

ORAL FOOD CHALLENGES IN ROUTINE CLINICAL PRACTICE

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ABSTRACT

The oral food challenge (OFC) is a vital tool in the accurate diagnosis of food allergy. While the OFC does come with the risk of a serious reaction, it is a much more specific test than other available allergy tests. When the OFC is carefully prepared and conducted under close physician supervision by an allergist/immunologist, the benefits of the test do outweigh the potential risks, as the result often leads to the elimination of unnecessary dietary restrictions and improved quality of life for our patients.

INTRODUCTION

Accurate diagnosis of food allergies is necessary both to prevent severe, life-threatening allergic reactions, and to avoid unnecessary dietary restrictions. The diagnosis of IgE-mediated food allergy can be difficult, as available testing results in many false-positive test results. The most common method of determining whether or not someone has a food allergy is to use the clinical history in combination with skin-prick testing (SPT) and/or immunoassays of serum food specific IgE (sIgE) levels. While these tests tend to be sensitive tools in the detection of IgE-mediated food allergy, false-positive test results to tolerated foods are not uncommon, as results can be affected by factors such as age, reagents used, or cross-reactivity between proteins found in pollens and foods. It is vital that physicians correctly identify patients who are not simply sensitised to an allergen, but actually clinically reactive to it, and often it is an oral food challenge (OFC) that is required to make that distinction.

WHAT IS THE OFC?

An OFC is an oral provocation procedure performed under physician supervision in a medical setting (hospital or outpatient office). During an OFC, a food is eaten as per a protocol of gradual feeding until an age-appropriate serving is reached. The OFC can be an open, single-blind, or double-blind placebo-controlled food challenge (DBPCFC). The DBPCFC is the most specific test for the diagnosis of a food allergy and it minimises the potential bias most effectively.¹ With the DBPCFC

the test food is prepared by a third party who is not involved in evaluating the patient, and the sequence of sessions administering either the placebo or the test food is random. This minimises bias, as the patient, the patient's family, and the observer are all unaware of when the test food is ingested. The food is masked by mixing it in with a masking vehicle such as mashed potato, apple sauce, oatmeal, or chocolate pudding, or by placing the food in capsules. The blinded session of the DBPCFC can be done on 1 day, separated by a 3-hour break, though administering the active and placebo challenges on separate days is preferred.² Only after both challenges have been completed is the code broken, and the results discussed with the patient. If the patient passes the blinded challenges, an open feeding with the tested food should also be done to definitively determine that there is tolerance. During an open feeding following the blinded session, the patient is fed an age-appropriate serving of food in its natural state, e.g. peanut butter sandwich or a cup of milk. While the DBPCFC is currently the gold standard test for diagnosing food allergy, it is time- and labour-intensive, requires a capacity for masking the foods and is therefore largely reserved for research studies and select cases in clinical practice.^{3,4}

In a **single-blind placebo-controlled OFC (SBPCFC)**, the patient is unaware of whether or not he or she is served the test food or a placebo. SBPCFC may be helpful if the patient is suspected of having a psychological response. The SBPCFC does leave the possibility of observer bias, and any inconsistency in the observer's attitude could lead to bias on the part of the patient. Similar to the DBPCFC, an open OFC with the tested food in its natural form should be administered after a negative blinded challenge.

Open food challenges are typically performed in the clinical setting. The open challenge has the benefit of being simple to plan and reproduces the natural exposure in quantity and method of preparation. Of the different OFC methods, it does have the highest potential for bias, which may depend on age, personality, and type of symptoms.³⁻⁶ A negative open OFC will rule out a reaction to a food, though a positive OFC where the patient manifests only subjective symptoms, such as itchy mouth or abdominal pain, may need to be confirmed with a blinded challenge.^{3,4} It is a reasonable first choice when the need for OFC is established, as less than one-third of suspected foods result in a positive challenge, and many of these will have objective symptoms.^{3,7,8}

OFC DOSING

In completing an OFC, the general target dose recommendations are 8-10 g protein for dry foods, 16-20 g for meats and 100 ml for wet food (Tables I,II).⁵ In our experience, OFCs are usually initiated with

0.1-1% of the total challenge food, although the European Academy of Allergy and Clinical Immunology did propose lower initial doses for OFCs to the following common food allergens: peanut 0.1 mg; milk 0.1 ml; egg 1 mg; cod 5 mg; wheat 100 mg; soy 1 mg; shrimp 5 mg; and hazelnut 0.1 mg.³ Unless the patient is considered to be at risk for a severe reaction to a very small amount of food, such low initial doses are probably not necessary. Following the initial dose, the challenge food is then given in gradually increasing increments every 15 minutes, although longer dosing intervals may be necessary for patients reporting reactions with delayed onset. A sample OFC for milk is included here (Table III). Once the feeding is complete, it is then followed by an observation period of about 1 to 2 hours.

WHEN TO PERFORM THE OFC

There are a number of factors that are considered in the decision to perform an OFC, including the patient's medical history, age, past adverse food reactions, SPT and serum food allergen-specific IgE results, in addition to the importance of the food to the patient, whether

it is due to its nutritional value or abundance of that food in a geographical location or ethnic diet. There are multiple indications for an OFC (Table IV); the OFC is usually performed when the patient's history does not correspond to the SPT or sIgE results, or when the results of these tests are positive but lower than the designated 95% positive predictive value (PPV) or 95% specificity for a particular food, although no specific cut-offs exist to indicate when one should consider an OFC. Researchers have been able to determine 95% PPVs for the likelihood of passing or failing an OFC based on a food sIgE level, using the ImmunoCAP system (Table V) in children.⁹⁻¹² It is important to note that these levels have only been established using the ImmunoCAP system and the results do not apply to other food sIgE platforms.¹³ Similar diagnostic cut-offs have been established for SPTs based on wheal diameters.^{14,15} These PPVs have been established for cow's milk, egg, and peanut, although levels are not as reliable for fish, wheat, soy or tree nuts. There are limitations to using the ImmunoCAP reference values in determining who should proceed with an OFC. Studies have shown international differences in the

Table I. Examples of portion sizes* for an open challenge with common food allergens⁵

Food	Portion size
Milk/dairy	180-240 ml milk or infant formula ½-1 cup yogurt ½-1 cup cottage cheese 15-30 g hard cheese
Soy/legumes	½-1 cup soy beverage ½-1 cup tofu ½-1 cup cooked beans (kidney, pinto, chickpeas, lentils)
Egg	1 slice of French toast (1 egg per 1 slice of bread) 1 hard boiled or scrambled egg
Grains (rice, corn, wheat, rye, barley, oat)	½-1 cup pasta/rice 15-30 g cereal ½-1 slice bread ½-1 muffin or bread roll
Meats	60-90 g cooked lean meat/poultry
Fish	60-90 g cooked fish
Shellfish	60-90 g shellfish
Peanut	30 g peanut butter = 2 tablespoons peanut butter
Tree nuts	30-40 g crushed tree nuts = 25-30 pieces
Seeds	10-15 g seeds = 1-2 tablespoons seeds
Vegetables	½-1 cup cooked vegetable ½-1 cup leafy raw vegetable 1 small baked white or sweet potato or 70 g French fries
Fruits	½-1 cup raw/cooked/canned fruit ½-1 small apple/banana/orange/pear 180-240 ml fruit juice

*Portion sizes may need to be adjusted depending on the age of the patient.

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Table II: Approximate protein content in common foods and food forms used in OFCs⁵

Food	Protein content in a serving	Challenge food form	Protein in 10 g challenge food
Egg, whole, cooked	1 egg = 6.1 g	Egg, whole, dried Egg white, powder	4.8 g 7.5 g
Milk, skim	240 ml = 8.4 g		
Milk, whole	240 ml = 8.0 g		
Peanut butter, generic, creamy	1 tablespoon (15 ml = 15 cc) = 4.6 g	Peanut flour, generic	5.25 g
Soy milk, generic	240 ml = 6.6 g	Soy flour, defatted	5.1 g
Isomil* soy formula	180 ml = 2.9 g	Isomil powder	1.3 g
Wheat bread, whole	1 slice (about 20 g) = 2.4 g	Wheat flour, whole grain	1.3 g

*Ross Laboratories, Abbott Nutrition, Columbus, Ohio.

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Table III. Sample schedule and dosing for OFC for IgE-mediated cow's milk allergy

Time (min)	% of total food	Amount of challenge food (ml of non-fat cow's milk)
0	0.1%	0.1
15	1%	1
30	4%	4
45	10%	10
60	20%	20
75	30%	30
90	34.9%	34.9
Total	100%	100 ml

Table IV. Indications for an OFC⁵

Identify foods causing acute reactions for initial diagnosis of food allergy and for monitoring resolution of food allergy.
Determine whether food allergens associated with chronic conditions such as atopic dermatitis or allergic eosinophilic oesophagitis will cause immediate reactions.
Expand the diet in persons with multiple dietary restrictions, usually because of subjective complaints such as headaches or hyperactive behaviour.
Assess the status of tolerance to cross-reactive foods.
Assess the effect of food processing on food tolerability, e.g. fruits and vegetables that may be tolerated in cooked form in the pollen-food allergy syndrome.

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Table V. 95% Predictive SPT and food sIgE levels

Food	Serum food sIgE (kU _A /l)	SPT wheal (mm)
Cow's milk if <1 year of age	≥15 ¹⁰ ≥5 ⁹	≥8 ¹³
Egg white if <2 years of age	≥7 ¹⁰ ≥2 ¹¹	≥7 ¹³
Peanut	≥14 ¹⁰	≥8 ^{13,14}
Fish	≥20 ¹⁰	

cut-off points, which suggest that the cut-offs are likely to be institutionally or regionally dependent.^{16,17} It is possible that PPVs established in the USA will not be useful in South Africa or Asia. It is also likely that PPVs derived from paediatric studies may not be applicable to adults with food allergy. Also, these cut-off values do help determine the probability of passing a challenge but not the severity of a reaction that may occur.^{18,19}

THE OPEN OFC

An important initial step in the OFC is determining the site and preparing the area. An OFC should be performed in a location where food may be heated and measured. To reduce the possibility of allergen cross-contamination, disposable plates, cups and utensils are used. The challenge area should be cleaned thoroughly in between challenges. Decisions regarding the location of the OFC should be based on risk assessment and capacity to treat anaphylactic reactions. Lower-risk challenges are appropriate for the office setting. Higher-risk challenges may be performed in the office setting as well, but factors should be considered, including the expertise of the person performing the challenge, availability of materials and support for the treatment of a severe reaction, distance from the hospital and response time of emergency medical services. Higher-risk challenges may need to be performed in the hospital in the inpatient or outpatient setting so that emergency treatment is immediately available.

The Adverse Reactions to Food Committee of the American Academy of Allergy, Asthma & Immunology published a standard risk assessment strategy in 2009.⁵ They defined patients with a low risk of reaction as those with recent accidental ingestion of a small amount of the food without clinical symptoms and those with favourable SPT and food sIgE results. They also defined those who have a low risk of a severe reaction as those with no past severe reactions, those being challenged with a food that is not usually implicated in severe food-induced anaphylaxis such as meat or a vegetable, and those without asthma. Those with a high risk of a reaction included patients with a reaction to the food in the past

6-12 months and those with high-positive SPT and food sIgE results. Patients with a high risk of a severe reaction were defined as those with a history of a severe reaction, those undergoing an OFC to a food that is frequently implicated in fatal and near-fatal food-induced anaphylaxis such as peanut or tree nuts, those with asthma, and those with conditions such as cardiovascular disease that may affect the resuscitation in case of a severe reaction.

FOOD PREPARATION

For the open OFC, the challenge food can be prepared at home by the patient or patient's family. The person preparing the food should be clearly instructed to be careful to avoid cross-contamination or contact with other foods to which the patient may react during the preparation. It is preferable to use single-ingredient foods for the OFC when possible. The person preparing the food should also be made aware that the form and degree of rawness of the food can affect the challenge outcome. Heating can change the protein conformation of a food and may result in a change in allergenicity.²⁰ This is seen with milk and egg, as will be discussed later in this review, as well as with a number of fruits and vegetables implicated in pollen-food allergy syndrome.²¹⁻²⁴

PATIENT PREPARATION

Patients must be properly prepared to undergo the OFC. They should be in good health, and in order to properly interpret the challenge and minimise the risk of a severe reaction, allergic diseases such as asthma, allergic rhinitis, and atopic dermatitis should be under optimal control. Patients must discontinue medications that may interfere with the OFC; this includes but is not limited to antihistamines, and duration of avoidance is specific to each medication (Table VI).⁵ Patients should also be made aware of the risks and benefits of the OFC, and consent should be obtained and documented. Discussion of the risks associated with the challenge should include the increased risk of recurrence of the allergy if the food is not incorporated into the diet, and that regular ingestion of the food seems to promote continued tolerance.^{25,26}

PERFORMING THE OFC

When the patient arrives for the OFC, there are several steps that must be performed before beginning. It should be confirmed that the patient is not sick and has not had any recent symptoms that could be mistaken for an allergic reaction during the OFC, such as sneezing, coughing, vomiting, or a rash. In patients with asthma, an exacerbation would be a reason to delay an OFC, and one should ask about the last time the patient used any rescue medications. It should also be confirmed that the

patient has not taken any medications that could mask an allergic reaction, giving a false-negative result.

A thorough physical exam should be performed, including baseline vital signs and weight, to enable accurate dosing of any medications that may be used to treat the patient during the OFC. The doses of the medications that may be used should be calculated prior to the start of the OFC, and written down in a place they will be visible during the procedure (Fig. 1).

Table VI. Guidelines for discontinuation* of medications that might interfere with interpretation of OFC⁵

Medication [†]	Last dose before OFC
Oral antihistamines	3-10 d
Cetirizine	5-7 d
Diphenhydramine	3 d
Fexofenadine	3 d
Hydroxyzine	7-10 d
Loratadine	7 d
Antihistamine nose spray	12 h
Oral H ₂ receptor antagonist	12 h
Antidepressants	3 d - 3 wks, drug-dependent and dose-dependent
Oral/intramuscular/intravenous steroids [‡]	3 d - 2 wks
Leukotriene antagonist	24 h
Short-acting bronchodilator (albuterol, metaproterenol, terbutaline, isoproterenol)	8 h
Long-acting bronchodilator (salmeterol, formoterol)	24 h
Inhaled cromolyn sodium	8 h
Nedocromil sodium	48 h
Theophylline (liquid)	12 h
Theophylline long-acting	24 h
Ipratropium bromide (inhaled/intranasal)	48 h
Oral/intranasal α-adrenergic agents	4-12 h depending on formulation and dosing interval
Oral β-agonist	12 h
Oral long-acting β ₂ -agonist	24 h
Drugs that may be continued	
Antihistamine eye drops	
Inhaled/intranasal corticosteroids	
Topical steroids	
Topical immunosuppressive preparations: pimecrolimus, tacrolimus	

*Risks of drug withdrawal should be considered and alternative treatments prescribed.

†Aspirin and other non-steroidal anti-inflammatory agents and angiotensin-converting enzyme inhibitors should be avoided because of their theoretical ability to enhance or induce allergic reactions and potential interference with an OFC outcome interpretation.

‡ This suggested guideline is based on the concern regarding the potential for suppression of the late-phase responses. In addition, a patient who received a short course of systemic corticosteroid may be going through an exacerbation that would either interfere with the OFC interpretation or potentially worsen the severity of a reaction. In patients who receive chronic therapy with systemic steroids, such as for inflammatory/rheumatological diseases, risk/benefit ratio for stopping steroid therapy and substituting an alternative therapeutic agent v. performing an OFC while the patient remains on steroid should be evaluated on an individual basis.

These medications should be readily available, in close proximity to where the OFC is taking place. While a nurse may administer the food, the physician should be immediately available to assess and treat the patient.

Before each dose during the OFC, the patient should be re-examined, including inspection of the skin, lung auscultation, abdominal auscultation, and vital signs. The patient should also be questioned for pruritus, laryngeal symptoms, abdominal pain, dizziness, and any other new complaints.² The physical exam should be documented each time, with the time of the feedings recorded as well. The OFC should be discontinued and the patient should be treated at the onset of an allergic reaction. The patient is usually observed for 2 hours after the full serving is ingested, or if the patient has a reaction, for 2 hours after symptoms have resolved. The observation period may need to be longer if the patient has a history of delayed symptoms, such as in patients with food protein-induced enterocolitis, where symptoms may not develop for 3-4 hours. If the patient does react during the OFC, he or she should be sent home with an updated emergency plan in case of any accidental ingestions at home, and arrangements for follow-up in a clinic should be discussed. If the OFC is passed, the patient should be instructed to ingest the tested food at home daily, or at least 2-3 times per week.

THE SAFETY OF IN-OFFICE OFCs

When considering whether or not to perform an OFC in the office setting, safety is, of course, a major concern. There are not many data on the results of OFCs performed in the office setting. In 2011, Lieberman *et al.* reported the results of all open OFCs performed at the Jaffe Food Allergy Institute, our university-based, outpatient practice, between August 2008 and May 2010.⁸ This was a retrospective chart review that included all patients referred by nine different allergists. Patients were typically not referred if the likelihood of a

reaction was thought to be greater than 50%, although there were no specific cut-offs for SPT size or sIgE that precluded challenge.

Most challenges were performed using doubling doses every 15 minutes until an age-appropriate serving size was administered. Altogether 701 OFCs were performed in 521 different patients who ranged in age from 8 months to 21.8 years (median 5.67 years). OFCs were performed to a wide variety of foods, with the majority being peanut, tree nuts, egg, milk, soy, fish, shellfish, sesame, and wheat.

Overall, 132 (18.8%) of the challenges elicited a reaction. The majority of those reactions were cutaneous (56.8%), and only 12 (9.1%) were treated with adrenaline, with one that required 2 doses of adrenaline. With a rate of only 1.7% of all challenges requiring treatment with adrenaline, it was concluded that open OFCs are a safe and effective method of establishing tolerance in patients with food allergy.

BAKED EGG AND BAKED MILK OFCs

In recent years studies have shown that a majority of children with milk and egg allergy can tolerate extensively heated milk and egg.^{23,24} Subjects with transient milk or egg allergy produce IgE antibodies primarily directed at conformational epitopes (amino acids brought into close proximity through protein folding) as opposed to sequential epitopes (contiguous amino acids). High temperatures break down conformational epitopes of milk and egg proteins, thus reducing the allergenicity of these foods for many individuals. The introduction of the extensively heated milk and egg into the diet not only has quality-of-life benefits, but also has therapeutic potential, as children incorporating baked milk or egg into their diet have been found to be more likely to develop tolerance to regular egg or milk than subjects who continued to avoid the extensively heated forms of these foods.^{27,28}

Patient Name:					
Age (years)					
Weight (kg)					
Medications	Concentration	Usual dosage	Calculated dosage (mg)	Volume (ml)	Max dose
Diphenhydramine PO	12.5 mg/5 ml	1.5 mg/kg			50 mg
Diphenhydramine IV	50 mg/1 ml	1 mg/kg			50 mg
Prednisone	5 mg/ml	1 mg/kg			60 mg
Adrenaline IM	1:1000 solution	0.01 ml/kg			0.3 ml
Flowsheet					
Time					
Dose					
Reaction					

Fig. 1. Sample OFC flowsheet with common medication doses to be printed prior to start.

These important discoveries have led allergists to consider not only traditional egg or milk OFCs, but OFCs to extensively heated forms of these foods as well.

Our group examined the outcomes of 100 consecutive open, baked-egg OFCs performed in the outpatient setting.²⁹ Patients were referred for open OFC by seven allergists on the basis of their clinical impression as well as family interests. There were no cut-offs used for sIgE or SPT size that precluded challenge. It was discovered that 66% of the patients tolerated baked egg, 31% reacted to baked egg, and 3 challenges were considered inconclusive. The patients who passed the OFC had lower serum egg white sIgE (median 2.81 kU_A/l) than those who reacted during the challenge (median 5.85 kU_A/l), $p=0.001$. The mean SPT wheal size was identical between the two groups (7 mm). Most of the reactions (80.6%) were mild and treated with an antihistamine alone. Four patients were treated with intramuscular adrenaline. No patient received more than one dose of adrenaline or required observation beyond 2 hours. Based on these results, it is our opinion that the benefits of performing outpatient OFCs to baked egg far outweigh the associated risk of the challenge for select patient populations.

Similar studies with milk have found that a majority of children with milk allergy can tolerate extensively heated milk. While studies performed in the outpatient clinic setting are limited, our group challenged 100 patients with milk allergy (age range 0.5-21 years) to heated milk in our research unit, an outpatient facility located within Mount Sinai's children's hospital.²³ Patients were enrolled if they had a positive SPT or detectable serum milk sIgE and a history of an allergic reaction to milk within 6 months before study entry; or milk-specific IgE levels or SPT highly predictive for clinical reactivity (if ≤ 2 years old, a level >5 kU_A/l; if >2 years old, a level >15 kU_A/l; SPT wheal diameter ≥ 8 mm). In this cohort, 68 children tolerated heated milk only, 23 reacted to heated milk, and 9 tolerated heated milk and unheated milk challenges. The heated-milk-reactive subjects did have significantly larger SPT mean wheal diameters and greater milk sIgE concentrations than heated- and unheated-milk-tolerant subjects. Eight of the 23 heated-milk-reactive subjects (35%) experienced anaphylaxis and received adrenaline.

A recent study by Bartnikas *et al.* retrospectively examined all challenges to baked milk done at Boston Children's Hospital from September 2009 to September 2011.³⁰ Of 35 children who underwent food challenges to baked milk, 29 (83%) passed and 6 (17%) failed. None of the children who failed baked-milk challenges in their clinic developed anaphylaxis or required adrenaline. They did not find any significant difference in milk-protein skin or blood test results among the groups who passed or

failed baked-milk challenges. The above studies indicate that performing OFCs to extensively heated egg or milk is safe in children with egg or milk allergy who have not had recent reactions to these forms of the foods and have lower food sIgE levels, and may be a wise initial step when one is considering an OFC to the unheated forms of these foods.

TREATING REACTIONS

If a patient does have an allergic reaction to an OFC, treatment should be administered promptly by the person observing the challenge, according to the guidelines for the treatment of anaphylaxis.³¹ Adrenaline is the treatment of choice for anaphylaxis. Intramuscular adrenaline has a more rapid absorption and achieves a higher plasma adrenaline level than subcutaneous adrenaline.³² Oral antihistamines should be used to treat mild reactions, but are slower in onset of action than adrenaline and have little effect on blood pressure, so are considered second-line treatment for anaphylaxis. They are useful in the symptomatic treatment of urticaria-angio-oedema and pruritus. In addition to adrenaline, intravenous fluids should be administered for reactions with hypotension and/or recurrent emesis. Positioning the patient in a recumbent position with elevated lower extremities is also helpful for severe hypotension, to increase the venous return to the heart. Other medications or treatments that may be required and should be available include glucagon for adrenaline-unresponsive reactors, supplemental oxygen for those with hypoxia, β -agonists for patients with bronchospasm refractory to adrenaline, and atropine for patients with bradycardia. Systemic steroids may be given for severe anaphylaxis, asthma, and significant angio-oedema, presumably to prevent late-phase responses, though there is no clear evidence to support this therapy.

Declaration of conflict of interest

The authors declare no conflict of interest.

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