

# Oral food provocation test

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## I. Introduction

Accurate diagnosis of patients with suspected food allergy (FA) is obviously important. The patient's health may be compromised if problem foods are left in the diet. Also, nutrition and quality of life may be negatively affected if foods are unnecessarily removed from the diet. In many cases of food allergy, the diagnosis is not clear based on the history, skin tests, and serologic tests, especially because these tests often yield falsely positive results. In these instances further testing will be needed, typically including oral food challenges, which are the gold standard for the diagnosis of food allergy.<sup>1)</sup>

## II. Purpose of oral food challenge testing

There are a number of reasons that oral food challenge (OFC) testing should be considered, both for clinical and for research purposes. In the clinical setting, challenges are typically done for 3 major reasons.

- 1) To establish an accurate diagnosis when the diagnosis is still not clear after performing other diagnostic tests, including history taking, skin testing, measurement of specific IgE levels, and/or elimination diets.
- 2) If a patient has a chronic allergic condition, such as atopic dermatitis or allergic gastrointestinal disease, skin tests or specific IgE levels that are not in the diagnostic range, and an unclear response to an elimination diet.
- 3) To determine if a patient with a known FA has developed tolerance to that food.

In the research setting, OFCs have been used with great success for numerous indications.

### III. Methodology

The general concepts underlying all OFC procedures are the same. The food in question is introduced in gradually increasing doses under observation in a controlled wetting until a specific dose is reached. The major differences among the various methods that are employed include the use of blinding and variations in dosing strategy.

#### 1) Open challenges

An open challenge refers to an OFC in which the suspect food is administered without blinding or use of placebo. The limitations of open challenge related to the chance of bias on the part of both the patient and the observer. This bias will most often result in falsely positive challenge results, and this is especially common when the patient has significant anxiety about the challenge or when the patient's prior symptoms have been more subjective in nature. Even with these limitations, open challenges do still have utility in the clinical settings for several reasons.<sup>2)</sup>

- a) When the probability of negative outcome is estimated to be high.
- b) In infants and young children, in whom the impact of anxiety and other psychological factors is likely to be minimal, the risk of bias is significantly reduced.
- c) For practical reasons, open challenges are far easier to perform. Especially when the reactivity to the foods is limited to the oral mucosa.

#### 2) Single-blind challenges

In a single-blind challenge, the patient is blinded to the challenge material, while the observer not.

#### 3) Double-blind, placebo-controlled challenges

The DBPCFC remains the gold standard for the diagnosis of FA since both patients and observer biases are minimized. It is preferred method for all scientific research protocols. The limitations of DBPCFCs are entirely practical, including considerable time requirements for staff in the preparation of adequately blinded challenge materials.

### IV. Preparations of OFC

OFCs should be performed in an environment that maximized comfort and safety. The risks and benefits of challenge should be discussed in detail; informed consent should be contained. The personnel involved in challenge procedures must be specially trained in the management of acute allergic reactions, and these trained personnel should continuously monitor patients undergoing challenge. Medications and equipment for

**Table 1.** Basic clinical requirements for the implementation of food challenges

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Medical doctor well-trained in the treatment of allergic disease/particular anaphylaxis
Anesthesiology team (or equivalent team particularly trained in resuscitation) on call; at hand within 5 minutes, possibility for hospitalization and longer observation
Laryngoscope, intubation tube, ventilation bag, O <sub>2</sub> at hand
Heart defibrillator at hand
Peak flow-meter, spirometry apparatus at hand
High skills in inserting infusion lines warranted
Infusion line, Infusion fluid at hand
Inhalative beta-2 mimeticum and corticosteroid inhaler at hand
Epinephrine inhaler at hand or 1mg epinephrine in 2ml NaCL to use in a nebulizer
Antihistamines and corticosteroids p.o. and i.v. at hand
Epinephrine i.m. (i.v.) at hand

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(From How to determine threshold clinically. In: Risk management of food allergy)

**Table 2.** Guidelines for discontinuation of medications before oral food challenges

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Medication	Last dose before OFC
Oral antihistamines	3-10 days
Cetirizine	5-7 days
Diphenhydramine	3 days
Fexofenadine	3 days
Hydroxyzine	7-10 days
Loratadine	7 days
Antihistamine nose spray	12 hours
Oral H <sub>2</sub> receptor antagonist	12 hours
Antidepressants	3 days-3 weeks, drug-dependent and dose-dependent
Oral/intramuscular/intravenous steroids	3 days-2 weeks
Leukotriene antagonist	24 hours
Short-acting bronchodilator	
Albuterol, metaproterenol	8 hours
Turbutaline, isoproterenol	24 hours
Long-acting bronchodilator	
Salmeterol, formoterol	48 hours
Inhaled cromolyn sodium	48 hours
Theophylline (liquid)	24 hours
Theophylline long-acting	48 hours
Ipratropium bromide (inhaled/intranasal)	4-12 hours depending on formulation and dosing
Oral intranasal $\alpha$ -adrenergic agents	Interval
Oral $\beta$ -agonist	12 hours
Oral long-acting $\beta$ <sub>2</sub> -agonist	24 hours
Drug that may be continued	
Antihistamine eye drops	
Inhaled/intranasal corticosteroids	
Topical steroids	
Topical immunosuppressive preparations:	
pimecrolimus, tacrolimus	

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(From Guidelines for the Oral Food Challenges in Children. *Pediatr Allergy Respir Dis(Korea)* 2012;22:3-20)

resuscitation must be available.<sup>3)</sup> (Table 1) Cases in which a severe reaction is suspected, the challenge should be performed in an inpatient setting or intensive care unit. Before proceeding with a challenge, patients should have a stable baseline examination, without significant symptoms of atopic dermatitis, rhinoconjunctivitis, urticaria. They should not have been treated for a significant asthma exacerbation within

a minimum of 1week prior to undergoing the challenge. They must have no current illness (e.g., fever, vomiting, diarrhea) at the time of the challenge. Prior to the challenges, patients should discontinue antihistamines and bronchodilators for appropriate periods.<sup>4)</sup> (Table 2)

## V. Challenge protocols and dosing

Food for an open OFC can be brought from home by the patient or parent, whereas for a blind OFC, the test material should be provided by a physician. The total amount administered during a gradually escalating OFC equals 8-10 g of the dry food, 16-26 g of meat or fish, and 100 mL of the wet food. The challenge food should be provided gradually, at 15-30 min intervals or longer, beginning with a dose unlikely to trigger a reaction and progressing stepwise with escalating doses, with an option to repeat doses or delay doses longer if symptoms may be developing. A few reports have been published dealing with the standardization of DBPCFC protocols. In 2004, a position paper of the European Academy of Allergy and Clinical Immunology was the first to provide general guidelines for the safe conduct of DBPCFC.<sup>5)</sup> A Korean guideline for the OFC in children has been published with the standardization of open food challenge protocols in 2012. This guideline has introduced case examples of challenge doses for oral food challenges in terms of egg white and cow's milk allergy. (Table 3-1, 3-2) Also, examples of portion sized for OFC with common food allergen and proposed starting dose for different foods have been suggested.<sup>6)</sup> (Table 4, 5)

## VI. Interpretation of OFC

Challenges should be stopped and medications administered in the event of any significant objective

**Table 3-1.** Case examples of challenge doses for egg challenge

Time (min)	Dose
0	Lip provocation
15	1/48
30	1/24
45	1/8
60	1/4
75	Rest
135	observation

(From Guidelines for the Oral Food Challenges in Children. *Pediatr Allergy Respir Dis(Korea)* 2012;22:3-20)

**Table 3-2.** Case examples of challenge doses for milk challenge

Time (min)	Dose (ml)
0	Lip provocation
15	1
30	2
45	6
60	18
75	54
90	Rest
135	observation

(From Guidelines for the Oral Food Challenges in Children. *Pediatr Allergy Respir Dis(Korea)* 2012;22:3-20)

**Table 4.** Examples of portion sizes for an open food challenge with common food allergens

Food	Portion size
Milk/diary	6-8 oz milk or infant formula 1/2-1 cup yogurt 1/2-1 cup cottage cheese 1/2-1 oz hard cheese
Soy/legumes	1/2-1 cup soy beverage 1/2-1 cup tofu 1/2-1 cup cooked beans (kidney, pinto, chickpeas, lentils)
Egg	1 slice of French toast (1egg per 1 slice of bread) 1 hard boiled or scrambled egg
Grains (rice, corn, wheat, rye, barley, oat)	1/2-1 cup pasta/rice 1/2-1 oz cereal 1/2-1 slice bread 1/2-1 muffin or roll bread
Meats	2-3 oz cooked lean meat/poultry
Fish	2-3 oz cooked fish
Shellfish	2-3 oz shellfish
Peanut	30 g peanut butter = 2 tablespoons peanut butter
Tree nuts	30-40 g crushed tree nuts = 25-630 pieces 10-15 g seeds = 1-2 teaspoons seeds
Seeds	10-15 g seeds = 1-2 teaspoons seeds
Vegetables	1/2-1 cup leafy raw vegetable 1 small baked white or sweet potato or 70 g french fries 1/2-1 cup raw/cooked/canned fruit
Fruits	1/2-1 small apple/banana/orange/pear 6-8 oz fruit juice

(From Oral food challenges in children. Korean J Pediatr. 2011;54:6-10.)

**Table 5.** Proposed starting dose for different foods

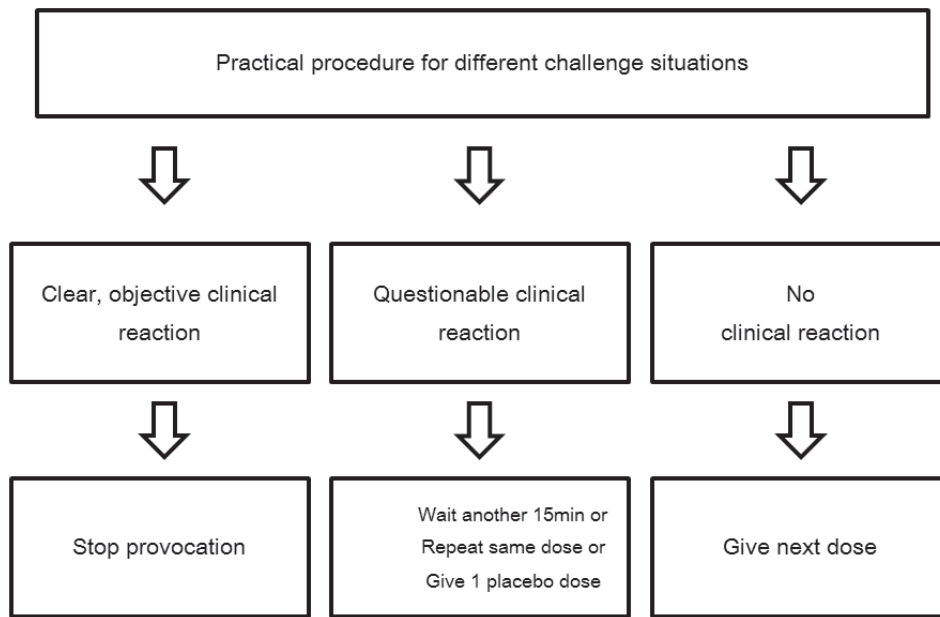
Food	Dose
Peanut	0.1mg
Milk	0.1ml
Egg	1mg
Cod	5mg
Wheat	100mg
Soy	1mg
Shrimp	5mg
Hazelnut	0.1mg

(From Oral food challenges in children. Korean J Pediatr. 2011;54:6-10.)

symptoms. However, despite controlled conditions, it is sometimes difficult to determine whether clinical symptoms are sufficiently clear to make a decision. Niggemann et al. proposed a decision tree for various situations during an OFC procedure, which is reproduced in Fig. 1.<sup>7)</sup> Table 6 summarized the subjective symptoms that might be observed under challenge, and the corresponding objective symptoms which might occur at the challenge.

## VII. Risk and treatment of OFC

The expected reactions are those seen with food induced reactions in general, involving some combination



(From Oral food challenges in children. Korean J Pediatr. 2011;54:6-10.)

**Fig. 1.** Decision tree for various situations during oral food challenge procedure

**Table 6.** Organ-related subjective and corresponding objective symptoms that might be observed under challenge

Organ	Subjective Symptoms	Objective Symptoms
Skin	Itch	Flush, urticaria, angioedema
Oral mucosa	Itch	Blisters, redness, swelling
GI tract	Nausea, pain, cramps	Diarrhea, vomiting
Eyes/ nose	Itch	Rhinitis, conjunctivitis
Lung	Tightness, chest pain. Dyspnea	Hoarseness, wheezing, reduction of lung
CVS	Dizziness, vertigo	Tachycardia, drops of blood pressure

(From How to determine threshold clinically. In: Risk management of food allergy)

of cutaneous, gastrointestinal, respiratory, and cardiovascular reactions. Skin and gastrointestinal reactions are most common, and severe or life-threatening reactions are rare. Many patients describe localized pruritus in the mouth, throat, or ears as their first symptoms, sometimes with visible urticarial in or around the mouth. While these symptoms do indicate a localized allergic response, they do not mean that the challenge must stop, as they are often transient. Distinct behavioral changes are very common, especially in young children. These signs should always be taken seriously, as they likely herald the onset of a reaction. While there is a risk that stopping too early will result in a false-positive challenge, the risk of waiting too long or giving an extra dose is much more significant. So, challenges should be terminated whenever the observer is reasonably convinced that reaction is occurring, and the treatment should be administered as indicated. Some challenges may have only minor, localized signs and symptoms, in which case treatment may not be

necessary. However, in the majority of cases, treatment with at least an antihistamine is warranted. Other therapies, including intramuscular epinephrine, oral or parenteral corticosteroids, inhaled or nebulized beta-agonists, and H<sub>2</sub> antagonist, oxygen, or intravenous fluids, should be administered at the discretion of the treating physician.

## VIII. Conclusion

OFCs are essential tools in the diagnosis of FA. The basic methodology underlying all OFCs relies on the administration of the suspect food in gradually increasing doses under close observation in a medical setting. Challenges should be terminated and treatment administered at the sign that a reaction is occurring. OFCs carry the potential risk but this risk can be minimized by appropriate dosing and by performing challenges in an appropriate setting with experienced personnel.

## 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;130:1260-74.
2. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, Blanco C, Ebner C, Hourihane J, et al. Standardization of food challenges in patients with immediate reactions to foods - position paper from the European Academy of Allergology and Clinical Immunology. *2007 2004;59:690-7.*
3. Ballmer-Weber BK, Knulst AC, Hourihane J, et al. How to determine threshold clinically. In: Bernard Madsen C, Crevel WR R, Mills C, Taylor SL, editors. *Risk management for food allergy. Food science and technology international series.* Elsevier, 2014:67-76.
4. Guidelines for the Oral Food Challenges in Children. Tae Won Song, Kyung Won Kim, Woo Kyung Kim, Jeong Hee Kim, Hyun Hee Kim, Yong-Mean Park, et al. *Pediatr Allergy Respir Dis(Korea)* 2012;22:3-20.
5. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, Blanco C, Ebner C, Hourihane J, et al. Standardization of food challenges in patients with immediate reactions to foods--position paper from the European Academy of Allergology and Clinical Immunology. *Allergy.* 2004;59:690-7.
6. Yum HY, Yang HJ, Kim KW, Song TW, Kim WK, Kim JH, et al. Oral food challenges in children. *Korean J Pediatr.* 2011;54:6-10.
7. Niggemann B, Beyer K. Diagnosis of food allergy in children: toward a standardization of food challenge. *J Pediatr Gastroenterol Nutr* 2007; 45:399-404.