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Allergology International. 2009;58:467-474
DOI: 10.2332/allergolint.09-RAI-0140

REVIEW ARTICLE

Diagnosis of Food Allergy Based on Oral Food Challenge Test

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ABSTRACT

Diagnosis of food allergy should be based on the observation of allergic symptoms after intake of the suspected food. The oral food challenge test (OFC) is the most reliable clinical procedure for diagnosing food allergy. The OFC is also applied for the diagnosis of tolerance of food allergy. The Japanese Society of Pediatric Allergy and Clinical Immunology issued the 'Japanese Pediatric Guideline for Oral Food Challenge Test in Food Allergy 2009' in April 2009, to provide information on a safe and standardized method for administering the OFC. This review focuses on the clinical applications and procedure for the OFC, based on the Japanese OFC guideline.

KEY WORDS

food hypersensitivity, guideline, immunoglobulin E, oral food challenge, tolerance

ABBREVIATIONS

OFC, oral food challenge test; IgE, immunoglobulin E; Japanese OFC Guideline, Japanese Pediatric Guideline for Oral Food Challenge Test in Food Allergy 2009; DBPCFC, double-blind placebo-controlled food challenge; GI, gastrointestinal; SPT, skin prick test; HRT, basophil histamine-releasing test; FPIES, food protein-induced enterocolitis syndrome.

INTRODUCTION

Food allergies affect 12.8% of infants, 5.1% of 3-year-olds[1] and 1.3-2.6% of school-age children in Japan. These allergies are associated with numerous social problems in nurseries, kindergartens and schools, particularly in terms of providing lunches to the affected children,[2] and in preparing for unexpected severe reactions after accidental ingestion of allergic foods.[3]

In 2008, the Japanese Society of School Health issued a guideline for the management of allergic diseases in schools (http://www.hokenkai.or.jp/). This guideline emphasized the importance of proper medical diagnosis for appropriate management of allergic students, especially with food allergy.

Definitions and diagnosis of food allergy should be based on the presence of clinical manifestations after ingestion of the offending food.[4] Proof of an immunological mechanism, typically as the detection of allergen-specific immunogloblin (Ig)E antibodies, should be associated with the diagnosis, but proof of sensitization itself without provocation is not diagnostic of food allergy.[5]

Clinical testing to detect allergen-specific IgE antibodies (ImmunoCAP FEIA®, Phadia KK., Tokyo) is widely used in Japanese pediatric practice, particularly for patients with infantile atopic dermatitis, to determine the allergic background of the eczema. Examinations have sometimes been performed before the introduction of solid foods to babies, not only for the management of eczema,[6] but also to avoid unexpected anaphylactic reactions at the first intake of foods to which the baby might already have been sensitized through breast milk.[7] Transient elimination of sensitized foods may help to control the allergic conditions of infants, but proper diagnosis of food allergy should follow.[8]

Diagnosis of food allergy should be based on a convincing history of allergic reactions or on the result of an oral food challenge test (OFC).[9] The OFC has been covered by public medical insurance in Japan

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Received 20 July 2009.
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since 2006, but too few institutions can provide the OFC to meet the needs of patients, and a standardized protocol for the OFC has been absent.[10]

The Japanese Society of Pediatric Allergy and Clinical Immunology issued the 'Japanese Pediatric Guideline for Oral Food Challenge Test in Food Allergy 2009' (Japanese OFC Guideline, available only in Japanese) in April 2009, providing for the first time information about a safe and standardized method for administering the OFC.[11] This review focuses on the role of and practical methods for the OFC in the diagnosis and management of food allergy, based on the Japanese OFC Guideline.

CHARACTERISTICS AND CROSS-REACTIVITIES OF FOOD ALLERGENS THAT AFFECT THE OCCURRENCE OF FOOD ALLERGY

Hen's eggs, cow's milk and wheat are the three major food allergens accounting for 70% of patients who required treatment for acute reactions in 2008 in Japan. Peanut, salmon roe, shrimp and buckwheat are the next most common food allergens.[12]

Reactivity of food allergens or allergenic components of the foods can be highly modified by cooking methods. Hen's egg allergens, particularly ovalbumin, are sensitive to denaturing by heating, resulting in loss of IgE-binding capacity. Ovomucoid, on the other hand, is relatively resistant to heating[13] and protease digestion.[14] As a result, some patients with egg allergy can tolerate extensively heated egg products, and IgE antibody to ovomucoid can offer a good diagnostic marker to predict whether a child can eat heat-treated eggs.[15]

Caseins constitute 76-86% of whole milk proteins, and among these, αs1-casein is the major milk allergen.[16] This protein does not contain disulfide bonds and shows no tertiary structure. This characteristic structure explains why most IgE-binding epitopes are sequential (linear) and not susceptible to heat denaturation.[17] Conversely, another milk allergen, β-lactoglobulin, is highly conformational, and extensive heating may decrease the reactivity of milk for some patients.[18]

Wheat allergens can be divided into two fractions: a water-salt soluble fraction (albumins and globulins); and gluten (gliadin and glutenin). Wheat and other cereal grains share a number of homologous proteins, mostly in the water-salt soluble fraction,[19] whereas gluten is a component exclusive to wheat. The fact that most patients with wheat allergy can consume other cereals, such as rice or corn, suggests that the dominant wheat allergens and IgE epitopes exist in components that are not cross-reactive with other cereals. Specific IgE testing for recombinant ω-5 gliadin can offer a good marker of immediate-type wheat allergy or anaphylaxis in children,[20] as well as wheat-dependent exercise-induced anaphylaxis in adults.[21]

Allergen components of peanut have been extensively characterized, and recombinant allergens are ready for use in research.[22] However, no single recombinant allergen is satisfactory for the diagnosis of peanut allergy in terms of sensitivity and specificity.[23] Cross-reactivity to homologous proteins in soybeans, Gly m 5 (vs. Ara h 1) and Gly m 6 (vs. Ara h 3),[24] and other tree nut allergens[25,26] requires more extensive study, particularly in terms of the relationship with clinical manifestations.

Taken together, knowledge of food allergens is required to interpret the results of allergen-specific IgE testing,[27] but no single in vitro test represents an alternative to a convincing history of allergic symptoms or the OFC.

ORAL FOOD CHALLENGE TEST

DEFINITION OF THE OFC

The general methodology for the OFC is to administer the suspected food in gradually increasing doses under a medical setting.[28] A single trial with intake of a small amount of the suspected food at home or in the office may help in the introduction of eliminated foods, but is not defined as an OFC, because it is not diagnostic of food allergy.

An open challenge refers to an OFC in which the patient can recognize the target food without blinding. The results can be definitive if the challenge yields either negative results or positive results with objective symptoms. This approach may be appropriate for most infants or young children, because psychological claims of symptoms are negligible at those ages. However, if the patient complains only of subjective symptoms such as abdominal pain or pruritus, particularly when the patient displays anxiety about the challenge, interpreting challenge result is difficult.

A single-blind challenge means that the patient does not know whether the food contains the suspected allergen, but the observer knows.[29] A masking effect sometimes helps to reduce psychological effects or difficulty eating in small children, but a single-blind challenge without placebo is essentially similar to an open challenge.

A double-blind placebo-controlled food challenge (DBPCFC), in which both the patient and observer are blinded to the challenge material, remains the gold standard for diagnosing food allergy for both clinical and scientific purposes.[30] A provocation kit containing dried powder[31] of each food (whole egg, cow's milk, wheat and soybean) and a masking material (strawberry puree) is provided through the Food Provocation Network in Japan by the National Food Allergy Research Group (Fig. 1).

AIMS AND INDICATIONS

The OFC is generally carried out for two purposes:

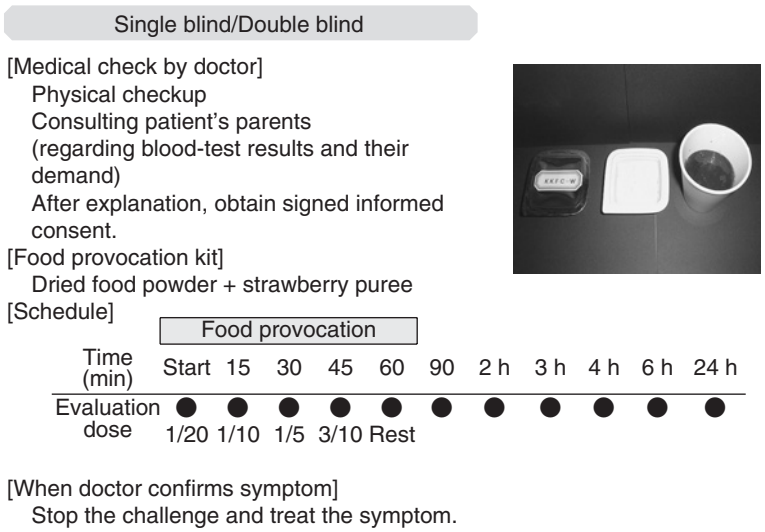

Fig. 1 Provocation kit and the protocol for blind food challenge.

diagnosis of food allergy; or determination of tolerance to the allergic food.

Diagnostic OFC is typically used in three situations. First, if a patient is suffering from chronic allergic conditions such as atopic dermatitis or persistent gastrointestinal (GI) symptoms, and elimination of the suspected food ameliorates the symptoms, an OFC to confirm the recurrence of symptoms is considered to establish an accurate diagnosis. Second, if a patient is suffering from acute allergic symptoms after eating multiple foods, and a precise history and/or in vitro diagnostic testing indicates some suspected foods, definitive diagnosis of the offending food may be achieved using the OFC. Third, and most frequently, is with the introduction of a sensitized food as confirmed by the presence of specific IgE antibody or positive results from a skin prick test (SPT), for the first time in life. This scenario is mostly the case in infants with atopic dermatitis, but patients and their family with known food allergy tend to avoid highly allergenic foods such as peanuts, buckwheat and shrimp, particularly if they have ever shown positive specific IgE titers. Careful setting of the OFC may be needed in this case, because introduction of a highly sensitized food for the first time in life can sometimes induce severe reactions.

Diagnosis of the achievement of tolerance (outgrowing the allergy) is another important indication for the OFC. Most infants with egg,[32] milk,[33] wheat[34] or soybean allergies tend to outgrow these allergies during childhood. Information on symptoms following accidental exposure helps determine an indication for the OFC. If the patient has experienced a severe reaction recently within 1 year, the OFC is not indicated. Patients with strict avoidance of the allergic food for more than 1 year may be considered for an OFC. Information about daily consumption of foods containing small amounts of the suspected component is also helpful to determine indications and procedures for the OFC.

Allergies to peanut,[35] tree nuts,[36] buckwheat or shrimp, especially in older children or adults, are thought to continue throughout life. An OFC to those foods may not be indicated unless loss of sensitization is confirmed by negative results from an SPT or specific IgE test.

DECIDING ON THE CHALLENGE PROTOCOL

Selection of a challenge protocol should be based on the safety and accuracy of the OFC.[37] The total provocation dose may be large enough compared to daily consumption of the suspected food for the proper diagnosis of food allergy, but is sometimes considered too high for a highly sensitized patient with a history of severe reaction, in terms of safety. Using step-wise procedures in the OFC may be an option, with challenge using a small amount preceding a full-dose challenge.

The challenged food should be standardized for diagnosis of the food allergy. However, processed food may be an option for patients with known food allergy. Introduction of extensively heated foods,[38] partially digested foods or fermented food such as "miso", "shoyu" or "natto", which are traditional Japanese soy products,[39] may be tolerated and even effective for the induction of tolerance in some patients. Although allergenic activities of these foods are generally decreased, OFC should be considered before introduction, because some patients experience severe reactions to these foods.

Precise information on the history of the patient, which has already been mentioned, and immunological laboratory data are essential for deciding on the indications and procedure for OFC.

1) Sampson[41] (U_A/ml)

Specific IgE	Egg white	Milk	Peanut	Fish
Diagnostic decision points	7	15	14	20

2) Komata[39]

Age (years)	<1	1	2≤
Egg white	13.0	23.0	30.0
Milk	5.8	38.6	57.3

3) Ando[14]

Food	Raw egg white		Heated egg white	
Specific IgE	Egg white	Ovomucoid	Egg white	Ovomucoid
Positive decision points	7.38	5.21	30.7	10.8

Fig. 2 Positive decision points for allergen-specific IgE titers to diagnose food allergy without food challenge.

Positive decision points for specific IgE antibodies, which indicate IgE titers with over 95% probability for positive challenge, have been proposed for some allergens (Fig. 2).[40] Patients with specific IgE titers above this point may be advised to continue a restricted diet without undergoing an OFC.[41] Probability curves for specific IgE titers are also helpful to predict the probability of positive challenge.[42] Even so, OFC might be performed for highly sensitized patients to identify the threshold amount of suspected food inducing allergic symptoms, and to provide the patient with advice on safe levels of the food. Emphasis is required on the fact that specific IgE titers do not always correlate to threshold amounts of food or the severity of allergic symptoms.

SPT also indicates sensitization to the suspected food,[43,44] sometimes in patients with negative results for specific IgE in serum. Results from an SPT help to predict a positive challenge in patients with negative or low specific IgE titers to milk or egg,[45] but false positive results are also common.

The basophil histamine-releasing test (HRT) is also commercially available in Japan.[46] High scores (Class 4) in HRT for egg white, milk and wheat suggest more than 90% probability for positive challenge, particularly in patients who have experienced anaphylaxis.[47] Decreased HRT titers in patients maintaining high specific IgE titers sometimes indicate the achievement of tolerance to the food.

SETTING AND PROCEDURES

All institutes at which OFCs are performed have to be fully equipped for access to emergency treatment. The site may be in-hospital, but an outpatient office or clinic may also be suitable for some patients in whom severe reactions are not predicted. A safe, clean and comfortable environment, hopefully free from contact with other patients with infectious diseases, needs to be provided for patients to spend a long period. Well-trained doctors or nurses should keep in touch with the patient throughout the procedure, and the contribution of a dietitian helps a great deal.[48]

The risks and benefits of OFC should be discussed with the patient and parents, and written informed consent needs to be obtained in most cases.

Before proceeding with the OFC, the patient needs to be stable in terms of allergic symptoms and free from any acute illness. Antihistamines should have been discontinued for >72 h and any other medications for the treatment or prevention of allergic diseases discontinued for an appropriate period based on the duration of action, except inhaled corticosteroids and topical corticosteroid ointments applied on small areas of skin lesions.

Typical challenge foods and total doses administered are listed in Table 1. The starting dose should be 1 g (1 ml) or less of the food.[49] The typical challenge scheme is to divide the total dose into 3-6 incremental doubling doses, such as 1, 2, 4, 8 and 16 g of boiled egg white or 1, 5, 10, 25, 50 and 100 ml of milk. A challenge with smaller doses should be considered for patients deemed to be at risk of severe reaction, such as 0.1 ml for the starting dose of milk.[50]

When processed food is used for a blind challenge, equivalent doses of allergen content should be considered and a standardized cooking method may be applied to minimize the variation of allergen activity.

Doses are generally given every 15-30 min over 1-2 h. A longer dosing interval might be applied for severe patients or for those who have experienced a late-onset allergic reaction after intake of the suspected food. If a sign of suspicious reaction appears, the next dose should be postponed to observe the progress of symptoms, or the same dose should be repeated to avoid overloading.

The patient may stay in hospital for more than 2 h after the final dose is given or the provoked symptoms disappear. Upon discharge, the patient needs to be instructed to observe the possibility of late-onset symptoms, even after a negative (passed) challenge.

SYMPTOMS AND TREATMENTS

The expected reactions during OFC involve cutaneous, mucosal, respiratory, GI, cardiovascular and neurological symptoms (Table 2). Parallel to the allergic reactions observed with accidental intake, cutaneous symptoms are most frequently observed in 80% of positive (failed) challenges, followed by respiratory (35%) and GI (25%) symptoms.[51]

Respiratory symptoms are common and need to be treated properly. Coughing might be divided into two categories: dry and staccato coughing estimated to be of laryngeal origin; and productive coughing associated with wheezing or asthma.[52]

Oral symptoms are frequently reported at the beginning of challenge, but sometimes disappear afterward. Distinguishing whether such symptoms are a

Table 1 Recommended protocol for open food challenge

Target foods	Challenge foods	Step†	Initial dose	Total dose	Scheme
Egg	Boiled egg yolk	1	1 g	15 g (1 egg yolk)	1-2-4-8 g
	Boiled egg white	2‡	0.1 g	2-4 g	0.1-0.2-0.5-1-2 g
		3	1 g	16-32 g (1 egg)	1-2-4-8-16 g
Milk	Raw milk	1	0.05-0.1 ml	15-30 ml	0.1-1-2-4-8-15 ml
		2	1-5 ml	100-200 ml	1-5-10-25-50-100 ml
Wheat	Udon noodle (boiled)	1	0.5 g	15-30 g	0.5-1-2-4-8-15 g
		2	1 g	50-100 g	1-2-5-15-25-50 g
Fish	Boiled or baked fish		1 g	30-60 g	1-2-4-8-15-30 g
Soy	Tofu (soy paste)		1 g	50-100 g	1-2-5-15-25-50 g

†A stepwise challenge protocol may be considered for high-risk patients.

‡Processed foods (cookies, cakes, etc.) are also available.

Table 2 Signs and symptoms observed in OFC

Cutaneous
Pruritus, erythema, urticaria, angioedema
Oral
Throat pain, itching of palate, tongue or lips, palatal redness or hives
Mucosal
Eye swelling, tears, conjunctivitis
Upper respiratory
Rhinorrhea, sneezing, and nasal obstruction
Lower respiratory
Coughing, wheeze, dyspnea, stridor, hoarseness, chest tightness
Gastrointestinal
Nausea, vomiting, diarrhea, abdominal pain or cramp
Cardiovascular
Hypotension, light-headedness, cold extremities, cyanosis, syncope, collapse
Neurological
Behavioral change, loss of activity, restlessness, dizziness, sleep

part of systemic reactions or an oral allergy syndrome induced by local absorption of water-soluble allergens is difficult, but may be important.

Neurological symptoms might be a sign of systemic reactions, particularly when a small child is violently frightened and crying, or suddenly turns quiet.[53] Overwhelming tiredness and sleepiness are sometimes observed in older children associated with GI symptoms, but without cardiovascular symptoms like hypotension or decreased oxygen saturations.

Grading symptoms is helpful for deciding on treatment strategies (Table 3). Treatment may not be necessary for localized skin or mild mucosal symptoms (Grade 1). Most skin and mucosal symptoms may be treated using antihistamines (oral or parenteral). Beta-agonist inhalation may be applied to mild respiratory symptoms, and oxygen should be administered if oxygen saturation falls below 95% (Grade 2, Step 1 treatment, Fig. 3).

When symptoms reach Grade 3, Step 2 treatment should be applied. Intramuscular adrenaline (0.01 mg/kg) is the first-line treatment in Step 2. Effects of adrenaline may be observed within 5 min, when most skin, respiratory, GI and even neurological signs tend to disappear. If the effect was insufficient or symptoms reappear after 10-15 min, repeat administration of intramuscular adrenaline may be considered, and additional treatments such as intravenous fluid, parenteral antihistamine or corticosteroids should be applied. Repeat inhalation of beta-agonists or adrenaline[54] may be an option for persistent but mild respiratory symptoms.

In cases of severe reactions accompanied by intractable hypotension or respiratory distress, full resuscitation with bolus rehydration (30 ml/kg normal saline), respiratory supports and catecholamine should be applied in the intensive care unit (Step 3).

DIET MANAGEMENT BASED ON RESULTS OF THE OFC

Based on the total dose and symptoms provoked in the OFC, patients should be instructed about restrictions or re-introduction of the challenge food. Even after a negative challenge, the amount of food intake at home may not exceed that of the total dose at least several times to confirm safety.

Positive challenge does not always suggest a need for complete elimination of the food from the diet.[55] Patients may introduce small amounts of the target food within the appropriate safety range, at 1-10% of the threshold level in general, or the processed food in which decreased allergic reactivity is expected.

Repeated follow-up visits are needed to confirm the benefits of the OFC, particularly when re-introduction of the eliminated food is in progress. In many cases, the patient and parents are anxious about the occurrence of allergic symptoms even after a negative challenge, or may actually experience some mild symptoms after eating the target food. Providing instructions to the patient's school about restrictions to the

Table 3 Grading of symptoms observed with oral food challenge

Grade	Skin	Gastrointestinal	Respiratory mucosal	Cardiovascular	Neurological
1	Faint rash Wheals (<3) Pruritus	Nausea Oral/pharyngeal discomfort, itch	–	–	–
2	Localized rash Wheals (3-10) Worsening of eczema Increased scratch	Vomiting/diarrhea (1-2) Transient colic	Sneeze Rhinorrhea/nasal obstruction Scratch nose/eyes Cough (<10)	–	Loss of activity
3	Systemic rash/wheals Severe itch Angioedema	Vomiting/diarrhea (≥3) Persistent colic	Cough (≥10) Wheeze Husky voice/Barking cough Difficulty swallowing	Increased heart rate (≥15 bpm) Pallor	Fatigue・sleep or irritability
4	As above	Vomiting/diarrhea with dehydration	Dyspnea Weak respiration Cyanosis	Arrhythmia Mild hypotension Cold extremities Sweat skin	Dizziness Distraction
5	As above	As above	Respiratory arrest	Severe bradycardia Severe hypotension Cardiac arrest	Loss of consciousness

Grading should be based on the most severe symptom.

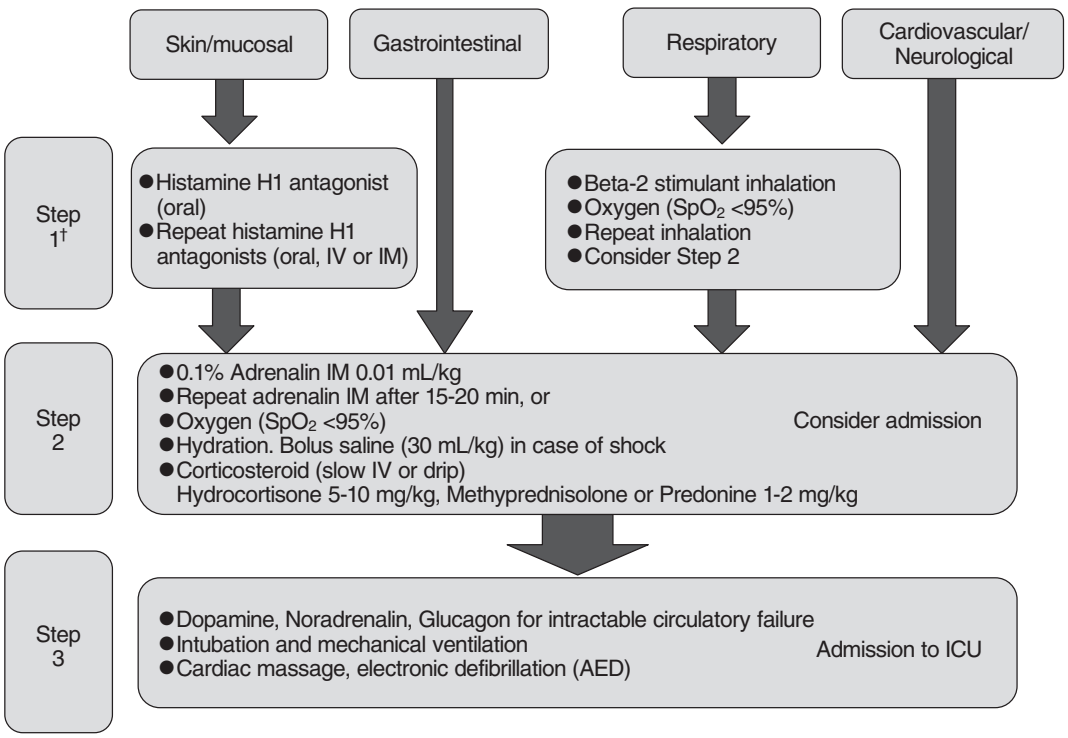

Fig. 3 Treatment plan for allergic symptoms. †Consider oral corticosteroid to prevent late reactions.

lunch menu is an important social activity to improve quality of life and safety of the patient.

FUTURE PROSPECTS

The Japanese OFC Guideline principally deals with the diagnosis of immediate food hypersensitivity. Diagnostic food challenge for non-IgE-mediated allergic reactions including food protein-induced enterocolitis syndrome (FPIES)[56] and late-onset worsening of eczema,[57] both of which are thought to be cell-mediated

immunological disorders, is not described in the guideline, because insufficient evidence is available to establish a standardized protocol at this time. Indirect food challenges such as provocation through breast milk after giving the target food to the lactating mother,[58] or labial food challenge[59] are also not dealt with.

The guideline does not recommend a single universal procedure, but places emphasis on users arranging their own protocol to meet the conditions of their institute and patient needs. In any case, safety remains the most important consideration, and the key safety point might be that OFC is conducted by experienced staff who are present throughout the procedure, continuously interacting with the patient.

ACKNOWLEDGEMENTS

This review was partially supported by a grant from Ministry of Health, Labour and Welfare, 2009. The author sincerely appreciates the cooperation of all production committee members of the Japanese OFC Guideline 2009.

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