Food challenges

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Because there is no *in vitro* test that can accurately predict the clinical relevance of a sensitization to food, the oral food challenge still remains the most reliable procedure to confirm or exclude food allergy and to assess the development of tolerance in children with potentially transient food allergies, such as to cow's milk, hen's egg, wheat, or soy. Although in the last few years component-resolved diagnostics have improved food allergy diagnostics, especially in patients with peanut and tree nut allergy, the majority of patients still need to undergo oral food challenge. This article will describe in whom and how to perform an oral food challenge, as well as its interpretation of the results, with a focus on suspected IgE-mediated food allergy.

WHO SHOULD UNDERGO ORAL FOOD CHALLENGE?

Patients of any age with suspected food allergy can be challenged. Food challenges in patients with a positive case history of an adverse reaction to food are especially important in cases in which the food eliciting the clinical reaction is uncertain or to determine the development of tolerance in the case of transient food allergies, such as to milk and egg in children. In case of a very severe (ie, anaphylactic) reaction by history, the benefit of a challenge has to be carefully weighed against the risk. Moreover, food challenges are often necessary in infants and children with eczema and food sensitization (based on skin testing or IgE measurement *in vitro*) if the food has thus far not been introduced into the diet and might cause immediate-type symptoms or has already been eaten but is highly suspected of causing worsening of eczema. Exclusion criteria for an oral food challenge are pregnancy; unstable asthma; medications that interfere with the treatment of a challenge-induced allergic reaction, such as β-blockers (see Table E1 in this article's Online Repository at www.jacionline.org); or confounding medical conditions that might interfere with interpretation of the challenge outcome or aggravate the extent of the allergic reaction, such as chronic urticaria; seasonal allergic rhinitis with current symptoms; severe uncontrolled eczema; acute infection, especially with fever; or mastocytosis. A careful prechallenge assessment is mandatory, including inspection of the oral cavity and the skin, pulse rate, blood pressure, lung auscultation, and, in older children or adults, peak flow value or FEV_1.

HOW TO PERFORM AN ORAL FOOD CHALLENGE

During the challenge, which is usually performed in a hospital setting, patients need to be under continuous supervision. Required medical skills and the appropriate equipment are summarized in Table E2 in this article's Online Repository at www.jacionline.org. Installation of intravenous access is highly recommended, at least in patients with a case history of a systemic reaction. The food is usually given to the patient in fasting conditions or after a light and defined meal (ie, toast and tea), especially in children. During the oral food challenge, no other food should be allowed.

Oral food challenges in patients with suspected IgE-mediated food allergy should be performed with titrated doses to avoid severe reactions. Various protocols have been used around the world, but a semi-log increase of the dose every 30 minutes with a starting dose of around 3 mg and a maximum dose of around 3 g of food protein seems to be a reasonable approach in regard to practicality and safety.[1] Although the 30-minute dosing interval is usually appropriate, it should be noted that the median latency time of clinical reactions to peanut has been shown to be 55 minutes.[2] Usually, 7 doses are given in which the cumulative dose represents a typical serving size (Table I). Fig 1 visualizes an example for titrating the oral food challenge for pasteurized whole hen's egg.

After a negative titrated challenge result, one serving of the whole amount (cumulative dose) should be given on another day (Table I) because it has been shown that 13% of challenge results were assessed as positive after having administered the cumulative dose on another day. This phenomenon of short-term nonreactivity might be induced by titrated intake of the allergenic food.

During the dose increases in titrated food challenges, the first response noted at a certain level is often a subjective symptom. By further increasing the dose, objective symptoms are observed, usually at higher amounts of the allergenic food.[3] Table II reports subjective and corresponding objective symptoms that can occur under challenge. A careful recording of symptoms is essential. A suggested oral food challenge protocol that visualized PRACTALL[1] consensus recommendations has been published recently.[4]

Oral food challenges can be performed openly, either single-blind or as a double-blind, placebo-controlled food challenge

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TABLE I. Dosing regimen with adequate amounts (for use, please recalculate with actual protein amount)

Dose	Protein (g)	Pasteurized or baked whole hen's egg (g)	Fresh whole cow's milk (g)	Peanut flour (g)	Wheat gluten (g)
1	0.003	0.023	0.1	0.006	0.004
2	0.01	0.078	0.3	0.02	0.014
3	0.03	0.23	1	0.06	0.04
4	0.1	0.78	3	0.2	0.14
5	0.3	2.3	10	0.6	0.4
6	1	7.8	30	2	1.4
7	3	23.4	100	6	4
Cumulative dose (on another day)	4.4	35	144	9	6

FIG 1. Titrated oral food challenge with pasteurized whole hen's egg.

TABLE II. Subjective and objective symptoms observed under challenge

Organ	Subjective symptoms	Objective symptoms
Skin	Itch	Flushing, erythema, hives, angioedema
Oral mucosa	Itch	Blisters, redness, swelling
Gastrointestinal tract	Nausea, pain, cramps	Vomiting, diarrhea
Nose	Itch	Bursts, sniffing, rhinorrhea
Eyes	Itch	Reddening, edema of conjunctiva
Lung	Tightness, chest pain, dyspnea	Wheezing, use of accessory muscles, reduction of lung function
Larynx	Throat tightness	Dry cough, stridor, hoarseness
Cardiovascular or neurologic system	Dizziness, vertigo, weakness	Tachycardia, decrease in blood pressure, collapse, loss of consciousness

(DBPCFC). The latter is regarded as the gold standard of food provocation and the benchmark to which other diagnostic procedures are compared. There are various recipes for blinding. Amino acid–based formulas, applesauce, and chocolate dessert are often used, with the blinding being optimized, if necessary, through use of allergen-free flavors and β-carotene. In case of DBPCFC, the blinding might influence the outcome of the challenge (ie, by degrading the allergenic protein when preparing the challenge meal), particularly in patients with birch pollen–related food allergies.[5] Moreover, the fat content of the matrix used to mask the allergenic food can interfere with the allergen uptake.[6] Therefore an open serving with the culprit food should follow a negative DBPCFC result, especially for unstable allergens. For some food allergens, especially hen's egg, an additional oral food challenge with heat-modified (baked) egg is recommended because about 80% of patients allergic to raw (pasteurized) egg will tolerate the heat-modified form.[1,7]

Additionally, false-negative challenges might be observed in patients who only have reactions in the context of an aggravating cofactor, such as after intake of certain drugs (ie, nonsteroidal anti-inflammatory agents) or alcohol, exercise, or viral infections. False-positive food challenge results can occur if the patient is allergic to a component of the matrix. Furthermore, positive placebo reactions are observed in DBPCFC settings in about 1% to 4% of patients[3] and at higher levels in younger patients.[8] DBPCFCs are especially useful in research settings but have also proved valuable in the clinic, especially if patients are anxious and can verbalize a number of subjective symptoms.

WHEN TO STOP AN ORAL FOOD CHALLENGE

The oral food challenge should be stopped if objective symptoms occur (eg, generalized urticaria); subjective symptoms are usually not a criterion for stopping the challenge.[1] When in doubt about the challenge result being positive, the time interval between the doses can be extended before the next dose is given. Moreover, the same dose can be repeated instead of increasing the amount. Reactions should be carefully recorded in regard to symptoms and time.[4]

IMPORTANT ISSUES AFTER THE CHALLENGE

Postchallenge monitoring usually lasts at least 2 hours, although it can last at least 4 hours or longer after recovery from a severe allergic reaction. Patients with an allergic reaction should be equipped with emergency drugs (self-injectable epinephrine, salbutamol, antihistamines, and corticosteroids, according to the judgement of the responsible physician), a management plan, and the contact details of the physician in charge at dismissal. Sensitized patients who were clinically tolerant in the oral food challenge and did not show allergic

reactions should receive advice to consume the food frequently (eg, 3 times per week) to maintain oral tolerance.

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TABLE E1. Drugs contraindicated for challenges (and treatment interval before challenge)

Antihistamines (3 d) except hydroxyzine and dexclorpheniramine (10 d)
Systemic corticosteroids (2 wk)
Tricyclic antidepressants (5 d)
Immunosuppressive treatment
β-Blocking agents (24 h)
Angiotensin-converting enzyme inhibitors (2 d)

TABLE E2. Required medical skills and appropriate equipment for implementation of food challenges

Medical staff trained in evaluation of allergic responses and treatment of allergic diseases, including anaphylaxis
Skills in inserting infusion lines and material for infusion lines
Team particularly trained in resuscitation on call: facilities for hospitalization and day clinic for postchallenge observation
Laryngoscope, intubation tube, ventilation bag, oxygen
Heart defibrillator
Peak flow meter, spirometric device
β_2-Agonist inhaler, epinephrine inhaler, or epinephrine in a nebulizer
Antihistamines and corticosteroids administered orally and intravenously, epinephrine administered intramuscularly (or intravenously if needed in intensive care settings)