

Japanese Guideline for Food Allergy 2014

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ABSTRACT

A food allergy is defined as “a phenomenon in which adverse reactions are caused through antigen-specific immunological mechanisms after exposure to given food.”

Various symptoms of food allergy occur in many organs. Food allergies are classified roughly into 4 clinical types: (1) neonatal and infantile gastrointestinal allergy, (2) infantile atopic dermatitis associated with food allergy, (3) immediate-type food allergy (urticaria, anaphylaxis, etc.), and (4) food dependent exercise-induced anaphylaxis and oral allergy syndrome (i.e., specific forms of immediate food allergy).

The therapy for food allergies includes treatment of and prophylactic measures against hypersensitivity such as anaphylaxis. A fundamental prophylactic measure is the elimination diet. However, elimination diets should be used only if necessary because of the patient-related burden. For this purpose, it is very important that causative foods be accurately identified. There are a number of means available to identify causative foods, including the history taking, a skin prick test, detection of antigen-specific IgE antibodies in the blood, the basophil histamine release test, the elimination diet test, and the oral challenge test, etc. Of these, the oral challenge test is the most reliable. However, it should be conducted under the supervision of experienced physicians because it may cause adverse reactions, such as anaphylaxis.

KEY WORDS

elimination diet, food allergy, IgE-mediated type, non-IgE-mediated type, oral food challenge

1. Definition of a Food Allergy

The Japanese Pediatric Guideline for Food Allergy 2012 (JPGFA2012),¹ published by the Japanese Society of Pediatric Allergy and Clinical Immunology (JSPACI) in 2011, provided the following definition: “a phenomenon in which adverse reactions are caused through antigen-specific immunological mechanisms after exposure to given food” (Fig. 1).

2. Clinical Symptoms and Related Diseases of Food Allergies

2.1. Symptoms of Food Allergies

Food allergy symptoms occur in many organs (Table

1). They are classified into immediate and non-immediate allergic reactions. The former refers to allergic reactions that develop within 2 hours after food intake, and the latter refers to those that develop more than 2 hours after food intake. However, this differentiation is only based on the elapsed time to symptom onset and does not necessarily describe a difference in mechanisms.

Of the symptoms, anaphylaxis is defined as a “severe hypersensitivity reaction that may cause a life-threatening risk with systemic symptoms induced in several organs.” Partly because of the fatal nature, prompt diagnosis and treatment are required.

While the grade/class² proposed by Sampson is

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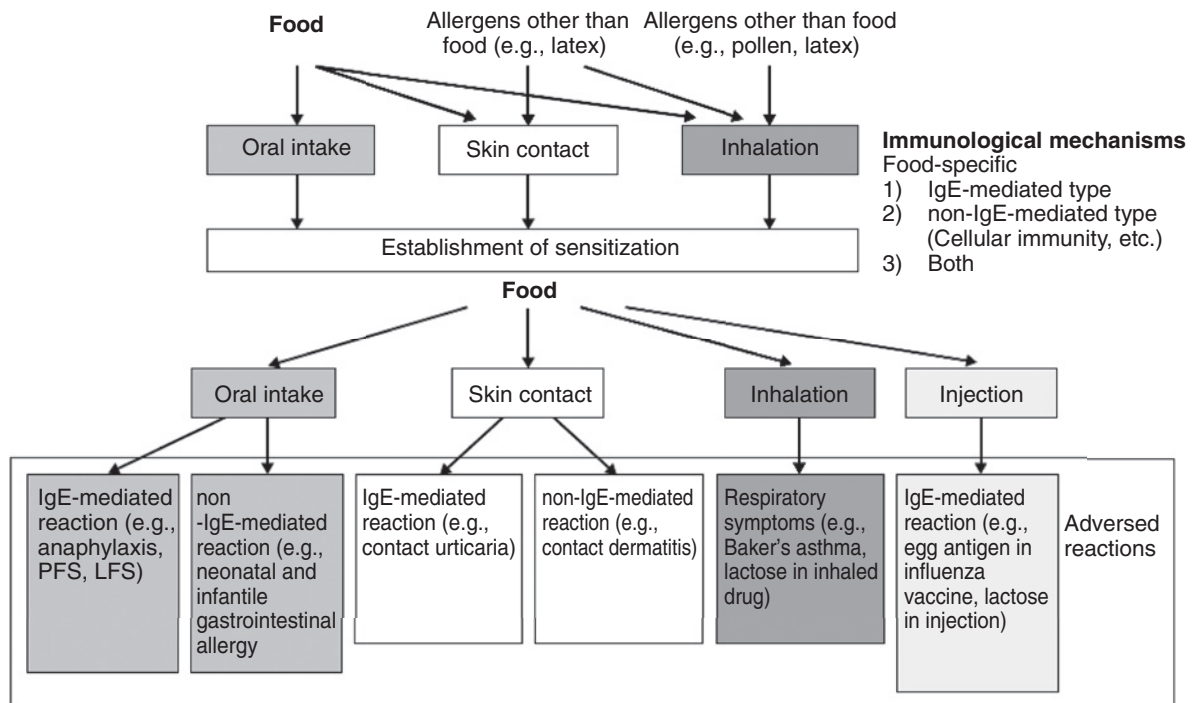


Fig. 1 Definition of food allergy. PFS, pollen food allergy syndrome; LFS, latex-fruit syndrome.

Table 1 Symptoms of food allergies

Organ	Symptoms
Skin	Erythema, urticaria, angioedema, pruritus, burning sensation, eczema
Mucous membrane	Eye symptoms: Conjunctival hyperemia and edema, pruritus, lacrimation, blepharedema Nasal symptoms: Rhinorrhea, nasal congestion, sneezing Oral symptoms: Discomfort/swelling of the oral cavity, lips, or 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
Circulatory organs	Decreased blood pressure, tachycardia, bradycardia, arrhythmia, coldness of limbs, pallor (peripheral circulatory failure)
Systemic	Anaphylaxis and anaphylactic shock

used as an indicator for the severity of anaphylactic symptoms, this guideline presents a version that has been partially revised (Table 2).

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 (Table 3).^{3,4}

Causative agents of anaphylaxis, besides foods, include medications, blood transfusions, insects, and latex. However, a food allergy is the most common cause. In Europe and United States, the causative foods of anaphylaxis include peanuts, nuts and seeds, seafood, eggs, and cow's milk. In Japan, the major

causative foods of anaphylaxis include eggs, cow's milk, wheat, crustacean, buckwheat, and peanuts.

Food-induced anaphylaxis is an immediate reaction associated with specific IgE antibodies. Symptoms typically occur within several minutes after intake. However, they occasionally occur more than 30 min later. Symptoms may occur either in a monophasic or biphasic pattern. Severe anaphylaxis symptoms accompanied by decreased blood pressure and impaired consciousness are called anaphylactic shock. Anaphylactic shock likely occurs in patients with food allergy complicated by asthma.

Decreased blood pressure is caused by a peripheral vasodilation and a decrease in the circulating

Table 2 Classification of anaphylaxis²

Grade	Skin	Digestive organ	Respiratory organ	Circulatory organ	Nerve
1	<Localized> • pruritus, erythema, urticaria, angioedema	• Oral itch and/or discomfort • Swelling of lips	• Pharyngeal pruritus and/or discomfort	-	-
2	<Systemic> • pruritus, erythema, urticaria, angioedema	• Nausea • 1-2 occurrences of vomiting and/or diarrhea • Transient abdominal pain	• Slight nasal congestion and/or rhinorrhea • Sneezing once or twice • Sporadic coughing	-	• Decrease in activity level
3	Above symptoms	• Repeated vomiting, and/or diarrhea • Persistent abdominal pain	• Marked nasal congestion and/or rhinorrhea • Repeated sneezing • Persistent cough • Laryngeal pruritus	• Tachycardia (increased ≥ 15 beats/minute)	• Sense of unease
4	Above symptoms	Above symptoms	• Laryngeal tightness • Hoarseness • Barking cough • Dysphagia • Wheezing • Dyspnea • Cyanosis	• Arrhythmia • Decreased blood pressure	• Unrest • Fear of death
5	Above symptoms	Above symptoms	• Respiratory arrest	• Severe bradycardia • Marked decrease in blood pressure • Cardiac arrest	• Unconsciousness

Not all symptoms are essential. The symptom grade will be determined according to the organ symptoms of the highest grade. Grade 1 will not be regarded as anaphylaxis.

Table 3 Diagnostic criteria for anaphylaxis⁴

- Acute onset of an illness (over minutes to several hours) involving skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
 - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
 - Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia (collapse), syncope, incontinence)
- Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
 - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
 - Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope, incontinence)
 - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
- Reduced BP after exposure to a known allergen for that patient (minutes to several hours). Reduced BP is defined:
 - In adults, as a systolic BP of less than 90 mm Hg or greater than 30 percent decrease from that person's baseline.
 - In infants and children, as a low systolic BP (age-specific) or greater than 30 percent decrease in systolic BP. Low systolic BP is defined as:
 - Less than 70 mm Hg for 1 month to 1 year of age
 - Less than (70 mm Hg plus twice the age) for 1 to 10 years of age
 - Less than 90 mm Hg for 11 to 17 years of age

Note: In infants and young children, hypotension may be a late manifestation of hypovolemic shock. Tachycardia, in the absence of hypotension, may also indicate shock.

Symptoms corresponding to any of the above three conditions indicate highly possibly anaphylaxis.

Table 4 Clinical type of food allergy⁵

Clinical type		Age of onset	Common causative foods	Acquisition of tolerance	Possibility of anaphylactic shock	Mechanism of food allergy
Neonatal and infantile gastrointestinal allergy		Neonatal period Infancy	Cow's milk (powdered milk for infants)	Mostly remittable	(±)	Mainly non IgE-mediated type
Infantile atopic dermatitis associated with food allergy [†]		Infancy	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: Chicken eggs, cow's milk, wheat, buckwheat, fish, peanuts, etc. School-aged children to adults: Shellfish, fish, wheat, fruit, buckwheat, peanuts, etc.	Chicken eggs, cow's milk, wheat, soybeans, etc. Mostly remittable Other allergens are mostly less remittable	(++)	IgE-mediated type
Specific type	Food-dependent exercise-induced anaphylaxis (FEIA/FDEIA)	School age-adulthood	Wheat, shrimp, squid, etc.	Less remittable	(+++)	IgE-mediated type
	Oral allergy syndrome (OAS)	Infancy-adulthood	Fruits, vegetables, etc.	Less remittable	(±)	IgE-mediated type

[†] Some cases are complicated by digestive symptoms, such as chronic diarrhea, and hypoproteinemia. Foods are not involved in all cases of infantile atopic dermatitis.

plasma volume related to plasma leakage (edema) in the skin, intestinal tract, or mesentery. In the early stage, peripheral vasoconstriction and tachycardia will compensate for the plasma leakage (compensated shock). However, once the compensation becomes unsustainable, bradycardia rapidly causes cardiac arrest. As a result, decreased cerebral blood flow and hypoxemia result in impaired consciousness.

Hypoxemia is induced by narrowing in the respiratory tract, especially in the distal airway from larynx. Throat tightness, hoarseness, a barking cough, dysphagia, wheezing, and dyspnea are symptoms that should not be overlooked in addition to symptoms of the circulatory organs and neurological system.

3. Clinical Types of Food Allergies

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

3.1. 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.^{6,7} 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.⁸ In light of this situation, the JPGFA2012 tentatively named this disease "neonatal and infantile gastrointestinal allergy."

The most common causative food is cow's milk. Others include soybeans and rice. Children who are exclusively breast-fed may develop this disease. Allergen-specific lymphocyte stimulation tests are positive for most patients. This indicates that the allergy is cell-mediated.⁹

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.

The prognosis is favorable. Approximately 70% of patients acquire tolerance at 1 year of age, and approximately 90% acquire tolerance by their second birthday.

3.2. 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. This type is the most common food allergy during childhood. It is associated with infantile atopic dermatitis. Eczema often remits with the elimination of allergen foods. The food allergy often improves with aging. Common

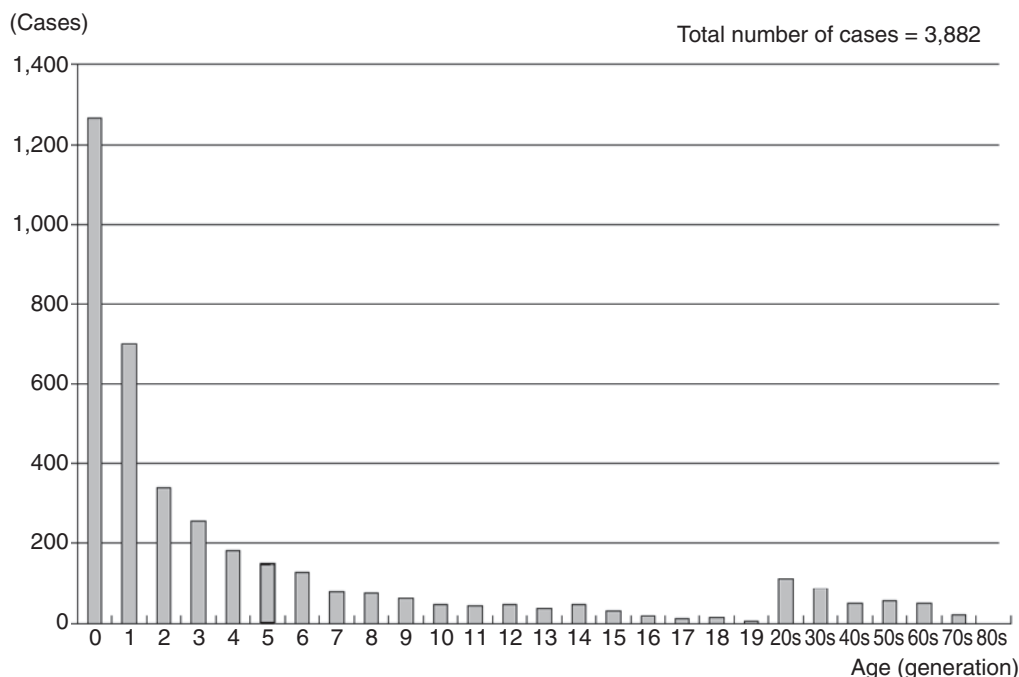


Fig. 2 Number of patients with immediate-type food allergy by age. The number of patients aged 0-19 years old are shown by age, and the number of patients aged ≥ 20 years are shown in 10-year increments.¹⁰

causative foods include eggs, cow's milk, wheat, and soybeans.

3.3. Immediate-type Food Allergy

This type develops immediate symptoms after ingestion. Infants may rarely develop immediate symptoms when they ingest hen's egg, cow's milk, wheat, and other causative foods for the first time. After infancy, common causative foods are buckwheat, peanuts, fish, crustacean, and fruit. Tolerance acquisition may be less common among infants.

3.4. Specific Forms

3.4.1. Food-dependent exercise-induced anaphylaxis (FEIAn or FDEIA)

Food-dependent exercise-induced anaphylaxis (FEIAn) is induced by exercise after food ingestion, but it does not occur after either food ingestion or exercise alone. The pathogenesis is IgE-mediated. FEIAn is mostly induced by exercise within 2 hours after food ingestion. It is a relatively rare disease with the deflection for junior high to high school adolescents.¹¹

Common causative foods are wheat products and crustacean. FEIAn is mostly induced after high-intensity exercise. Nonsteroidal anti-inflammatory drugs, such as aspirin, can exacerbate the condition.

It is desirable to narrow down the causative foods by history taking and allergy testing, and conduct a provocation test. No drug has been established that

can prevent FEIAn.

3.4.2. 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 and vegetables. OAS is often complicated by pollinosis. OAS complicated by pollinosis is called pollen-associated food allergy syndrome or pollen-food allergy syndrome (PFS). OAS is established through sensitization to the pollen allergen protein, and a hypersensitivity reaction develops after ingestion of vegetables or fruit that share cross reactivity with the pollen allergen protein. A definitive diagnosis can be made by 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. 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 for pollinosis has also been initiated to treat OAS. However, a conclusion has not yet been reached regarding the therapeutic effect.

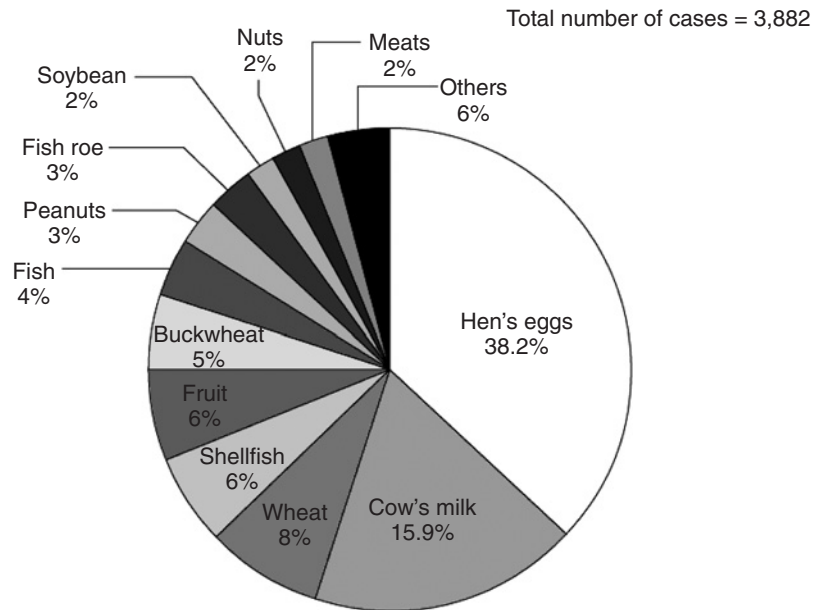


Fig. 3 Breakdown of causative foods of immediate-type food allergy (subjects are patients who developed symptoms within 60 minutes after food ingestion and visited medical institutions).¹⁰

Table 5 Causative foods of immediate-type food allergy by age¹⁰

Age group	<1 year old	1 year old	2-3 years old	4-6 years old	7-19 years old	≥20 years old	Total
Sample size	1270	699	594	454	499	368	3892
First	Hen's egg 62.1%	Hen's egg 44.6%	Hen's egg 30.1%	Hen's egg 23.3%	Crustacean 16.0%	Crustacean 18.0%	Hen's egg 38.3%
Second	Cow's milk 20.1%	Cow's milk 15.9%	Cow's milk 19.7%	Cow's milk 18.5%	Hen's egg 15.2%	Wheat 14.8%	Cow's milk 15.9%
Third	Wheat 7.1%	Wheat 7.0%	Wheat 7.7%	Crustacean 9.0%	Buckwheat 10.8%	Fruit 12.8%	Wheat 8.0%
Fourth		Fish roe 6.7%	Peanuts 5.2%	Fruit 8.8%	Wheat 9.6%	Fish 11.2%	Crustacean 6.2%
Fifth			Crustacean 5.1%	Peanuts 6.2%	Fruit 9.0%	Buckwheat 7.1%	Fruit 6.0%
Sixth				Buckwheat 5.9%	Cow's milk 8.2%	Hen's egg 6.6%	Buckwheat 4.6%
Seventh				Wheat 5.3%	Fish 7.4%		Fish 4.4%

This table lists causative foods that account for >5% in each age group.

4. Diseases Associated with Food Allergies

Urticaria, atopic dermatitis, eosinophilic gastroenteritis, 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 rela-

tionship between the ingestion of a specific food and the disease condition should be analyzed with the involvement of a food allergy taken into consideration.

5. Epidemiology of Food Allergies

On the basis of a large-scale epidemiological survey in Japan, the prevalence of food allergy is estimated to be 5-10% in infants, 5% in young children, and 1.5-3% in schoolchildren. Food allergies are common

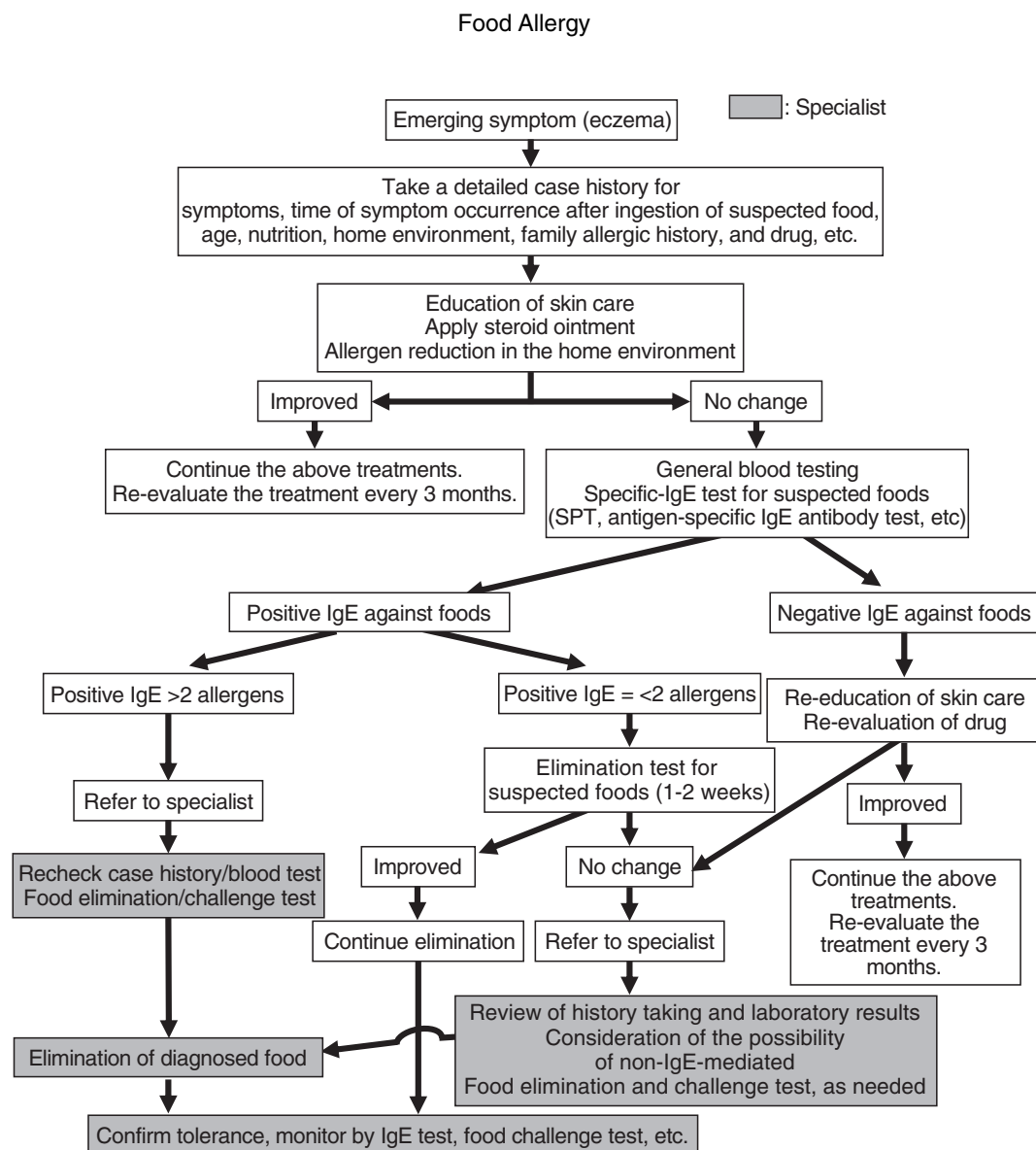


Fig. 4 Procedure for diagnosis of food allergy (for “Infantile Atopic Dermatitis associated with Food Allergy”).⁵ SPT, skin prick test.

among infants and young children and significantly decrease with aging (Fig. 2). This indicates that tolerance is mostly likely to be acquired during infancy. To the best of our knowledge, no epidemiological survey has been conducted regarding food allergies among adults. However, given that the rate of adult patients newly affected by food allergy is not as high as that in infants and young children and that tolerance is less likely to be acquired after school age, the prevalence among adults is estimated to be similar to that among school-aged children.

According to the national survey on immediate food allergy conducted by the Health and Labour Sciences Research in 2001 and 2002, causative foods include hen’s eggs, cow’s milk, and wheat in that order (Fig. 3). These 3 foods account for approximately 60% of all causative foods and are thus considered the 3

major causative foods in Japan. These 3 foods are followed by crustacean, fruit, buckwheat, fish, and peanuts. There are age-specific trends for the causative foods (Table 5). In infants aged <1 year, the above-mentioned 3 major causative foods (hen’s eggs, cow’s milk, and wheat) represent approximately 90% of the total list of causative foods. In children aged ≥1 year, the rates of hen’s egg and cow’s milk allergies rapidly decrease. In contrast, some food allergies increase with age. In school-aged children, the probability of crustacean and fruit allergies increases while that for hen’s egg and cow’s milk allergies decrease. The frequency of wheat allergy remains high for all age groups. In terms of symptoms, cutaneous symptoms such as urticaria are the most likely to occur, followed by respiratory, mucous membrane, digestive, and shock symptoms. Shock symptoms are observed

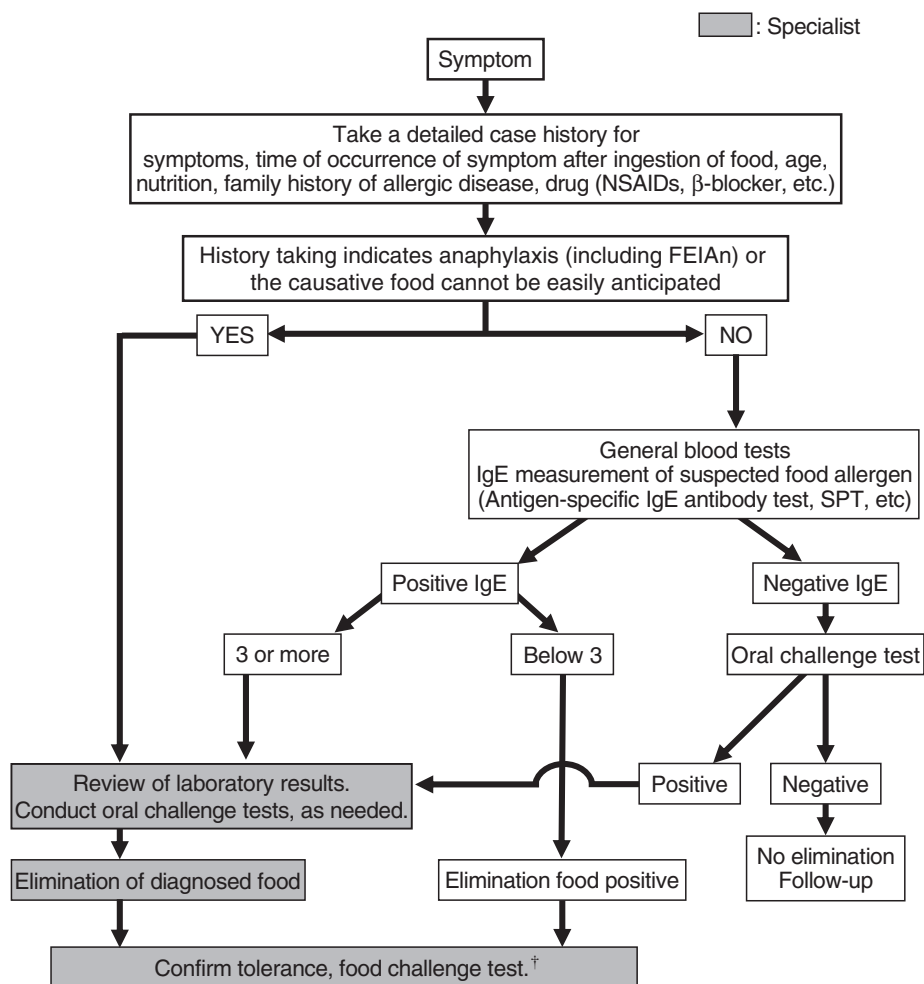


Fig. 5 Procedure for diagnosis of food allergy (for “Immediate-Type Reaction”).

NSAIDs, non-steroidal anti-inflammatory drugs; FEIAN, food-dependent exercise-induced anaphylaxis; SPT, skin prick test.

† Generally, patients who demonstrate immediate-type reaction in later childhood are less likely to acquire tolerance.⁵

in 10.9% of patients, indicating that immediate food allergy confers a high risk of anaphylactic shock symptoms.

6. Diagnosis and Oral Food Challenge Test

Figure 4, 5 provide flowcharts for food allergy diagnosis.

6.1. 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. Food diaries are useful for this purpose.

6.2. Exclusion of Factors Influencing Symptoms, Other than Diet

Factors other than diet that cause or exacerbate symptoms should be removed by indoor environmental improvement, proper skin care, and pharmacotherapy in subjects with chronic and nonimmediate symptoms such as atopic dermatitis.

6.3. Skin Test

A skin prick test (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. However, for patients with a history of symptoms or high antigen-specific IgE antibody levels, avoid even the SPT because it may cause systemic symptoms. Reportedly, an atopy patch test, in which a food antigen is applied on the skin, is use-

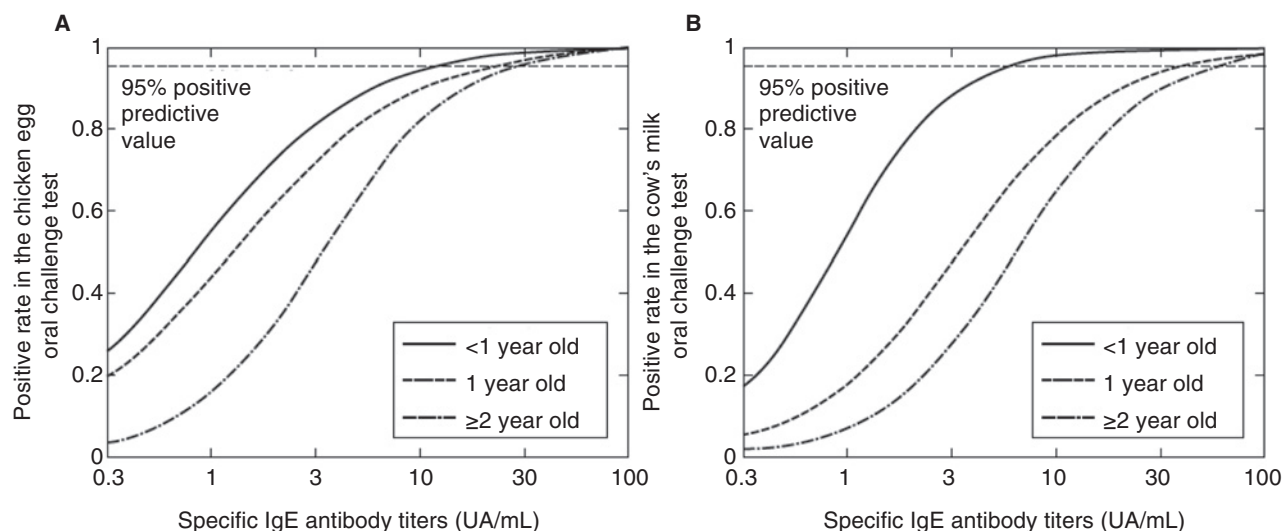


Fig. 6 Probability curve of heated chicken egg/cow's milk allergy and specific IgE antibody titers. **A.** Egg white. **B.** Cow's milk.

ful for predicting nonimmediate 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 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 note, during early infancy, some patients negative for antigen-specific IgE antibodies in the blood may have a positive SPT. Vegetables and fruit, which cause OAS, are unstable allergens. Thus, employ a prick-prick test using fresh vegetables and fruit (skin is pricked with the needle which is 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.

6.4. Antigen-Specific IgE Antibodies in the Blood

The presence of specific IgE antibody titers suggest antigen sensitization and do not necessarily indicate induced symptoms. However, for some antigens (hen's eggs, cow's milk, and peanuts), refer to probability curves indicating correlations between specific IgE antibody titers and the positive rates of immediate reactions in food challenge tests. Furthermore, some reports suggest specific IgE values, with which an immediate reaction in oral challenge test is positive at a probability of 95%.¹² However, since the values differ between reports, they should only be used as reference values.

6.4.1. Hen's eggs

Komata *et al.*¹³ provided probability curves for egg white-specific IgE antibody titers by age (Fig. 6). According to those curves, the Class 3 rating of egg white-specific IgE antibodies at age ≥ 2 years indicates that the positive rate in the hen's egg food challenge is approximately 70-80%. On the other hand, more than half of infant patients <1 year old in the Class 2 rating showed positive results in the food challenge, demonstrating that the positive rate for the same antibody titer is higher at a younger age. Ando *et al.*¹⁴ reported that the ovomucoid-specific IgE antibody test is more useful than the egg white-specific IgE antibody test as an indicator for ingestibility of heated eggs. A part of subjects with hen's egg allergy in infants may give a negative result of egg white-specific IgE antibody. In this case, an SPT may be useful for diagnosis. It has been reported that the higher the egg white-specific IgE antibody titers, the slower the acquisition of tolerance against hen's egg allergy. A high ovomucoid-specific IgE level also serves as an indicator for prolonged hen's egg allergy.

6.4.2. Cow's milk

Probability curves for cow's milk-specific IgE antibody titers were also reported (Fig. 6). While the casein-specific IgE antibody titers are superior to cow's milk in sensitivity and specificity, β -lactoglobulin- and α -lactalbumin-specific IgE antibodies are inferior to cow's milk in both sensitivity and specificity. SPT is useful for diagnosis of infants with a negative cow's milk-specific IgE antibody test but are still suspected of cow's milk allergy.

The higher the cow's milk-specific IgE antibody titers, the longer the delay in the tolerance acquisition against the cow's milk allergy. While the antibody titers will gradually decrease in subjects acquiring tol-

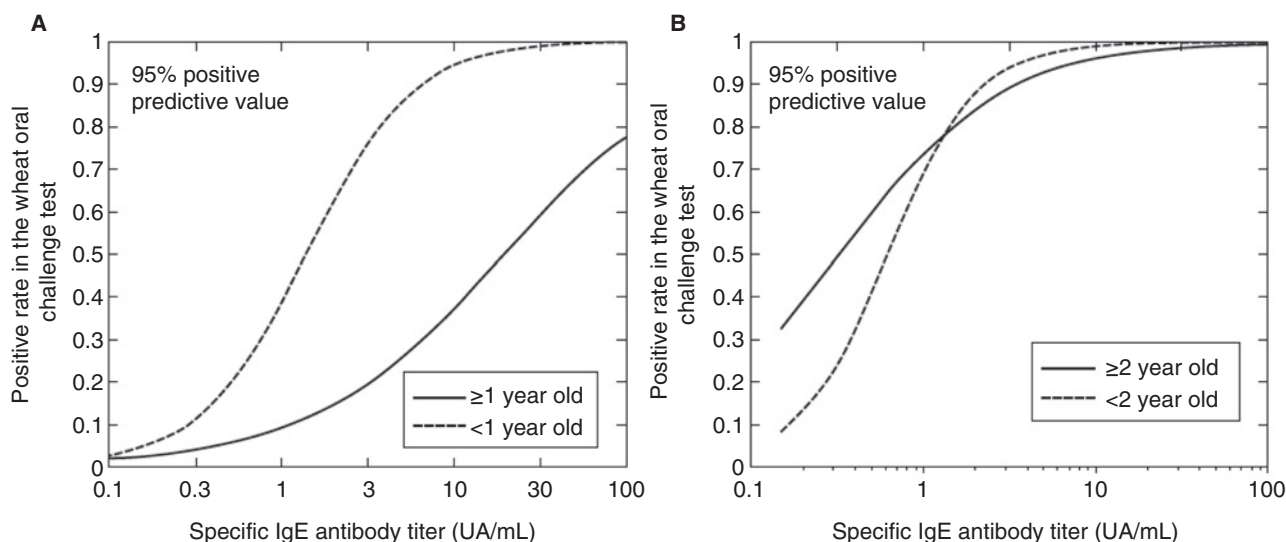


Fig. 7 Probability curves of wheat-specific and omega-5 gliadin-specific IgE antibodies. **A.** Wheat. **B.** Omega-5 gliadin.

erance, the antibody titers will remain high in subjects with delayed tolerance acquisition.

6.4.3. Wheat

Wheat-specific IgE antibody titers are correlated with positive predictive values in challenge tests. However, even if titers are >100 UA/mL at ages ≥ 1 year, the positive rates are approximately 75%. Antibody titers which are predicted that positive rates in challenge tests are $\geq 95\%$ cannot be calculated (Fig. 7). On the other hand, omega-5 gliadin-specific IgE antibody titers show positive predictive values of 90% for Class 3 and almost 100% for Class 4 and above. However, the diagnostic sensitivity is around 77%; thus, wheat allergy cannot be ruled out even with negative results.^{15,16} However, omega-5 gliadin-specific IgE antibody titers are often negative with the acquisition of tolerance against wheat and are thus useful as a follow-up indicator.

6.4.4. Buckwheat

It is quite rare that buckwheat allergy clinically cross-reacts with wheat or rice. Buckwheat-specific IgE antibody titers are primarily high on their own. Conversely, if the buckwheat-specific IgE antibody titers value is similar to that of other cereals, it is less likely that the patient is allergic to buckwheat.

6.4.5. Soybean

Soybean-specific IgE antibody titers are less sensitive and specific for the diagnosis of soybean allergy; therefore, it is important to collect an adequate medical history and results of an oral challenge test for definitive diagnosis. Soybean allergy associated with birch pollen sensitization reportedly induces anaphylaxis associated with the ingestion of soybean milk, chiefly among adults, with Gly m 4 (PR-10) function-

ing as an allergen even when soybean-specific IgE antibodies are negative.

6.4.6. Peanuts and nuts

As allergens, peanuts and nuts often induce anaphylaxis. A definitive diagnosis of the allergy can be made when the patient demonstrates a definite history of symptoms and positive specific IgE antigen titers. It has been reported in the United States that a 99% positive predictive value is achieved at 13.0 UA/mL for peanuts and 18.5 UA/mL for walnuts. In Japan, however, the positive predictive value may be slightly lower than that. The Ara h 2 of peanuts has higher diagnostic accuracy than the crude antigen.¹⁷

6.4.7. Crustaceans/mollusks/shellfish

Clinical symptoms of crustacean/mollusk/shellfish allergy are often typical of an immediate food allergy. However, the specific IgE antibody titers have insufficient sensitivity and specificity, and a detailed history taking regarding the reproducibility of induced symptoms and oral challenge test results are essential for an accurate diagnosis. Approximately 65% of patients with shrimp allergy also show symptoms with crab. While mollusks (octopus/squid) and shellfish share tropomyosin as a primary allergen with crustaceans, the possibility of clinical cross-reactivity is approximately 20%; therefore, it is recommended that a diagnosis be made for each type.

6.4.8. Fish

Because there is a strong cross antigenicity of allergens between fish, the specific IgE antibody titers are positive in several fish species. However, owing to poor correlations between the antibody titer levels and the presence of induced symptoms, the presence of induced symptoms needs to be confirmed individu-

Table 6 Objectives of oral food challenge test

1. Definitive diagnosis of a food allergy (identification of the causative allergen)	2. Diagnosis of tolerance acquisition
(1) Identification of the causative allergen in the case of an immediate reaction after ingestion of several foods	(1) Determination of the time to discontinue an elimination diet that continued for a period of time after the definitive diagnosis of a food allergy
(2) Challenge test to follow the elimination test for atopic dermatitis where involvement of a food allergy is suspected	3. Assessment of the risks of induced symptoms
(3) Identification of induced symptoms to foods that have been proven of sensitization but have not been ingested	(1) Determine safe intake quantity (ideally conducted at a specialized facility)
	(2) Assessment of the risks of accidental ingestion for safety management at kindergartens and schools

ally for each fish species.

6.4.9. Fruit and vegetables

In the case of OAS associated with pollen sensitization, some patients may be positive for specific IgE antibodies of several fruits and vegetables, and others may be negative for all specific IgE antibodies. In such a case, a prick-prick test using fresh juice is useful. On the other hand, in a Class 1 fruit allergy that develops systemic symptoms as a reaction to a single species of fruit (kiwi fruit, banana, etc.), specific IgE antibody titers are also mostly positive to the single species of fruit and are useful for diagnosis.

6.5. 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.¹⁸ 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. 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.

6.6. Elimination Tests

In an elimination test, the potential causative foods are eliminated for approximately 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.

6.7. Oral Food Challenge Test

An oral food challenge test is the most reliable for

identifying the causative foods of a food allergy. However, there is a risk for 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 make a notification according to them.

6.7.1. Objectives

The objectives for the oral food challenge test are provided in Table 6.

6.7.2. Ensuring safety

(1) Conduct the tests under the supervision of physicians and nurses. (2) Prepare agents for emergency, such as adrenaline (Bosmin®, Adrenaline Syringe®), steroids, antihistamines, bronchodilators (inhaled β_2 stimulants, aminophylline), and transfusion sets. (3) Postpone the test if symptoms such as fever or diarrhea occur. (4) Start with a small dose and titrate it. (5) If symptoms occur, discontinue the tests and conduct treatment, if needed. If the patient's background indicates that severe symptoms are likely to be induced, consider the need for a challenge test and conduct it only if necessary with appropriate safety measures. The food challenge tests should be conducted by physicians skilled in the treatment of food allergies and anaphylaxis. For tests conducted at outpatient departments or clinics, it is recommended to prepare for immediate hospitalization.

6.7.3. Preparation

(1) Prepare for tests (staff, equipment, medicines, etc.), considering the risks of anaphylaxis. (2) Explain the objectives, methods, risks, and measures for hypersensitivity and obtain informed written consent. (3) Before the tests, discontinue the use of agents that could influence the test results, such as antiallergics, histamine H1 receptor antagonists, β_2 stimulants, theophylline, oral disodium cromoglycate, Th2 cytokine inhibitors, leukotriene receptor antagonists, and steroids.

6.7.4. Administration methods

(1) 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. (2) 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. (3) DBPCFC (double-blind placebo-controlled food challenge test): Both the subjects and examiners who assess the symptoms are blinded to the challenge food. The challenge food should be prepared by people (controller) other than examiners. In addition to the challenge tests using the foods of interest, a test using a placebo should be conducted on different day.

6.7.5. Protocol for the challenge test

(1) Administration method: Provocation thresholds in food challenge tests cannot be predicted even when based on a combination of history and data of various tests. Therefore, divide the total amount of the challenge food into 3 to 6 portions and gradually increase the amount that is administered. To ensure safety, conduct a preliminary challenge test with a small dose. If negative results are obtained, a challenge test using a standard dose may be needed on a different day.

(2) Administration intervals and total challenge dose: Safety can be improved by increasing the administration intervals, making it more likely that unnecessary administration will be avoided before symptoms develop. Foods are usually given at intervals of 15-30 min because of the time restriction in challenge tests. Within the scheduled observation period, make note of possible indications of symptoms such as mild redness and small wheals around the mouth or a mild cough. Make flexible judgments such as prolonging the observation period or reducing the dose, as needed. The total challenge dose is determined as a sufficient amount based on intake per meal according to age.

(3) Observation period after the last 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. The rate of nonimmediate reactions induced in a food challenge test varies significantly between reports. If nonimmediate reactions are predicted, prolong the observation period, as needed (e.g., hospitalization for 1 day).

(4) Classification of induced symptoms (Table 2).

7. Prediction, Prophylaxis, and Follow-Up of Food Allergy

7.1. Prediction of a Food Allergy

Reportedly, a family history of allergy is most useful for screening of child at high risk for food allergy. The measurement of the total IgE level in cord blood is not sensitive enough to predict the development of allergic diseases and is not recommended for screening test.

7.2. Prophylaxis for Food Allergies

7.2.1. Effects of maternal food allergen elimination in late pregnancy

There is no evidence that the incidence of allergic diseases in childhood is reduced by eliminating food allergens from the mother's diet during pregnancy. Thus, dietary restriction during pregnancy is not recommended. No significant difference has been observed in the incidence of allergic diseases, total IgE level in cord blood, or specific IgE level between mothers who completely eliminated eggs and cow's milk and those who did not.

7.2.2. Effects of food allergen elimination in the mother and child while breastfeeding

There have been many reports indicating that the elimination of food allergens from the diet of breastfeeding mothers does not reduce the incidence of allergic diseases after infancy. Thus, dietary restriction during nursing is not recommended as a prophylactic measure for food allergy. In some reports, when mothers and their children undergo dietary restriction during lactation, the incidence of atopic dermatitis temporarily declines and there are significant effects on specific IgE levels. However, these effects are temporary. In addition, dietary restriction continued from late gestation through lactation has no persistent prophylactic effects. Instead, it is important to establish a well-balanced diet.

7.2.3. Cautions with food allergen elimination

There is no evidence that an elimination diet reduces the incidence of childhood allergic diseases over long periods. In addition, nutritional deficiencies may occur if an elimination diet is followed during pregnancy, resulting in poor weight gain in pregnant women and impaired fetal growth. Thus, caution should be exercised with the use of elimination diets. Proper nutritional instruction should be provided if an elimination diet is needed.

The "Support Guide on Lactation and Weaning 2007" of Japan recommends the commencing time of baby foods approximately 5-6 months after birth. Advance or delay of this timing is not recommended.

Table 7 Labeling of foods containing allergic substances

Specific raw materials	
Mandatory	Buckwheat, crab, egg, milk, peanut, shrimp, wheat
Recommended	Abalone, apple, banana, beef, cashew nut, chicken, gelatin, kiwi fruits, mackerel, matsutake mushroom, orange, peach, pork, salmon, salmon roe, sesame, soybean, squid, walnut, yam

From Allergy Labeling Q&A. Available at: <http://www.caa.go.jp/foods/pdf/syokuhin12.pdf> (in Japanese).

7.3. Natural Course and Allergic March

7.3.1. Natural course

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 eggs, cow's milk, wheat, and soybeans is more likely to be acquired. However, tolerance to allergens in buckwheat, peanuts, nuts, crustacean, 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. Common factors for delayed tolerance acquisition include complications with multiple food allergies, high levels of specific IgE antibody titers, past history of anaphylaxis, and complications with other allergic diseases (e.g., atopic dermatitis).

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.

7.3.2. 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.

8. Management of Food Allergy

8.1. Key Points for Management of Food Allergy

In order to prevent symptoms and ensure safety, the

elimination of causative foods forms the basis of food allergy treatment. However, this places a burden on the patients and their family. The minimum amount of elimination based on the correct identification of the causative food is important. Prevention of nutritional problems or growth disorders should be carefully considered by providing alternative foods and achieving basic nutritional requirements with the aim of "eating."

In addition, it plays an important in improving the quality of dietary life to consider when and how to discontinue the elimination diet.

Instruction on social issues such as mental burden arising from food elimination, food services at nursery, kindergarten, and school life is also required.

8.2. Basics of Management of Food Allergy

8.2.1. Minimal elimination diet

Minimal food elimination based on the correct identification of the causative allergen with the aim of "eating" is fundamental.

(1) Elimination of causative foods: Even foods to be generally considered as highly allergenic should not be eliminated for prevention of development of food allergy.

(2) Reduction in allergenicity by cooking or processing: Instruct elimination level in accordance with patient's tolerance. For example, while raw foods may cause symptoms, sufficiently heated or processed foods may not cause symptoms.

(3) Use of hypo-allergenic foods: In infants with cow's milk allergy in whom breast milk is not sufficient, a formula free of cow's milk allergens is essential.

8.2.2. Consideration of the nutritional aspects and quality of life through substitution in the elimination diet

Substitution is easily achieved by use ingenuity in cooking and providing alternative foods. In order to maintain quality of life, use foodstuffs that are available at an ordinary retail shop with reference to allergenic substances on food labels, except for a formula free of cow's milk allergens.

8.2.3. Dietary instruction and system formation with the aim of safe ingestion

Ingestion of causative foods should be avoided. If

Table 8 Key points for diet therapy, listed by food

1. Hen's egg
Ingestion of several animal/vegetable proteins helps to replace the nutritional contents in hen's eggs.
For its excellent cooking characteristics, hen's eggs are frequently used for cooking and food processing.
• Consider cooking ways to eliminate or to substitute hen's eggs.
Allergenicity will be reduced by heating.
• It should be noted that the reduction in allergenicity of egg white protein may differ according to the cooking conditions.
2. Cow's milk
Use cow's milk allergen-free formula as a substitution for cow's milk-allergic infants.
Instruct nutritional supplementation of calcium. Formula free of cow's milk allergens is useful for the purpose.
Eliminate processed foods including casein as an additive substance because casein allergenicity is less likely to be reduced by heating.
3. Wheat
Use rice as the staple food instead of wheat. Bread and noodles made from rice flour are also available. Avoid processed foods containing gluten.
Wheat allergenicity is less likely to be reduced by heating.
Wheat contained in soy sauce as a raw material will not usually induce symptoms.
Barley tea can be safely drunk by most.
4. Soybean
Miso, soy sauce, and soybean oil are mostly usable for soybean-allergic patients.
A wide variety of soybean foods are available but ingestible foods differ among individuals.
5. Fish
Fish is a major source of Vitamin D and n-3 polyunsaturated fatty acids such as EPA and DHA. These fatty acids inhibit allergic inflammation. The ways to ingest fish should be found.
• Fresh fish should be purchased and refreezing at home should be avoided. Increased histamine in preserved fish may induce toxication associated with urticaria and eruption.
• Soup stock from dried bonito and similar ingredients can be ingested by most.
• Canned fish meat can be ingested by most.
6. Crustaceans
The clinical cross-allergenicity between shrimp and crab, which are crustaceans, is high. Whereas the clinical cross-allergenicities between crustaceans and mollusks, such as squid and octopus, and between crustaceans and shellfish are low.
7. Meat
It is rare that the elimination of meat is required. Meat should be eliminated only when meat clearly induces symptoms.
Well-heated beef is ingestible by most children who are allergic to cow's milk.
Elimination of chicken meat is usually unnecessary for children allergic to eggs.

symptoms are induced by a small amount of the antigen in a processed food, accidental ingestion can be easily avoided by instructing the patient to cook fresh foodstuffs.

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 7 shows the items for which labeling is mandatory (specific raw materials) and items for which labeling is recommended (quasi-specific raw materials). 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.

8.2.4. Discontinuation of the elimination diet at an appropriate time in consideration of tolerance acquisition with age

An elimination diet places a burden on both the mother and pediatric patient. After the elimination diet starts, it should not be continued indefinitely but should be discontinued according to age and severity of hypersensitivity.

In the case of a less severe infant food allergy, an elimination diet can be discontinued at the age of 12-18 months. Indicators for the possibility of discontinuation include a reaction to accidental ingestion, the presence of antigen-specific IgE antibodies in the blood and the results of the skin prick test, basophil histamine release, or oral challenge tests. Of these, the most reliable test is the oral challenge test.

For foods with a negative result in the oral challenge test, the possibility of safe ingestion at home can be examined. In particular, given that atopic dermatitis may worsen after several days of continuous

Table 9 Countermeasures for allergy symptoms induced at home, kindergarten, or school

	Mild	Moderate	Severe
Skin symptoms	• Localized pruritus and/or flushing • Several urticaria areas • Slightly swollen lips	• Severe pruritus • Development of flushing • >10 urticaria areas • Swelling of eyelids and lips	• Generalized severe pruritus, flushing and/or urticaria
Digestive symptoms	• Oral pruritus, uncomfortable feeling	• Nausea or 1 occasion of vomiting • Loose stool or 1 occasion of diarrhea • Intermittent abdominal pain	• Repeated vomiting • Several occasions of diarrhea • Severe abdominal pain
Respiratory symptoms	• Sporadic coughing • Sneezing	• Intermittent coughing • Snuffles, rhinorrhea • Throat pruritus	• Hoarseness, dysphonia • Continuous hard coughing • Barking cough • Wheezing • Dyspnea
Circulatory symptoms	Nil	Nil	• Tachycardia • Irregular pulse • Pallor of the face • White or purple lips or nails
Neurological symptoms	Nil	• Sluggishness	• Anxiety, fear • Fatigue • Confusion
Treatment stages	[Stage of careful observation with orally administered antihistaminics]	[Stage of a medical institution visit]	[Stage of an urgent medical institution visit]
	• Follow-up with orally administered antihistaminics. * If symptoms progress, the treatment for moderate cases should be applied.	• Visit a medical institution following administration of household medicine for emergency (antihistaminics, steroid drug, or bronchodilator). * If symptoms progress, the treatment for severe cases should be applied.	• Administer Epipen® in combination with antihistaminics, steroids, or bronchodilator, if possible. • Transfer the patient to a medical institution by ambulance.
Points to note	1. Patients and their guardians should carry household medicines for emergency so that the patients may administer the drugs while not at home or at kindergarten/school. 2. Consider carrying an Epipen® for patients with a past history of anaphylaxis. 3. If a causative food remains in the mouth, encourage the patient to bring up the food. Then, rinse the mouth. 4. If the patient was exposed to the food in the eye, wash the eyes with clean water. Apply a steroid eye-drop, if available. Then, visit an ophthalmologist. 5. Anaphylaxis is progressive and may rapidly worsen from the mild symptoms experienced in the early stage. 6. If a patient has a previous history of severe symptoms, such as anaphylaxis and shock, treat the patient quickly even if the present symptoms are mild.		

ingestion, the final decision should be made after eating the causative food at home.

Even after remission of the allergic reaction, the pediatric patient may refuse the causative food. Accordingly, it is less stressful to discontinue the elimination diet at nursery, kindergarten or school after confirming that the pediatric patient has come to eat the causative food normally at home. Table 8 lists the

key points for diet therapy by food.

9. Measures against Symptoms in the Acute Phase

9.1. Measures for Accidental Ingestion Other than Medical Institutions

Table 9 lists the symptoms caused by a food-induced anaphylactic reaction and the measures against them.

How to use EpiPen®



Fig. 8 How to use EpiPen®.

Table 10 Indication of EpiPen® for general persons (Japanese Society of Pediatric Allergy and Clinical Immunology-JSPACI)

The EpiPen® should be applied to patients suspected of anaphylactic shock, for whom the EpiPen® is prescribed, with at least 1 of the following symptoms:

Digestive symptoms	• Repeated vomiting	• Persistent severe (intolerable) abdominal pain
Respiratory symptoms	• Tightening in the throat or chest • Persistent severe coughing	• Husky voice • Breathing with wheeze • Barking cough • Difficulty in breathing
Systemic symptoms	• Pale lips or nails • Confusion	• Hardly palpable pulse • Fatigue • Incontinence

JSPACI will provide the explanation to patients indicated for EpiPen® and their guardians and prepare all guidelines and manuals for nurseries, kindergartens, and schools regarding measures to deal with allergic symptoms and anaphylaxis in accordance with the above.

In the event of accidental ingestion, force the patient to bring up the accidentally ingested food to minimize absorption of the antigen(s). If ocular symptoms occur after rubbing the eyes with hands exposed to causative foods, wash the eyes and place a drop of antiallergics or steroids in the eyes. In addition, orally administer household medicines for emergency, prescribed by physicians, such as histamine H1 receptor antagonists and steroids.

If symptoms are exacerbated or developed in multiple organs, immediately consult a medical institution. At this time, consider calling an ambulance and using an adrenaline for self-injectable (EpiPen®) (Fig. 8). An emergency life-saving technician is allowed to use an EpiPen® as part of the duty of care, if it is carried by the patient. If anaphylactic shock is suspected, place the patient in the shock posture with the lower limbs raised approximately 30 degrees. Then, wait for an ambulance. Provide resuscitation if the patient is in cardiopulmonary arrest.

9.2. Timing of Adrenaline for Self-Injection and Instructions for Use

After the use of an adrenaline for self-injection, the patient should be immediately transported to a doctor by ambulance. If symptoms do not improve, adrenaline can be administered again after arrival at the medical institution. Even after recovery, the patient needs to be followed up with caution given to the appearance of a biphasic anaphylactic reaction.

Because adrenaline is a powerful drug with a sudden peripheral vasoconstriction activity and vasopressor activity, it cannot be prescribed for patients with an underlining disease such as diabetes, arteriosclerosis, hyperthyroidism, or severe arrhythmia associated with ventricular tachycardia. Judicious use of adrenaline is required for patients with hypertension, pulmonary emphysema, cardiac disease, and elderly people. The expiry date should be reviewed and heeded. Re-prescription is recommended until remission is observed.

The adrenaline for self-injection is produced only for intramuscular injection into the anterolateral

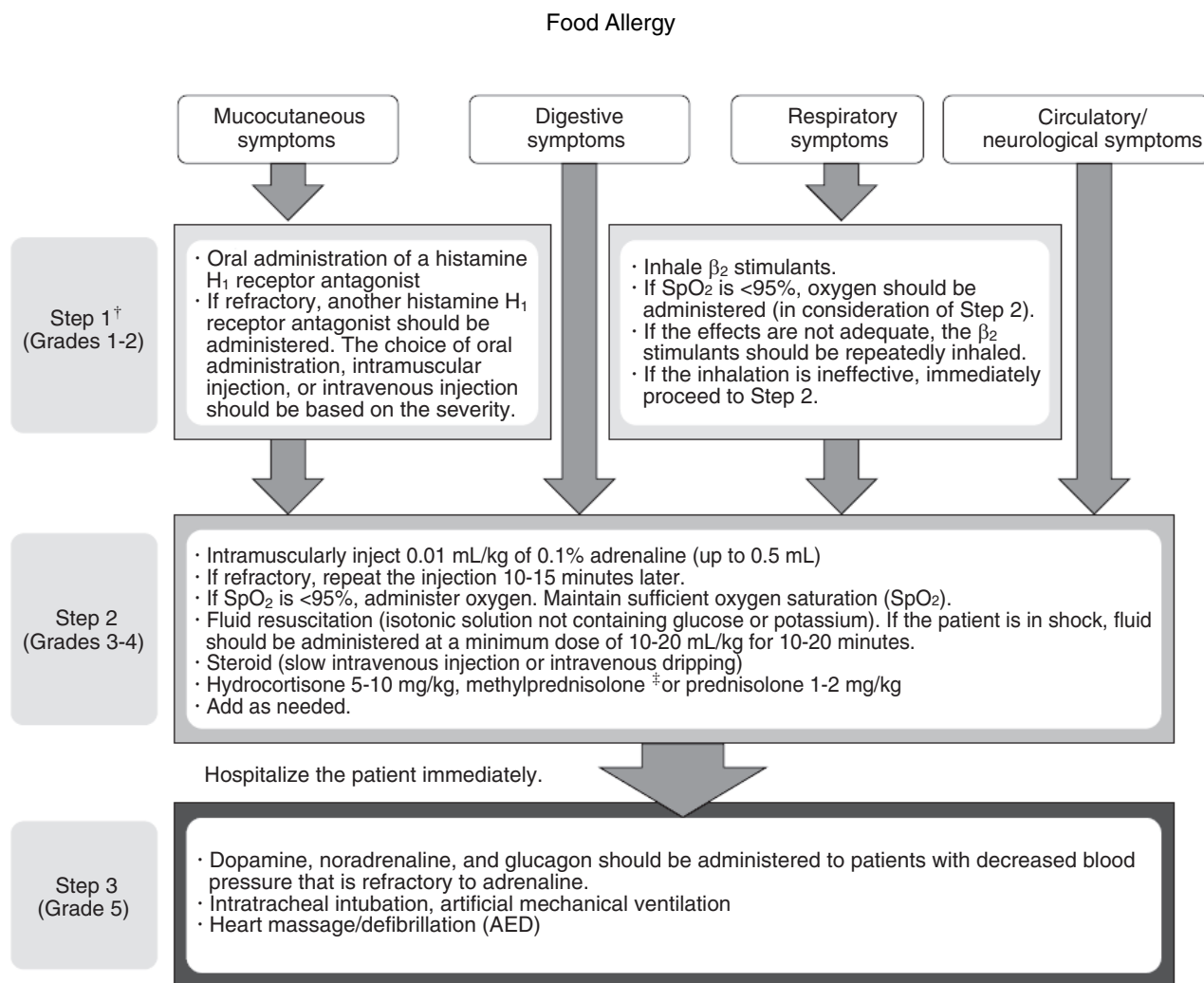


Fig. 9 Treatments to be applied when immediate reaction/anaphylaxis develops.

[†] If there is a concern about a non-immediate reaction after the treatments in Step 1, orally administer a steroid drug.

[‡] It should be noted that Solu-Medrol® 40 mg contains lactose.

thigh. In order to prevent an accident, the safety cap should be kept closed except for when in use.

JSPACI proposed symptoms that are indicators for the use of Epipen® other than medical staff (Table 10).

9.3. Treatment at a Medical Institution (Fig. 9)

If the effects of adrenaline for self-injection are not adequate, 0.005-0.01 mg/kg of 0.1% adrenaline should be intramuscularly injected after a lapse of 10-15 min. If oxygen saturation (SpO₂) is <95%, oxygen should be administered. After vascular access and fluid replacement (10-20 mL/kg for 10-20 min, more if the patient is in shock), hydrocortisone (5-10 mg/kg) should be intravenously injected and repeatedly injected at a dose of 5 mg/kg every 4-6 hours, as needed. Methylprednisolone (1-2 mg/kg) may also be intravenously dripped. It should be noted that Solu-Medrol® 40 contains lactose. Metabolic acidosis should be corrected. 0.1% adrenaline should be re-

administered, as needed. In patients with urticaria and vascular edema, antihistamines is administered intravenously, and in patients with bronchoconstriction, β₂ stimulant is inhaled and aminophylline is administered intravenously.

10. Antigen-Specific Oral Immunotherapy

10.1. Positioning of Antigen-Specific Oral Immunotherapy

Tolerance is more likely to develop for orally administered antigens. Antigen-specific oral immunotherapy has also been initiated to treat food allergy. Elimination diet is a passive treatment, while this immunotherapy is considered to be an active treatment with the goal of inducing remission of the food allergy. The clinical effects of oral immunotherapy have been recognized, but problems with safety remain.

Table 11 Food allergy and anaphylaxis in certificate for school life management (for allergic diseases)

Name _____		Male/Female _____		Birth day (age) _____ () _____		School name _____		Grade/Class _____		Date of submission: _____	
Food allergy (+/-) Anaphylaxis (+/-)		Disease type and treatment A. Type of food allergy (if you have food allergy) 1. Immediate-type 2. Oral allergy syndrome 3. Food-dependent exercise-induced anaphylaxis B. Type of anaphylaxis (if you have a history of anaphylaxis) 1. Food (causative food:) 2. Food dependent exercise induced anaphylaxis 3. Exercise-induced anaphylaxis 4. Insects 5. Medicines 6. Others						Points to remember for school life A. School meals 1. No need for management 2. Consult with guardians for decision. B. Classes and activities regarding foods and food materials 1. No need for considerations 2. Consult with guardians for decision. C. Exercise (gymnastics, extracurricular activities, etc.) 1. No need for management 2. Consult with guardians for decision. D. Overnight extracurricular activities 1. No need for considerations 2. Caution should be exercised for meals and events. E. Other considerations/Management items (optional)		[Emergency contact number] Guardians TEL: _____ Contact medical institution Name of medical institution: _____ TEL: _____	
		C. Causative foods/Grounds for diagnosis: Circle the number of causative food and describe grounds for diagnosis in < >. 1. Egg < > 2. Cow's milk/Dairy products < > 3. Wheat < > 4. Buckwheat < > 5. Peanut < > 6. Nuts and seeds < > 7. Shellfishes (shrimp and crab) < > 8. Fruits < > 9. Fish < > 10. Meat < > 11. Others 1 < > 12. Others 2 < > D. Prescriptions for emergency 1. Oral medicines (antihistaminics and steroids) 2. Adrenaline self-injection "Epipen" 3. Others ()						Date of description Name of physician Name of medical institution			
• Do you agree to have the information described in this table shared with all school staff to be used for daily activities and emergency measures at the school? 1. Yes, I do 2. No, I do not Guardian's signature: _____											

Prepared by the Japanese Society of School Health.

Table 12 Food allergy and anaphylaxis in certificate for nursery life management (for allergic diseases)

<Reference form>

Name _____ M/F Birthday: _____ (age) _____ grade/class _____ Submitted on: YY/MM/DD

This life management instruction table will be prepared only when special consideration or management becomes necessary in the nursery.

Type/treatment		Points to note in nursery	[Emergency contact number]	★Guardians TEL:	
A. Food allergy type (to be described only when the child has food allergy) 1. Infantile atopic dermatitis associated with food allergy 2. Immediate-type food allergy 3. Others (neonatal digestive symptom/oral allergy syndrome/food-dependent exercise-induced anaphylaxis/others)	B. Anaphylaxis type (to be described only when the child has a past history of anaphylaxis) 1. Food Cause: 2. Others (drug/food-dependent exercise-induced anaphylaxis/latex allergy)	A. School meals/baby food 1. No need for management. 2. Consult with guardians for decision.	★Contact medical institution Name of medical institution:		
		B. Formula for allergic infants 1. Unnecessary 2. Necessary Circle the corresponding formula below or describe in () Milfee/New MA-1/MA-mi/PEPDIET elemental formula Others ()			
C. Grounds for elimination of the causative food Circle the number of the corresponding food and describe the grounds for elimination within < >. 1. Chicken egg < > 2. Milk/dairy products < > 3. Wheat < > 4. Buckwheat < > 5. Peanuts < > 6. Soybean < > 7. Sesame < > 8. Nuts < > 9. Crustaceans < > 10. Mollusks/shellfish < > 11. Fish roe < > 12. Fish < > 13. Meat < > 14. Fruit < > 15. Others ()		C. Classes and activities regarding food and food materials 1. No need for management 2. Consult with guardians for decision.	TEL:		
D. Prescription drugs to be prepared for emergency use 1. Internal medicine (antihistaminics, steroid drug) 2. Self-injectable adrenaline "Epipen® 0.15 mg" 3. Others ()		D. Elimination foods that cannot be ingested Of the causative foods described in Type/Treatment C, circle the foods that cannot be ingested during elimination 1. Chicken eggs: Eggshell calcium 2. Milk/dairy products: Lactose 3. Wheat: Soy sauce/vinegar/barley tea 5. Soybeans: soybean oil/soy sauce/miso 6. Sesame: Sesame oil 11. Fish: bonito soup stock/sardine soup stock 12. Food extract			Date of description
		E. Other considerations/Management items		Name of physician	
				Name of medical institution	

This life management instruction table will be improved in the future to reflect regional activities and emerging evidence.

Table 13 Points to remember in referral to specialists

1. Accurate diagnosis (request of an oral food challenge test)
2. Instructions on diets, including elimination and alternative diets
3. Instructions on elimination diet, requested by nursery, kindergarten, school, etc.
4. Nutrition guidance to discontinue elimination diet and to gradually introduce usual diet
5. Instructions on adrenaline (epinephrine) self-injection for anaphylaxis

10.2. Desensitization and Permanent Oral Tolerance

In desensitization, the tolerant status is maintained after the achievement of the maintenance dose and while the treatment is continued; however, the tolerant status disappears or is attenuated once the treatment is discontinued. In addition, attenuation of the tolerance occurs in the presence of factors associated with increased intestinal permeability such as exercise, viral gastrointestinal infectious disease, stress, or menstruation.

In desensitization, specific IgG4 increases, specific IgE decreases, and the activation of mast cells and basophils are attenuated.

In permanent oral tolerance, tolerance is maintained even if the maintenance therapy is discontinued. It is unknown if permanent oral tolerance can be obtained by the currently available oral immunotherapy for food allergy.

10.3. Future Issues

This therapy is still being investigated, and the development of antigens and study on administration methods for immunotherapy are urgently required not only in terms of effectiveness but also in terms of safety. Further, mechanisms for immunotherapy need to be determined.

11. Measures at Nurseries, Kindergartens, and Schools

The “Certificate for school life management” (Table 11) is now being used at kindergartens and schools, and the “Certificate for nursery life management” (Table 12) 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”) (Table 11) was prepared for schools to advance activities for school children with allergic diseases, and the “Guideline on Measures for Aller-

gic 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” (Table 12) 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.

12. Timing of Referring to Specialists

Table 13 summarizes the timing of referring to a specialist. In addition to, referring to a specialist is recommended when there are complications.

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

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