Allergology International 66 (2017) 248–264

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Invited review article

Japanese guidelines for food allergy 2017☆

Motohiro Ebisawa [a,*], Komei Ito [b], Takao Fujisawa [c], on behalf of Committee for Japanese Pediatric Guideline for Food Allergy, The Japanese Society of Pediatric Allergy and Clinical Immunology, The Japanese Society of Allergology

[a] Department of Allergy, Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, Kanagawa, Japan
[b] Aichi Children's Health and Medical Center, Aichi, Japan
[c] Mie National Hospital, Mie, Japan

ARTICLE INFO

Article history:
Received 6 October 2016
Available online 10 March 2017

Keywords:
Food allergy
Guidelines
Oral food challenge
Oral immunotherapy
Prevention

ABSTRACT

Five years have passed since the Japanese Pediatric Guideline for Food Allergy (JPGFA) was first revised in 2011 from its original version. As many scientific papers related to food allergy have been published during the last 5 years, the second major revision of the JPGFA was carried out in 2016. In this guideline, food allergies are generally classified into four clinical types: (1) neonatal and infantile gastrointestinal allergy, (2) infantile atopic dermatitis associated with food allergy, (3) immediate-type of food allergy (urticaria, anaphylaxis, etc.), and (4) special forms of immediate-type of food allergy such as food-dependent exercise-induced anaphylaxis and oral allergy syndrome (OAS). Much of this guideline covers the immediate-type of food allergy that is seen during childhood to adolescence. Infantile atopic dermatitis associated with food allergy type is especially important as the onset of most food allergies occurs during infancy. We have discussed the neonatal and infantile gastrointestinal allergy and special forms of immediate type food allergy types separately. Diagnostic procedures are highlighted, such as probability curves and component-resolved diagnosis, including the recent advancement utilizing antigen-specific IgE. The oral food challenge using a stepwise approach is recommended to avoid complete elimination of causative foods. Although oral immunotherapy (OIT) has not been approved as a routine treatment by nationwide insurance, we included a chapter for OIT, focusing on efficacy and problems. Prevention of food allergy is currently the focus of interest, and many changes were made based on recent evidence. Finally, the contraindication between adrenaline and antipsychotic drugs in Japan was discussed among related medical societies, and we reached an agreement that the use of adrenaline can be allowed based on the physician's discretion. In conclusion, this guideline encourages physicians to follow the principle to let patients consume causative foods in any way and as early as possible.

Copyright © 2017, Japanese Society of Allergology. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Definition of a food allergy

The Japanese Pediatric Guideline for Food Allergy 2016 (JPGFA 2016),[1] published by the Japanese Society of Pediatric Allergy and Clinical Immunology (JSPACI) in 2016, ratifies the definition used in JPGFA 2012[2] "a phenomenon in which adverse reactions are caused through antigen-specific immunological mechanisms after exposure to a given food."

2. Mechanisms of food allergy

The most common mechanism of food allergy is IgE-mediated reactions, which cause immediate reactions within 2 h after the exposure to food allergens. Non-IgE mediated reaction is a food allergic reaction that occurs independent of IgE.

3. Clinical symptoms

Food allergy symptoms occur in various organs, as shown in Table 1. They are classified into immediate and non-immediate allergic reactions. Symptoms described in Table 1 are mostly immediate allergic reactions.

☆ This article is an updated version of "Japanese guideline for food allergy 2014" published in Allergol Int 2014:63:399-419.

* Corresponding author. Department of Allergy, Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, 18-1 Sakuradai, Minami-ku, Sagamihara, Kanagawa 252-0392, Japan.
E-mail address: m-ebisawa@sagamihara-hosp.gr.jp (M. Ebisawa).

Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2017.02.001

1323-8930/Copyright © 2017, Japanese Society of Allergology. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Table 1
Symptoms of food allergies.

Organ	Symptoms
Skin	Erythema, urticaria, angioedema, pruritus, burning sensation, eczema
Mucous membrane	Conjunctival hyperemia and edema, pruritus, lacrimation, blepharedema
	Rhinorrhea, nasal congestion, sneezing
	Discomfort/swelling of the oral cavity/pharynx/lips/tongue
Respiratory organs	Discomfort/itch/tightness in the pharyngolarynx, hoarseness, dysphagia, coughing, wheezing, retractive breathing, feeling of chest tightness, dyspnea, cyanosis
Digestive organs	Nausea, vomiting, abdominal pain, diarrhea, hematochezia
Nerve	Headache, lowered vigor, unrest, impaired consciousness, incontinence
Circulatory organs	Decreased blood pressure, tachycardia, bradycardia, arrhythmia, coldness of limbs, pallor (peripheral circulatory failure)

4. Definition of anaphylaxis

Of the symptoms, anaphylaxis is defined as "severe hypersensitivity reaction that may cause a life-threatening risk with systemic symptoms induced at several organs."

The European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology proposed the combination of symptoms that are diagnosed as anaphylaxis.[3]

5. Clinical types of food allergies

Food allergies are roughly classified into 4 representative clinical types (Table 2).[4]

5.1. Neonatal and infantile gastrointestinal allergy

Neonatal and infantile gastrointestinal allergy is one type of food allergy that induces digestive symptoms such as emesis, hematochezia, and diarrhea in neonates and infants mainly through non-IgE-mediated (cell-mediated) mechanisms. A classification of this type of food allergy has already been proposed in the United States. However, this classification cannot be immediately introduced in Japan, because there are many cases in Japan that do not meet this classification. In light of this situation, the JPGFA 2012 tentatively named this disease "neonatal and infantile gastrointestinal allergy." The most common causative food is cow's milk. Other causes include soybeans and rice. Children who are exclusively breast-fed may develop this disease. The number of reported cases has increased rapidly in the last 10 years. In both a multicenter survey conducted in Tokyo in 2009 and case-accumulation study at facilities for neonate infants, the disease incidence was reportedly 0.21%.[5,6] Allergen-specific lymphocyte stimulation tests are positive for most patients. This indicates that the allergy is cell-mediated. The diagnosis is based on (i) the development of digestive symptoms after causative food ingestion, (ii) the disappearance of symptoms by eliminating causative foods, and (iii) a positive food challenge test. Approximately 30% of the cases are C-reactive protein (CRP) positive. An increased CRP level has been reported in cases presenting with systemic symptoms such as fever, which also differentiates it from septic poisoning.[7,8] The prognosis is favorable. Approximately 70% of patients acquire tolerance at 1 year of age, and approximately 90% acquire tolerance by their second birthday.

5.2. Infantile atopic dermatitis associated with food allergy

Infantile atopic dermatitis associated with food allergy, as a name, was proposed by the study group of the Ministry of Health, Labour and Welfare.[4] This type is the most common food allergy during childhood. It is associated with infantile atopic dermatitis. Eczema often remits with the elimination of allergenic foods. The food allergy often outgrows as age increases. Common causative foods include egg, cow's milk, wheat, and soybeans.

5.3. Immediate-type food allergy

This type develops immediate symptoms after ingestion through IgE-dependent mechanisms. Infants may develop immediate symptoms when they ingest hen's egg, cow's milk, wheat, and other causative foods for the first time. In periods other than infancy, the common causative foods are crustaceans, fish, peanuts, buckwheat, and fruit. Tolerance acquisition may be less common in adolescents and adults.

5.4. Special forms

5.4.1. Food-dependent exercise-induced anaphylaxis (FDEIA)

Food-dependent exercise-induced anaphylaxis (FDEIA) is induced by exercise after food ingestion, but does not occur after either food ingestion or exercise alone. The pathogenesis is IgE-mediated. FDEIA is mostly induced by exercise within 2 h after

Table 2
Clinical type of food allergy.

Clinical type		Age of onset	Common causative foods	Acquisition of tolerance (remission)	Possibility of anaphylactic shock	Mechanism of food allergy
Neonatal and infantile gastrointestinal allergy		Neonatal period Infancy	Cow's milk (baby formula)	Mostly remittable	(±)	Mainly non-IgE mediated type
Infantile atopic dermatitis associated with food allergy		Infancy	Hen's egg, cow's milk, wheat, soybean, etc.	Mostly remittable	(+)	Mainly IgE mediated type
Immediate-type food allergy (urticaria, anaphylaxis, etc.)		Infancy adulthood	Infancy to young child: Hen's egg, cow's milk, wheat, buckwheat, fish, peanut, etc. School-aged children to adults: Crustacean, fish, wheat, fruit, buckwheat, peanut, etc.	Hen's egg, cow's milk, wheat, soybean, etc. are mostly remittable. Other allergens are mostly less remittable	(++)	IgE-mediated type
Special type	Food-dependent- exercise induced anaphylaxis (FDEIA)	School age adulthood	Wheat, Crustacean, etc.	Less remittable	(+++)	IgE-mediated type
	Oral allergy syndrome (OAS)	Infancy adulthood	Fruit, vegetable, etc.	Less remittable	(±)	IgE-mediated type

food ingestion. It is a relatively rare disease that occurs most often among junior high and high school adolescents. In surveys of junior high school students in Yokohama city in 1998 and 2012, the prevalence was reported to be 0.017% and 0.018%, respectively (approximately 1 per 6000 students), indicating an unchanged disease prevalence. The prevalence was 0.0046% among elementary school students (2003; approximately 1 per 20,000 students) and 0.0086% among senior high school students (2001; approximately 1 per 12,000 students).[9] Common causative foods are wheat products and crustaceans in Japan. FDEIA is mostly induced after high-intensity exercise. Non-steroidal anti-inflammatory drugs, such as aspirin, can exacerbate the condition.

It is desirable to narrow down the causative foods through history taking, allergy testing, and conducting a provocation test. No drug has been determined to prevent FDEIA.

Currently, no methods exist to predict the initial episode of FDEIA; thus, the emphasis is on the prevention of second or later episode(s). Lifestyle guidance for disease prevention instructs not to consume any causative food within 2 h prior to exercising. However, caution is required to avoid instructing complete elimination of the causative foods and restriction of physical exercise.

5.4.2. Oral allergy syndrome (OAS)

Oral allergy syndrome (OAS) is an immediate food allergy localized to the mucous membrane via IgE antibodies. Common causative foods are fresh fruit, vegetables, and legumes. OAS is often complicated by pollinosis. OAS complicated by pollinosis is also called pollen food allergy syndrome (PFAS). PFAS is established through sensitization to the pollen allergen protein, and a hypersensitivity reaction develops after ingestion of fruit or vegetables that share cross reactivity with the pollen allergen protein. Causative allergens include Bet v1 homologs and profilin, which show cross-antigenicity with pollens and others. A definitive diagnosis can be reached through history taking and identifying antigen-specific IgE antibodies. A prick–prick test using fresh vegetables and fruit to identify specific IgE antibodies is superior to the measurement of antigen-specific IgE antibodies in the blood.[10] In the oral challenge test for definitive diagnosis, a fresh food is sublingually administered. While an elimination diet is the basis of treatment, many heat-treated foods can be orally ingested. The symptoms are alleviated by administration of histamine H1 receptor antagonist. Antigen-specific oral immunotherapy (OIT) for pollinosis has also been initiated to treat PFAS. However, a conclusion has not yet been reached regarding the therapeutic effect. Since 30–50% of patients with latex allergy are reported to have some form of hypersensitive reaction (immediate symptoms including anaphylaxis and OAS) to fruit or vegetables, these cases are also called latex-fruit syndrome.[11]

6. Diseases associated with food allergies

Urticaria, atopic dermatitis, eosinophilic gastrointestinal disorders (EGIDs) protein-losing enteropathy, celiac disease, and primary pulmonary hemosiderosis (Heiner syndrome) complicated with milk allergy have been associated with ingestion of specific foods, but an immunological mechanism has not necessarily been established. When these diseases are diagnosed, the causal relationship between the ingestion of a specific food and the disease condition should be analyzed with the involvement of a food allergy taken into consideration. EGIDs are roughly segregated into eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), and eosinophilic colitis (EC) on the basis of the affected sites. In Europe and the United States, EoE has increased rapidly, so that the disease is no longer rare. In Japan, adult EoE cases have tended to increase, and the prevalence rate is 17.1 per 100,000 persons.[6] The endoscopic disease-detection rate in Asia is about 20 per 100,000 persons,[5] which is significantly less than the rate observed in Europe and the United States (about 500 per 100,000 persons). Only a small number of pediatric EoE cases have been reported in Japan, and the characteristic symptoms of EoE are known to vary depending on patient age. Pediatric EoE is likely to present with suckling disorders in babies and toddlers, vomiting in infants and school-age children, abdominal pain and swallowing disorder in school-age children and children in their early teens, and deglutition disorder and food impaction in teenagers, adults, and older people. In Europe and the United States, EGE is rarer than EoE, while in Japan, there are more reported cases of EGE than EoE; approximately 24 cases of adult EGE are reported annually.[12] Pediatric EGID, as a whole, is more common in children of school age or older ages, and there have been approximately 100 published cases in Japan since 2005, as revealed on a search of the Igaku Chuo Zasshi (ICHUSHI).

7. Epidemiology of food allergies

7.1. Prevalence

On the basis of a large-scale epidemiological survey in Japan, the prevalence of food allergy is estimated to be 5–10% in infants,[13] 5% in young children, and 4.5% in school children.[2] To the best of our knowledge, no epidemiological survey has been conducted regarding food allergies among adults.

7.2. Nationwide survey of immediate-type food allergies

According to the national survey on immediate food allergy conducted by the Consumer Affairs Agency, Government of Japan in 2011, total of 2954 cases were reported from 1079 doctors who agreed to participate in the study.[14] The category of food allergy cases was "the case whose onset was within 60 min after ingestion of a certain food, and which was seen by doctors."

7.2.1. Incidence rate at different ages (Fig. 1)

The highest incidence of immediate type food allergies occurred in the children aged <1 year, 34.1% (1009 cases), and then decreased gradually with age – 20.4% (600) in the 1-year-old and 10.1% (297) in the 2-year-old. Food allergy incidence was 64.5% in ≤2-year-old children, 80.3% in ≤5-year-old children, and 90.1% in ≤10-year-old children. The incidence was 5.4% (160) in people aged ≥18 years. The ratio of male to female food allergy patients was 1.4 (1724:1230).

7.2.2. Proportion of causative foods (Fig. 2)

Most frequent causative foods were hen's egg (1153 cases, 39.0%), cow's milk (645 cases, 21.8%), and wheat (347 cases, 11.7%). The top 10 antigens included these three in addition to peanut, fruit, fish roe, crustacean, nut, buckwheat, and fish. The three top-ranking antigens accounted for 72.5%; the five top-ranking antigens accounted for 81.7%; and the 10 top-ranking antigens accounted for 95.4%, of all food allergy cases.

7.2.3. Causative foods in different ages

(1) Initial onset (Table 3)

The initial-onset food allergy accounts for 58.1% of all cases. The highest rate of initial-onset food allergy is seen in <1-year-old children (88.1%); the rate decreases rapidly thereafter, and most food allergy cases in older age groups are a result of accidental ingestion. Three major causative foods were predominant in the <1-year-old age group, while various other causative foods were seen in the older age groups.

Fish roe was the second-ranking causative food in the 1-year-old age group. Fish roe was ranked first in the 2–3 years age group, while peanut was ranked third. Causative foods in other age groups were fruit (first) and peanut (third) in the 4–6 years age group;

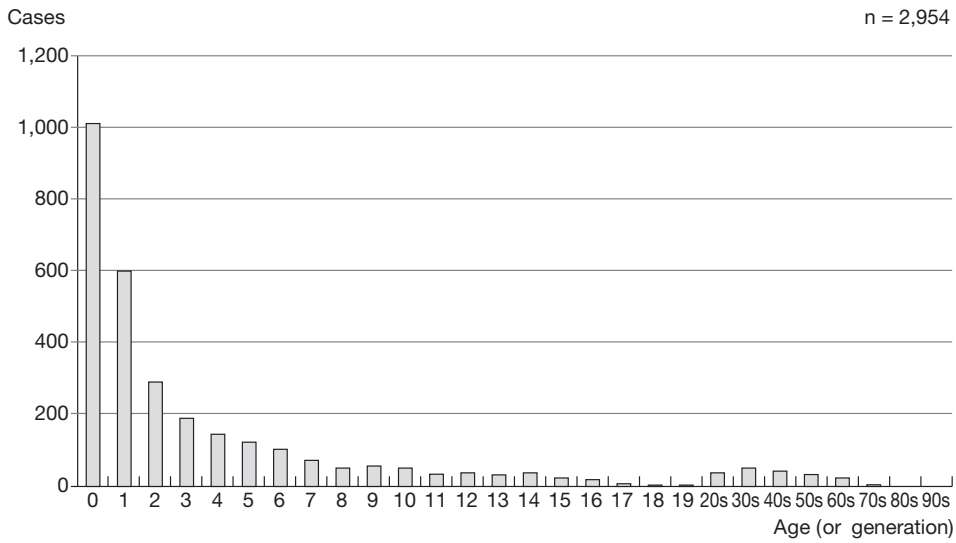

Fig. 1. Number of patients with immediate-type food allergy by age. The number of patients aged ≥20 years is shown in 10-year increments.

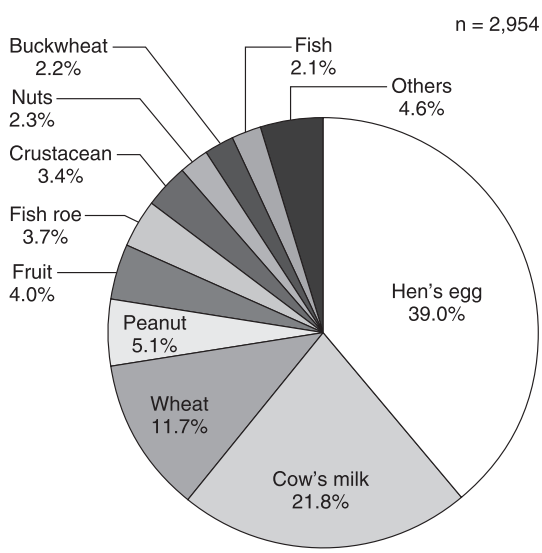

Fig. 2. Breakdown of causative foods of immediate-type food allergy.

crustaceans (first) and fruit (second) in the 7–19 years age group; and wheat (first), fish (second), and crustaceans (third) in the ≥20 years age group.

(2) Accidental ingestion (Table 4)

Accidental ingestion occurred in 41.9% of the food allergy cases, and the causative foods did not differ among the age groups. Hen's egg, cow's milk, and wheat were the most common causative foods in infants and toddlers, while peanuts and buckwheat were more common in early childhood and older ages.

7.2.4. Symptom appearance rate in different organs

The manifestation of food allergies occurs most frequently as skin symptoms, appearing in 92.0% of the cases, followed by respiratory symptoms in 33.6%, mucosal symptoms in 28.0%, digestive symptoms in 18.6%, and shock in 10.4%.

8. Natural history and allergic march

8.1. Natural history

The progression of food allergy is very diverse. Most patients with food allergy that developed during infancy achieve tolerance as they age. The acquisition of tolerance in food allergy depends on factors such as the causative food, age of onset, severity of hypersensitivity, and recognition of allergen ingredients. In general, tolerance to allergens in hen's egg, cow's milk, wheat, and soybeans

Table 3
Causative foods of new-onset food allergies.

	<1 year old (884)	1 year old (317)	2–3 years old (173)	4–6 years old (109)	7–19 years old (123)	≥20 years old (100)
1	Hen's egg 57.6%	Hen's egg 39.1%	Fish roe 20.2%	Fruit 16.5%	Crustacean 17.1%	Wheat 38.0%
2	Cow's milk 24.3%	Fish roe 12.9%	Hen's egg 13.9%	Hen's egg 15.6%	Fruit 13.0%	Fish 13.0%
3	Wheat 12.7%	Cow's milk 10.1%	Peanut 11.6%	Peanut 11.0%	Hen's egg Wheat 9.8%	Crustacean 10.0%
4		Peanut 7.9%	Nuts 11.0%	Buckwheat Fish roe 9.2%		Fruit 7.0%
5		Fruit 6.0%	Fruit 8.7%		Buckwheat 8.9%	

This table lists the causative foods that account for ≥5% in each group, ranked from 1st to 5th, from the top. N = 1706.

Table 4
Causative foods of accidental ingestion.

	<1 year old (119)	1 year old (280)	2–3 years old (311)	4–6 years old (265)	7–19 years old (203)	≥20 years old (50)
1	Hen's egg 49.6%	Hen's egg 48.6%	Hen's egg 37.0%	Hen's egg 40.0%	Hen's egg 19.2%	Wheat 34.0%
2	Cow's milk 32.8%	Cow's milk 34.3%	Cow's milk 36.3%	Cow's milk 30.6%	Cow's milk 17.2%	Crustacean 22.0%
3	Wheat 16.8%	Wheat 11.4%	Wheat 14.1%	Peanut 11.7%	Peanut 16.3%	Buckwheat 10.0%
4				Wheat 9.8%	Wheat 11.3%	Fruit Fish 8.0%
5					Crustacean 9.4%	

This table lists the causative foods that account for ≥5% in each group, ranked from 1st to 5th, from the top. N = 1228.

is more likely to be acquired. However, tolerance to allergens in buckwheat, peanuts, nuts, crustaceans, and fish is less likely to be acquired. The time to acquire tolerance for the same food differs significantly between reports, probably owing to differences in allergy severity in the study patients and the diagnostic techniques that were used.[15–18] Common factors for delayed tolerance acquisition include complications with multiple food allergies, high levels of specific IgE antibody titers, a history of anaphylaxis, and complications with other allergic diseases (e.g., atopic dermatitis).[15,17–20]

The time to tolerance acquisition for each food depends on the allergen proteins recognized by specific IgE antibodies and antibody binding sites (epitope). For example, in cases of high levels of ovomucoid-specific IgE antibodies, hen's egg allergy is less likely to spontaneously remit. In addition, specific IgE antibodies in pediatric patients with persistent cow's milk allergy primarily recognize a certain epitope.

On the other hand, some infant-onset cases of peanut allergy, for which tolerance is less likely to be acquired, may acquire tolerance. However, the peanut allergy may recur with later ingestion, if the patient restricts ingestion after tolerance acquisition.

8.2. Food allergy and allergic march

Childhood allergic disease exhibits a natural course, in which various diseases, such as food allergy, atopic dermatitis, asthma, and allergic rhinitis, develop with age. This natural course is called the allergic march. Food allergy occurs at an early stage. Progression of the allergic march may be inhibited by alleviating the sensitization to the food allergen. Percutaneous sensitization is increasingly being recognized as an onset risk for food allergies as well as atopic dermatitis. In fact, the allergic march can be explained by this pathologic condition. For instance, the breakdown of the skin barrier accompanied by a mutation in the Filaggrin gene is reportedly associated with an odds ratio of 5.3 for the onset of peanut allergy, 3.1 for atopic dermatitis, and 1.5 for asthma.[21,22]

9. Prediction and prevention

9.1. Risk factors for food allergy

Studies have investigated family history, genetic predisposition, skin barrier function, and the season of birth as risk factors for food allergy onset. Especially, the presence of atopic dermatitis is an important risk factor. Recently, Tsakok *et al.* reported in a systematic review that children with atopic dermatitis were 6.18 times more easily sensitized against food than healthy children.[23] Based on a large-scale cohort study, Flohr reported that the severity of eczema increased the risk of food sensitization in 3-months old infants.[24] These reports indicated that the presence of dermatitis poses a risk of percutaneous sensitization.

9.2. Prevention of food allergy (Table 5)

9.2.1. Primary prevention

Guidelines do not recommend food elimination as a prevention measure to pregnant and lactating mothers. Previous cohort studies have demonstrated that peanut consumption by mothers during pregnancy or lactation did not influence peanut sensitization or the clinical onset of peanut allergy in their 4- to 6-year-old children.[28] Similarly, the Cochrane reviews noted that food elimination in pregnant and lactating mothers confers no preventive benefits on the onset of food allergies in their children.[29] There are both positive and negative reports on the impact of complete maternal feeding in preventing food allergies, and sufficient evidence does not exist to support either.[30–33] As delaying the introduction of specific foods into the diet of high-risk infants did not reduce the onset risk,[34,35] this measure is not recommended.

The Learning Early About Peanut allergy (LEAP) study, a randomized comparison study reported in 2015, investigated whether peanut intake or avoidance was effective in preventing the onset of peanut allergy in high-risk infants (infants with atopic dermatitis or hen's egg allergy along with a risk of peanut allergy onset, even though allergy was absent at the start of the study).[25] The study reported a significantly lower incidence of peanut allergy at 5 years of age in the intake group (3.2%) compared to the avoidance group (17.2%), and this effect persisted for a year after complete elimination at the age of 5 years.[26] On the basis of this report, an international consensus statement advised that in countries with a high onset risk of peanut allergy, the introduction of peanuts after weaning should be sooner rather than later.

Moreover, the Enquiring About Tolerance (EAT) study conducted in infants who were not high-risk, the early introduction (3–5 months of age) of foods associated with high onset risk decreased the sensitization rates in skin prick tests (SPTs) with hen's egg and peanut compared with a standard introduction (6 months of age or later). Further, early introduction had a preventive effect on the onset of food allergies, as assessed using the oral food challenge (OFC) test, in compliant subjects compared with a standard introduction. However, when a group of dropped out subjects was included in the analysis, the difference in prevention no longer remained significant, and seven subjects in the early introduction group tested positive in an OFC test at 3 months. Thus, caution should be exercised in analyzing and interpreting the efficacy and safety of early introduction.[27] In another study assessing the impact of introducing raw hen's egg to infants, cases of anaphylaxis were reported in some high-risk infants.[36] Thus, an indiscriminate and careless early introduction of onset risk-associated foods is not recommended.

In a randomized comparison study conducted in Japan on children with atopic dermatitis (Prematurity's Effect on Toddlers,

Table 5
A summary of prevention measures for the onset of food allergy.

Items	Comments by JPGFA 2016
Food elimination in pregnant or lactating mothers	It is not recommended to conduct food elimination for prevention of the onset of food allergies in pregnant and lactating mothers as it may cause harmful nutritional disorders in the mother and baby.
Complete breast feeding	Although breast feeding has significant benefits, sufficient evidence to indicate its superiority in the prevention of allergic diseases is not available.
Artificial formula	There is insufficient evidence on the usefulness of hydrolyzed milk in preventing the onset of food allergies.
Timing of weaning foods	Weaning is appropriate at 5–6 months of age (according to the Support Guidelines for Breast-feeding and Complementary feeding, 2007). Delaying in weaning due to concerns regarding the onset of food allergies is not recommended.[†,‡]
Moisture retention from the early stages of infancy	Although the use of moisturizing agents from early infancy may prevent atopic dermatitis in 30–50% of the cases, its preventive effect on the onset of food allergies has not been proven.
Probiotics/prebiotics	Although the use of probiotics during pregnancy and lactation reportedly reduces infantile eczema, there is insufficient evidence supporting its role in the prevention of food allergy onset.

[†] It was reported that delayed peanut consumption might increase the risk of developing peanut allergy,[25,26] and in countries where peanut allergy occurs frequently, the early peanut consumption (4–10 months after birth) is recommended.

[‡] Although it was reported that the intake of foods which may induce allergies (peanut, hen's egg) from 3 months after birth may reduce the onset risk of food allergies in comparison with the start at 6 months or later after birth,[27] the amount and quality of foods to safely induce tolerance are still unknown and under study.

Infants and Teens; the PETIT study), the group of children in whom cooked hen's egg was introduced stepwise in very small amounts, starting at 6 months of age, demonstrated a significant decrease in the onset of hen's egg allergy compared to a group of children in whom cooked hen's egg was eliminated until 12 months of age. In this study, no adverse events were reported, and atopic dermatitis was maintained in remission through active eczema control, including proactive therapy.[37]

9.2.2. Secondary prevention

Few studies have assessed intervention strategies for the prevention of food allergy onset in food-sensitized infants with no history of causative food intake. Although two possible intervention methods have been reported, the insufficient supporting evidence makes the assessment of their preventive effects difficult.

(1) Oral tolerance induction

In the LEAP study mentioned previously, for the 98 subjects with a positive peanut SPT result (indicated by a wheal of 1–4 mm diameter; cases with larger diameters and cases positive for OFC test were excluded), the intake group showed a higher inhibitory effect on the onset of peanut allergy.[25] In the PETIT study for egg-white specific IgE antibody-positive group at 6 months of age, the earlier introduction group of cooked hen's egg showed higher prevention of the onset of hen's egg allergy. However, in cases where a food allergy onset is suspected, caution should be exercised in introducing food at home; OFC tests may also be considered.[37]

(2) Active anti-inflammatory treatment for eczema and the maintenance of remission.

As a compromised skin barrier and the presence of dermatitis constitute percutaneous sensitization risk to food antigens, the possibility that skin cares aiming at active eczema control against atopic dermatitis decrease allergen sensitization and subsequent allergy march has been considered.[38] However, at present, supporting evidence is scarce.

Table 5 shows a summary of the recommended prevention measures.

10. Food allergens

10.1. Structure of food allergen

Most food allergens are proteins contained in the food. Proteins consist of about 20 different amino acids, which string together like a chain (primary structure). The primary structure is folded into spirals (α-helix) or arranged as sheets (β-sheet) (secondary structure), which is then configured into specific three-dimensional structures (tertiary structure). Moreover, multiple protein molecules may bind (quaternary structure) to form a large molecule. A specific IgE antibody recognizes a specific site of these structures (an antigenic determinant or epitope) to bind. An epitope with a linear alignment of amino acids is called a linear epitope, and an epitope with a three-dimensional, discontinuous alignment of amino acids is called a conformational epitope. When the epitopic structure is shared by more than one protein, the antibody binds to all common epitopic structures, a phenomenon called cross antigenicity. Among the multiple proteins composing any food, the protein molecules with allergenicity (IgE antibody binding ability) are called the allergenic component of the food.[39] An allergenic component recognized by specific IgE antibodies to induce symptoms in 50% or more of allergy patients is called a major allergen.

The three-dimensional structure of food proteins changes on heating, or on treatment with acids and hydrolytic or other enzymes during food processing or cooking (alteration). Proteins are cleaved through the actions of digestive enzymes (proteases) such as pepsin, trypsin, and chymotrypsin (digestion). The change in the structure of the epitope decreases its IgE antibody binding ability, and the attenuation of an allergic reaction due to decreased IgE antibody binding ability is termed hypoallergenicity.

Recently, the bioinformatic analysis of allergen structure and function has revealed that food allergens belong to limited protein families. Sixty percent or more of plant-derived food allergens belong to four protein families (prolamin, cupin, Bet v1 homologs, and profilin),[40] while animal-derived food allergens belong to three protein families (tropomyosin, parvalbumin, and casein).[41]

10.2. Food allergens in medicinal products and personal care products

Food-derived components may be present in medical care products, general medicinal products, or personal care products (oral care products, cosmetics, bath agents, and soaps among others). Specifically, these components are hen's egg white-derived lysozyme chloride and cow's milk-derived albumin tannate. Lactose is a disaccharide consisting of glucose and galactose and is a component of raw cow's milk, and thus contains several micrograms of milk protein. Lactose is used to blend powdered medicines and is added to various drugs (inhalants, capsules, tablets, powdered medicines, and intravenous products). In patients who are highly allergic to cow's milk, symptoms may be induced on rare occasions.[42]

11. Diagnosis and examination

Two types of flowcharts demonstrating the steps in the diagnosis of food allergy for infantile atopic dermatitis associated with food allergy (Fig. 3) and for immediate-type reaction (Fig. 4) are proposed by the research group of the Ministry of Health Labour and Welfare,[4] since the diagnostic procedure differs between the two types of food allergies. In an elimination test, the potential causative foods are eliminated for approximately 1–2 weeks. Then, observation of the symptoms is made to determine if there are improvements. In infants receiving mother's milk or mixed feeding, the potential causative foods are eliminated from the mother's diet. In cases where symptoms are alleviated by food elimination (positive by elimination test), an OFC test is recommended to obtain a definitive diagnosis.

11.1. History taking

Key points in history taking are causative foods and their intakes, age at symptom onset, reproducibility, the last time when symptoms occurred, details of the induced symptoms, time from food ingestion to onset of symptoms, other causative conditions (exercise, medication, etc.), past test results, and present ingestion of the causative foods.

11.2. Immunological examination

The presence of specific IgE antibodies can be confirmed through specific serum IgE antibody test, SPT, basophil histamine release test, etc. Although the diagnostic values of these tests have been evaluated in many studies, their results vary depending on the selection of the general population and the diagnostic methods used. The presence of specific IgE antibodies indicates sensitization to the relevant food allergen, which is not always the actual allergen involved in the onset.

11.2.1. Antigen-specific IgE antibodies in the blood

At present, the ImmunoCap® assay is widely used to detect blood IgE antibodies. The assay increases the efficacy of converting allergen into solid phase using cellulose polymer and has a high detection sensitivity through the use of fluorescent enzyme-labeled antibodies (fluorescent enzyme immunoassay, FEIA). The AlaSTAT 3 g Allergy® also detects specific IgE antibodies, and in this test, the liquid phase allergen binds to the solid-phased beads and detection

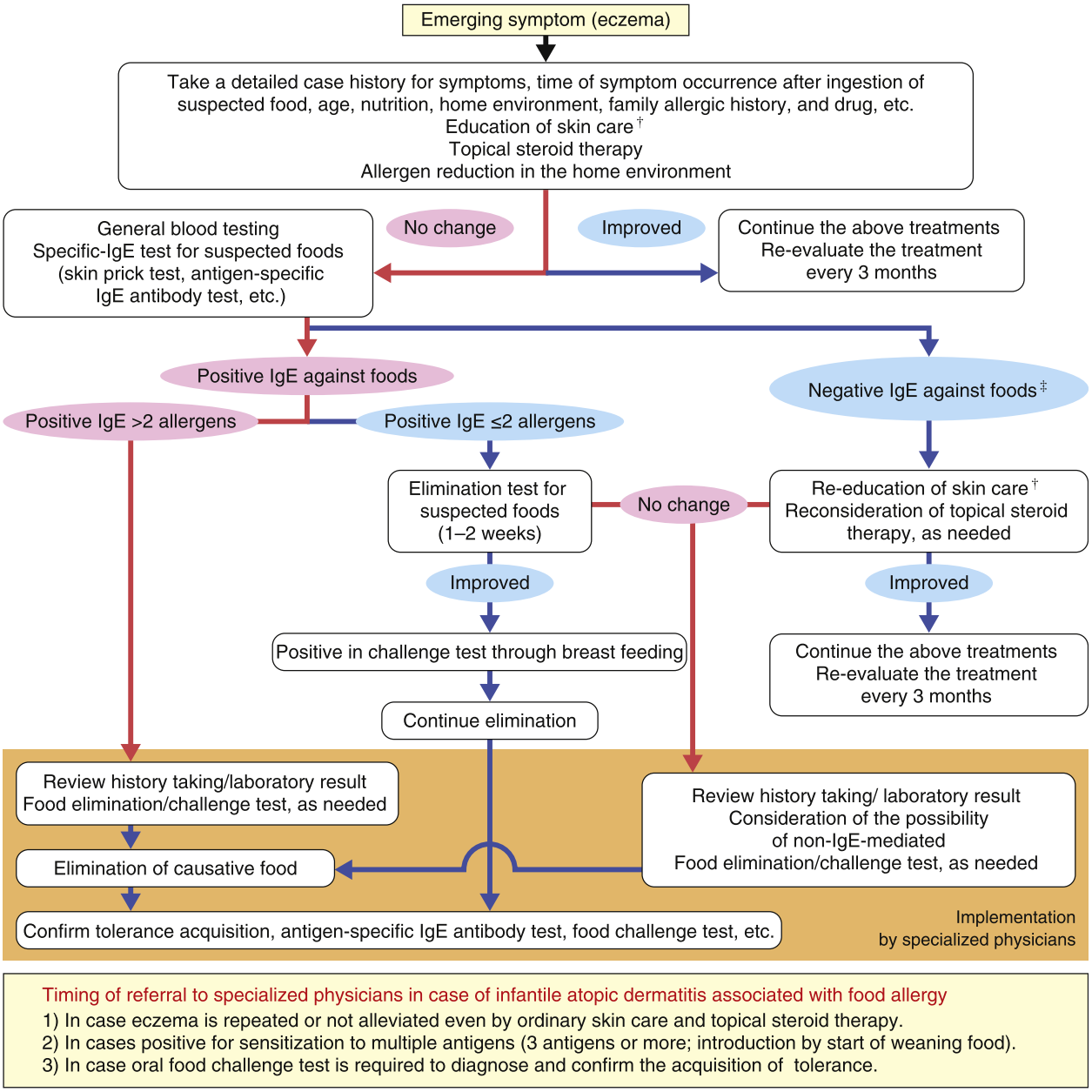

Fig. 3. Flow chart for diagnosis of food allergy (Infantile atopic dermatitis associated with food allergy). †Instruction for skin care. Fundamentals of skin care are skin cleansing and moisturizing. The details are discussed in the "Guidelines for the Management of Atopic Dermatitis 2012." ‡Positive for specific IgE antibody. As infants aged <6 months may have negative value for blood antigen specific IgE antibody, the prick test is useful.

is based on a chemiluminescent enzyme immunoassay (CLEIA). Both testing methods have nearly equivalent accuracies. Another assay, the Oriton IgE®, uses a porous glass filter as the solid phase. In either assay, the relative antigen-binding capacity is measured based on a World Health Organization-provided IgE standard. As the antibody measurement is not a direct quantitative estimation of the antibody molecules, the results used for diagnosis and monitoring are concentration-dependent.

To interpret the results of a specific IgE antibody test, information on the probability curves, sensitivity, and specificity serve as useful references.[43–47] In addition to a crude antigen, measurement of the allergen component-specific IgE antibody confers higher diagnostic accuracy.[48–51] Table 6 shows food allergen components for which testing is covered by nationwide insurance in Japan, including ovomucoid of egg white, ω-5 gliadin of wheat, and Ara h2 of peanut.

11.2.2. Skin test

A SPT is recommended to determine the causes of food allergy. Avoid intradermal tests using food antigens, because they are more likely to yield false positive results and cause anaphylactic reactions than the SPT. Reportedly, an atopy patch test, in which a food antigen is applied on the skin, is useful for predicting non-immediate reactions in the diagnosis of atopic dermatitis. However, no consensus has been reached on this finding. Before testing, the use of agents such as antihistamines, antiallergics, and steroids should be withdrawn for at least 3 days, because these influence in vivo tests. While a positive SPT indicates the presence of antigen-specific IgE antibodies, this result alone does not substantiate the diagnosis of a food allergy. However, even if the blood test is negative for antigen-specific IgE antibodies, a positive SPT may provide helpful information for the diagnosis of food allergy. Of

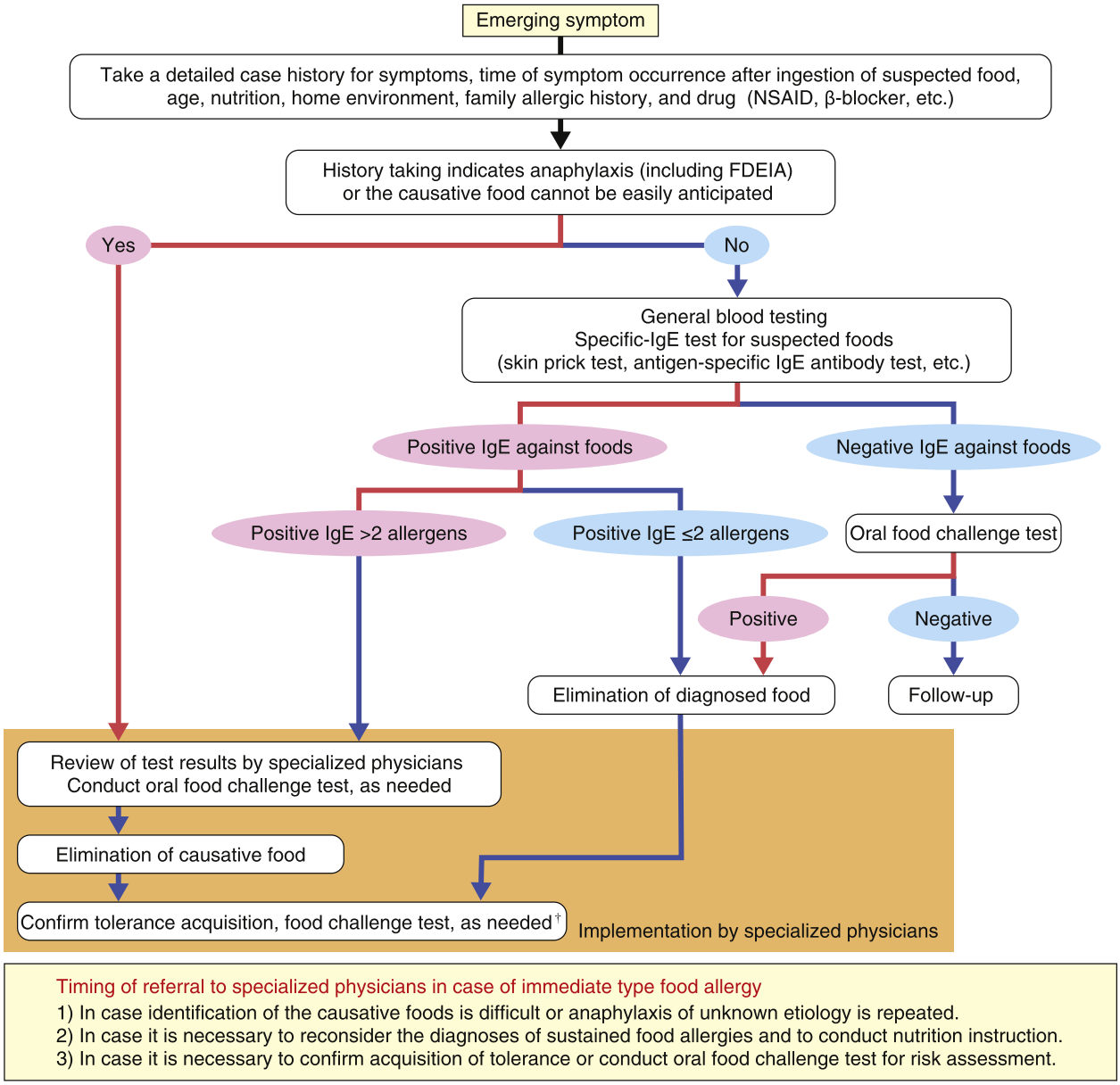

Fig. 4. Flow chart for diagnosis of food allergy (Immediate-type). †Generally, patients who demonstrate immediate-type reaction in later childhood are less likely to acquire tolerance.

Table 6
Food allergen component-specific IgE tests covered by nationwide health insurance.

Crude antigen	Allergenic component
Egg white	Gal d 1 (Ovomucoid)
Cow's milk	Bos d 4 (α-Lactoalbumin)
	Bos d 5 (β-Lactoglobulin)
	Bos d 8 (Casein)
Wheat	Tri a 19 (ω-5 gliadin)
Soybean	Gly m 4 (PR-10)
Peanut	Ara h 2 (2S albumin)
Latex	Hev b 6.02

note, during early infancy, some patients negative for antigen-specific IgE antibodies in the blood may have a positive SPT.[52,53] Fresh fruit and vegetables, which cause OAS, are unstable allergens. Thus, a prick–prick test is performed using fresh fruit and vegetables (the skin is pricked with the needle that has pricked the suspected food). More than 95% of SPT-negative patients do not present with immediate food allergy. However, as infants are less responsive to SPT, symptoms may be actually induced in infants negative for SPT.[52,53]

11.2.3. Basophil histamine release test

A basophil histamine release test (HRT) is used to measure the amount of histamine released from peripheral blood basophils after a reaction to an allergen. This is an in vitro test, which most accurately reflects specific IgE antibodies in a living body. Clinical laboratory tests covered by health insurance include HRT Shionogi® and Allerport® HRT, which use an automatic analysis system based

on the same measurement principle. HRT Shionogi® allows simultaneous testing for egg white, cow's milk, wheat, soybean, and rice. Allerport® HRT allows for measurement of 18 items, including the foods listed above. HRT Shionogi® is useful for diagnosis of egg, cow's milk, and wheat allergies.[54] It is also useful as an ancillary test for diagnosis of causative foods without challenge tests in patients who are at a higher risk of severe symptoms.[55] This kit is expected to have higher specificity than antigen-specific IgE antibody tests for other foods, but sufficient information has not yet been obtained for clinical assessment.

11.2.4. Basophil activation test, BAT

Similar to HRT, this is a quantitative estimation of IgE-dependent basophilic activation. In place of histamine release, the expression of activation markers CD63 and CD203c are measured by flow-cytometry. For quantitative estimation of CD203c, the Allegenicity kit® (Beckmann Coulter) is often used.[56,57] Although not covered by nationwide insurance, a CD203c test can be entrusted to an laboratory company.

11.2.5. Antigen-specific IgG4 antibodies in the blood

The IgG4 antibody is not usable for diagnosis of food allergies as it can be detected in asymptomatic patients and healthy persons as well.[58,59] Due to the false-positive test results, some non-causative foods may be eliminated, which for multiple food items, may cause health damage. Ingesting specific foods might lead to deconditioning, and it is named as “delayed food allergy”, which is not an established pathologic condition and examination method. The specific IgG4 antibodies may be used as markers of treatment efficacy for OIT.

12. Oral food challenge test

An OFC is the most reliable for identifying the causative foods of a food allergy. However, there is a risk for adverse reactions including anaphylaxis; therefore, it is important to ensure the patient's safety. Criteria for facilities are determined to conduct food challenge tests as healthcare services provided by health insurance. Thus, it is necessary to notify them.

12.1. Definition and objectives

OFC is an examination to investigate the presence or absence of induced symptoms in a subject following the administration of an ascertained or suspected causative food in single or multiple doses.[1] The objectives for OFC are summarized in Table 7.

12.2. Risk assessment

When an OFC is indicated, the medical history, the kind of planned challenge food, results of immunological examinations, and presence of underlying diseases are evaluated as risk factors, and the implementation schedule, challenge foods, and total challenge amounts are decided. Table 8 shows factors that may induce critical symptoms during an OFC.

12.3. OFC in practice

12.3.1. Preparation

(1) Ensuring safety
  a) Conduct the tests under the supervision of physicians and nurses. OFC should be conducted by physicians skilled in the treatment of food allergies and anaphylaxis. For OFC conducted at outpatient departments or clinics, it is recommended to prepare for immediate hospitalization.
  b) Prepare agents for emergency, such as adrenaline (Bosmin®, Adrenaline Syringe®), steroids, antihistamines, bronchodilators (inhaled β2 stimulants), and transfusion sets.

Table 7
Objectives of oral food challenge test.

1. Definitive diagnosis of a food allergy (identification of the causative allergen)
   (1) Identification of the foods that have been proven of sensitization but have not been ingested
   (2) Identification of foods suspected as causes of immediate reaction
   (3) Definitive diagnosis of infantile atopic dermatitis associated with food allergy (Conduct subsequently after elimination test)
   (4) Evaluation of symptom-inducing threshold level
2. Determination of the safe intake quantity and judgement of tolerance acquisition
   (1) Determination of the safe intake quantity (Small to medium dose)
   (2) Judgement of tolerance acquisition (Full dose)

(2) Before OFC, discontinue the use of agents that could influence OFC results (Table 9).
(3) Control basic allergic diseases, such as bronchial asthma and atopic dermatitis, since symptom induced by OFC may be difficult to judge and can be severe.
(4) Explain the objectives, methods, risks, and measures for hypersensitivity and obtain informed written consent.

12.3.2. OFC methods

(1) Open or blinded OFC
  a) Open test: Both the examiners and the subjects know the contents of the challenge food. However, if the symptoms are subjective, the test should be performed in a blind manner. In preschoolers, as the possibility of a psychogenic reaction can be neglected, the open OFC method is acceptable.
  b) Single-blind food challenge: The examiners know the content of the challenge food, while the subjects do not. For blinding, mix the challenge food with masking vehicle, such as juice, puree, oatmeal, or hamburger. Powdered food materials may be used as challenge food. The challenge test is conducted using a placebo (e.g., masking vehicle alone or a mixture of masking vehicle and food, other than the challenge food) in addition to the challenge food of interest on different days.
  c) DBPCFC (double-blind placebo-controlled food challenge test): Both the subjects and examiners who assess the symptoms are

Table 8
Factors associated with inducing severe symptoms.

1. Medical history associated with food intake
   (1) Medical history of severe symptoms such as anaphylaxis, anaphylactic shock, and respiratory symptoms
   (2) Short period from the experience of induced severe symptoms
   (3) History of induced symptoms by a small dose
2. Item of foods
   Cow's milk, wheat, peanut, buckwheat, etc., often cause severe symptoms.
3. Immunological tests
   (1) High specific IgE antibody titer
   (2) High release percentage in a basophilic histamine release test
4. Underlying diseases and complications
   (1) Bronchial asthma
   (2) Exacerbations of asthma, allergic rhinitis, or atopic dermatitis
   (3) Underlying diseases such as cardiac, respiratory, and psychotic diseases

Table 9
Drugs to be discontinued before an oral food challenge test and the discontinuation periods.

Histamine H1 receptor antagonists	72 h
Leukotriene receptor antagonists	24 h
β_2 stimulants	12 h
Th2 cytokine inhibitors	12 h
Theophylline	48 h
Oral sodium cromoglycate (DSCG)	48 h
Oral steroids	7–14 days

blinded to the challenge food. The challenge food should be prepared by people (controller) other than the examiners. In addition to the challenge tests using the foods of interest, a test using a placebo should be conducted on a different day.

(2) Total challenge dose (Tables 10 and 11)

The total allergen amount administered as a single dose, or as several fragmented doses, is called as the total challenge dose. Table 10 shows examples of total challenge doses used for common food items, and Table 11 shows examples of total challenge doses used for other foods.[1] In high-risk cases where symptoms may be induced by a small dose, a low total dose is recommended for an OFC test, while for negative cases, the OFC should be conducted subsequently with a medium or full dose.[60]

(3) Administration intervals and dividing method

Table 12 shows examples of administration intervals and dividing method for the total dose. Generally, the allergen is administered at 20–60-min intervals.[61,62] In cases where safely administered doses have been already known or to determine whether a small dose can be administered safely, a single dose OFC test can be considered.

Table 10
Examples of total challenge doses in oral food challenge test (open method).

Doses	Hen's egg	Cow's milk	Wheat
Low dose	One cooked egg yolk, about 1/32 cooked whole egg	About 3 mL	Udon noodle (50–75 mg wheat protein)
Medium dose	About 1/8–1/2 cooked whole egg	15–50 mL	Udon noodle (375–1250 mg wheat protein)
Full dose	One cooked whole egg 50 g (corresponding to one egg)	200 mL	Udon noodle 200 g, one of six slices of 5000 mg wheat protein

The full challenge dose is assumed a dose to confirm the tolerance acquisition, as assuming single meal amount in elementary-school pupils. In infants, it is taken into consideration to reduce the total challenge dose when necessary. The low challenge dose is set a dose that may mix in case of accidental ingestion and initial challenge test in high risk cases is assumed. As for administration interval, 20 min or longer is desirable.

Table 11
Examples of total challenge doses in an oral food challenge test (open method).

	Total challenge dose	Special instructions
Fish	Fish stock (Dashi), fish 50–100 g	Most patients do not react to fish stock.
Shrimp	20–40 g	
Potatoes	50–100 g	
Fruit	50–100 g	
Shellfish/Molluscs	10–20 g	
Meats	20–50 g	Very few patients react to meats.
Soybeans	Boiled soybeans 5–10 g, Tofu 50–100 g, soy milk 200 mL	Very few patients react to soy sauce and miso.
Buckwheat	2–80 g (boiled)	Severe reactions may occur.
Peanut, sesame, and other nuts	0.1–10 g	As a measure against accidental ingestion, the test may be conducted with a total challenge dose of 0.1–0.5 g. Food elimination can be released at school in a case that patient can intake 10 g. Each peanut weighs approximately 1 g.

Table 12
Administration intervals and dividing methods in oral food challenge tests.

Dosing method	Administration interval	Dose dividing method
Single dose	–	1/1
Two doses	60 min	1/4 → 3/4, 1/3 → 2/3
Three doses	30–60 min	1/8 → 3/8 → 1/2
Five doses	20–40 min	1/16 → 1/16 → 1/8 → 1/4 → 1/2

(4) Observation period after the final intake: Immediate reactions primarily occur within 1–2 h after intake. Thus, even if no symptoms occur, patients should remain in the hospital for approximately 2 h after the last intake. Explain to patients that symptoms may occur within the following 24 h. Then, instruct them about what measures to take before going home. If non-immediate reactions are predicted, prolong the observation period as needed (e.g., hospitalization for 1 day).

12.3.3. Handling OFC-induced symptoms

If symptoms are induced after administering the first dose of an OFC test, the next administration is discontinued, and necessary treatment is started based on the symptoms. Following appropriate treatment, the patient is followed up until symptoms settle down (see Evaluation of symptoms induced by foods and treatment).

12.3.4. Evaluation of the results of an OFC test and instruction for patients

(1) Evaluation of a positive result

In cases where obvious symptoms are induced within several hours after the administration in the OFC test, the OFC test result is interpreted as positive.

(2) Diagnosis of indeterminate cases

In cases where slight or subjective symptoms are induced, a food allergy diagnosis may not be confirmed using a single OFC test. In such indeterminate cases, the OFC test is repeated, or the reproducibility of symptoms is investigated by repeated concerned food administration at home.

(3) Diagnosis of negative cases

Following negative results in an OFC test, the dose administered at the challenge is repeatedly taken at home to confirm that the food can be safely consumed.

(4) Instruction for the patient after an OFC

Based on the results of the OFC test, the patient is instructed on foods that are safe to consume and on efforts required to improve the quality of life (QOL). The patient is permitted the consumption of specific food up to a ceiling of the total challenge dose in the OFC test.[1]

13. Dietary and nutritional instruction

13.1. Principle of dietary and nutritional instruction

13.1.1. Minimum avoidance of causative foods

Although eliminating causative foods is the principal treatment for food allergies, caution should be exercised in not eliminating these foods excessively. Even for foods that demonstrate confirmed positive results in an OFC, the patient is instructed to take in lower amounts or hypoallergenic forms (heated or cooked).[63–65]

13.1.2. Consideration of nutritional aspects and QOL

Food elimination may sometimes result in nutritional imbalance. Patients are instructed to supplement nutrients that become insufficient in their diets due to the elimination. Where sufficient nutritional management cannot be provided by a physician alone, instructions are provided in cooperation with nationally registered dietitians. An elimination of foods decreases the QOL of the patients as well as their families. The dietitian instructs the patient on food elimination, taking into consideration the non-allergic family members living with the patient. The patient is instructed on ways to share meals with family or reduce food preparation burden through the use of commercially available products.

13.2. Dietary instruction for safe ingestion

13.2.1. Prevention of accidental ingestion

In successfully executing food elimination from daily life, it becomes necessary for the patient's family members to take preventive measures against accidental eating. As preventive measures, two methods are commonly employed: preventing the mixing of allergens into the foods consumed by the patients and not eating allergen-mixed food.

13.2.2. Labeling of foods containing allergenic substances

With the aim of preventing health hazards caused by processed foods containing allergic substances, the labeling of allergic substances in packed processed foods was institutionalized in April 2002 by the Food Sanitation Act. Table 13 shows the items for which labeling is mandatory and items for which labeling are recommended. It should be noted that the items for which labeling is recommended are not always labeled. Instruct patients to check food labels for processed foods prior to their purchase in order to prevent accidental ingestion.[66]

13.3. Evaluation of nutritional status

To prevent iatrogenic malnourishment after initiating food elimination, the nutritional status of the patient is regularly evaluated, and appropriate instruction is to be imparted.

13.3.1. Evaluation of physical development

The simplest method of nutritional status evaluation is the evaluation of physical growth. The patient's height and body weight are measured at the initial examination and are assessed at each follow-up visit to evaluate the growth curve.

13.3.2. Evaluation of diet

A direct estimation of the nutrients consumed during a meal may also be made to assess patient's nutritional status. For example, the content of the meals consumed during 3 days are calculated to determine the nutritional value, which then enables the evaluation of the total amount consumed of various nutrients such as calcium and vitamins.

Table 13
Allergenic ingredients designated by the Consumer Affairs Agency, Government of Japan.

	Allergenic ingredients
Mandatory by ministerial ordinance	Egg, milk, wheat, shrimp/prawn, crab, buckwheat, peanut
Recommended by ministerial notification	Abalone, squid, salmon roe, orange, cashew nut, kiwi fruit, beef, walnut, sesame, salmon, mackerel, soybean, chicken, banana, pork, matsutake mushroom, peach, yam, apple, gelatin

The subjects for labeling are those that allergens of ingredients in foods are contained with concentration levels of several μg/g or several μg/mL as total protein value.

13.3.3. Confirmation of abnormal findings

The following points are to be kept in mind: the presence or absence of nutritional disorder signs should be assessed during physical examinations, and blood tests should be performed to effectively evaluate nutritional condition by monitoring hemoglobin and albumin levels, etc.

13.3.4. Nutritional guidance by dietitian

When a nutritional deficiency is suspected, a prompt and accurate nutrient evaluation is conducted in cooperation with the dietitian. Nutritional instructions are given to supplement the shortfall by alternative foods. In cases where multiple food items need to be eliminated, the dietary menu becomes limited, and can easily result in malnutrition. In fact, reports from various countries, including Japan, have noted an impairment in gain in height with the prolonged elimination of cow's milk.

13.4. Dietary instruction to aim at eating

13.4.1. Dietary instruction after evaluating the possible intake amount

In the case where an OFC test or history taking has ascertained that the patient can take a certain amount of the causative food, the amount, as well as specific examples of eatables are presented to the patient, in cooperation with a dietitian, if possible.

13.4.2. Dietary instruction after the OFC test

In the case where an OFC test has been conducted, dietary instructions and safe consumption amounts are presented based on the results.

(1) In the case of a negative OFC test result

Following a negative OFC test result, the patient repeatedly takes the causative food at an amount not exceeding the total challenge dose at home to confirm its safety. Moreover, to increase the intake amount, repeat OFC test with a higher total challenge dose is desirable.

(2) In the case of a positive OFC test result

Following a positive OFC test result, taking the severity of symptoms and the intake amount into consideration, a complete elimination or limited elimination of the causative food is advised. However, in cases where the symptom-inducing threshold level is small, even if the induced symptoms are mild, allowable amounts should be decided carefully.

(3) Intake exceeding the threshold level

In most children with food allergies, the symptom-inducing threshold level increases with time, and acquisition of tolerance may be anticipated in such cases. The daily intake amount is estimated through accurate history taking, the allergen amount that can be safely taken and its reproducibility are evaluated, eatable amounts are advised, and further challenge tests are conducted when necessary. Physicians should not advise intake of amounts exceeding these thresholds unless the patient's safety has been considered sufficiently. In severe cases where an early acquisition of resistance is not expected, instructing intake exceeding the threshold level corresponds to OIT.[1]

14. Oral immunotherapy

14.1. Current situation and problems

14.1.1. OIT in Japan

In Japan, OIT in children with allergies to hen's egg, cow's milk, wheat, and peanuts has been reported. However, currently, in Japan, OIT has widely been conducted as investigative care using the

causative food products. In a nationwide survey conducted in 2011 to assess the state of implementation of OIT in training and teaching facilities of the Japan Pediatric Society, OIT with inpatient management was conducted at 20 facilities with 511 patients, and OIT with only outpatient management was conducted at 32 facilities with 889 patients. Subsequently, the JPGFA 2012 positioned OIT and advised to not implement the therapy carelessly. However, in similar nationwide surveys conducted in 2015, OIT with inpatient management was conducted at 27 facilities with 1544 patients, and OIT with only outpatient management was conducted at 67 facilities with 6429 patients, with an increase of 5.7 times the number of OIT cases.

14.1.2. Problems

Table 14 shows problems in OIT at the current time.

14.2. Theory and mechanisms

14.2.1. Definition

OIT is defined as a treatment method for cases where the early acquisition of tolerance during the natural course cannot be anticipated. After a symptom induction threshold has been determined during an earlier OFC, causative foods are taken under a physician's instruction aiming to acquire the conditions of increased threshold or desensitization. The therapy is ultimately aimed at acquiring tolerance to the causative foods. Accordingly, OIT should be conducted after conditions set forth in Table 15 are met.

14.2.2. Mechanisms

The mechanism of action of OIT is not clarified yet in many aspects. The reactive changes observed in antigen-specific IgE, IgG, and IgG4 antibodies, mast cells, basophils, and lymphocytes are similar to changes seen during immune response to subcutaneous immunotherapy of inhalant antigens.[67–69] These responses are thus considered to be associated with the treatment effects of OIT (Table 16). During OIT, a desensitization condition (no symptom-induction with causative food) can be achieved by daily or periodically consuming the causative foods.[68,70] However, in some of the desensitized patients, if causative foods have not been taken in a while, symptoms may appear when the causative food is consumed again.[70] Thus, a challenge test is conducted after causative foods intake has been discontinued to evaluate the treatment effect. However, even in cases where symptoms are not induced in these challenge tests, as desensitization is not the same as acquiring tolerance during the natural course, it is reasonable to assume that the treatment-induced desensitization is obtained temporarily.[71]

14.3. Indication for OIT

In international guidelines, clear standards for the selection of subjects for OIT have not been described. Thus, based on the natural history of food allergies and previously reported clinical studies, the Food Allergy Committee states that the current indications of OIT in Japan are cases of (1) patients with immediate-type food allergy diagnosed by an OFC test, and (2) patients in whom early acquisition of tolerance during the natural course is not expected.

Table 14
Problems with oral immunotherapy.

Problems in treatment
(1) In most cases, although treatment effects could be seen, the evidence level is low.
(2) Induction of symptoms are unavoidable during treatment.
(3) Anaphylaxis may be induced unexpectedly.
(4) After completion of oral immunotherapy, symptoms may be induced by intake of treatment foods in some cases.
Problems associated with oral immunotherapy specifically in Japan
(1) Some facilities provide oral immunotherapy as a research-oriented care which has not been approved by an ethics committee.
(2) Safety measures during the treatment course are insufficient at some facilities.
(3) In cases where the symptom induction threshold is unknown, patients are sometimes imprudently instructed to increase intake at home by some doctors.

Table 15
Requirements for facilities where oral immunotherapy is conducted.

(1) Specialized physicians familiar with the medical care of food allergies (who routinely conduct OFC tests and are sufficiently capable of dealing with induced symptoms) are present.
(2) Physicians have experience and are knowledgeable in oral immunotherapy, the selection of subjects, mechanism of action, efficacy, associated side effects, and management of these side effects.
(3) After approval by the ethics committee, therapy is administered only with informed consent from the patient or his/her guardian.
(4) All possible emergency treatments and measures are available whenever the therapy-induced symptoms appear.

14.4. Method

International guidelines and systematic reviews do not propose a unified method of the OIT, and various treatment periods, methods of dose escalation, and foods used have been reported.[72,73] Most of studies report that after desensitization has been achieved through periods of escalation- and maintenance-dose administration, an OFC test is conducted after discontinuation of treatment for a certain period of time to evaluate treatment efficacy.

14.5. Efficacy

Based on the results obtained from previous clinical studies, we know that many patients can achieve increased symptom-induction threshold or desensitization through OIT.[67,70,74,75] Moreover, in a subset of these patients, it is apparent that desensitization can be maintained even when the continuous intake of causative food is discontinued. However, as symptoms may be induced in some cases after treatment completion, it is inferred that the desensitization obtained through OIT in severe food allergy is different from the tolerance obtained in the natural course.[76] Thus, it is necessary to carefully follow up the patients after successful completion of OIT.

14.6. Adverse reactions

Some OIT-induced symptoms are seen in many cases during the treatment. Although the most of induced symptoms were mild to intermediate, there were some reported cases in which severe symptoms were induced that required an intramuscular injection

Table 16
Immune response to oral immunotherapy.

	Factors	Immunological changes
Humoral	Specific IgE antibody	Temporal increase after treatment initiation, followed by decrease
	Specific IgG antibody	Increase several months after treatment initiation
	Specific IgG_4 antibody	Increase several months after treatment initiation
Cellular	Mast cell	Reduction in wheal diameter in a skin prick test
	Basophil	Reduction in the expression of CD63 and CD203c Reduction in the spontaneous histamine release level
	Lymphocyte	Reduction in the production of IL-2, IL-4, IL-5, IL-13 Increase in the production of IL-10 and TGF-β Increase in the number of $FOXP3^+$ T cells

of adrenaline.[67,74] Although these symptoms appear mainly during the dose-escalation period, symptoms may also be induced during the dose-maintenance period in some cases. In addition, exercise or bathing before or after causative food intake, acute infections, the pre-menstrual period, and the use of analgesics may induce treatment-related side effects. Reported side effects include non-immediate eosinophilic esophagitis and enterocolitis as well as immediate symptoms. In a systematic review by Lucendo *et al.*,[77] eosinophilic esophagitis occurred in 2.7% of patients who received OIT, and also occurred following OIT with hen's egg, cow's milk, or peanuts. The risk factors associated with non-immediate adverse effects have not yet been clarified, and it is thus difficult to predict the side effects in advance.

15. Evaluation of symptoms induced by foods and treatment

15.1. Symptom severity and treatment

It is necessary to appropriately evaluate the severity of immediate-type symptoms of food allergies in each organ in order to be able to promptly start treatment, and re-evaluate changes in symptoms over time. Early treatment of anaphylaxis with adrenaline improves hospitalization rate and mortality.

15.1.1. Grading symptom severity

Immediate-type symptoms in each organ (skin/mucosa, respiratory system, digestive system, nerves, and the circulatory system) are classified as follows: grade 1 (mild), grade 2 (moderate), and grade 3 (severe), based on the classification of severities detailed in Table 17.[3,78,79] The symptom severity grading is performed on the basis of the most severe symptoms observed for each affected organ.

15.1.2. Treatment based on symptom severity

The severity of induced symptoms in each organ is evaluated appropriately, and treatment is administered according to the severity (Fig. 5). An intramuscular injection of adrenaline is indicated in cases with grade-3 symptoms. However, in cases of grade-2 symptoms with a history of severe anaphylaxis, rapidly progressive symptoms, circulatory symptoms, or respiratory symptoms that cannot be alleviated by inhalation of bronchodilating agents, adrenaline administration should be considered.

15.1.3. Evaluation of organ specific symptoms

(1) Skin/mucosal symptoms

In the case of skin or mucosal symptoms, second-generation histamine H1 receptor antagonists with low intracerebral transitivity and low sedative action are desirably administered orally as treatment.

(2) Respiratory symptoms

In the case of life-threatening critical respiratory symptoms, caution should be paid in detecting and diagnosing them. The upper respiratory tract symptoms include tightness in the pharyngolarynx, barking cough, and hoarseness; pharyngeal edema is suspected with these findings, and asphyxia may occur rapidly in some cases. In cases where this sign is seen, it is regarded as a grade-3 symptom, and intramuscular injection of adrenaline, administration of oxygen, and airway stabilization, as needed, are administered as soon as possible. In cases of sporadic coughing as a lower respiratory tract associated symptom, patient should be followed-up carefully, and the patient with a history of critical immediate respiratory symptoms or asthma should be treated with inhalation of β2 stimulants at an early stage. Grade-2 symptoms such as mild wheezing and intermittent coughing should be promptly treated with inhalation of β2 stimulants, and the patient's respiratory rate and blood oxygenation (SpO_2) should be checked, and oxygen should be administered if necessary. If symptoms are not alleviated by inhalation of β2 stimulants, adrenaline should be injected intramuscularly.

(3) Digestive symptoms

Although nausea and vomiting may occur immediately after causative food intake, the symptoms may also occur several hours later in some cases. Mild abdominal pain, a single vomiting/

Table 17
Classification of severities according to clinical symptoms.

		Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)
Skin/mucosal symptoms	Erythema, urticaria, and wheal	Localized	Generalized	←
	Pruritus	Mild itch (self-controlled)	Severe pruritus (out of self-control)	←
	Swollen lip or eyelid	Localized	Swollen whole face	←
Gastrointestinal symptoms	Discomfort of the oral cavity or throat	Discomfort, itch of the oral cavity or throat	Throat pain	←
	Abdominal pain	Mild abdominal pain	Severe abdominal pain (Self-controlled)	Continuous severe abdominal pain (out of self-control)
	Vomiting, diarrhea	Nausea, single vomiting, diarrhea	Recurrent vomiting, diarrhea	Continuous vomiting, loss of bowel control
Respiratory symptoms	Cough, rhinorrhea, nasal congestion, sneezing	Intermittent cough, rhinorrhea, nasal congestion, sneezing	Repetitive cough	Persistent severe cough, "barking" cough
	Wheezing, dyspnea	–	Wheezing detectable via auscultation, mild feeling of smothering	Audible wheezing, dyspnea, cyanosis, asphyxia, SpO2 ≤92%, throat tightness, hoarseness, dysphagia
Cardiovascular symptoms	Pulse, blood pressure	–	Tachycardia (increase >15 beats/min), mild hypotension[†], pale face	Dysrhythmia, hypotension[‡], severe bradycardia, cardiac arrest
Neurological symptoms	Consciousness status	Change in activity level, tiredness	Somnolence, mild headache, fear	Fatigue, anxiety, incontinence, loss of consciousness

[†] Mild hypotension: <80 mmHg in age of less than one, <[80 + (2× age)] mmHg in age of 1–10, <100 mmHg in age of 11-adult.
[‡] Hypotension: <70 mmHg in age of less than 1, <[70 + (2× age)] mmHg in age of 1–10, <90 mmHg in age of 11-adult.

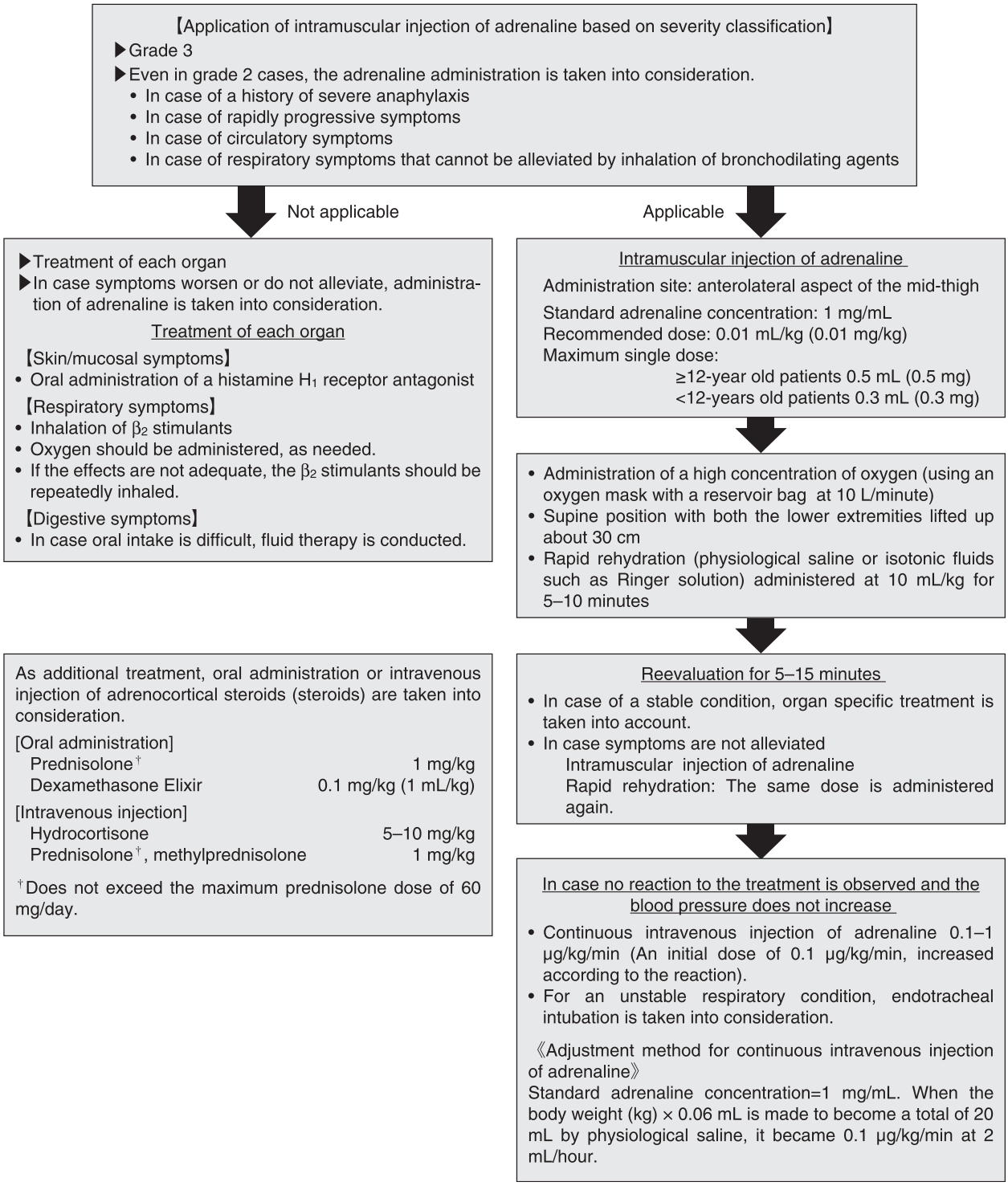

Fig. 5. Treatment based on the severity.

diarrhea constitute grade 1 symptoms that may be alleviated without treatment. However, for grade-2 symptoms, control with fasting and rehydration is taken into consideration. For grade-3 symptoms, adrenaline should be injected intramuscularly.

15.2. Management of anaphylaxis in a health care setting

Following a diagnosis of anaphylaxis, the affected patient should be treated immediately, according to the procedure outlined in Figure 5. The procedures from "Confirmation of vital signs" (15.2.1. described as below) to "Body position of the anaphylaxis patients" (15.2.4.) are conducted simultaneously.[3]

15.2.1. Confirmation of vital signs

Administration of oxygen, wearing a SpO_2 monitor and an electrocardiographic monitor is directed, and based on the ABCDE approach (Airway, Breathing, Circulation, Disability, Exposure) of Pediatric Advanced Life Support (PALS), the presence or absence of physiologic abnormalities and abnormalities in vital signs are

assessed and severity of respiratory and circulatory symptoms is evaluated.

15.2.2. Ensuring staffs and treatment by a team

In the case of respiratory failure or shock, as endotracheal intubation and securing the infusion route must be conducted concomitantly, the patient should be treated by a team of medical staff. To the extent possible, specialized resuscitation and emergency medical teams should be ensured.

15.2.3. Intramuscular injection of adrenaline

Adrenaline is the first-line treatment option for anaphylaxis.[3,78,80] Its administration at the early stage is known to decrease anaphylaxis-related mortality and hospitalization rates.[81]

Thus, once anaphylaxis is diagnosed, adrenaline administration is conducted as soon as possible.[82] The administration site is the anterolateral aspect of the mid-thigh. Compared to a subcutaneous injection, intramuscular injection results in a rapid increase in the blood concentration, allowing for a rapid effect.[83] The recommended dose is 0.01 mL/kg (0.01 mg/kg), and the maximum single dose is 0.5 mL (0.5 mg) in ≥12-year-old patients and 0.3 mL (0.3 mg) in <12-year-old patients. If symptoms are not alleviated by multiple intramuscular adrenaline injections (~three times), a continuous intravenous injection of adrenaline should be considered.

15.2.4. Body position of the anaphylaxis patients

At the onset of anaphylaxis, as the blood pressure may change rapidly due to postural changes, as a rule, the patient is placed in a dorsal position with the lower extremities lifted up to about 30 cm. If an increased respiratory rate is present, the patient's upper body may be lifted slightly. If the patient has vomiting, his/her face should be turned sideways.

15.2.5. Administration of oxygen

Respiratory and circulatory symptoms, as well the impaired consciousness should be treated with oxygen administration using an oxygen mask with a reservoir bag. The oxygen is started at a high flow volume (10 L/min) to meet the patient's immediate oxygen demand.

15.2.6. Securing the intravenous infusion route and rapid rehydration

At the onset of anaphylaxis, maintenance of an effective circulating blood volume is difficult due to vascular dilation and hyperpermeability, and can easily result in a hypovolemic shock. A decrease in the circulating blood volume would decrease the effect of adrenaline. Therefore, an intravenous infusion route is secured, and rapid rehydration is conducted with 10 mL/kg of Ringer's solution or physiological saline for 5–10 min.

15.2.7. Cessation of respiration

If the patient has no pulse or if his/her respiration ceases, cardiopulmonary resuscitation should be started in accordance with the Basic Life Support (BLS) protocol.

15.2.8. Measurement of vital signs: reevaluation

As an anaphylaxis patient's condition changes over time, it is necessary to evaluate vital signs frequently and regularly.

15.3. Contraindication of adrenaline

The package inserts included with adrenaline injections (Bosmin® injection, adrenaline 0.1% injection syringe [Thermo®], EpiPen®) in Japan state that its concomitant use with antipsychotic drugs such as butyrophenones and phenothiazines, or with α blockers, may cause hypotension due to the reversal of the adrenaline vasopressor action. These combinations are thus contraindicated.

The incidence of pediatric food allergies and developmental disorders has increased in recent years. In cases of anaphylactic reactions in patients being treated with α receptor-blocking antipsychotic drugs (such as risperidone), the administration of adrenaline is contraindicated as per the drug's package insert, as mentioned previously. The Committee for Food Allergy of the Japanese Society of Pediatric Allergy and Clinical Immunology directed the relevant pharmaceutical companies to provide background data regarding this contraindication. The following was concluded after discussion among the committee. Furthermore, the committee contacted several medical societies relevant to this issue and asked their views.

"Physicians must recognize that a combination of α receptor-blocking antipsychotic drugs and adrenaline are contraindicated as per the package insert. Adrenaline is thus contraindicated in food allergy patients with a high risk of anaphylaxis and who are treated with antipsychotic drugs, which are the contraindication for the combined use with adrenaline, in close communication with relevant medical organizations, care should be taken to avoid this contraindicated situation as much as possible by using alternative drugs. However, if anaphylaxis develops in a patient who treated with the antipsychotic drugs mentioned above, the use of adrenaline is considered allowable based on the physician's discretion. In case that adrenaline is administrated, vital signs (cardiac rate, blood pressure, respiratory rate, body temperature, etc.) and SpO_2 should be monitored to control anaphylaxis. If adrenaline administration does not result in an increase in blood pressure, a resuscitation team should provide an alternative treatment using noradrenaline or dopamine."[1]

16. Measures at nurseries, kindergartens, and schools[11]

The "Certificate for school life management" is now being used at kindergartens and schools, and the "Certificate for nursery life management" is being used at nurseries. On the basis of the "Research Report on Allergic diseases" published in 2007, the Ministry of Education, Culture, Sports, Science and Technology stated that "Measures need to be taken based on the recognition that allergic diseases are not rare but many children with various allergic diseases are enrolled in schools." In light of the above, the "Certificate for school life management (for allergic diseases)" (hereinafter referred to as the "Certificate") was prepared for schools to advance activities for school children with allergic diseases, and the "Guideline on Measures for Allergic Diseases at Schools" was prepared to enable kindergartens and schools to cope with food allergies and anaphylaxis.

In a manner pursuant to the Certificate for school life management, the "Guideline on Measures against Allergy at Nursery" and the "Certificate for nursery life management" were published in March 2011 by the Ministry of Health, Labour and Welfare. As a result, kindergartens and schools share a similar philosophy and methods to deal with allergic symptoms and anaphylaxis.

It is desirable for physicians involved in the medical care of food-allergic patients to be able to sufficiently recognize the ways for lunch boxes provided at schools, preschools, and nurseries in a community and be able to advise individual patients. At schools and nurseries, it is mandatory to provide lunch boxes to all children with food allergies. As the ways providing lunch boxes in schools differ from the necessary minimum elimination conducted in the home setting, it places the highest priority in ensuring food safety, the alternative of complete elimination or release of food elimination is recommended.

Committee for Japanese Pediatric Guideline for Food Allergy, Japanese Society of Pediatric Allergy and Clinical Immunology (JSPACI)

Members: Motohiro Ebisawa, Chair of the Committee; Komei Ito, Vice-Chiar; Takao Fujisawa, President of JSPACI; Yukoh Aihara (Aihara Allergy & Pediatric Clinic, Kanagawa); Setsuko Ito (Department of Food Science and Nutrition, Doshisha Women's College of Liberal Arts, Kyoto); Takanori Imai (Department of Pediatrics, Showa University School of Medicine, Tokyo); Yusei Ohshima (Department of Pediatrics, Faculty of Medical Sciences, University of Fukui, Fukui); Yukihiro Ohya (Division of Allergy, Department of Medical Subspecialties, National Center for Child Health and Development, Tokyo); Hideo Kaneko (Department of Clinical Research, National Hospital Organization Nagara Medical Center, Gifu); Yasuto Kondo (Department of Pediatrics, Fujita Health University, The Second Teaching Hospital, Nagoya); Naoki Shimojo (Department of Pediatrics, Graduate School of Medicine, Chiba University, Chiba); Mizuho Nagao (Institute for Clinical Research, Mie National Hospital, Mie).

Collaborators: Yasunori Ito (Department of Pediatrics, Faculty of Medicine, University of Toyama, Toyama), Yuzaburo Inoue (Department of Pediatrics, Eastern Chiba Medical Center, Chiba), Ikuo Okafuji (Department of Pediatrics, Kobe City Medical Center General Hospital, Kobe), Sakura Sato (Department of Allergy, Clinical Research Center for Allergology and Rheumatology, Sagamihara National Hospital, Kanagawa), Yoichi Nakajima (Department of Pediatrics, Fujita Health University, The Second Teaching Hospital), Hajime Nishimoto (Department of Pediatrics, Saitama Citizens Medical Center, Saitama), Tatsuki Fukuie (Division of Allergy, Department of Medical Subspecialties, National Center for Child Health and Development), Masaki Futamura (Division of Pediatrics, Nagoya Medical Center, Nagoya), Tetsuharu Manabe (Department of Pediatrics, Sagamihara National Hospital), Noriyuki Yanagida (Department of Pediatrics, Sagamihara National Hospital), Yoshiyuki Yamada (Division of Allergy and Immunology, Gunma Children's Medical Center, Gunma).

Adviser: Atsuo Urisu (Urisu Clinic/Fujita Health University, Aichi, Japan).

Conflict of interest

ME received honorarium from DBV Technologies and Pfizer. The rest of the authors have no conflict of interest.

References

1. Ebisawa M, Ito K, Fujisawa T, Food Allergy Committee, Japanese Society of Pediatric Allergy and Clinical Immunology. *[Japanese Pediatric Guideline for Food Allergy 2016]*. Tokyo: Kyowa Kikaku; 2016 (in Japanese).
2. Urisu A, Ebisawa M, Ito K, Aihara Y, Ito S, Mayumi M, et al. Japanese guideline for food allergy 2014. *Allergol Int* 2014;**63**:399–419.
3. Simons FE, Ardusso LR, Bilò MB, El-Gamal YM, Ledford DK, Ring J, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J* 2011;**4**:13–37.
4. Ebisawa M. Management of food allergy in Japan "food allergy management guideline 2008 (revision from 2005)" and "guidelines for the treatment of allergic diseases in schools". *Allergol Int* 2009;**58**:475–83.
5. Miyazawa T, Itahashi K, Imai T. Management of neonatal cow's milk allergy in high-risk neonates. *Pediatr Int* 2009;**51**:544–7.
6. Nomura I, Morita H, Hosokawa S, Hoshina H, Fukuie T, Watanabe M, et al. Four distinct subtypes of non-IgE-mediated gastrointestinal food allergies in neonates and infants, distinguished by their initial symptoms. *J Allergy Clin Immunol* 2011;**127**:685–8.e1-8.
7. Kimura M, Shimomura M, Morishita H, Meguro T, Seto S. Serum C-reactive protein in food protein-induced enterocolitis syndrome versus food protein-induced proctocolitis in Japan. *Pediatr Int* 2016;**58**:836–41.
8. Kimura M, Ito Y, Tokunaga F, Meguro T, Shimomura M, Morishita H, et al. Increased C-reactive protein and fever in Japanese infants with food protein-induced enterocolitis syndrome. *Pediatr Int* 2016;**58**:826–30.
9. Aihara Y. [Food-dependent exercise-induced anaphylaxis]. *Arerugi* 2007;**56**:451–6 (in Japanese).
10. Ortolani C, Ispano M, Pastorello EA, Ansaloni R, Magri GC. Comparison of results of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome. *J Allergy Clin Immunol* 1989;**83**:683–90.
11. Wagner S, Breiteneder H. The latex-fruit syndrome. *Biochem Soc Trans* 2002;**30**:935–40.
12. Kinoshita Y, Furuta K, Ishimaura N, Ishihara S, Sato S, Maruyama R, et al. Clinical characteristics of Japanese patients with eosinophilic esophagitis and eosinophilic gastroenteritis. *J Gastroenterol* 2013;**48**:333–9.
13. Ebisawa M, Sugizaki C. Prevalence of pediatric allergic diseases in the first 5 years of life. *J Allergy Clin Immunol* 2008;**121**:S237.
14. Imai T, Sugizaki C, Ebisawa M. [A report on 2011 nationwide survey of immediate type food allergies in Japan (Supported by a grant from "Consumer Affairs Agency, Government of Japan")]. *Arerugi* 2016;**65**:942–6 (in Japanese).
15. Ohtani K, Sato S, Syukuya A, Asaumi T, Ogura K, Koike Y, et al. Natural history of immediate-type hen's egg allergy in Japanese children. *Allergol Int* 2016;**65**:153–7.
16. Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2007;**120**:1172–7.
17. Wood RA, Sicherer SH, Vickery BP, Jones SM, Liu AH, Fleischer DM, et al. The natural history of milk allergy in an observational cohort. *J Allergy Clin Immunol* 2013;**131**:805–12.
18. Peters RL, Allen KJ, Dharmage SC, Koplin JJ, Dang T, Tilbrook KP, et al. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: a population-based assessment. *J Allergy Clin Immunol* 2015;**135**:1257–66.e1-2.
19. Sicherer SH, Wood RA, Vickery BP, Jones SM, Liu AH, Fleischer DM, et al. The natural history of egg allergy in an observational cohort. *J Allergy Clin Immunol* 2014;**133**:492–9.
20. Elizur A, Rajuan N, Goldberg MR, Leshno M, Cohen A, Katz Y. Natural course and risk factors for persistence of IgE-mediated cow's milk allergy. *J Pediatr* 2012;**161**:482–7.e1.
21. Brown SJ, Asai Y, Cordell HJ, Campbell LE, Zhao Y, Liao H, et al. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. *J Allergy Clin Immunol* 2011;**127**:661–7.
22. Brough HA, Simpson A, Makinson K, Hankinson J, Brown S, Douiri A, et al. Peanut allergy: effect of environmental peanut exposure in children with filaggrin loss-of-function mutations. *J Allergy Clin Immunol* 2014;**134**:867–75.e1.
23. Tsakok T, Marrs T, Mohsin M, Baron S, du Toit G, Till S, et al. Does atopic dermatitis cause food allergy? A systematic review. *J Allergy Clin Immunol* 2016;**137**:1071–8.
24. Flohr C, Perkin M, Logan K, Marrs T, Radulovic S, Campbell LE, et al. Atopic dermatitis and disease severity are the main risk factors for food sensitization in exclusively breastfed infants. *J Invest Dermatol* 2014;**134**:345–50.
25. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;**372**:803–13.
26. Du Toit G, Sayre PH, Roberts G, Sever ML, Lawson K, Bahnson HT, et al. Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med* 2016;**374**:1435–43.
27. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med* 2016;**374**:1733–43.
28. Lack G, Fox D, Northstone K, Golding J, Avon Longitudinal Study of Parents and Children Study Team. Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 2003;**348**:977–85.
29. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Evid Based Child Health* 2014;**9**:447–83.
30. Muraro A, Dreborg S, Halken S, Høst A, Niggemann B, Aalberse R, et al. Dietary prevention of allergic diseases in infants and small children. Part III: critical review of published peer-reviewed observational and interventional studies and final recommendations. *Pediatr Allergy Immunol* 2004;**15**:291–307.
31. Brew BK, Kull I, Garden F, Almqvist C, Bergström A, Lind T, et al. Breastfeeding, asthma, and allergy: a tale of two cities. *Pediatr Allergy Immunol* 2012;**23**:75–82.
32. Paton J, Kljakovic M, Ciszek K, Ding P. Infant feeding practices and nut allergy over time in Australian school entrant children. *Int J Pediatr* 2012;**2012**:675724.
33. Katz Y, Rajuan N, Goldberg MR, Eisenberg E, Heyman E, Cohen A, et al. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. *J Allergy Clin Immunol* 2010;**126**:77–82.e1.
34. Boyle RJ, Ierodiakonou D, Khan T, Chivinge J, Robinson Z, Geoghegan N, et al. Hydrolysed formula and risk of allergic or autoimmune disease: systematic review and meta-analysis. *BMJ* 2016;**352**:i974.
35. Vandenplas Y, Alarcon P, Fleischer D, Hernell O, Kolacek S, Laignelet H, et al. Should partial hydrolysates be used as starter infant formula? A working group consensus. *J Pediatr Gastroenterol Nutr* 2016;**62**:22–35.
36. Palmer DJ, Metcalfe J, Makrides M, Gold MS, Quinn P, West CE, et al. Early regular egg exposure in infants with eczema: a randomized controlled trial. *J Allergy Clin Immunol* 2013;**132**:387–92.e1.
37. Natsume O, Kabashima S, Nakazato J, Yamamoto-Hanada K, Narita M, Kondo M, et al. Two-step egg introduction for preventing egg allergy in high-risk infants with eczema (PETIT study): a double-blind, placebo-controlled, parallel-group randomised clinical trial. *Lancet* 2017;**389**:276–86.
38. Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol* 2014;**134**:824–30.e6.

39. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, Valenta R, Hilger C, Hofmaier S, et al. EAACI molecular allergology user's guide. *Pediatr Allergy Immunol* 2016;**27**(Suppl 23):1–250.
40. Jenkins JA, Griffiths-Jones S, Shewry PR, Breiteneder H, Mills EN. Structural relatedness of plant food allergens with specific reference to cross-reactive allergens: an in silico analysis. *J Allergy Clin Immunol* 2005;**115**:163–70.
41. Jenkins JA, Breiteneder H, Mills EN. Evolutionary distance from human homologs reflects allergenicity of animal food proteins. *J Allergy Clin Immunol* 2007;**120**:1399–405.
42. Takei M, Yanagida N, Asaumi T, Sato S, Ebisawa M. [Oral lactose challenge tests for cow's milk allergy]. *[Jpn J Pediatr Allergy Clin Immunol]* 2015;**29**:649–54 (in Japanese).
43. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;**107**:891–6.
44. Haneda Y, Kando N, Yasui M, Kobayashi T, Maeda T, Hino A, et al. Ovomucoids IgE is a better marker than egg white-specific IgE to diagnose boiled egg allergy. *J Allergy Clin Immunol* 2012;**129**:1681–2.
45. Sato S, Ogura K, Takahashi K, Sato Y, Yanagida N, Ebisawa M. Usefulness of antigen-specific IgE probability curves derived from the 3gAllergy assay in diagnosing egg, cow's milk, and wheat allergies. *Allergol Int* 2017;**66**:296–301.
46. Komata T, Soderstrom L, Borres MP, Tachimoto H, Ebisawa M. The predictive relationship of food-specific serum IgE concentrations to challenge outcomes for egg and milk varies by patient age. *J Allergy Clin Immunol* 2007;**119**:1272–4.
47. Furuya K, Nagao M, Sato Y, Ito S, Fujisawa T, IPAD3g investigators. Predictive values of egg-specific IgE by two commonly used assay systems for the diagnosis of egg allergy in young children: a prospective multicenter study. *Allergy* 2016;**71**:1435–43.
48. Ebisawa M, Shibata R, Sato S, Borres MP, Ito K. Clinical utility of IgE antibodies to omega-5 gliadin in the diagnosis of wheat allergy: a pediatric multicenter challenge study. *Int Arch Allergy Immunol* 2012;**158**:71–6.
49. Ebisawa M, Moverare R, Sato S, Borres MP, Ito K. The predictive relationship between peanut- and Ara h 2-specific serum IgE concentrations and peanut allergy. *J Allergy Clin Immunol Pract* 2015;**3**:131–2.e1.
50. Maruyama N, Sato S, Yanagida N, Cabanos C, Ito K, Borres MP, et al. Clinical utility of recombinant allergen components in diagnosing buckwheat allergy. *J Allergy Clin Immunol Pract* 2016;**4**:322–3.e3.
51. Maruyama N, Nakagawa T, Ito K, Cabanos C, Borres MP, Movérare R, et al. Measurement of specific IgE antibodies to Ses i 1 improves the diagnosis of sesame allergy. *Clin Exp Allergy* 2016;**46**:163–71.
52. Ogata M, Shukuya A, Sugizaki C, Ikematsu K, Imai T, Tachimoto H, et al. [Usefulness of skin prick test using bifurcated needle for the diagnosis of food allergy among infantile atopic dermatitis – second report. In the case of cow's milk allergy]. *Arerugi* 2010;**59**:839–46 (in Japanese).
53. Ogata M, Sukuya A, Sugizaki C, Ikematsu K, Imai T, Tachimoto H, et al. [Usefulness of skin prick test using bifurcated needle for the diagnosis of food allergy in infantile atopic dermatitis – first report. Case of egg allergy]. *Arerugi* 2008;**57**:843–52 (in Japanese).
54. Sato S, Tachimoto H, Shukuya A, Ogata M, Komata T, Imai T, et al. Utility of the peripheral blood basophil histamine release test in the diagnosis of hen's egg, cow's milk, and wheat allergy in children. *Int Arch Allergy Immunol* 2011;**155**(Suppl 1):96–103.
55. Sato S, Ito K, Urisu A, Kando N, Nakagawa T, Tsuge I, et al. [Utility of the allerport(R) hrt in the diagnosis of hen's egg allergy: a pediatric multicenter challenge study]. *Arerugi* 2015;**64**:136–48 (in Japanese).
56. Nagao M, Hiraguchi Y, Hosoki K, Tokuda R, Usui T, Masuda S, et al. Allergen-induced basophil CD203c expression as a biomarker for rush immunotherapy in patients with Japanese cedar pollinosis. *Int Arch Allergy Immunol* 2008;**146**(Suppl 1):47–53.
57. Sato S, Tachimoto H, Shukuya A, Kurosaka N, Yanagida N, Utsunomiya T, et al. Basophil activation marker CD203c is useful in the diagnosis of hen's egg and cow's milk allergies in children. *Int Arch Allergy Immunol* 2010;**152**(Suppl 1): 54–61.
58. Bock SA. AAAAI support of the EAACI position paper on IgG4. *J Allergy Clin Immunol* 2010;**125**:1410.
59. Stapel SO, Asero R, Ballmer-Weber BK, Knol EF, Strobel S, Vieths S, et al. Testing for IgG4 against foods is not recommended as a diagnostic tool: EAACI Task Force Report. *Allergy* 2008;**63**:793–6.
60. Yanagida N, Okada Y, Sato S, Ebisawa M. New approach for food allergy management using low-dose oral food challenges and low-dose oral immunotherapies. *Allergol Int* 2016;**65**:135–40.
61. Ito K, Futamura M, Takaoka Y, Morishita M, Nakanishi K, Sakamoto T. [Open food challenge with milk, egg white and wheat]. *Arerugi* 2008;**57**:1043–52 (in Japanese).
62. Yanagida N, Imai T, Sato S, Ebisawa M. Do longer intervals between challenges reduce the risk of adverse reactions in oral wheat challenges? *PLoS One* 2015;**10**:e0143717.
63. Okada Y, Yanagida N, Sato S, Ebisawa M. Better management of cow's milk allergy using a very low dose food challenge test: a retrospective study. *Allergol Int* 2015;**64**:272–6.
64. Okada Y, Yanagida N, Sato S, Ebisawa M. Better management of wheat allergy using a very low-dose food challenge: a retrospective study. *Allergol Int* 2016;**65**:82–7.
65. Okada Y, Yanagida N, Sato S, Ebisawa M. Heated egg yolk challenge predicts the natural course of hen's egg allergy: a retrospective study. *World Allergy Organ J* 2016;**9**:31.
66. Akiyama H, Imai T, Ebisawa M. *Japan Food Allergen Labeling Regulation—History and Evaluation. Advances in Food and Nutrition Research*, *Vol. 62*. Amsterdam: Elsevier; 2001. p. 140–72.
67. Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *J Allergy Clin Immunol* 2008;**121**:343–7.
68. Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. *J Allergy Clin Immunol* 2009;**124**:292–300.e1-97.
69. Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, Gorelik M, Schroeder J, Hamilton RG, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. *J Allergy Clin Immunol* 2015;**135**:1275–82.e1-6.
70. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, et al. Oral immunotherapy for treatment of egg allergy in children. *N Engl J Med* 2012;**367**:233–43.
71. Rolinck-Werninghaus C, Staden U, Mehl A, Hamelmann E, Beyer K, Niggemann B. Specific oral tolerance induction with food in children: transient or persistent effect on food allergy? *Allergy* 2005;**60**:1320–2.
72. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. *J Allergy Clin Immunol* 2010;**126**:1105–18.
73. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, et al. ICON: food allergy. *J Allergy Clin Immunol* 2012;**129**:906–20.
74. Sato S, Utsunomiya T, Imai T, Yanagida N, Asaumi T, Ogura K, et al. Wheat oral immunotherapy for wheat-induced anaphylaxis. *J Allergy Clin Immunol* 2015;**136**:1131–3.e7.
75. Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. *Lancet* 2014;**383**: 1297–304.
76. Gorelik M, Narisety SD, Guerrerio AL, Chichester KL, Keet CA, Bieneman AP, et al. Suppression of the immunologic response to peanut during immunotherapy is often transient. *J Allergy Clin Immunol* 2015;**135**:1283–92.
77. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2014;**113**:624–9.
78. Ebisawa M. [JSA anaphylaxis guideline – importance of basic management and prevention]. *Arerugi* 2015;**64**:24–31 (in Japanese).
79. Yanagida N, Shukuya A, Sato S, Nagakura K, Emura S, Asaumi T, et al. [Evaluation of a portable manual for parents of children with food allergies that assesses the severity of allergic symptoms]. *[Jpn J Pediatr Allergy Clin Immunol]* 2014;**28**:201–10 (in Japanese).
80. Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernández Rivas M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy* 2014;**69**:1026–45.
81. Fleming JT, Clark S, Camargo Jr CA, Rudders SA. Early treatment of food-induced anaphylaxis with epinephrine is associated with a lower risk of hospitalization. *J Allergy Clin Immunol Pract* 2015;**3**:57–62.
82. Soar J, Pumphrey R, Cant A, Clarke S, Corbett A, Dawson P, et al. Emergency treatment of anaphylactic reactions–guidelines for healthcare providers. *Resuscitation* 2008;**77**:157–69.
83. Simons FE, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol* 1998;**101**:33–7.