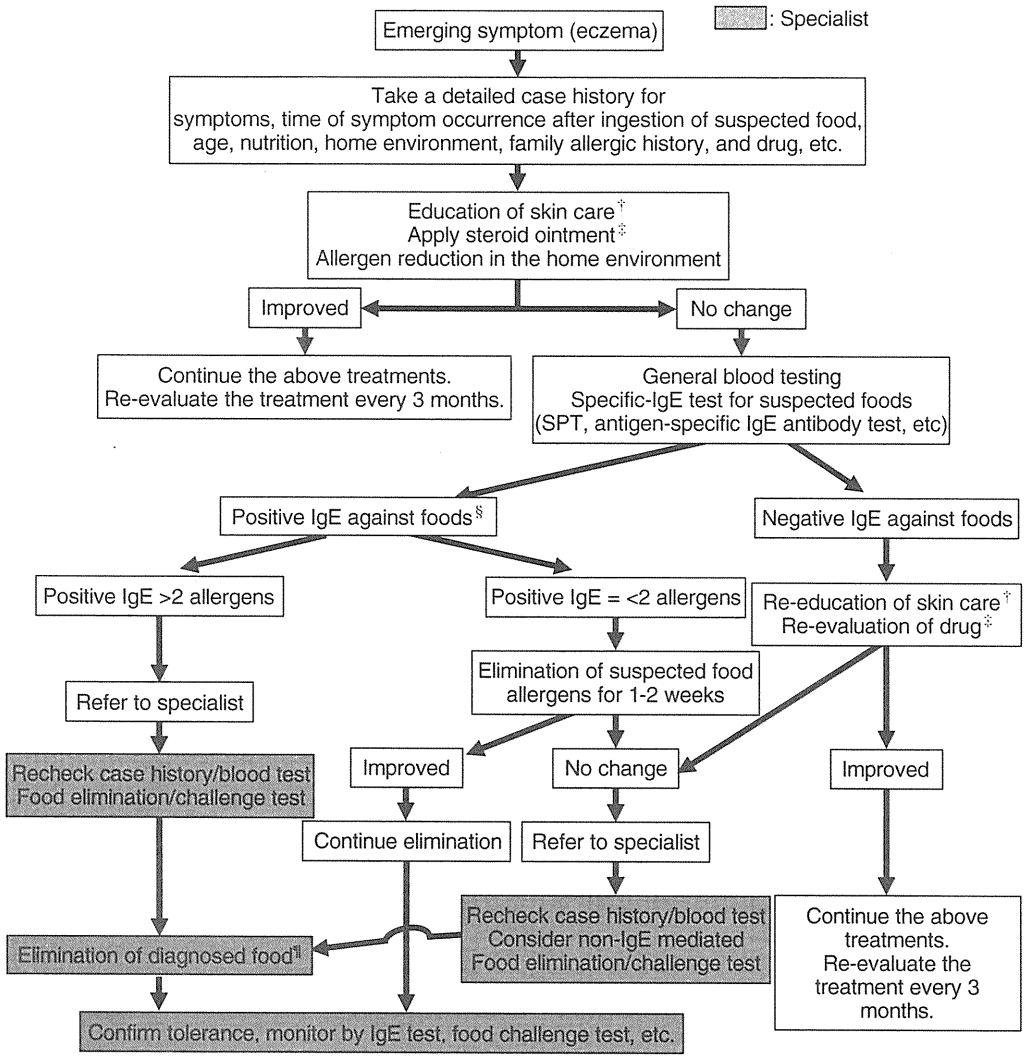

Fig. 4 Procedure for Diagnosis of Food Allergy (for "Infantile Atopic Dermatitis associated with Food Allergy"). SPT, skin prick test.

†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

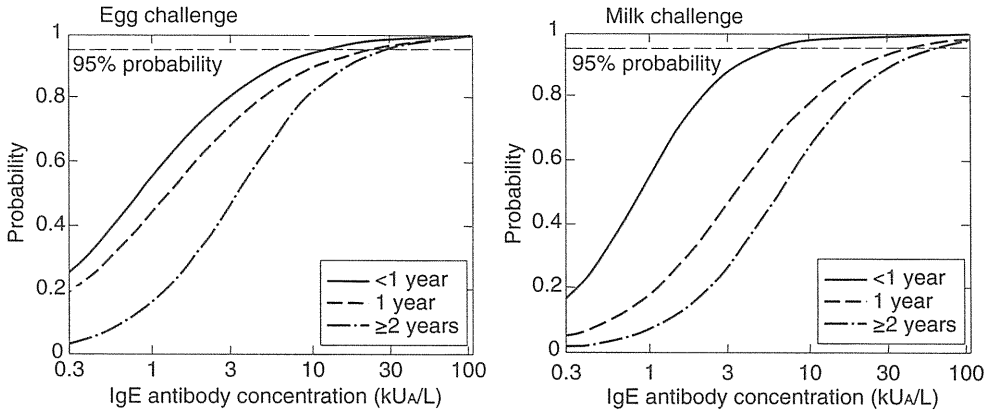

Fig. 5 Probability curves of egg white-specific and cow's milk-specific IgE antibody titers by age. Specific IgE antibody titers indicate the rate of positive immediate reaction (probability) in the food challenge test. However, these values should be used as reference, because they vary by reporters.

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

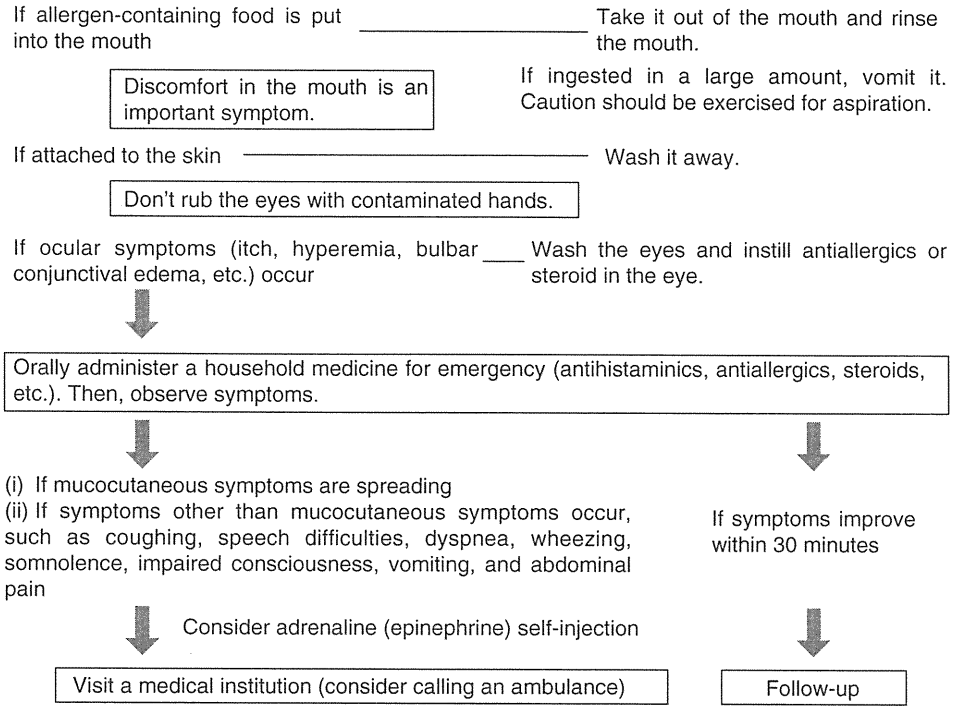

Fig. 6 Treatment out of medical institutions.

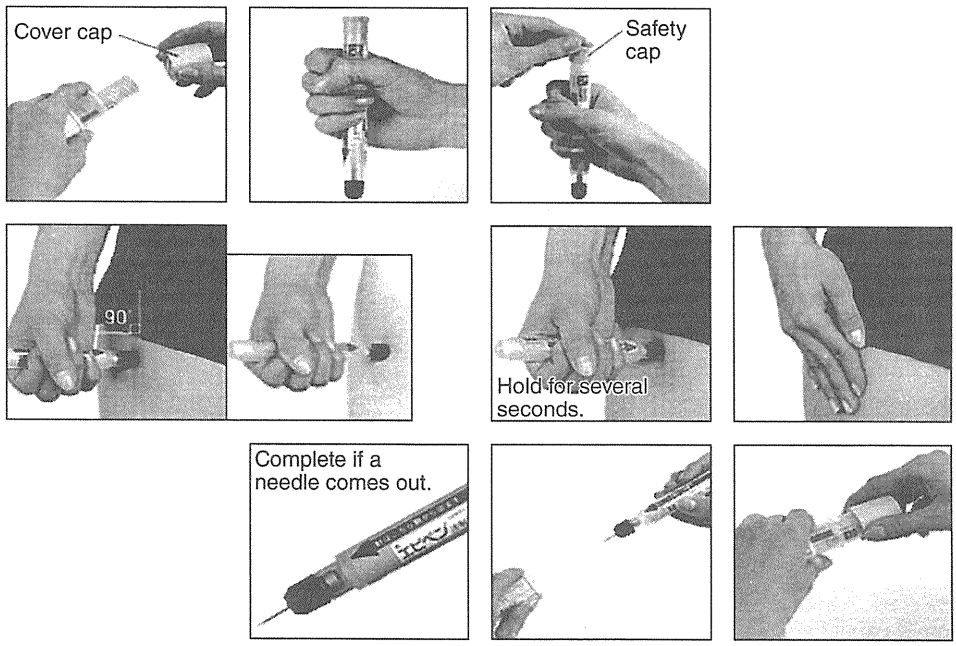

Fig. 7 Injection of Epipen®. Caution should be exercised for thumb positioning to prevent accidental injection on the thumb. Thigh muscle is the recommended injection site.

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)

Certificate for school life management (for allergic diseases)

Name _____ Male/Female Birthday (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

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.

REFERENCES

1. Food Allergy Committee, Japanese Society of Pediatric Allergy and Clinical Immunology. *[Japanese Pediatric Guideline for Food Allergy 2005]*. Tokyo: Kyowa Kikaku, 2005 (in Japanese).
2. Mukoyama T, Nishima S, Arita M *et al*, and Food Allergy Committee, Japanese Society of Pediatric Allergy and Clinical Immunology. Guidelines for diagnosis and management of pediatric food allergy in Japan. *Allergol Int* 2007;**56**:349-61.
3. Sampson HA. Food allergy: when mucosal immunity goes wrong. *J Allergy Clin Immunol* 2005;**115**:139-41.
4. Kondo N, Fukutomi O, Agata H *et al*. The role of T lymphocytes in patients with food-sensitive atopic dermatitis. *J Allergy Clin Immunol* 1993;**91**:658-68.
5. Burks AW, Laubach S, Jones SM. Oral tolerance, food allergy, and immunotherapy: implications for future treatment. *J Allergy Clin Immunol* 2008;**121**:1344-50.
6. Kondo Y, Urisu A. Oral allergy syndrome. *Allergol Int* 2009;**58**:485-91.
7. Nowak-Węgrzyn A, Muraro A. Food protein-induced enterocolitis syndrome. *Curr Opin Allergy Immunol* 2009;**9**: 371-7.
8. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol* 2010;**125**:S116-25.
9. Ohtsuka Y, Shimizu T, Shoji H *et al*. Neonatal transient eosinophilic colitis causes lower gastrointestinal bleeding in early infancy. *J Pediatr Gastroenterol Nutr* 2007;**44**:501-5.
10. Heiner DC, Sears JW, Kniker WT. Multiple precipitins to cow's milk in chronic respiratory disease. A syndrome including poor growth, gastrointestinal symptoms, evidence of allergy, iron deficiency anemia, and pulmonary hemosiderosis. *Am J Dis Child* 1962;**103**:634-54.
11. Aihara Y, Takahashi Y, Kotoyori T *et al*. Frequency of food-dependent exercise-induced anaphylaxis (FEIAn) in Japanese junior high school students. *J Allergy Clin Immunol* 2001;**108**:1035-9.
12. Ebisawa M. Management of food allergy in Japan. "Food Allergy Management Guideline 2008 (Revision from 2005)" and "Guidelines for the Treatment of Allergic Diseases in Schools". *Allergol Int* 2009;**58**:475-83.
13. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;**107**:891-6.
14. Komata T, Soderstrom L, Borres MP, Tachimoto H, Ebisawa M. The predictive relationship of food-specific serum IgE concentrations to challenge outcomes for egg and milk varies by patient age. *J Allergy Clin Immunol* 2007;**119**:1272-4.
15. Ando H, Movérare R, Kondo Y *et al*. Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy. *J Allergy Clin Immunol* 2008;**122**:583-8.
16. Ito K, Futamura M, Borres MP *et al*. IgE antibodies to omega-5 gliadin associate with immediate symptoms on oral wheat challenge in Japanese children. *Allergy* 2008; **63**:1536-42.
17. Food Allergy Committee, Japanese Society of Pediatric Allergy and Clinical Immunology. *[Japanese Pediatric Guideline for Oral Food Challenge Test in Food Allergy 2009]*. Tokyo: Kyowa-Kikaku, 2009 (in Japanese).
18. Ito K, Urisu A. Diagnosis of food allergy based on oral food challenge test. *Allergol Int* 2009;**58**:467-74.
19. Nowak-Wegrzyn A, Fiocchi A. Is oral immunotherapy the cure for food allergies? *Curr Opin Allergy Clin Immunol* 2010;**10**:214-9.

8. Hofmann SC, Pfender N, Weckesser S, Huss-Marp J, Jakob T. Added value of IgE detection to rApi m 1 and rVes v 5 in patients with Hymenoptera venom allergy. J Allergy Clin Immunol 2011;127:265-7.
9. Sturm GJ, Heinemann A, Schuster C, Wiednig M, Groselj-Strele A, Sturm EM, et al. Influence of total IgE levels on the severity of sting reactions in Hymenoptera venom allergy. Allergy 2007;62:884-9.
10. Blum S, Gunzinger A, Müller UR, Helbling A. Influence of total and specific IgE, serum tryptase, and age on severity of allergic reactions to Hymenoptera stings. Allergy 2011;66:222-8.

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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.

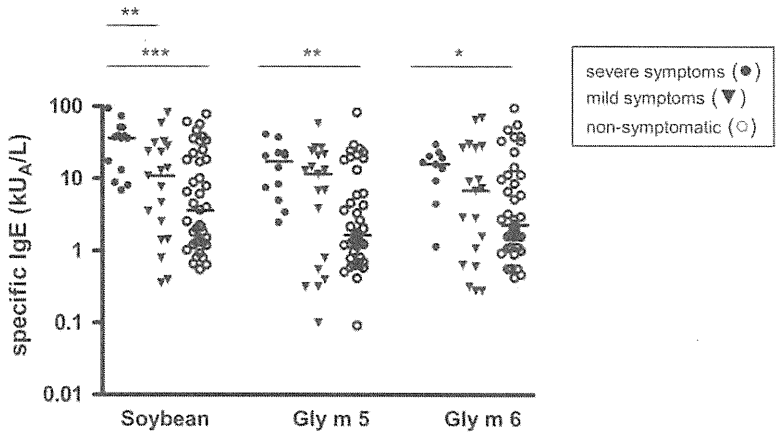

FIG 1. Quantitative IgE measurement for soybean, Gly m 5, and Gly m 6. Comparison of IgE antibody levels between children with severe symptoms, mild symptoms, and no symptoms is shown. The Mann-Whitney *U* test (2-tail) was used to compare the statistical differences between the study groups, and significant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

1. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol 2001;107:891-6.
2. Ikematsu K, Tachimoto H, Sugisaki C, Syukuya A, Ebisawa M. Feature of food allergy developed during infancy (2)-acquisition of tolerance against hen's egg, cow's milk, wheat, and soybean up to 3 years old. Arerugi 2006;55:533-41.
3. Imamura T, Kanagawa Y, Ebisawa M. A survey of patients with self-reported severe food allergies in Japan. Pediatr Allergy Immunol 2008;19:270-4.
4. Holzhauser T, Wackermann O, Ballmer-Weber BK, Bindslev-Jensen C, Scibilia J, Perono-Garoffo L, et al. Soybean (Glycine max) allergy in Europe: Gly m 5 (beta-conglycinin) and Gly m 6 (glycinin) are potential diagnostic markers for severe allergic reactions to soy. J Allergy Clin Immunol 2009;123:452-8.
5. Ballmer-Weber BK, Vieths S. Soy allergy in perspective. Curr Opin Allergy Clin Immunol 2008;8:270-5.
6. Ito K, Urisu A. Diagnosis of food allergy based on oral food challenge test. Allergol Int 2009;58:467-74.
7. Adachi A, Horikawa T, Shimizu H, Sarayama Y, Ogawa T, Sjolander S, et al. Soybean beta-conglycinin as the main allergen in a patient with food-dependent exercise-induced anaphylaxis by tofu: food processing alters pepsin resistance. Clin Exp Allergy 2009;39:167-73.
8. Thanh VH, Shibasaki K. Major proteins of soybean seeds. A straightforward fractionation and their characterization. J Agric Food Chem 1976;24:1117-21.
9. Komata T, Soderstrom L, Borres MP, Tachimoto H, Ebisawa M. Usefulness of wheat and soybean specific IgE antibody titers for the diagnosis of food allergy. Allergol Int 2009;58:599-603.
10. Matricardi PM, Bockelbrink A, Beyer K, Keil T, Niggemann B, Grüber C, et al. Primary versus secondary immunoglobulin E sensitization to soy and wheat in the Multi-Centre Allergy Study cohort. Clin Exp Allergy 2008;38:493-500.

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

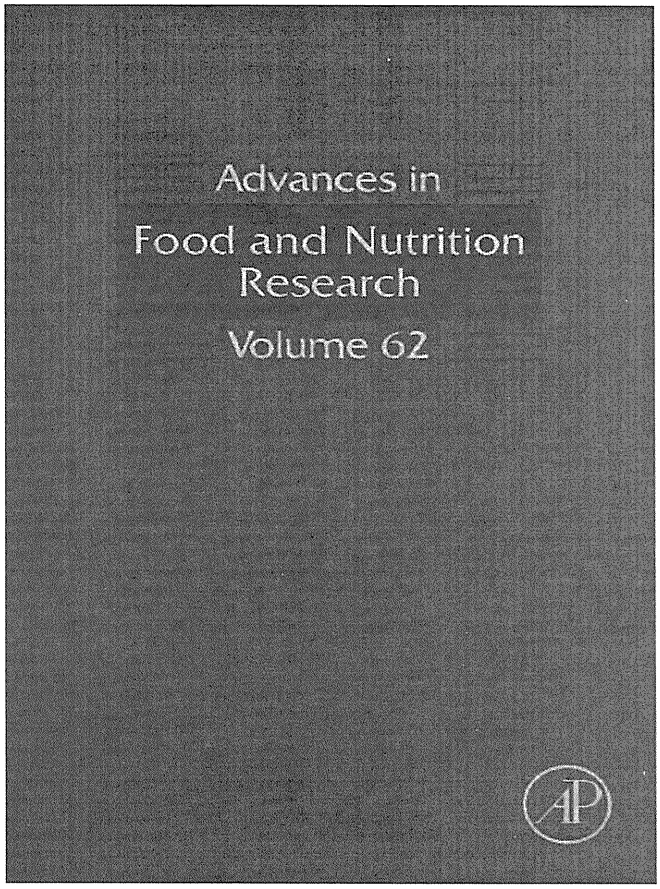
To the Editor:

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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CHAPTER 4

Japan Food Allergen Labeling Regulation—History and Evaluation

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Abstract

According to a national survey of food allergy cases, the food-labeling system for specific allergenic ingredients (i.e., egg, milk, wheat, buckwheat, and peanut) in Japan was mandated under law on April 1, 2002. By Japanese law, labeling of allergens is designated as mandatory or recommended based on the number of cases of actual illness and the degree of seriousness. Mandatory labeling is enforced by the ministerial ordinance, and the ministerial notification recommends that foods containing walnut and soybean be labeled with subspecific allergenic ingredients. Additional labeling of shrimp/prawn and crab has also become mandatory since 2008. To monitor the validity of the labeling system, the Japanese government announced the official methods for detection of allergens in a November 2002 ministry notification. These official methods, including two kinds of enzyme-linked immunosorbent assay kits for screening, Western blotting analyses for egg and milk, and polymerase chain reaction analyses for wheat, buckwheat, peanut, shrimp/prawn and crab as confirmation tests, have provided a means to monitor the labeling system. To standardize the official methods, the Japanese government described the validation protocol criteria in the 2006 official guidelines. The guidelines stipulate that any food containing allergen proteins at greater than 10 mg/kg must be labeled under the Law. This review covers the selection of the specific allergenic ingredients by the Japanese government, the implementation of regulatory action levels and the detection methods to support them, and the assessment of the effectiveness of this approach.

I. ASSESSMENT OF IMMEDIATE-TYPE FOOD ALLERGIES IN JAPAN

Food allergies that cause immediate reactions had already been under investigation prior to any discussion of "allergy food labeling" under the food sanitary law for prepackaged processed foods and food additives. Before implementation of the allergy food-labeling system in Japan, a research group supported by the Ministry of Health and Welfare of Japan had collected epidemiological data on immediate-type food allergies during both childhood and adulthood in Japan in 1998 and 1999. This retrospective study asked hospitals with more than 200 beds to report all immediate-type food allergy cases treated by the emergency department. The questionnaire included information on age, sex, cause of the food allergy, symptoms, IgE CAP RAST, and type of treatment. To focus on the

immediate-type, only cases in which symptoms occurred within 60 min after ingestion of the suspected food were included. Of the 2623 hospitals surveyed, 1623 hospitals responded and 1420 cases were analyzed. As shown in Table 4.1, hen's eggs were the most common allergen, followed by cow's milk, wheat, buckwheat, fishes, fruits, and shrimp. The top three major food allergens were most prevalent among the pediatric population, whereas fishes, buckwheat, and shrimp were mainly reported in adults. Based on these data, the Ministry of Health and Welfare selected 24 candidates that caused more than four cases of adverse reaction for the allergy food-labeling system. Following roundtable discussions among specialists and regulatory officers of the Ministry of Health and Welfare, hen's eggs, cow's milk, wheat, buckwheat, and peanuts were selected as items for mandatory labeling by the 2000 ministerial ordinance; the remaining 19 allergens were designated as items for recommended labeling by a ministerial notification.

To further understand the real-time condition of food allergies in Japan, we investigated prospectively the immediate-type food allergy cases in collaboration with more than 2000 doctors between 2001 and 2002 to account for recall bias in the previous study. The contributing doctors included those working in hospitals with more than 200 beds as well as allergy specialists working in clinics. Contributing doctors were asked to respond to a questionnaire every 3 months for 2 years from 2001 to 2002 and report immediate-type food allergy cases by mail. The same questionnaire as that in the previous studies was used, and only immediate-type food allergies as defined in the previous study were included. A total of 3882 cases were reported within the 2 years (Table 4.2). The cases ranged from 0 to 80 years of age, with 50% (1969) of them below 2 years of age. The most common cause of food allergy was hen's eggs (38.3%), followed by cow's milk (15.9%), wheat (8%), shellfish (6.2%), fruits (6%), buckwheat (4.6%), fishes (4.4%), and peanuts (2.8%). Notably, the cause of food allergy differed greatly among age groups. Food-induced anaphylaxis was seen in 10.9% of the reported cases. As shown in Table 4.3, hen's eggs, cow's milk plus its products, wheat, buckwheat, and peanuts were the major causes of food-induced anaphylaxis in Japan. Compared to our previous investigation, fruit allergies against kiwi and banana seemed to be an increasing trend. Thus, the present Ministry of Health, Labor, and Welfare of Japan (MHLW) has been implementing countermeasures against food allergies to improve the quality of life of afflicted patients. This prospective investigation on immediate-type food allergies has been repeated every 3 years as a means to monitor the condition of food allergies in Japan. The results of these investigations have improved the allergy food-labeling system by including banana as a recommended item by a ministerial notification and shrimp and crab as mandatory items for labeling by a ministerial ordinance.

TABLE 4.1 Immediate type of food allergy cases reported from 1998 to 1999

Offending food, *n* (%)	Total	>1 year	1 year	2–3 years	4–6 years	7–19 years	20+ years
Egg	420 (29.6)	197 (47.4)	72 (30.4)	89 (30.8)	35 (25.0)	19 (9.2)	8 (6.1)
Milk product	324 (22.8)	128 (30.8)	66 (27.8)	70 (24.2)	34 (24.3)	21 (10.1)	5 (3.8)
Wheat	147 (10.4)	40 (9.6)	20 (8.4)	35 (12.1)	12 (8.6)	27 (13.0)	13 (9.9)
Buckwheat	82 (5.8)	1 (0.2)	10 (4.2)	16 (5.5)	10 (7.1)	29 (14.0)	16 (12.2)
Fish	73 (5.1)	15 (3.6)	9 (3.8)	10 (3.5)	5 (3.6)	13 (6.3)	21 (16.0)
Fruits	66 (4.6)	6 (1.4)	13 (5.5)	13 (4.5)	8 (5.7)	19 (9.2)	7 (5.3)
Shrimp	51 (3.6)	0 (0.0)	2 (0.8)	4 (1.4)	4 (2.9)	22 (10.6)	19 (14.5)
Meat	44 (3.1)	9 (2.2)	2 (0.8)	4 (1.4)	4 (2.9)	14 (6.8)	11 (8.4)
Peanut	34 (2.4)	3 (0.7)	12 (5.1)	5 (1.7)	6 (4.3)	5 (2.4)	3 (2.3)
Soybean	27 (1.9)	5 (1.2)	8 (3.4)	4 (1.4)	3 (2.1)	4 (1.9)	3 (2.3)
Other	152 (10.7)	12 (2.9)	23 (9.7)	39 (13.5)	19 (13.6)	34 (16.4)	25 (19.1)
Total	1420	416	237	289	140	207	131

TABLE 4.2 Immediate type of food allergy cases reported from 2001 to 2002

Offending food, *n* (%)	Total	>1 year	1 year	2–3 years	4–6 years	7–19 years	+20 years
Egg	1486 (38.3)	789 (62.1)	312 (44.6)	179 (30.1)	106 (23.3)	76 (15.2)	24 (6.6)
Milk product	616 (15.9)	255 (20.1)	111 (15.9)	117 (19.7)	84 (18.5)	41 (8.2)	8 (2.2)
Wheat	311 (8.0)	90 (7.1)	49 (7.0)	46 (7.7)	24 (5.3)	48 (9.6)	54 (14.8)
Fruits	232 (6.0)	40 (3.1)	30 (4.3)	30 (5.1)	40 (8.8)	45 (9.0)	47 (12.8)
Buckwheat	179 (4.6)	4 (0.3)	23 (3.3)	45 (7.6)	27 (5.9)	54 (10.8)	26 (7.1)
Fish	171 (4.4)	21 (1.7)	32 (4.6)	22 (3.7)	18 (4.0)	37 (7.4)	41 (11.2)
Shrimp	161 (4.1)	4 (0.3)	10 (1.4)	20 (3.4)	29 (6.4)	59 (11.8)	39 (10.7)
Peanut	110 (2.8)	4 (0.3)	22 (3.1)	31 (5.2)	28 (6.2)	22 (4.4)	3 (0.8)
Soybean	76 (2.0)	22 (1.7)	16 (2.3)	9 (1.5)	8 (1.8)	9 (1.8)	12 (3.3)
Meat	71 (1.8)	13 (1.0)	6 (0.9)	7 (1.2)	7 (1.5)	19 (3.8)	19 (5.2)
Other	469 (12.1)	28 (2.2)	88 (12.6)	88 (14.8)	83 (18.3)	89 (17.8)	93 (25.4)
Total	3882	1270	699	594	454	499	366

TABLE 4.3 Anaphylaxis cases reported from 2001 to 2002

No.	Offending food	*n* (%)
1	Egg	109 (27.6)
2	Milk product	93 (23.5)
3	wheat	70 (17.7)
4	Buckwheat	28 (7.1)
5	Peanuts	18 (4.6)
6	Shrimp	14 (3.5)
7	Salmon roe	8 (2.0)
	Peach	8 (2.0)
9	Soybean	7 (1.8)
	Kiwi	7 (1.8)
11	Banana	4 (1.0)
	Yam	4 (1.0)
–	Other	25 (6.3)
	Total	395

II. JAPANESE FOOD ALLERGY-LABELING SYSTEM

Food allergies represent an important health problem in industrialized countries. In Japan, the number of people with food allergies is increasing, especially among young children, due to major changes in dietary habits with the introduction of western foods after World War II.

In 1999, the Joint FAO/WHO Codex Alimentary Commission Session agreed to recommend labeling of eight kinds of food which contain ingredients known to be allergens. This movement has led the Japanese government to take new measures to tackle food allergies in Japan.

A. Japanese regulations for labeling of food allergenic ingredients

The special subcommittee of MHLW held a meeting on the labeling of the Food Sanitation Investigation Council and stated that, "From the viewpoint of preventing the occurrence of health hazards, mandatory labeling of foods containing specific allergenic ingredients should be required." Accordingly, the MHLW decided that the Food Sanitation Law should provide for the mandatory labeling of foods containing allergenic ingredients designated in the 2000 ministerial ordinance.

Since the only therapy for a food allergy is avoidance of the responsible food, it is essential for food allergy patients to eliminate food allergens from their diet. Therefore, the Japanese MHLW decided to improve the