soy milk[E36]		
34 mL of pasteurized liquid egg white	—	34 mL of pasteurized liquid egg white (equivalent 1 whole egg white)
206 mL of ultra high heated chocolate soy milk	240 mL of ultra high heated chocolate soy milk	Total: ∼260 mL
9 g of milk hydrolysate	9 g of milk hydrolysate	
9 g of vanilla sugar	9 g of vanilla sugar	

tsp, Teaspoon.
Dark milk-free chocolate: eg, Enjoy Life Chocolate chips.
Custard powder: eg, Birds Custard Powder.
Peanut flour: eg, Golden Brand.
Peanut flavor: eg, Silver Cloud Estates peanut flavor (peanut free).
Hazelnut flavor: eg, Silver Cloud Estates hazelnut flavor (tree nut free).
Lupine flour: eg, Lupina brand lupine flour.
Milk-free margarine: eg, Fleischmann's Unsalted Stick Margarine.
Milk-free, soy-free cocoa: eg, Hershey's unsweetened cocoa powder.
Pasteurized liquid egg white: eg, Egg Beaters.
Creamed coconut: eg, Edward and Sons Creamed coconut.
Desiccated coconut: eg, Bob's Red Mill fine macaroon coconut.
Vanilla sugar: eg, Dr Oetker brand.
Milk hydrolysate: eg, Nutramigen powder.
Dried whole egg: eg, Hoosier Hills Farm.
Potato starch: eg, Authentic foods Potato starch.
Beet sugar syrup: eg, Goldsafter Original Goldsaft Beet Sugar Syrup.
*These recipes were developed in research settings and measurements are provided in precise amounts (eg, milligram and milliliter) rather than in standard household measures.
†BE in gingerbread (recipe not shown), peanut in gingerbread, cashew nut in gingerbread, and hazelnut in gingerbread muffins are also commercially available, produced according to these recipes.[E37]
‡Brand used in these recipes: Golden Peanut Company, Alpharetta, Ga.
§Brand used in these recipes: Internatio Möller, Mechelen, Belgium, to be obtained at Allergie Supermarkt.[E38]
‖Brand used in these recipes: Dutch Spices to be obtained at Allergie Supermarkt.[E38]
¶Brand used in these recipes: Zeeuwse boerin keukenstroop.[E39]
#Heating may reduce allergenicity of hazelnut; therefore, this recipe may not be suitable for diagnosis of PFS.[E40] The recipe has been validated for diagnosis of systemic reactions.[E34]

TABLE E15. Recommendations following a positive OFC (ie, individual reacts to the challenge food)

You/your child had a reaction during a food challenge—Recommendations from your doctor
You/your child did not tolerate the challenge food today. This means you/your child is still allergic to the food.
Activity level should be minimal for the rest of the day. Resume normal activity tomorrow.
You/your child's next meal should consist of foods unlikely to cause stomach discomfort because this may be confused with a delayed allergic reaction.
Please make sure you/your child has epinephrine available for the rest of the day.
Please monitor yourself/your child for the rest of the day. Rarely, you/your child may develop a delayed allergic reaction hours after eating the food. If you/your child has symptoms of an allergic reaction such as hives, cough, breathing problems, vomiting, or diarrhea later today, treat according to your emergency action plan first and go to the emergency department.
You/your child must continue to avoid the challenge food and carry epinephrine autoinjectors at all times.
Reminders about epinephrine:
Always have 2 epinephrine injectors available at all times.
Practice how to use epinephrine.
Make sure the school or day care has 2 epinephrine autoinjectors.
Resume any medications held for the food challenge. Return for Allergy follow-up as instructed by your doctor.
It is normal to feel disappointed after experiencing a reaction during a food challenge. However, it also can be a valuable learning experience in helping you/your child recognize symptoms of an allergic reaction and experience the effectiveness of immediate treatment with epinephrine. For parents, try to be as encouraging as possible when discussing the experience with your child. Please do not use the word "fail" in front of your child. Rather, praise your child for participating in the food challenge and helping to answer the question of whether or not he/she is allergic to the food. It is also possible that you/your child will experience increased worry about food allergy after an allergic reaction. This is also normal, and most patients typically feel better in a few days. If you/your child continue to feel more worry than is typical for you/your child, contact your doctor or mental health professional.
If you have any questions or concerns, please call _____.

TABLE E16. Recommendations following a negative OFC (ie, individual completes the food challenge without having a reaction)

You/your child did not have a reaction during a food challenge—Recommendations from your doctor
Congratulations! You/your child did not have a reaction during your OFC. This means you/your child does not have an allergy to the food tested. You/your child may eat this food in any amount in the future.
Do not eat/feed additional servings of the challenge food on the day of the challenge.
You/your child may start eating the food tomorrow.
You/your child's next meal should consist of foods unlikely to cause stomach discomfort because this may be confused with a delayed allergic reaction.
Please carry epinephrine autoinjectors twin pack today in the rare chance of delayed symptoms. Call your doctor if you/your child develop symptoms after discharge.
If there are no symptoms, begin regular consumption of the food starting the day after the challenge as directed by your doctor. This food should be reincorporated as a normal part of your/your child's diet. Some patients continue to experience worry about eating the food that they ate in the food challenge. This is normal and typically subsides after eating the food a few times after the food challenge. Remember that you/your child tolerated the food during the food challenge, which means that you/your child is no longer allergic to the food. It is also normal to not immediately like the taste of the food that you/your child ate during the food challenge. If you have concerns about incorporating the food into you/your child's diet, contact your doctor.
If you/your child notice an increase in allergy symptoms over the next few weeks, please call your doctor to discuss whether this may be related to ingesting the new food.
If you/your child do not have other food allergies, your doctor may advise you to carry your epinephrine autoinjector twin pack for 1 y or until the expiry date. Make sure to continue carrying your epinephrine autoinjector twin pack if you have other food allergies.
Continue to use caution to avoid cross-contact if you have other food allergies.
Resume any medications held for the food challenge. Return for Allergy follow-up as instructed by your doctor.
If you have any questions or concerns, please call _____.

TABLE E17. Ingestion challenge coding[E41]

Code	Description for ingestion challenge	Relative value units	Notes
95076	First 2 h (at least 61 min)	3.39	Includes pretest and posttest evaluation
95079	Each additional hour (at least 31 min)	2.38	May be charged more than once per challenge

The pretest period includes a brief updated history and physical including medication history, review of records and labs, review of procedure and risks with patient/family, obtaining consent, confirming supply and equipment available in the event of a reaction, and writing orders for testing.

The intratest portion of the challenge covers the time necessary to provide 6-7 test doses of the food being tested. This allows assessment of the patient and a note in the chart. In the posttest period, there should be discussion of the test results, also discussion of the possibility of a delayed reaction and what to do if one occurs, performance of a final brief examination of the patient before the patient leaves the office, and completion of medical records with a copy to the primary care physician (verbal and written). The typical patient (representing more than 50% of patients challenged) has a negative OFC. Reimbursement for the intratest and posttest services is also built into the new code 95076. CPT 95079 is an add-on code that describes each additional 60 min of test time. This add-on code is intended to be used for challenges lasting beyond the 2-h base code. CPT rules require that an add-on must last at least 1 min more than 50% of the total duration of the code. This means you could not use 95079 until the additional time equaled at least 31 min beyond the first 2-h OFC.

If an ingestion challenge test is completed in under 61 min, according to CPT/RUC rules, an evaluation/management (E/M) code should be used instead of 95076. If a patient has a reaction requiring intervention therapy (ie, injection of epinephrine), the challenge is over. Any continuing symptoms consistent with a positive challenge test should be reported using appropriate E/M coding. If epinephrine or a steroid injection is required, these may be separately billed. For patient assessment/monitoring (eg, blood pressure testing and peak flow meter testing), these are not reported separately.

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