

Accepted Manuscript

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PII: S0091-6749(17)31196-X

DOI: [10.1016/j.jaci.2017.06.038](https://doi.org/10.1016/j.jaci.2017.06.038)

Reference: YMAI 12934

To appear in: *Journal of Allergy and Clinical Immunology*

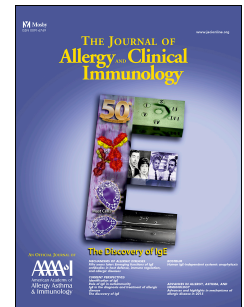
Received Date: 25 April 2017

Revised Date: 7 June 2017

Accepted Date: 20 June 2017

Please cite this article as: Ballmer-Weber BK, Beyer K, Methods in Allergy/Immunology: Food Challenges, *Journal of Allergy and Clinical Immunology* (2017), doi: 10.1016/j.jaci.2017.06.038.

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Methods in Allergy/Immunology

Food Challenges

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Since there is no in vitro test, which 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 diagnostic has improved the food allergy diagnostics, especially in peanut and tree nut allergy, the majority of patients still need to undergo oral food challenge. The following paper 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 where 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, i.e. 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 so far not been introduced into the diet and might cause immediate type symptoms or ~~is~~ has already been eaten but is highly suspected of causing worsening of the eczema. Exclusion criteria for an oral food challenge are pregnancy, unstable asthma, medications, which interfere with the treatment of a challenge induced allergic reaction such as betablockers (Online repository Table E1) or confounding medical conditions that might interfere with the interpretation of the challenge outcome or aggravate the extent of the allergic reaction such as chronic urticaria, seasonal allergy rhinitis with current symptoms, severe uncontrolled eczema, acute infection, especially with fever or mastocytosis. A careful pre-challenge 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 (PEF) or FEV₁.

How to perform an oral food challenge: During the challenge, which is usually performed in a hospital setting, the patients need to be under continuous supervision. Required medical skills and the appropriate equipment are summarized (Online repository Table E2). The installation of an i.v. 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 (i.e. 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 using 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 around 3 mg and a maximum dose of around 3 g food protein seems to be a reasonable approach in regard to practicality and

safety¹. While the 30 minutes dosing interval is usually appropriate, it should be noted that the median latency time of clinical reactions to ~~in~~ peanut has been shown to be 55 minutes². Usually seven doses are given where the cumulative dose represents a typical serving size (table 1). Figure 1 visualizes an examples for titrating the oral food challenge for pasteurized whole hen's egg.

After a negative titrated challenge one serving of the whole amount (cumulative dose) should be given on another day (table 1) as it has been shown that 13% of challenges were assessed as positive after having administered the cumulative dose on another day. This phenomenon of short-term non-reactivity might be induced by the 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 food³. Table 2 reports subjective and corresponding objective symptoms that might occur under challenge. A careful recording of symptoms is essential. A suggested oral food challenge protocol that visualized PRACTALL¹ consensus recommendations has recently been published⁴.

Oral food challenges can be performed openly, single blinded or as a double-blinded-placebo-controlled food challenge (DBPCFC). The latter is regarded to be 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 the usage of allergen-free flavours and β -carotin. In case of DBPCFC the blinding might influence the outcome of the challenge, i.e. by degrading the allergenic protein when preparing the challenge meal particularly in patients with birch pollen related food allergies⁵. Moreover, the fat content of the matrix used to mask the allergenic food can interfere with the allergen uptake⁶. Therefore, an open serving with the culprit food should follow a negative DBPCFC especially for unstable allergens. For some food allergens, especially hen's egg, an additional oral food challenge with heat modified (baked) egg is recommended as about 80% of the 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 develop reactions in the context of an aggravating co-factor, such as after the intake of certain drugs (i.e. non-steroidal anti-inflammatory agents), alcohol, exercise or viral infections. False positive food challenges can occur if the patient is allergic to a component of the matrix. Furthermore, positive placebo reactions are observed in DBPCFC settings in about 1-4% of patients³ and higher in younger patients⁸. DBPCFC are especially useful in research settings but have also been proven to be valuable in the clinic especially if patients are anxious and may verbalize a number of subjective symptoms.

When to stop an oral food challenge: The oral food challenge should be stopped if objective symptoms occur (e.g. generalized urticaria), subjective symptoms are usually not a criterion for ~~no~~ stopping the challenge¹. When in doubt about the challenge 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 time⁴.

Important issues after the challenge: The post challenge monitoring usually lasts at least 2 hours, and after recovery from a severe allergic reaction at least 4 hours or longer. Patients who had an allergic reaction should be equipped with emergency drugs (self-injectable epinephrine, salbutamol, antihistamines and corticosteroids, according 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 get the advice to consume the food now frequently (e.g. 3-times per week) in order to maintain the oral tolerance.

References:

1. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol*. 2012 Dec;130(6):1260-1274.
2. Blumchen K, Beder A, Beschorner J, Ahrens F, Gruebl A, Hamelmann E, et al. Modified oral food challenge used with sensitization biomarkers provides more real-life clinical thresholds for peanut allergy. *J Allergy Clin Immunol* 2014; 134(2):390-398.
3. Ballmer-Weber BK, Fernandez-Rivas M, Beyer K, Defernez M, Sperrin M, Mackie AR, Salt LJ, et al. How much is too much? Threshold dose distributions for 5 food allergens. *J Allergy Clin Immunol*. 2015 Apr;135(4):964-971.
4. Grabenhenrich LB, Reich A, Bellach J, Trendelenburg V, Sprickelmann AB, Roberts G, et al. A new framework for the documentation and interpretation of oral food challenges in population-based and clinical research. *Allergy*. 2017 Mar;72(3):453-461.
5. Ballmer-Weber BK, Holzhauser T, Scibilia J, Mittag D, Zisa G, Ortolani C, et al. Clinical characteristics of soybean allergy in Europe: a double-blind, placebo-controlled food challenge study. *J Allergy Clin Immunol*. 2007 Jun;119(6):1489-96.
6. Mackie A, Knulst A, Le TM, Bures P, Salt L, Mills EN, et al. High fat food increases gastric residence and thus thresholds for objective symptoms in allergic patients. *Mol Nutr Food Res*. 2012 Nov;56(11):1708-1714.
7. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol* 2011;127:668–76.
8. Ahrens B, Niggemann B, Wahn U, Beyer K. Positive reactions to placebo in children undergoing double-blind, placebo-controlled food challenge. *Clin Exp Allergy* 2014; 44, 572–578.

126 Figure legend:

127 Figure 1:

128 Titrated oral food challenge with pasteurized whole hen's egg

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Table 1**Dosing regimen with adequate amounts**

(for usage please recalculate with actual protein amount)

Dose	Amount 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

Table 2

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, drop of blood pressure, collapse, loss of consciousness



Online repository Table E1

Drugs contraindicated for challenges (and treatment interval before challenge)

antihistamines (3 days) except hydroxyzine and dexchlorfeniramine (10 days)
systemic corticosteroids (2 weeks)
tricyclic antidepressants (5 days)
immunosuppressive treatment
betablocking agents (24 hours)
angiotensin-converting enzyme (ACE) inhibitors (2 days)

Online repository Table E2

Required medical skills and appropriate equipment for the implementation of food challenges

Medical staff trained in the evaluation of the allergic responses and the treatment of allergic diseases inclusive anaphylaxis
Skills in inserting infusion lines and material for infusion lines
Team particularly trained in resuscitation on call; facilities for hospitalisation and day clinic for post-challenge observation
Laryngoscope, intubation tube, ventilation bag, O ₂
Heart defibrillator
Peakflow-meter, spirometry device
Beta-2 agonist inhaler, epinephrine inhaler or epinephrine in a nebuliser
Antihistamines and corticosteroids p.o. and i.v., epinephrine i.m. (or i.v. if needed in intensive care settings)