**Table 3** Symptoms of food allergy by organ

| Organ | Symptoms |
|---|---|
| Digestive system | Oral discomfort, lip swelling, abdominal pain, nausea and vomiting, diarrhea |
| Respiratory system | Sneezing, rhinorrhea, nasal congestion, coughing, wheezing, dyspnea, chest tightness, laryngopharyngeal edema |
| Eyes | Conjunctival hyperemia and edema, blepharedema, and lacrimation |
| Skin | Erythema, urticaria, angioedema, itch, burning sensation, blister, eczema |
| Nervous system | Headache |
| Urinary system | Hematuria, proteinuria, nocturnal enuresis |
| Systemic | Anaphylaxis |

### 3.2.1. Skin Symptoms: Skin Symptoms Are Most Common in Food Allergy

(1) Urticaria and angioedema: Acute urticaria and angioedema are common. Rash often occurs within several minutes after ingestion, accompanied by itch.

(2) Atopic dermatitis: Atopic dermatitis is not caused by a single factor. There are various exacerbation factors. Many papers have been published regarding the involvement of food allergies. Reports of its incidence vary widely, depending on the methods used to select subjects (e.g., selection based on severity, history, specific IgE antibodies, or skin test results), methods used for the oral challenge test (open food challenge, double-blind, placebo-controlled food challenge (DBPCFC), and test timing, i.e., before or after the remission of skin symptoms).

### 3.2.2. Digestive Symptoms

(1) Immediate-type gastrointestinal allergy: Nausea, vomiting, abdominal pain, colic and diarrhea occur during food ingestion or at about 2 h after food ingestion. These are often accompanied by skin and airway symptoms. Some infants present with intermittent vomiting and poor weight gain. Most affected infants ($\geq$95%) are positive for specific IgE antibodies against causative foods and in a skin test.

(2) Oral allergy syndrome (OAS)[6]: OAS is caused by contact urticaria in the oral mucosa. IgE antibodies are involved. Itch, redness, tingling, swelling, etc., often occur in the mouth, lips, and throat mostly within 15 min after ingestion. Some patients present with systemic symptoms, such as throat constriction, generalized urticaria, cough, wheezing, dyspnea, and anaphylactic shock. These may be caused by food antigens absorbed from the oral mucosa and distributed throughout the body. OAS occurs in infants, schoolchildren, and adults. Common causative foods are fruits (kiwi, banana, melon, peach, pineapple, apple, etc.) 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). Reportedly, in Hokkaido (Japan), 16% of patients with birch pollinosis develop OAS due to fruits, such as apple.

(3) Eosinophilic gastroenteritis: Eosinophilic gastroenteritis is a rare disease with eosinophil infiltration in the intestinal mucosa from the esophagus to the rectum. Abdominal pain, nausea and diarrhea occur. Eosinophilic gastroenteritis is accompanied by malabsorption, protein leakage and iron deficiency anemia caused by intestinal hemorrhage. While an infiltration of eosinophils is usually localized to the mucous membrane, it may spread to submucosa or muscle layer, being complicated by eosinophilic ascites. Food allergy is involved in 25-50% of these cases.

(4) Neonatal and infantile gastrointestinal allergy: In Europe and America, several disease types have been reported, which mainly present with digestive symptoms and occur among newborns and infants, and in which IgE is not involved.[7,8] Many Japanese patients also fall into these categories regarding their symptoms and test results. However, some patients do not fall into any of these disease types. Thus, the Guideline Committee for Food Allergy in the Japanese Society of Pediatric Allergy and Clinical Immunology bracket together these food allergies, which mainly present with digestive symptoms and occur among newborns and infants, into "neonatal and infantile gastrointestinal allergy." Many patients are negative for IgE antibodies and are positive for an allergen-specific lymphocyte stimulation test (ALST). Thus, this disease may be mainly caused by the hyperreactivity of cellular immunity.

About 70% of patients develop symptoms during the newborn period, while some do at several months after birth. Half of neonatal patients develop symptoms until 7 days after birth. Symptoms may develop after the first milk ingestion on the day of birth. Common symptoms are vomiting, bloody stool, diarrhea, and abdominal fullness. Other symptoms include shock, dehydration, sluggishness, hypothermia, acidosis, and methemoglobinemia. Of note, some patients present with fever and positive CRP. Differential diagnosis of these patients from those with severe infections, such as bacterial enteritis, is difficult. Some patients develop neonatal transient eosinophilic colitis, which causes bloody stool immediately after birth (before nursing). This disease may occurs in utero.[9]

The most common causative food is cow's milk.

**Table 4** Classification of food allergy

| Clinical type | | Age of onset | Common causative foods | Tolerance acquisition (remission) | Possibility of anaphylactic shock | Mechanism of food allergy |
|---|---|---|---|---|---|---|
| Neonatal and infantile gastrointestinal allergy | | Neonatal and infantile period | Cow's milk (powdered milk for infants), soybean, rice | (+) | (±) | Mainly non IgE-mediated type |
| Infantile atopic dermatitis associated with food allergy† | | Infancy | Egg, cow's milk, wheat, soybean, etc. | (+) in many cases | (+) | Mainly IgE-mediated type |
| Immediate-type (urticaria, anaphylaxis, etc.) | | Infancy-adulthood | Infants-young children: egg, cow's milk, wheat, buckwheat, fishes, etc. School children-adults: crustacean shellfish, fish, wheat, fruits, buckwheat, peanut, etc. | Egg, cow's milk, wheat, soybean, etc.(+) Others (±) | (++) | IgE-mediated type |
| Specific type | Food-dependent exercise-induced anaphylaxis (FEIAn/FDEIA) | School age-adulthood | Wheat, shrimp, squid, etc. | (±) | (+++) | IgE-mediated type |
| | Oral allergy syndrome (OAS) | Infancy-adulthood | Fruits, vegetables, etc. | (±) | (+) | 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.

Modified from Food Allergy Management Guideline 2008.

Others include soybean milk and rice. Some cases were fed by mother's milk or hydrolyzed whey formula.

Diagnosis is made based on i) development of digestive symptoms after causative food ingestion, ii) improvement and disappearance of symptoms by eliminating causative foods (positive elimination test), and iii) positive food challenge test.

To treat gastrointestinal allergy caused by cow's milk in an early stage, therapeutically effective products, such as amino-acid-based formula and extensively hydrolyzed formula, are preferably used.

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

### 3.2.3. Respiratory Symptoms

Upper respiratory tract symptoms include symptoms of allergic rhinitis, such as nasal discharge, nasal congestion, and sneezing. Lower respiratory tract symptoms include symptoms of airway narrowing (wheezing) and laryngeal edema.

The Heiner syndrome is characterized by pulmonary hemosiderosis caused by milk,[10] Heiner syndrome a rare disease, which causes hemoptysis due to alveolar hemorrhage and features chronic cough, dyspnea, wheezing, fever, and bloody sputum, resulting in iron deficiency anemia. Precipitating antibodies against cow's milk proteins are detected in the sera of affected infants.

### 3.2.4. Ocular Symptoms

Symptoms of allergic conjunctivitis, such as conjunctival hyperemia and edema, blepharedema, and lacrimation, may occur.

### 3.2.5. Systemic Symptoms

(1) Anaphylaxis: Severe allergic symptoms occurring in multiple organs are called anaphylaxis. The most severe symptoms result in shock accompanied by decreased blood pressure and impaired consciousness. Causative agents of anaphylaxis, besides foods, include medicines, blood transfusion, bee, and latex. Food allergy is the most common cause. Food-induced anaphylaxis is an immediate reaction, in which IgE antibodies are involved. While symptoms usually occur within several minutes after ingestion, they occasionally occur 30 min or later. Symptoms may occur either in monophasic or biphasic. In Europe and America, causative foods of anaphylaxis include peanuts, nuts and seeds, seafood, eggs, and cow's milk. In Japan, they include eggs, cow's milk, seafood, shellfish, buckwheat, and peanuts in this order.

(2) Food-dependent exercise-induced anaphylaxis (FEIAn or FDEIAn): FEIAn is induced by exercise after food ingestion (mostly within 2 h after ingestion), but does not occur after either food ingestion or exercise alone. Nonsteroidal antiinflammatory drugs, such as aspirin, are an exacerbation factor. FEIAn occurs in an IgE-mediated manner.

The prevalence of FEIAn in schoolchildren and students is 0.0085%, i.e., one incidence per 12,000 per-

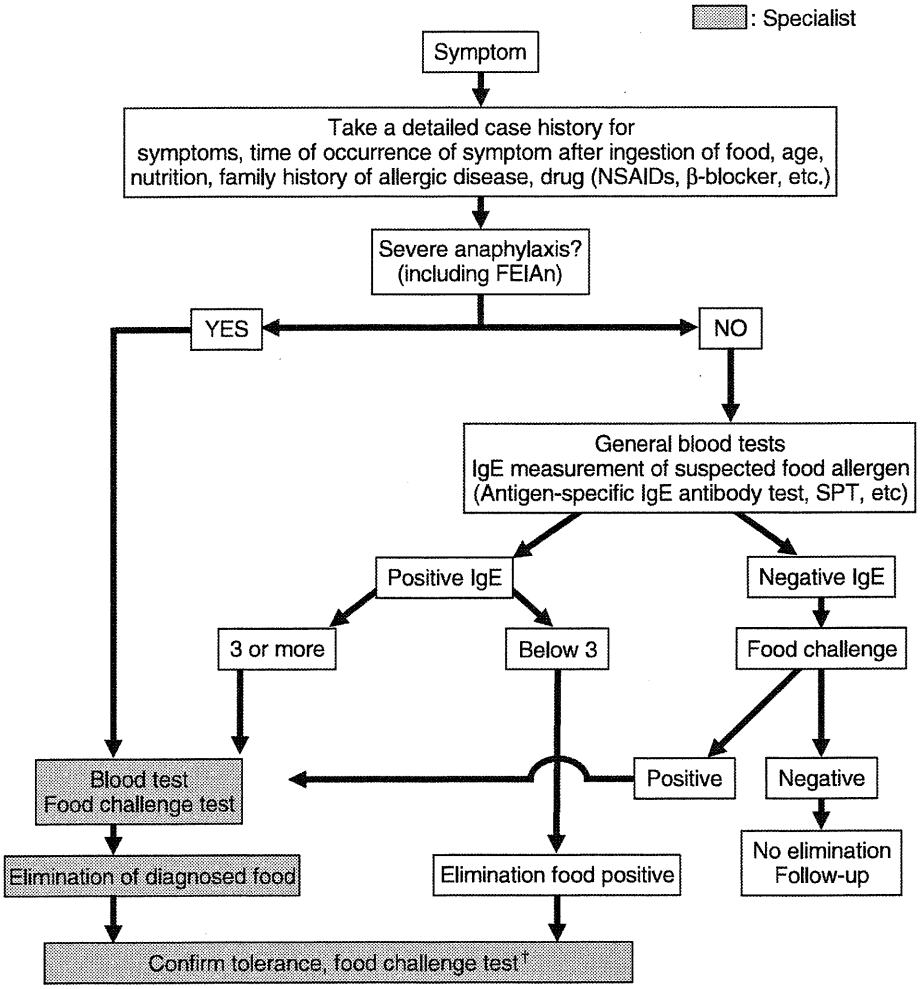


**Fig. 3** Procedure for Diagnosis of Food Allergy (for "Immediate Type Reaction"). NSAIDs, non-steroidal antiinflammatory drugs; FEIAn, food-dependent exercise-induced anaphylaxis; SPT, skin prick test.
†Generally, patients who demonstrate immediate type reaction in later childhood are less likely to acquire tolerance.
Adapted from reference 12.

sons. FEIAn is most common among junior high school students, and is more common in males than in females (male-female ratio, 4 : 1). Common causative foods are shellfish (55%) and wheat products (45%).[11]

Definitive diagnosis can be made by presuming the causative foods through history taking, allergy testing, and checking hypersensitivity in a provocation test with food challenge followed by exercise loading. Few patients have a positive provocative test. In patients with negative results, consider administering aspirin before the food challenge.

### 3.3. CLINICAL TYPES OF FOOD ALLERGY

Four representative clinical types of food allergy are shown in Table 4, a revision to "Food Allergy Management Guideline 2008".[12]

"Neonatal digestive symptoms" in the Food Allergy Management Guideline 2008 was altered to "neonatal and infantile gastrointestinal allergy" after approval by the Guideline Committee for Food Allergy in the Japanese Society of Pediatric Allergy and Clinical Immunology.

Atopic dermatitis during infancy is often associated with food allergy, of which symptoms become immediate type and is usually resolved with aging. This type atopic dermatitis is called "infantile atopic dermatitis associated with food allergy." Common causative foods are eggs, cow's milk, wheat, and soybeans.

The food allergy which promptly develop after ingestion of causative food are "immediate-type food allergy which is common in young children to adulthood." The causative foods are buckwheat, peanuts, fish, curastacean shellfish, and fruits. Tolerance ac-

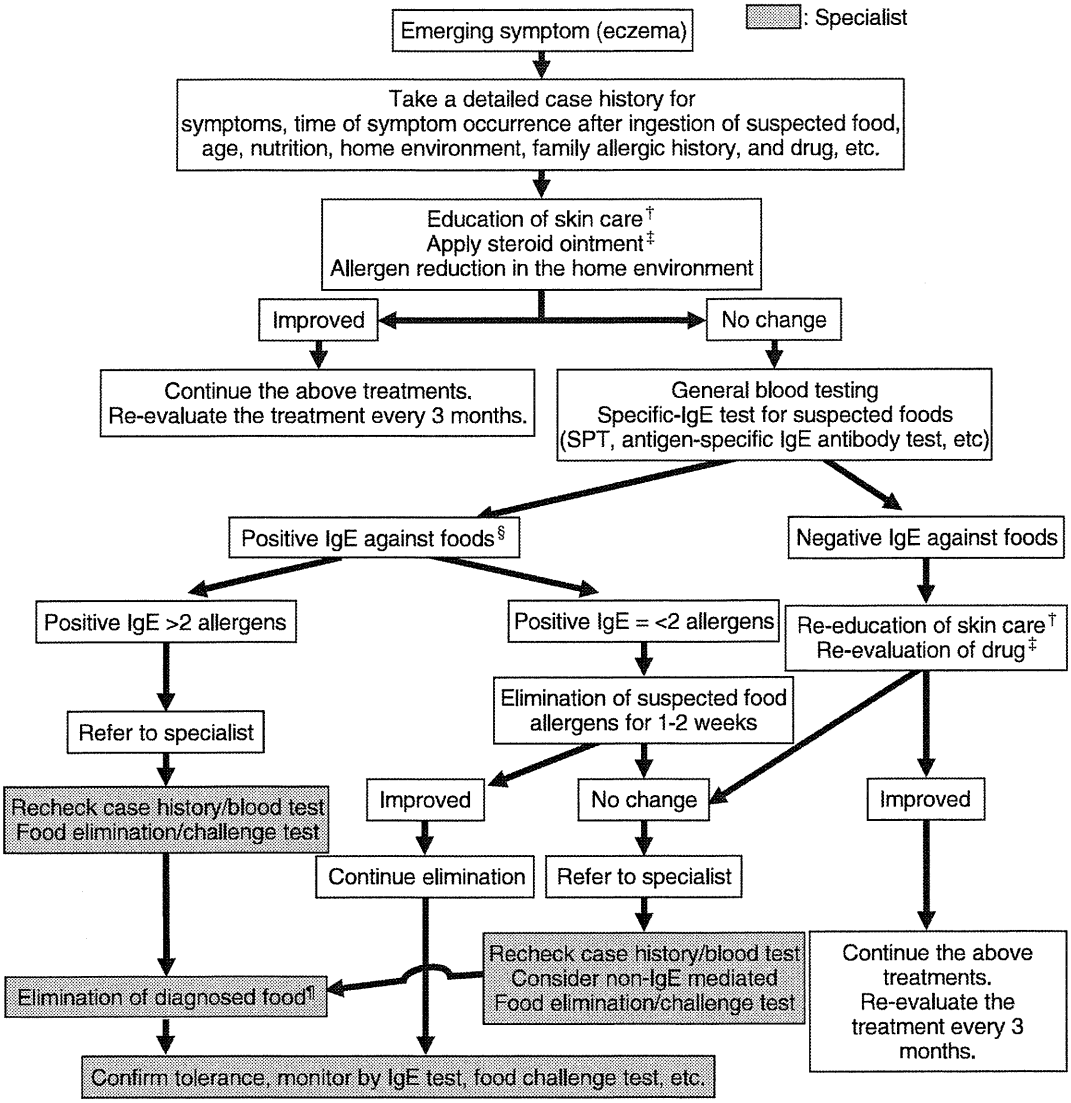


**Fig. 4** Procedure for Diagnosis of Food Allergy (for "Infantile Atopic Dermatitis associated with Food Allergy"). SPT, skin prick test.

† Skin care. Cleaning with soap and moisturizing is essential for skin care.

‡ Drug treatment. Steroid ointment is the essential treatment for infantile atopic dermatitis.

§ SPT is useful for a baby under six months of age because an IgE antibody tends to become negative.

¶ Precautions for practicing the elimination diet. Monitor child's growth and development. Always look for the possibility of ceasing the elimination diet.

Adapted from reference 12.

quisition may be less common compared with food allergy in infants.

"Food-dependent, exercise-induced anaphylaxis" and "oral allergy syndrome" are specific forms of immediate-type food allergy.

## *4. DIAGNOSIS AND CHALLENGE TEST OF FOOD ALLERGY*

The flowcharts of food allergy diagnosis are shown in Figure 3, 4.[12]

### 4.1. HISTORY TAKING

In history taking, causative foods and their intakes, time from food intake to onset of symptoms, reproducibility, other causative conditions (exercise, medication, etc.) and time when last symptoms occurred, should be recorded. Food diaries are useful for history taking.

### 4.2. EXCLUSION OF FACTORS INFLUENCING SYMPTOMS OTHER THAN DIETS

For chronic nonimmediate symptoms (e.g., atopic

**Table 5** Cutoff values of specific IgE antibody titers, which enable food allergy diagnosis even if no challenge test is conducted

| 1) Sampson (JACI 2001) | | | | ($U_A$/mL) |
|---|---|---|---|---|
| Specific IgE | Egg white | Cow's milk | Peanut | Fish |
| Diagnositic decision points | 7 | 15 | 14 | 20 |
| 2) Komata (JACI 2007) | | | | |
| Age | <1 year | 1 year | | ≥2 years |
| Egg white | 13.0 | 23.0 | | 30.0 |
| Cow's milk | 5.8 | 38.6 | | 57.3 |
| 3) Ando (JACI 2008) | | | | |
| Challenge diet | Raw egg white | | Heated egg white | |
| Specific IgE | Egg white | Ovomucoid | Egg white | Ovomucoid |
| Positive decision point | 7.38 | 5.21 | 30.7 | 10.8 |

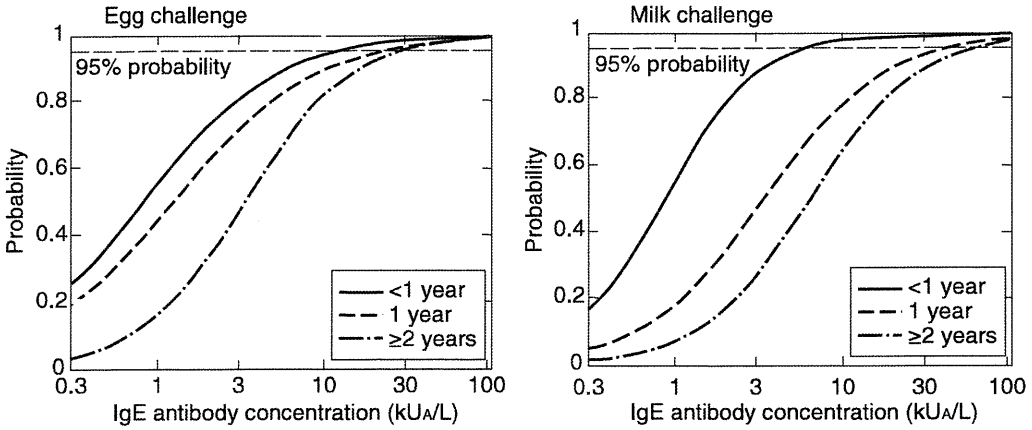


**Fig. 5** Probability curves of egg white-specific and cow's milk-specific IgE antibody titers by age. Specific IgE antibody titers indicate the rate of positive immediate reaction (probability) in the food challenge test. However, these values should be used as reference, because they vary by reporters.

dermatitis), factors other than diet causing or exacerbating symptoms should be removed by indoor environmental improvement, proper skin care, pharmacotherapy, etc.

### 4.3. SKIN TEST

A skin prick test (SPT) is recommended for examining the causes of food allergy. Intradermal tests using food antigens are not recommended because they are more likely to yield false positive results and cause anaphylactic reactions than SPT. However, for patients with a history of symptoms or high antigen specific IgE antibody levels, even SPT should be avoided because it may cause systemic symptoms.

Reportedly, an atopy patch test is useful for predicting nonimmediate reactions in the diagnosis of causative food of atopic dermatitis. However, no consensus has been reached on this finding.

Before testing, the use of agents such as antihistaminics, antiallergic drugs, and steroids should be avoided because these influence *in vitro* tests.

SPT-negative patients present with no immediate-type food allergy at the possibility of 95% or more. While a positive SPT indicates the presence of antigen-specific IgE antibodies, this result alone does not substantiate the diagnosis of food allergy. However, even if the antigen-specific IgE antibodies in blood is negative, a positive SPT may provide a clue to the diagnosis of food allergy. Of note, during early infancy, some patients negative for antigen-specific IgE antibodies in blood may give positive results in SPT.

Vegetables and fruits, which cause oral allergy syndrome, are unstable allergens. Thus, employ a prick-prick test using fresh vegetables and fruits (a needle used to prick food is used to prick the skin).

### 4.4. ANTIGEN-SPECIFIC IgE ANTIBODIES IN BLOOD

The presence of specific IgE antibody titers suggests antigen sensitization and do not necessarily indicate the induction of hypersensitive reactions. However, for some antigens (eggs, cow's milk, and peanuts), it is possible to depict the 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 antibody titers, with which food allergy can be diagnosed without food challenge tests (Table 5, Fig. 5).[13-16] However, since the values differ with reports, they should only be used as reference values.

Wheat and soybean-specific IgE antibody titers are correlated with positive predictive values in challenge tests. However, even if titers are above 100 UA/mL, positive rates do not exceed 95%. Wheat-specific IgE antibody titers are correlated with positive predictive values in challenge tests. Even if titers are above 100 UA/mL, positive rates are around 75%. Antibody titers which are predicted that positive rates in challenge tests are $\geq$95% cannot be calculated. IgE antibody titers specific for omega-5 gliadin show positive predictive values of 90% for Class 3 and almost 100% for Class 4 or above. However, the diagnostic sensitivity is around 77%, thus wheat allergy cannot be ruled out even if results are negative.[16]

Reportedly, a titer of 65 UA/mL of soybean-specific IgE antibody shows a positive predictive value of 86% in a challenge test. Antibody titers are weakly correlated with positive rates in challenge tests. A titer of 20 UA/mL of fish-specific IgE antibody shows a positive predictive value of 100% in a challenge test, but this has not been sufficiently reexamined.

These positive and negative predictive values were calculated using immediate reactions as parameters, thus they cannot be applied to nonimmediate reactions.

Reportedly, the incidence of induced symptoms requiring treatment becomes higher as specific IgE antibody titers increase. Many reports show that specific IgE antibody titers do not reflect provocation thresholds or the severity of induced symptoms in challenge tests.

### 4.5. BASOPHIL HISTAMINE RELEASE TEST

A basophil histamine release test is used to measure the amount of histamine released from peripheral blood basophils after reactions with allergens. This is an *in vitro* test which most accurately reflects specific IgE antibodies in the living body. "HRT Shionogi®," covered by health insurance, can be used for clinical laboratory tests. This kit allows simultaneous tests of response to egg white, cow's milk, wheat, soybean and rice. HRT Shionogi® greatly differs in its diagnostic usefulness depending on antigens. This kit is very useful for eggs, cow's milk, and wheat. The diagnostic sensitivity of immediate reactions is 93.0% for egg white (Class 4), 93.9% for cow's milk (Class 3 or above), and 93.8% for wheat (Class 4). Thus, this kit, combined with the above specific IgE antibody titers, is useful for conducting antigen detections without challenge tests in patients at higher risk of severe symptoms. However, this kit is less diagnostically useful for soybean and rice.

### 4.6. ELIMINATION TEST

Eliminate potential causative foods for about two weeks. Then, observe whether symptoms are improved. In infants receiving mother's milk or mixed feeding, eliminate the potential causative foods from the mother's diet.

### 4.7. ORAL FOOD CHALLENGE TEST[17,18]

An oral food challenge test is the most reliable in identifying the causative foods of food allergy. However, this test carries a risk of anaphylaxis in patients,[17] so it is important to ensure safety. Preferably, the food challenge tests should be conducted by physicians skilled in the treatment of food allergy and management of anaphylaxis. For treatment at outpatient departments or clinics, prepare for immediate hospitalization. Criteria for facilities are determined to conduct food challenge tests as healthcare services provided by health insurance. Thus, make a notification according to them.

#### 4.7.1. Objectives

(1) Identification of the causative foods of food allergy:

i) Challenge tests, conducted following elimination tests if food allergy may be involved in atopic dermatitis, etc.
ii) Determination of causative allergens if immediate reactions are predominant symptoms.
iii) Challenge tests, conducted when sensitization to foods of interest was demonstrated by positive specific IgE antibodies, but the presence of induced symptoms is unknown because the foods are not consumed.

(2) Determination of tolerance acquisition.

#### 4.7.2. Ensuring Safety

(1) Conduct tests under the supervision of physicians and nurses.

(2) Prepare agents for emergency, such as adrenaline (epinephrin) (Bosmin®, Adrenaline Syringe®), steroids, antihistaminics, bronchodilators (inhaled β2 stimulants, aminophylline), and transfusion sets.

(3) Postpone the test if symptoms such as fever and diarrhea occur.

(4) Start with small dosage and increase gradually.

(5) If symptoms occur, discontinue tests to conduct treatment if needed.

**Table 6** Induced symptoms and their grades in an oral challenge test

| Grade | Skin | Digestive system | Respiratory system (mucous membrane) | Circulatory system | Nervous system |
|---|---|---|---|---|---|
| 1 | - Mild small erythema<br>- Wheal (≤3)<br>- Itch of eczema | - Mild nausea<br>- Discomfort and itch in the mouth and pharynx | - | - | - |
| 2 | - Localized erythema<br>- Wheal (3-10)<br>- Slight exacerbation of eczema<br>- Increased scratching | - Vomiting (once or twice) or diarrhea<br>- Temporary abdominal pain | - Sneezing<br>- Rhinorrhea and nasal blockade<br>- Scratching of the nose and eyes<br>- Cough (<10 times) | - | - Mild depression |
| 3 | - Systemic erythema and wheal<br>- Marked itch<br>- Angioedema | - Vomiting (≥3 times) or diarrhea<br>- Persistent abdominal pain | - Cough (≥10 times)<br>- Wheezing<br>- Hoarseness and barking cough<br>- Dysphagia | - Tachycardia (increase of ≥15 times/min)<br>- Ill complexion | - Decreased activity level or dysphoria |
| 4 | Same as the above | - Frequent vomiting and diarrhea | Add the following to the above:<br>- Dyspnea<br>- Reduced wheezing<br>- Cyanosis | - Arrhythmia<br>- Slight pressure decrease<br>- Coldness of limbs<br>- Sweating | - Vertigo<br>- Agitation and confusion |
| 5 | Same as the above | Same as the above | Add the following to the above:<br>- Respiratory arrest | - Severe bradycardia<br>- Severe hypotension<br>- Cardiac arrest | - Unconsciousness |

### 4.7.3. Preparation

(1) Prepare for tests (staff, equipments, medicines, etc.) considering the risks of anaphylaxis.

(2) Explain objectives, methods, risks, and measures for hypersensitivity, etc., and obtain informed consent in written form.

(3) Before tests, discontinue the use of agents, which influence test results, such as antiallergic drugs, histamine H1 receptor antagonists, β2 stimulants, theophylline, oral disodium cromoglicate, Th2 cytokine inhibitors, leukotriene receptor antagonists and steroids.

### 4.7.4. Administration Methods

(1) Open test: Both the examiners and the subjects know the content of the challenge food. If the symptoms are subjective, reexamine in a blind manner.

(2) Single-blind food challenge: Examiners know the content of the challenge food, while the subjects do not. For blinding, mix a challenge food with masking stuff, such as juice, puree, oatmeal and hamburger. Powdered foods may be used as challenge tests. A challenge test is conducted using a placebo (e.g., masking food alone or a mixture of masking food and food other than what is in the challenge test), in addition to the challenge test of interest, on a different day.

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

### 4.7.5. Protocol of 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. Thus, divide the total amount of challenge diet into 3-6 portions and gradually increase the amount fed. 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, thus it will be more likely to prevent unnecessary dose-up before symptoms develop. Foods are given at intervals of 15-30 min because of the time restriction of challenge tests. Within the scheduled observation period, make note of possible signs of induced symptoms such as mild redness and small wheals around the mouth and mild cough. Make flexible judgments such as prolonging the observation period or reducing the dosage 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 mostly occur within 1-2 h after intake. Thus, even if no symptoms occur, patients should remain in hospitals for about 2 h after the last intake. Explain to patients that symptoms may occur within 24 h. Then, instruct them about what measures to take before going home. If nonimmediate reactions are predicted, prolong the observation period as needed, e.g., one-day hospitalization.

(4) Classification of induced symptoms (Table 6): Not all symptoms are prerequisites. Severity is classified based on the most severely affected organ. For example, if respiratory symptoms of Grade 3 and gastrointestinal symptoms of Grade 1 are noted, the severity is Grade 3.

## 5. PREDICTION, PROPHYLAXIS, AND NATURAL HISTORY OF FOOD ALLERGY

### 5.1. PREDICTION OF FOOD ALLERGY

Although a few of studies have reported that the measurement of cord blood total IgE level, combined with a family history of allergy, is useful in predicting the development of allergic disorders, the measurement of cord blood total IgE level is not sensitive enough to predict the development of allergic disorders. Therefore, the measurement of cord blood total IgE level is not recommended for screening test.

### 5.2. SUBJECTS AND METHODS OF THE PROPHYLAXIS OF FOOD ALLERGY

There is no evidence that the incidence of childhood allergic diseases is reduced by eliminating food allergens from the mother's diet during pregnancy. Thus, dietary restriction during pregnancy is not recommended.

There have been many reports that eliminating food allergens from the diets of breast-feeding mothers does not reduce the incidence of allergic diseases after infancy. Thus, dietary restriction during breast-feeding is not recommended as a prophylactic measure for food allergy. If mothers and their children undergo dietary restriction during lactation, the incidence of atopic dermatitis temporarily declines, and specific IgE levels significantly are decreased. However, these effects are temporary. In addition, dietary restriction continued from late gestation through lactation has no long-term prophylactic effects. There is no evidence that an elimination diet reduces the incidence of childhood allergic diseases over long periods. In addition, there are case reports from showing poor weight gain in pregnant women and impairment in fetal growth due to nutritional deficiency during pregnancy. Thus, caution should be exercised for elimination diets.

### 5.3. NATURAL HISTORY OF FOOD ALLERGY

#### 5.3.1. Food Allergy and Allergic March

Childhood allergic diseases exhibits a natural history, in which various diseases, such as food allergy, atopic dermatitis, asthma and allergic rhinitis, develop with aging. This natural course is called allergic march. Food allergy occurs at an early stage.

#### 5.3.2. Tolerance of Food Allergy

Most patients with food allergy, which developed during infancy, become tolerant with aging to be able to eat causative foods. High remission rates are noted for eggs, cow's milk, wheat, and soybeans. However, the reported age of remission varies, mainly due to subject differences. Allergies to peanuts, nuts, sesame, and fish, which may continue for a long time, also remit although at lower rates.

## 6. THERAPY OF FOOD ALLERGY

Therapy of food allergy includes treatments to improve hypersensitivity due to causative foods (anaphylaxis, etc.) and those to prevent hypersensitivity (eliminate causative foods).

### 6.1. TREATMENTS TO IMPROVE HYPERSENSITIVITY DUE TO CAUSATIVE FOODS

#### 6.1.1. Treatments at Medical Institutions

Oral administration of a histamine H1 receptor antagonist (antihistaminics) is effective for local urticaria. An intramuscular injection of adrenaline (epinephrine) (1 : 1,000) (Bosmin® or Adrenaline syringe®; 0.005-0.01 mL/kg for children to a maximum of 0.3 mL, 0.2-1 mL for adults) is the first choice for anaphylaxis. Injections can be repeated every 10-15 min. The anterolateral part of the thigh is the preferred injection site because of rapid absorption. Reportedly, immediate adrenaline injection (within 30 min) after the onset of symptoms is important for patients with the potentially fatal prognosis of anaphylaxis.

The timing of adrenaline injection is still controversial. Histamine H1 receptor antagonist can be orally administered to patients in Grades 1 and 2 as described in Table 6. Intramuscular adrenaline injection is required for patients in Grade 3 or above. For patients with a history of severe anaphylactic symptoms (Grade 4 or above), such as respiratory symptoms, decreased blood pressure, and impaired consciousness, adrenaline should be injected even if no symptoms occur after intake of causative food.

Place a patient with anaphylactic shock in the supine position with the lower limbs raised by 15-30 cm (shock posture). Perform oxygen inhalation for dyspnea (<95% $SpO_2$). In patients with laryngeal edema, administer adrenaline, inhaled corticosteroid, and intravenous steroid. In patients with bronchoconstriction, conduct β2 stimulant inhalation.

Steroids, such as methylprednisolone (Solu-

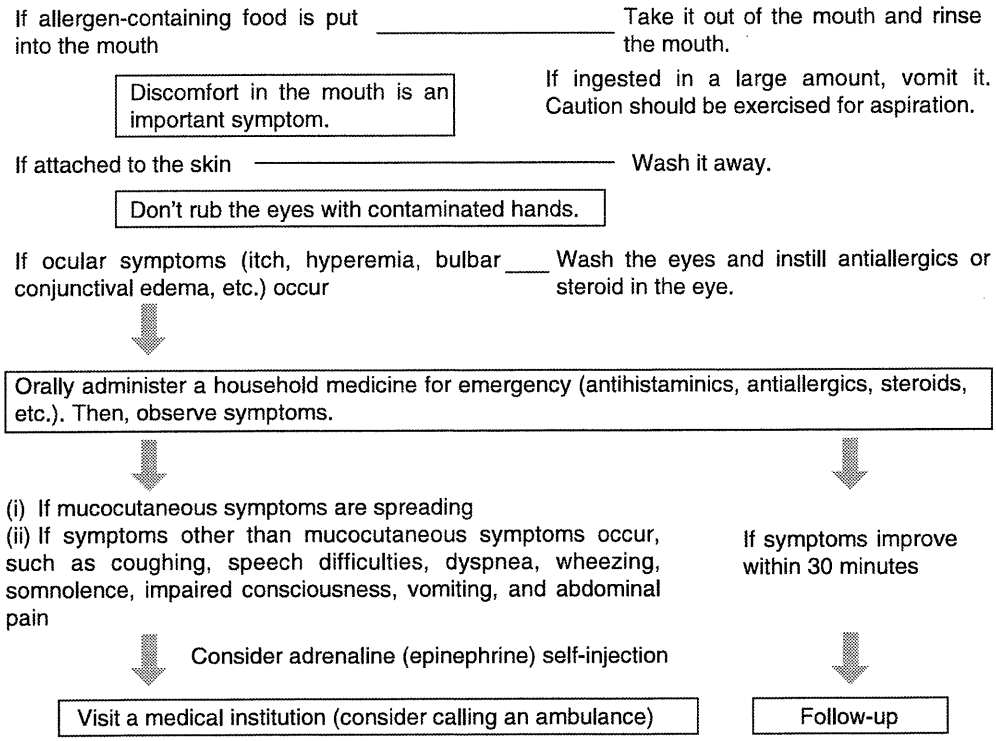


**Fig. 6** Treatment out of medical institutions.

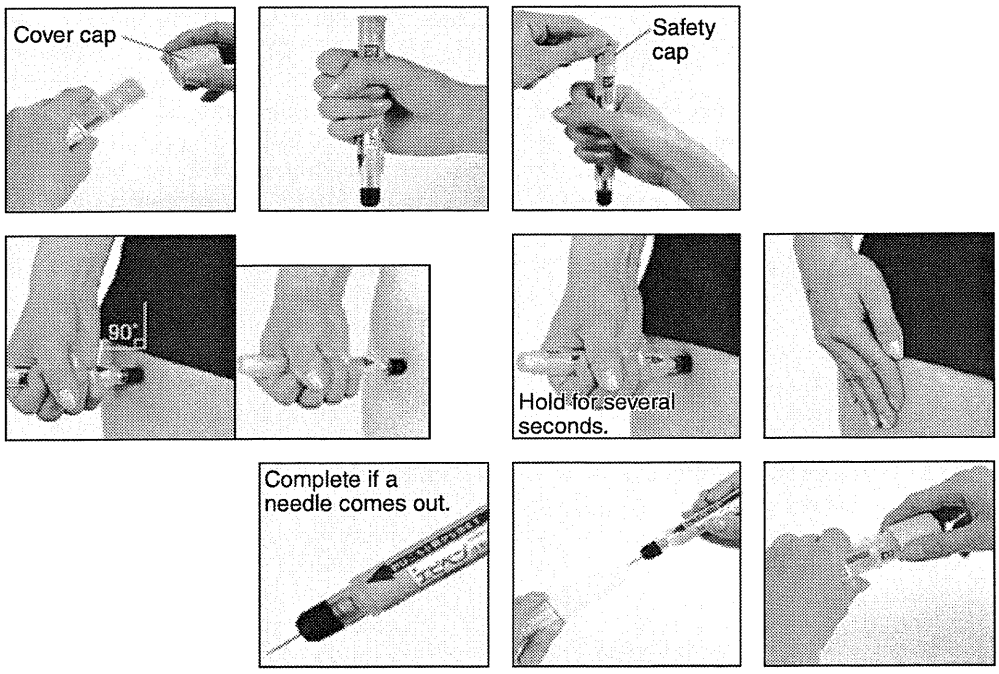


**Fig. 7** Injection of Epipen®. Caution should be exercised for thumb positioning to prevent accidental injection on the thumb. Thigh muscle is the recommended injection site.

Medrol®, 1-2 mg/kg) and hydrocortisone (5-10 mg/kg), are intravenously injected.

Dual response may occur. Thus, even if patients with anaphylaxis recover after ambulatory treatment, they should be observed for at least 4 h.

### 6.1.2. Measures at Places Other than Medical Institutions (Fig. 6)

Instruct patients with a history of anaphylaxis to carry medicines for the first-aid treatment of hypersensitivity (histamine H1 receptor antagonists, oral corticosteroids [prednisolone], or adrenaline for self-injection [Epipen®]). For patients with food allergy complicated by asthma, inhaled β2 stimulants are also needed.

According to the "Guidelines for the Treatment of Allergic Diseases in Schools",[16] there is no legal problem with school staff injecting Epipen® if patients cannot inject it themselves. However, there are many other problems with injection, so staff should receive technical training. In March 2009, the Ministry of Health, Labour and Welfare issued a notification that ambulance staff can inject Epipen® if patients carry it. Epipen® (0.15 mg of Epipen® injection for 15-30 kg body weight; 0.3 mg for ≥30 kg body weight) can be prescribed only by qualified physicians who received training. Before prescription, patients and their guardians should receive technical training (Fig. 7).

Measures for accidental ingestion are shown in Figure 6. First, cause the patient to bring up an accidentally ingested food by beating the back. At this time, caution should be exercised for aspiration. Then, rinse the mouth. If ocular symptoms occur after rubbing the eyes with hands exposed to causative foods, wash the eyes and administer eye-drops such as antihistaminics or steroids. In addition, orally administer household medicines for emergency, prescribed by physicians, such as histamine H1 receptor antagonists and steroids. If symptoms are exacerbated or symptoms occur in multiple organs, immediately consult a medical institution. At this time, consider calling an ambulance and using an Epipen®.

If anaphylactic shock is suspected, place the patient in the shock position with the lower limbs raised by about 30 degrees. Then, wait for an ambulance. Start resuscitation to help patients in cardiopulmonary arrest.

## 6.2. TREATMENT TO PREVENT HYPERSENSITIVITY

The elimination of causative foods is the most reliable prophylactic method of hypersensitivity caused by food allergy. However, this places various burdens on patients and their guardians. Ensuring safety by causative food elimination, preventing nutritional disorders, and improving the quality of dietary life are essential for diet therapy. For these purposes, consider eliminating minimal causative foods.

### 6.2.1. Minimal Elimination Diet

(1) Correctly identify causative foods.

To minimize the number of causative foods to be eliminated, it is important to identify causative foods correctly (see the method to identify causative foods).

(2) Even if the food is positive for specific IgE antibodies and in a skin prick test, do not eliminate the foods if it is negative in an oral challenge test.

(3) Periodically check tolerance to foods that patients tend to outgrow.

Tolerance to buckwheat, peanuts, nuts, fish, shellfish, sesame, etc., is unlikely to develop. On the other hand, allergies to eggs, cow's milk, soybeans, etc., often remit with aging. Do not continue the elimination diet, but rather conduct a challenge test once or twice a year to determine continuance of symptoms. Even if infants have allergies to peanuts and fish, a part of them may develop tolerance.

(4) Not all the foods with cross-reactivity with allergenic ones should be eliminated.

Wheat and rice are both gramineous plants and cause cross-reactivity in terms of IgE-binding capacity. However, most patients with wheat allergy can eat rice. Alternate kinds of beans and fish may be consumed even if a single species of them cause symptoms.

(5) Don't eliminate all foods even if they are of the same biological lineage.

The burden on patients can be reduced by determining elimination in reference to the degree of allergenicity of foods belonging to the same biological lineage.

The allergenicity of egg white is reduced by heating. Thus, about half of patients, for whom raw eggs should be eliminated, can consume heated eggs.

The allergenicities of fermented foods (e.g., miso and soy sauce) are reduced. Thus, many patients can consume them even if they are hypersensitive to soybeans and tofu. The allergenicity of natto (fermented soybeans) is also reduced compared with soybeans.

Fruits (e.g., apples and tomatoes) can be often consumed because their allergenicities are reduced by heating and processing. For example, most patients can consume tomato juice and ketchup even if they cannot consume fresh tomatoes. About 90% of patients with milk allergy can eat beef without hypersensitive reactions.

### 6.2.2. Elimination Diet without Nutritional Problem

(1) Instruction of alternative foods.

Elimination diet therapy may cause nutritional poblem in affected children. Caution should be exercised particularly for patients with allergy to multiple foods. Instruct them about suitable edible foods, as

**Table 7** Specific raw materials, for which labeling is mandated or recommended

| | Specific raw materials | Reasons for selection |
|---|---|---|
| Mandatory | Egg, milk, wheat, shrimp, crab | Allergies to these foods are common. |
| | Buckwheat, peanut | Caution should be exercised because of severe and life-threatening symptoms. |
| Recommended | Abalone, squid, salmon roe, orange, kiwi fruits, beef, walnut, salmon, mackerel, soybean, chicken, pork, matsutake mushroom, peach, yam , apple, banana | Allergies to these foods are less common. Thus, further surveys are needed for the ministerial ordinance to designate them. |
| | Gelatin | Many public comments demand independent labeling as "gelatin." Many specialists also request this labeling. |

Adapted from Food Sanitation Act, revised in June 2008.

well as eliminated foods, for nutritional management. Here, dietitians familiar with food allergy play a major role.

(2) Use of alternative foods.

Alternative foods for patients with food allergy include low allergenic foods and allergen-free or allergen-reduced foods, produced using low allergenic food materials.

Low allergenic foods include stuff using peptides and amino acids, reduced in molecular sizes by enzyme treatment. For example, hydrolyzed casein formula (New MA-1®), hydrolyzed whey formula (MA-mi®, Milfee HP®), amino acid formula (Elemental Formula®), etc., are available.

Commercially available main allergen-free packaged foods include those in which 25 food allergens are not used as raw materials. Allergen-reduced foods include low allergenic rice.

(3) Assessment of growth and development.

The growth and development of children must be assessed. Measure weight and height over time and graph them on charts. Growth graphs in maternal and child health handbooks are useful.

#### 6.2.3. Check Food Labels before Purchase

Table 7 shows 7 items for which labeling is mandated and 18 items for which labeling is recommended. Instruct patients to check food labels before purchase.

### 6.3. ANTIGEN SPECIFIC ORAL IMMUNOTHERAPY OF FOOD ALLERGY

Tolerance is more likely to develop to orally administered antigens. Antigen specific oral immunotherapy has also been initiated to treat food allergy. Elimination diet therapy is a negative treatment, while this immunotherapy is called active treatment, with the goal of causing remission of food allergy. The effects of oral immunotherapy have been recognized, but problems with safety and permanent tolerance remain.[19]

## *7. SOCIAL MEASURES FOR FOOD ALLERGY*

Hand instructions (medical certificates), which indicate foods to be eliminated, to guardians. Instruct staff of kindergarten and schools to have a discussion based on the instructions. Use the instruction table attached to the "Guidelines for the Treatment of Allergic Diseases in Schools" for management (Table 8).[16]

## *8. POINTS TO REMEMBER IN TREATING ALLERGIES COMPLICATED BY OTHER DISEASES*

### 8.1. ATOPIC DERMATITIS

The exacerbation factors of atopic dermatitis vary with age. Atopic dermatitis, associated with food allergy, is common among infants and decreases with aging.

The basic therapy of atopic dermatitis, associated with food allergy, is the same as that outlined in the Guidelines for the Management of Atopic Dermatitis 2009. The following comprehensive therapies are essential.

#### 8.1.1. Pharmacotherapy

This entails the proper use of topical steroids or Protopic ointment® (for children aged ≥2 years), histamine H1 antagonists for itching, antimicrobials to treat skin infection.

#### 8.1.2. Skin Care

Ensure that skin is protected by bathing and showering, applying moisturizer, using bandages or supporter, etc.

#### 8.1.3. Diet Therapy (e.g., Eliminating Causative Foods) and Measures Against Causative and Exacerbation Factors

Many patients with atopic dermatitis associated with food allergy are simultaneously involved in other causative and exacerbation factors. Thus, measures other than eliminating causative foods are often taken.

Causative foods, including the exacerbating foods of atopic dermatitis and the causative foods of immediate-type allergy, should be eliminated.

**Table 8** Food allergy and anaphylaxis in certificate for school life management (for allergic diseases)

Name _____ Male/Female Birthday (age)_____( ___) School name _____ Grade/Class_____ Date of submission:_____

Certificate for school life management (for allergic diseases)

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

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 < > ( )

[Grounds for diagnosis] Describe all relevant items in <>.
(i) History of marked symptoms
(ii) Positive for food challenge test
(iii) Positive for IgE antibody test

D. Prescriptions for emergency
1. Oral medicines (antihistaminics and steroids)
2. Adrenaline self-injection "Epipen®"
3. 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:

Date of description

Name of physician

Name of medical institution

Adapted from http://www.gakkohoken.jp./book/bo0002.html.

**Table 9** Points to remember in referral to food allergy specialists

| |
|---|
| 1. Accurate diagnosis by 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 |

Examine whether specific IgE antibody-positive foods can be consumed, referring to the degree of sensitization at the time of initial intake. Carefully start feeding from small amounts based on the results of oral challenge test.

Infants with severe atopic dermatitis, positive for various food antigen specific IgE antibodies, may suffer from malnutrition and growth disorder, including hypoproteinemia and poor weight gain. Some patients may develop hypersensitivity because they are positive for IgE antibodies specific for various food antigen, and may suffer from malnutrition because they cannot consume baby foods. Although rare, some infants suffer from atopic dermatitis caused by unnecessary excessive dietary restrictions, delayed start of baby foods, and inappropriate folk medicine.

Early intervention is desired to prevent severe atopic dermatitis. Specifically, points to remember include: (i) appropriate application of steroid ointment and skin care at an early stage for favorable management; (ii) appropriate diet therapy, aimed at minimal elimination diets and nutrition management by edible foods; (iii) check of growth (weight and height) and development; and (iv) mental support for guardians, especially mothers.

### 8.2. BRONCHIAL ASTHMA

Remember that anaphylactic shock is common among patients with food allergy complicated by bronchial asthma.

### 8.3. ALLERGIC RHINITIS

OAS is established through sensitization to pollen, and is developed after intake of foods that share cross reactivity with pollen. Thus, OAS is often complicated by pollinosis. At the consultation, examine nasal symptoms. In patients with pollinosis, examine abnormalities in the mouth after ingestion of fruits and vegetables.

## *9. POINTS TO REMEMBER IN REFERRAL TO SPECIALISTS*

Table 9 summarizes the issues to consider when making a referral to a specialist.

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## IgE to Gly m 5 and Gly m 6 is associated with severe allergic reactions to soybean in Japanese children

*To the Editor:*

Soybean is 1 of 8 foods believed to cause a majority of food-induced allergic reactions in children.[1,2] However, the prevalence of soybean allergy in Japan might be higher than in Europe and the United States, with soybean reported as the fifth most common food allergen causing anaphylaxis.[3] Soybeans contain about 40% protein, the majority of which is composed of the 2 storage proteins β-conglycinin and glycinin, which have been recently designated Gly m 5 and Gly m 6.[4] Four other proteins are officially accepted as allergens, and at least an additional 12 have been reported as IgE-reactive proteins.[5] Data regarding soybean allergens associated with clinical symptoms in children are limited. In this study we have examined the IgE reactivity pattern to 5 soybean and 3 cross-reactive allergens in a group of children with and without soybean allergy. Furthermore, we have investigated the clinical usefulness of analyzing specific IgE antibodies to Gly m 5 and Gly m 6.

There were 74 subjects (range, 0.6-16.3 years), of whom 33 were given diagnoses of soybean allergy (symptomatic group) based on challenge outcome (n = 29) or clinical history after intake (n = 4; 3 experienced apparent skin symptoms and 1 experienced anaphylaxis). The symptomatic group was further divided into subjects with severe symptoms (n = 14) and mild symptoms (n = 19). Severe symptoms were defined as a combination of skin, respiratory, or gastrointestinal symptoms, whereas mild symptoms were defined as isolated skin symptoms, oral symptoms, or both (Table I). The remaining 41 subjects were sensitized to soybean without any symptoms from soybean (nonsymptomatic group). Tolerance in the nonsymptomatic group was either confirmed by means of food challenge (n = 22) or a history of daily ingestion of soybean products (n = 19). Food challenges were conducted in accordance with the Japanese guidelines.[6]

IgE reactivity to 8 different allergens was tested in an in-house, qualitative multiplexed immunoassay, essentially as reported elsewhere.[7] The 8 allergens included in the setup were Gly m 5, Gly m 6, rGly m 4, soybean Kunitz trypsin inhibitor (Sigma-Aldrich, St Louis, Mo), soybean agglutinin (Vector Laboratories, Peterborough, United Kingdom), Cross-reactive carbohydrate determinants (CCDs) purified from digested bromelain (essentially MUXF3), profilin from timothy pollen (rPhl p 12), and lipid transfer protein from peach fruit (rPru p 3). Native Gly m 5 and Gly m 6 were essentially purified according to the method of Thanh and Shibasaki.[8] All recombinant allergens, as well as the CCD reagent, were produced at Phadia AB (Uppsala, Sweden).

IgE antibody levels to soybean, Gly m 5, and Gly m 6 were analyzed in serum by using ImmunoCAP (Phadia AB), all of which were commercially available. The lower limit of quantitation of the tests was 0.10 $kU_A/L$. The Fisher exact test was used to determine differences regarding the prevalence of IgE reactivity analyzed by using the multiplex assay (categorical data). The Spearman rank correlation test was used in the analysis of associations between IgE concentrations. The relationship between IgE concentrations and clinical status outcome was analyzed by using logistic regression analysis. Odds ratios were estimated by using regression models, and 95% CIs were generated according to the Wald test.

Among the children in the symptomatic group with mild symptoms, all had skin symptoms, and 3 had oral symptoms (Table I). Respiratory symptoms, mostly coughing and wheezing, were the most frequent symptoms (n = 12) in the severe group. The multiplex immunoassay showed that among the children in the symptomatic group, 67% had IgE reactivity to Gly m 5 (49% in the nonsymptomatic group), 58% to Gly m 6 (39% in the nonsymptomatic group), 21% to Gly m 4 (20% in the nonsymptomatic group), and 6% to soybean agglutinin and soybean trypsin inhibitor (7% and 10%, respectively, in the nonsymptomatic group). The number of subjects with IgE reactivity to lipid transfer protein, profilin, and CCDs varied between 12% and 15% (7% to 17% in the nonsymptomatic group). No significant difference in the frequency of IgE reactivity between the symptomatic and nonsymptomatic groups was observed for any of the allergens included in the study. However, a tendency toward a higher frequency of IgE reactivity in the symptomatic group was noted for both Gly m 5 and Gly m 6 ($P = .16$ for both). Therefore quantitative analysis of IgE to Gly m 5 and Gly m 6 was performed to investigate the true prevalence.

Analysis with ImmunoCAP demonstrated that all children had IgE levels to soybean, Gly m 5, and Gly m 6 of greater than 0.1 $kU_A/L$, except one in the nonsymptomatic group. The IgE levels to both Gly m 5 and Gly m 6 correlated with the IgE levels to soybean ($r_S = 0.89$ and $r_S = 0.86$, respectively). The IgE levels to soybean and Gly m 5 were significantly higher in the symptomatic group than in the nonsymptomatic group ($P < .01$). With respect to the specific IgE levels in the 2 groups, the risk of being allergic to soy increased significantly with increasing levels of IgE. For IgE to soybean, the odds increased 1.51-fold (95% CI, 1.10-2.08), and for IgE to Gly m 5, the odds increased 1.48-fold (95% CI, 1.08-2.02) per logarithmic unit increase, respectively. Significant differences were noticed between the severe and nonsymptomatic groups in IgE levels to soybean, Gly m 5, and Gly m 6 (Fig 1). The IgE responses to soybean, Gly m 5, and Gly m 6 were not statistically different between the children with mild symptoms and the nonsymptomatic children. Significant differences in the IgE levels to soybean were detected between the mild and severe symptom groups but not in the IgE levels to Gly m 5 and Gly m 6.

Knowledge about specific soybean allergens associated with clinical symptoms is restricted to a few publications. Many studies demonstrating IgE reactivity to soybean proteins in sera from soybean-sensitized subjects have been published, but the patient material has generally been small and often with an unclear diagnosis. In this study we have examined IgE reactivity to 5 soybean and 3 cross-reactive allergens in sera from 74 Japanese children. To the best of our knowledge, this group, consisting of symptomatic and nonsymptomatic subjects, is the largest defined clinical sample tested with the aim of identifying important soybean allergens.

**TABLE I.** Demographic, serologic, and clinical characterization of study subjects

| Patients' characteristics | | Symptomatic (n = 33) | Nonsymptomatic (n = 41) |
|---|---|---|---|
| Sex | Male/female | 20/13 | 32/9 |
| Age | Median (y [range]) | 2.3 (0.7-16.3) | 2.0 (0.6-10.3) |
| Total IgE | Median (kU/L [range]) | 1,282 (29-22,300) | 900 (15-15,360) |
| Specific IgE to soybean | Median ($kU_A$/L [range]) | 17.1 (0.36-92) | 3.6 (0.54-77.3) |
| Diagnosis of soybean allergy | Oral food challenge | 29 | 22 |
| | History | 4 | 19 |
| Graded symptoms | Severe/mild* | 14/19 | — |
| Symptoms after challenge or intake (severe/mild) | Skin | 11/19 | — |
| | Mucosal | 2/3 | — |
| | Respiratory | 12/0 | — |
| | Gastrointestinal | 3/0 | — |

Symptoms after challenge or intake are specified in the symptomatic children.
*Severe symptoms are defined as a combination of skin, respiratory, or gastrointestinal symptoms, and mild symptoms are defined as isolated skin symptoms, oral symptoms, or both.

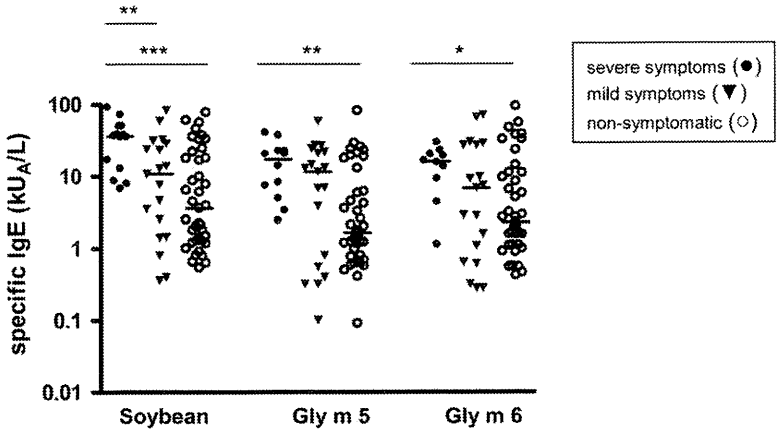


**FIG 1.** Quantitative IgE measurement for soybean, Gly m 5, and Gly m 6. Comparison of IgE antibody levels between children with severe symptoms, mild symptoms, and no symptoms is shown. The Mann-Whitney *U* test (2-tail) was used to compare the statistical differences between the study groups, and significant differences are indicated as follows: $*P < .05$, $**P < .01$, and $***P < .001$.

Of the 5 soybean allergens included in the multiplex assay, only the 2 storage proteins Gly m 5 and Gly m 6 were defined as major allergens. In fact, when using the more sensitive ImmunoCAP system, it was found that all children in the symptomatic group had IgE to Gly m 5 and Gly m 6. Holzhauser et al[4] also found a large number of subjects with IgE antibodies to the same 2 proteins in European children and adults with soybean allergy, but they were not considered to be major allergens in their study group. The reason for Gly m 5 and Gly m 6 being found as major allergens in the present study might be the study group composition of children only or might depend on Japanese eating habits, with soybean being part of the daily food intake.

We found that IgE levels to Gly m 5, but not to Gly m 6, were significantly higher in the symptomatic group when compared with those in the nonsymptomatic group. Because of the significant overlap of individual values between the symptomatic and nonsymptomatic groups, it was not possible to decide on a predictive IgE level for clinical symptoms. In earlier studies Sampson[1] showed that the positive predictive level for specific IgE to soybean was estimated at 30 $kU_A$/L, and Komata et al[9] showed an association between the level of IgE to soybean and positive challenge outcomes for soybean. In the present study it was shown that increasing IgE levels to both soybean and Gly m 5 correlated with increasing risk for clinical reactions.

Significant differences between the IgE levels to Gly m 5 and Gly m 6 were seen between the group of children with severe symptoms and the nonsymptomatic children. A similar trend was seen in the study by Holzhauser et al,[4] in which severe symptoms correlated with the presence of IgE to Gly m 5 and Gly m 6.

It is worthwhile noting that measurement of IgE levels to soybean extract provides the best differentiation between the symptomatic and nonsymptomatic groups. This is also true after dividing the symptomatic group into subjects with severe and mild symptoms. The major constituents in the soybean extract are the 2 storage proteins Gly m 5 and Gly m 6, and there was also a very good correlation between the IgE levels to soybean and those 2 proteins. Nevertheless, this might reflect that there are other nonidentified components present in the soybean extract to which IgE might have a predictive value. However, the well-recognized problem with IgE analysis based on soybean extract is the poor sensitivity, probably because of the presence of cross-reacting IgE antibodies primarily induced to allergens from other allergen sources, such as pollen, resulting in many sensitized subjects without symptoms from

soybean.[1,10] Analysis of IgE antibodies to Gly m 5 and Gly m 6 will therefore most likely better predict soybean allergy than an extract-based test.

Interpretation of the severity of allergic symptoms through the level of sensitization is a complex matter, but this risk assessment is of great importance for the prediction of severe and potentially fatal reactions. In this study the levels of IgE responses to Gly m 5 and Gly m 6 were found to be associated with severe clinical reactions caused by soybean in Japanese children.

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## TNF-α blockade in chronic granulomatous disease–induced hyperinflammation: Patient analysis and murine model

*To the Editor:*

Chronic granulomatous disease (CGD), a genetic deficiency in the phagocyte nicotinamide adenine dinucleotide phosphate oxidase 2 (NOX2), leads to severe recurrent infections but also to exuberant inflammatory responses. Because infections have a major effect on mortality, they have been the main focus of CGD research and therapies, resulting in markedly increased survival. Because of the improved management of infections, inflammatory complications are now an increasingly important problem. Almost any organ can be affected, with the gut being probably the most common site.[1,2] Although hyperinflammation might not lead to a major increase in mortality, it is associated with high morbidity.

A breakthrough in research on CGD-induced hyperinflammation was the generation of Nox2-deficient mice with CGD, leading to the development of a skin model of inflammatory complications by Dinauer.[4] Indeed, injection of sterile fungal cell wall and more specifically β-glucan into the skin of mice with CGD leads to massive hyperinflammation and ultimately granuloma formation.[4,5] Note that injection of sterile bacterial cell wall components did not lead to hyperinflammation.[5] Underlying mechanisms are still poorly understood; however, a common observation is an increase in levels of proinflammatory cytokines, particularly TNF-α,[6,7] which is often cited as a possible culprit in CGD-induced inflammatory states.[3]

The following lines of argument suggest that TNF-α inhibition might be a pertinent treatment approach: (1) inflammatory cells from patients with CGD release increased amounts of proinflammatory cytokines, particularly TNF-α; (2) anti–TNF-α treatments have been successfully used in other types of inflammatory diseases (eg, rheumatoid arthritis and Crohn disease); and (3) inflammatory complications in the context of other immunodeficiencies are improved by TNF-α blockers. However, it is not clear whether the increased secretion of TNF-α by leukocytes from patients with CGD is a causative mechanism in hyperinflammation. Yet despite the lack of information about the role of TNF-α in CGD-induced hyperinflammation, there is an increasing off-label use of anti–TNF-α treatments in patients with CGD. Indeed, the use of these compounds in the treatment of CGD-induced inflammatory complications has been suggested in several publications and is included in recent algorithms of CGD management. In fact, short-term treatment with infliximab has been proposed as the second-line treatment in patients with steroid-refractory chronic granulomatous colitis.[8]

We first performed a literature review on the treatment of CGD-induced inflammatory complications with TNF-α inhibitors (see Table E1 in this article's Online Repository at www.jacionline.org). We found indications for off-label use of TNF-α inhibitors in patients with CGD; indeed, we could identify a total of 17 published cases. Patients with autosomal recessive mutations are overrepresented in the collection (11/17 [65%]), and 7 of these presented with inflammatory bowel disease or arthritis as initial symptom (see patients marked by asterisks in Table E1). Note that in general autosomal recessive mutations represent approximately 30% of patients with CGD. Only in 5 patients was a clear and sustained response to treatment observed. The treatment response seemed genotype dependent: 4 (36%) of 11 autosomal

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# The usefulness of casein-specific IgE and IgG4 antibodies in cow's milk allergic children

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# Abstract

**Background:** Cow's milk allergy is one of the most common food allergies among younger children. We investigated IgE antibodies to milk, and IgE and IgG4 antibodies to casein, α-lactalbumin and β-lactoglobulin in cow's milk allergic (CMA) and non-allergic (non-CMA) children in order to study their clinical usefulness.

**Methods:** Eighty-three children with suspected milk allergy (median age: 3.5 years, range: 0.8-15.8 years) were diagnosed as CMA (n=61) or non-CMA (n=22) based on an open milk challenge or convincing clinical history. Their serum concentrations of allergen-specific (s) IgE and IgG4 antibodies were measured using ImmunoCAP®. For the sIgG4 analysis, 28 atopic and 31 non-atopic control children were additionally included (all non-milk sensitized).

**Results:** The CMA group had significantly higher levels of milk-, casein- and β-lactoglobulin-sIgE antibodies as compared to the non-CMA group. The casein test showed the best discriminating performance with a clinical decision point of 6.6 $kU_A/L$ corresponding to 100% specificity. All but one of the CMA children aged >5 years had casein-sIgE levels >6.6 $kU_A/L$. The non-CMA group had significantly higher sIgG4 levels against all three milk allergens compared to the CMA group. This was most pronounced for casein-sIgG4 in non-CMA children without history of previous milk allergy. These children had significantly higher casein-sIgG4 levels compared to any other group, including the non-milk sensitized control children.

**Conclusions:** High levels of casein-sIgE antibodies are strongly associated with milk allergy in children and might be associated with prolonged allergy. Elevated casein-