

Guidelines for Diagnosis and Management of Pediatric Food Allergy in Japan

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ABSTRACT

In Japan, the prevalence of food allergy has been increasing and a variety of problems have emerged regarding what should be considered a food allergy. A treatment regimen consists of avoiding the offending food (elimination diet therapy) and receiving nourishment from alternative foods (substitutional diet therapy). There is a growing concern that confusion has resulted from the lack of a consensus on the procedures for diagnosing and treating food allergies. The Food Allergy Committee of the Japanese Society of Pediatric Allergy and Clinical Immunology established the "Guidelines for Diagnosis and Management of Pediatric Food Allergy." Definition, classification, pathophysiology, clinical disorders and management of food allergy are discussed and determined.

KEY WORDS

anaphylaxis, diet therapy, food allergy, guideline, IgE

INTRODUCTION

In Japanese children, the prevalence of food allergies and other allergic diseases is increasing. This trend appears to be associated with changes in eating habits and alterations in the environment. Globalization of food product distribution has allowed us to eat a variety of foods that were once unfamiliar to us, and consumption of food additives has led to adverse food reactions that were not experienced in the past.

As public interest in food allergy grows, more people are seeking medical attention for even minor symptoms, and ordinary clinics and hospitals are now frequently performing serological specific IgE test-

ing. Under these circumstances, a variety of problems have emerged regarding what should be considered a food allergy.

Manifestation of a food allergy naturally requires appropriate treatment. In principle, a treatment regimen consists of avoiding the offending foods (elimination diet therapy) and receiving nourishment from alternative foods (substitutional diet therapy).

In an effort to treat food allergies, some mothers, however, put their children on an excessive elimination diet without receiving appropriate guidance, resulting in malnutrition or even developmental disorders in the children. In addition, placing children on an elimination diet creates a considerable burden for

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Table 1 Classification of adverse reactions to food

Reactions to toxic substances.....	toxic reactions
(Phenomena occurring in every human)	
Bacterial toxins, natural poison, etc.	
Reactions to nontoxic substances.....	nontoxic reactions
(Phenomena limited to particular humans)	
Food allergy	
(Phenomena result of an immunological mechanism)	
• IgE-mediated reactions	
• Non IgE-mediated reactions	
Food intolerance	
(Phenomena result of an immunological mechanism)	
• Reactions to pharmacologically active substances	
• Metabolic diseases (lactose intolerance, etc.)	

mothers, causing anxiety for the mother and emotional problems for the child. On the other hand, some allergic reactions to foods are overlooked without proper diagnosis of a food allergy.

There is a growing concern that this confusion has resulted from the lack of a consensus on the procedures for diagnosing and treating a food allergy, including the use of elimination diets. In April 2000, members of the Japanese Society of Pediatric Allergy and Clinical Immunology discussed the clinical problems of diagnosis and treatment of food allergies and established the Food Allergy Committee to provide guidelines for evidence-based, appropriate treatment. These efforts resulted in the "Guidelines for Diagnosis and Management of Food Allergy".

DEFINITION AND CLASSIFICATION

Food allergy is defined as "a phenomenon in which symptoms (involving the skin, mucous membranes, digestive and respiratory systems, anaphylactic reactions, etc.) adverse to the living body are induced through an immunological mechanism after ingestion of a food."¹

The immunological mechanism is not solely responsible for the variety of symptoms and diseases induced by contact with or ingestion of a specific food. A food allergy is a phenomenon that belongs to the category of adverse reactions to food, and the physician needs to understand the classification of such reactions for differential diagnosis of food allergies.

Table 1 illustrates the classification of adverse food reactions. Adverse reactions are roughly classified according to the mechanism into reactions to toxic substances and reactions to nontoxic substances. Reactions to toxic substances occur in every human, such as reactions to bacterial toxins and natural poisons. Reactions to nontoxic substances are phenomena limited to particular humans.

Reactions to nontoxic substances are then classified into food allergies mediated by an immunological

mechanism and food intolerance in which the mechanism is not immunological. Food allergies are further divided into IgE-mediated and Non IgE-mediated reactions. Most food allergies are IgE-mediated and the diagnostic procedures are relatively well established.

Non IgE-mediated reactions are assumed to involve immunoglobulins other than IgE, complements, or cell-mediated immunity but the diagnostic procedures have not been established yet.

Food intolerance includes hyper-reactions (pharmacological intolerance) to amines and other vasoactive substances in foods and lactose intolerance caused by metabolic factors.

EPIDEMIOLOGY

Large-scale morbidity surveys conducted in Japan demonstrated that food allergy occurs in 5%–10% of infants and preschool children and 1%–2% of school children.^{2,3}

Concerning the proportion of morbidity by age, infants under 12 months account for 29.3%, constituting the largest group among all age brackets. The proportion then gradually diminishes with age, and children aged 0–8 years constitute 80.1%. However, adults over 20 still account for 9.2%, which is not negligible. Figure 1 depicts the results of a national survey of food allergy conducted by the Ministry of Health, Labour, and Welfare (MHLW) in 1998–1999.⁴

The three major food allergens are hen eggs, milk and wheat, followed by buckwheat, fish, fruit, prawns, meat, and soybeans. While the most common allergens in children under the age of 6 remain eggs, milk and wheat, the kinds of allergens increase with age to include buckwheat, prawns, and fish. In older children, no predominant antigen, such as eggs, exists that affect infants with overwhelming frequency (Table 2).

PATHOPHYSIOLOGY AND CLINICAL DISORDERS

Clinically, food allergy is broadly classified into im-

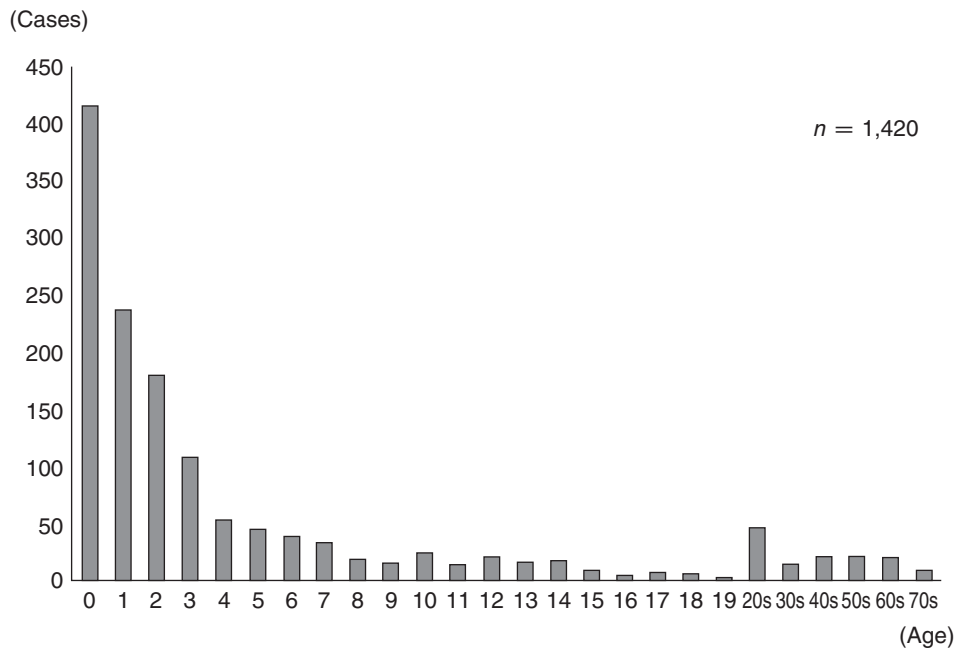


Fig. 1 Distribution of immediate food allergies by age (the national survey of food allergy conducted by the MHLW in 1998–1999)

Table 2 Allergens inducing immediate food allergy classified by age

	0 years (n = 416)	1 year (n = 237)	2–3 years (n = 289)	4–6 years (n = 140)	7–19 years (n = 207)	Over 20 years (n = 131)
1st	Eggs 47.4%	Eggs 30.4%	Eggs 30.8%	Eggs 25.0%	Buckwheat 14.0%	Fish 16.1%
Second	Dairy products 30.8%	Dairy products 27.8%	Dairy products 24.2%	Dairy products 24.3%	Prawns 13.0%	Prawns 14.5%
Third	Wheat 9.6%	Wheat 8.4%	Wheat 12.1%	Wheat 8.6%	Wheat 10.6%	Buckwheat 12.2%
Total	87.8%	66.6%	67.1%	57.9%	37.6%	42.7%

mediate and non-immediate reactions on the basis of the length of time from food ingestion to symptom manifestation.⁵ Immediate symptoms occur within 1 or 2 hours after ingestion; most symptoms are IgE-mediated reactions that belong to type I allergy in the Coombs & Gell classification. This type of allergy results from the predominant reaction of Th2 cells among helper T cells. On the other hand, the pathology of non-immediate reactions is mostly unknown. Frequent failures in identifying a relationship between non-immediate reactions to IgE imply that those reactions may not be mediated by IgE.^{6,7} This issue is being studied through the analyses of T cells and secreted cytokines. Figure 2 presents the reaction systems of two types of helper T cells in food allergies, symptom manifestation, and kinds of tests.

Skin symptoms are most common in immediate food allergy. Respiratory, mucous membrane, and gastrointestinal (GI) symptoms are also commonly

observed. Anaphylactic shock is relatively rare but serious and can be fatal.

The MHLW's national survey of food allergy in 1998–1999 demonstrated skin symptoms (82.5%) as the most common reaction in immediate food allergy, followed by respiratory, mucous membrane, and GI symptoms (Fig. 3).⁴

Skin reactions occur most frequently in food allergies. Acute urticaria and angioedema are common skin symptoms. In most cases, an itchy rash develops within a few minutes after food ingestion.

For respiratory reactions, allergic rhinitis symptoms may develop as nasal discharge, congestion, and sneezing. Symptoms in the lower respiratory tract include airway constriction, laryngeal edema, and bronchial asthma.

GI complaints include nausea, vomiting, abdominal pain, and diarrhea, which occur within a few minutes to 2 hours after ingestion of food allergens. Infants

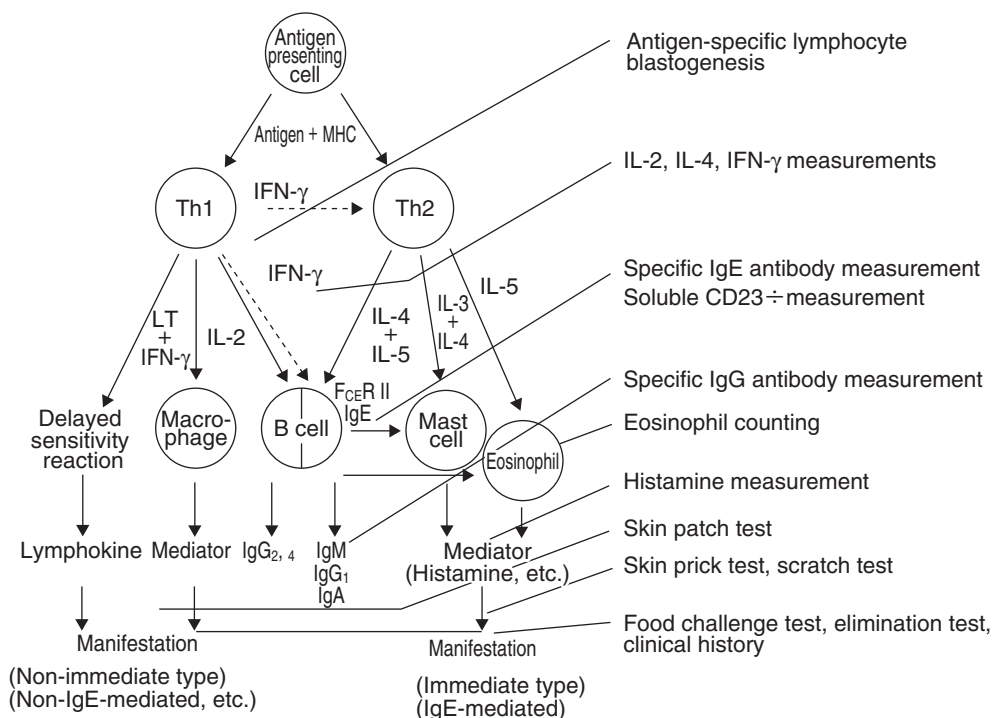


Fig. 2 Reaction systems of two types of helper T cells in food allergy conditions. Th1- and Th2-mediated reactions, manifestation of symptoms, and examination (Dotted lines work suppressive)

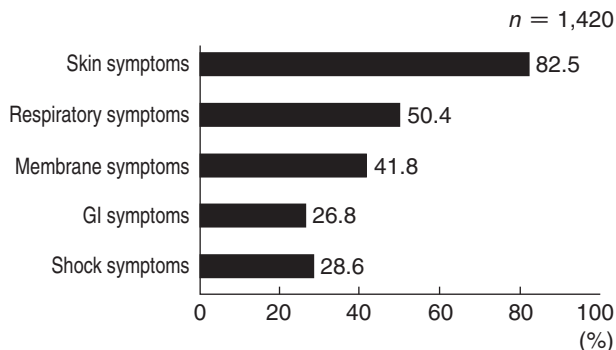


Fig. 3 Immediate food allergy symptoms (the national survey of food allergy conducted by the MHLW in 1998–1999)

vomit intermittently and have poor weight gain.

Anaphylaxis is a systemic reaction. Overall, food is the major cause of anaphylaxis, accounting for 33% of all anaphylactic episodes.⁸ Though the length of time to onset varies, anaphylaxis typically occurs within a few minutes. Some anaphylactic food reactions, however, develop more than 30 minutes after ingestion and, therefore, require special caution. Initial symptoms include swelling and an itchy sensation on the lips, tongue, and pharynx; nausea; and vomiting. The skin, GI, and respiratory reactions are accompanied by circulatory symptoms such as blood pressure decrease, vascular collapse, and arrhythmias.

Peanuts, tree nuts, fish, eggs, and milk are listed in the United States as major allergens causing life-threatening anaphylactic reactions, while in Japan, buckwheat, fish, shellfish, peanuts, eggs, and milk are responsible for such reactions.

In non-immediate food allergies, cause-and-effect relationships between foods and chronic symptoms are often overlooked. Eosinophilic gastroenteritis,⁹ protein-losing gastroenteropathy,¹⁰ and celiac disease are reported as GI disorders.

DIAGNOSTIC PROCEDURES

Procedures for diagnosing food allergies and identifying food allergens basically consist of the following: an in-depth patient history, review of the patient's food diary to understand how symptoms occur, estimation of a suspicious substance based on a skin test and a serum-specific IgE test, and determination of the responsible allergen by eliminating and reintroducing the food with the suspected allergen. Figure 4 illustrates the diagnostic procedures for identifying allergens responsible for food allergies.

First, the physician should grasp how the symptoms occur and identify the suspicious allergen through a detailed patient history and analysis of a food diary. Obtaining a patient history should focus on the kind and intake of symptom-inducing food, the time gap between food ingestion and onset of symptoms, reproducibility, presence or absence of any

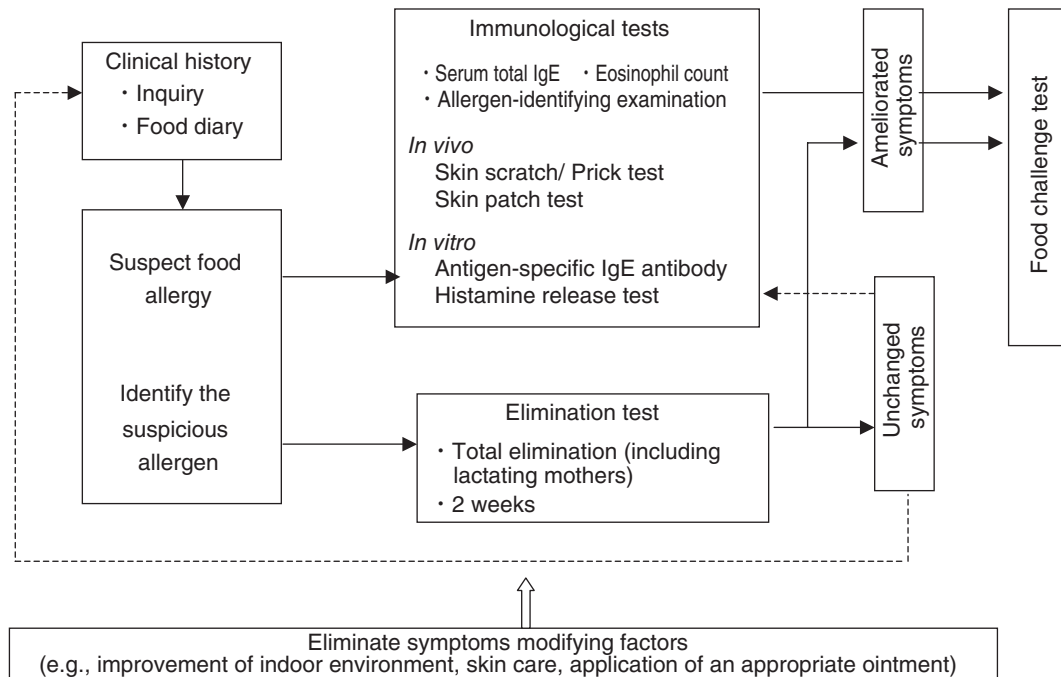


Fig. 4 Procedures for diagnosis of food allergy

other symptom-inducing conditions (e.g., infection, exercise), and the time of the last symptom.¹¹

A skin prick test, which is highly sensitive but less specific,¹² is useful as a screening test when conducted in appropriate combination with other tools. A skin patch test is superior both in sensitivity and specificity for delayed reactions and is thus of greater value than a specific IgE test and a skin prick test. Since those tests are all performed *in vivo*, the absence of any influence from drugs and systemic conditions must be confirmed for analysis of the test results. Emergency measures to treat anaphylactic reactions should be ready when a skin prick test is performed. Similar to a skin prick test, a serum-specific IgE test is highly sensitive but less specific. The presence of an allergen-specific IgE antibody in serum merely indicates that the individual is sensitized by the allergen.

The physician should perform a food elimination test in which the foods containing the suspected allergen are excluded from the patient's diet and then monitor the symptoms to identify the responsible allergen. If the symptoms improve, an oral food challenge will follow for definite diagnosis.

ORAL FOOD CHALLENGE TEST

Oral food challenge tests are performed in the manner of open-label, blind, or double-blind placebo-controlled studies. A double-blind placebo-controlled food challenge (DBPCFC) is considered the most accurate challenge test. The selection of the appropriate test type should be based on symptoms, age, and the

course of the allergy.

INDICATIONS FOR CHALLENGE TEST

A challenge test is usually performed (1) to identify a suspected food allergen in the patient's clinical history, (2) to determine the existence of a food allergy caused by an uneaten food with a positive food allergen-specific IgE test (mainly for infants with atopic dermatitis), and (3) to verify acquired resistance after an allergen elimination diet. It is desirable to avoid a challenge test in patients with a history of anaphylactic shock. Given an anaphylaxis inducing risk, the physician must be ready for emergency treatment of possible life-threatening reactions when performing a challenge test. Table 3 shows the periods of elimination diets and the timing of challenge tests for patients with a history of immediate allergies. A challenge test should preferably be performed at a special clinic on an infant with atopic dermatitis who experienced anaphylaxis or has a positive allergen test for multiple foods.

The severity of induced symptoms cannot be predicted from specific IgE levels or the results of a skin prick test. Furthermore, no correlation has been found between inducing doses and specific IgE antibody titers.^{13,14}

The relationship between specific IgE levels and rates of induction from challenge tests have been re-examined to develop a safe DBPCFC test, and CAP antibody levels are being used as decision values. For eggs, milk, peanuts, and fish, antibody levels above a certain value can be an indicator of a positive chal-

Table 3 Timing of food challenge testing on children with immediate food allergy

Offending Food Allergen	Timing of Food Challenge Tests	Remarks
Eggs Milk Wheat Soybeans	12 to 18 months After an allergen elimination diet	A food challenge test may be conducted after 6 months, in consideration of changes over time in specific IgE antibody measurements.
Peanuts Fish Nuts	After a 3-year allergen elimination diet	A food challenge test may be conducted after 1 to 2 years, in consideration of changes over time in specific IgE antibody measurements.
Other food	Every 12 to 18 months	

* A food challenge test can be conducted 1 to 3 months after an elimination diet on a child with atopic dermatitis who does not ingest CAP-positive allergen foods, in consideration of specific IgE antibody measurements.

allenge test and thereby makes the challenge test unnecessary.¹⁵⁻¹⁸ The induction probability is higher than 95% when the specific IgE level is higher than 7 UA/mL for eggs, 15 UA/mL for milk, and 20 UA/mL for fish. In infants under the age of 2 years, the induction rate is even higher at lower specific IgE levels. Thus, food challenge tests for young infants are recommended at lower egg and milk-specific IgE titers, less than 2 UA/mL or 5 UA/mL, respectively.¹⁶⁻¹⁸

On the other hand, it is difficult to predict induction for wheat and soybeans from IgE levels; consequently, a challenge test should be performed with caution. In the case of an allergy to peanuts, an induction risk remains unclear even with negative IgE levels; therefore, a challenge test should be carefully introduced, taking into consideration the patient's history of anaphylaxis and food intake. Some children with atopic dermatitis or acquired resistance can ingest the food without any problem even with IgE levels higher than the CAP values. IgE antibody levels should thus serve as a reference to ensure safety when a challenge test is required.

In the case of an allergy to egg white, high ovomucoid IgE levels were reported to be associated with a high rate of positive challenge tests for egg whites.¹⁹ The ovomucoid CAP antibody level of 6.22 UA/mL (CAP level of 10.5 for egg white) has a greater than 95% probability for a positive challenge test with freeze-dried egg white.

PREPARATION FOR CHALLENGE TEST

EXPLANATION OF CHALLENGE TEST AND PREPARATION OF WRITTEN INFORMED CONSENT

The following information should be provided:

1. The challenge test is intended for diagnosis of a food allergy or discontinuation of the ongoing elimination diet (evaluation of acquisition of resistance).
2. Ingestion of the allergen may induce symptoms.
3. If an immediate adverse reaction occurs, treatment will be required.

4. The challenge test is useful in planning the most appropriate treatment.

Then, the written informed consent is prepared with the signatures of the patient (signed by their family) and their family.

DETERMINATION AND PREPARATION OF DRUGS TO TREAT POSSIBLE REACTIONS

- Ready for peripheral venous access
- Antihistamines, adrenocorticosteroids, and inhalation bronchodilators
- Adrenaline (Epinephrine) and hydrocortisones

PRETEST EXAMINATION

- Presence or absence of infections, accidental anaphylaxis, asthmatic attacks, and diarrhea. (Inquiries should cover symptoms that occurred in the past 1 to 2 weeks. If any of these symptoms are present, a challenge test should be avoided.)
- Physical examination: fever, diarrhea, vomiting, rales, skin condition
- Discontinuation of oral drugs: anti-allergic agents (starting 5 days before the test), antihistamines, and oral disodium cromoglycate (DSCG) (3 days before the test)

If anti-allergic medications need to be continued, the ongoing medications should be recorded on the medical chart before performing the test.

- Confirmation of 2-week-long pretest avoidance of the allergen to be used in the challenge

TYPES OF CHALLENGE TESTS

OPEN-LABEL

An open-label test is easy to perform because the test food can be used in the ordinary, commercially available form. This test is usually performed (1) on infants, (2) on those with a negative skin test, (3) on those with a confused history, (4) when the patient suspects many kinds of foods consumed at home, (5) to form a plan for daily food ingestion after an elimination diet (guidance for discontinuation of food avoidance), or (6) on those with a negative blind

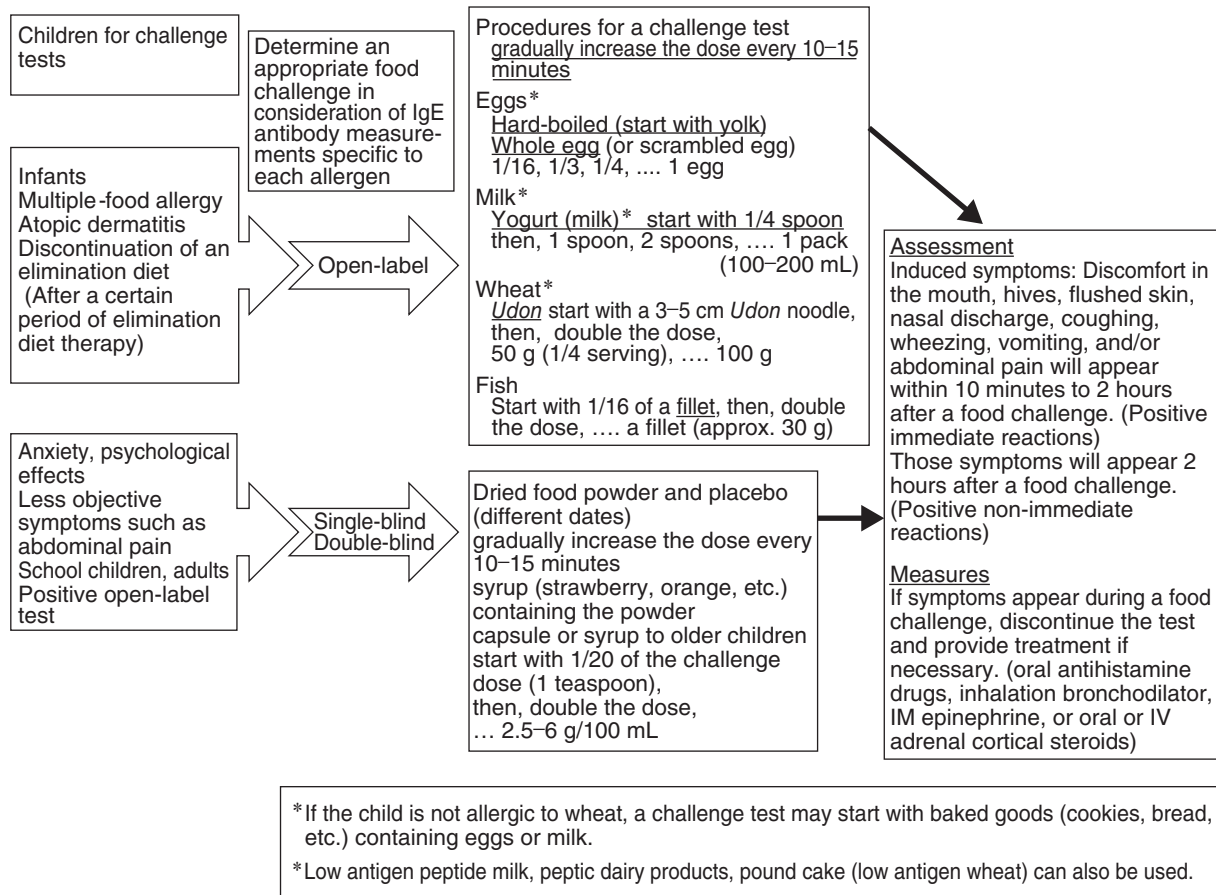


Fig. 5 Indications, methods, and procedures for food challenge tests

test.²⁰

Open-label tests are commonly used in Japan and useful in determining whether eggs, milk, or wheat, among the various allergens, must be avoided because they are the main constituents of an infant's diet. In a challenge test with eggs, the test starts with hard-boiled yolks and gradually shifts to hard-boiled egg white. Yogurt or milk is easy to use in a challenge test for dairy products; likewise, *udon* (noodles) for wheat, cooked soybeans for soybeans, and cooked fish for fish are convenient.²¹

The advantage of an open-label test is that it is helpful in discontinuing an elimination diet by allowing a wide range of food selections particularly when the patient has numerous allergens because, if a challenge test with a food in a certain cooked form is negative, the food in that form can be safely used in the patient's dietary life. The test should be performed under a physician's supervision. If the test is negative, oral ingestion will follow at home to verify the test results. It is important to ensure that the patient ingests a safe amount of the food at home because high levels of consumption may induce an allergy.

The disadvantage of this test is that since the aller-

gen is known to the child, if there is a medical history related to the test food, the child may refuse to eat it or anxiety by the child or family may influence the onset of symptoms. A negative open-label test precludes a blind test, whereas if the open-label test is positive, a blind test for verification is recommended.²² In infants, however, an open-label test is usually sufficient for assessment.²⁰

An open-label test usually starts with about 1/20 or 1/16 of the challenge dose. For a patient with a history of anaphylaxis or who may develop hypersensitivity, it is safe to start with a minimal amount on the back of the lower lip. Figure 5 shows the procedures for challenge tests with eggs, milk, and wheat.²³

SINGLE-BLIND AND DBPCFC

Blind and DBPCFC tests are desirable for older children or adults. Many researchers believe that an open-label challenge test by a specialist is sufficient for infants and a double-blind test is unnecessary.^{11,20,24} An initial challenge test on infants is likely to produce induction, and the initial dose should therefore be carefully determined.

"Single-blind" means that the investigator (test performer) knows what the challenge food is, while

Time (minutes)	Prior to challenge	0	15	30	45	60	90	120	180...
Challenge dose		1/20* 1sp (5 mL)* 0.25 g *	1/10 2sp (10 mL) 0.5 g	1/5 4sp (20 mL) 1 g	1/3 6sp (30 mL) 1.5 g *	The entire remaining amount 35 mL 1.75 g	Observation after challenge		
Symptom observation	○	○	○	○	○	○	○	○	○..
Skin symptoms	Presence and severity of flushed skin, eczema, itching sensation, hives, or angioedema (on a scale of 3 to 0)								
Nasal symptoms	Presence and severity of sneezing, congestion, or nasal discharge (3 to 0)								
Chest symptoms	Presence and severity of coughing or wheezing (3 to 0)								
Abdominal symptoms	Presence and severity of subjective symptoms (3 to 0)								
	Presence and severity of objective symptoms (3 to 0)								

* Dried food powder 5 g/100 mL of strawberry puree

Start with a minimal amount less than 1 mL (0.05 g) to 0.1 mL (5 mg) on an hypersensitive child.

Fig. 6 Protocol for a blind test using strawberry puree^{25, 27}

“double-blind” means that a third party determines the challenge food so that even the investigator is unaware of the content.

The challenge food is used in the form of dried food powder, and the powder and placebo in a specified amount are placed into capsules or syrup. For infants, their favorite fruit (e.g., orange, strawberry) is commonly used in the form of juice or paste. The challenge food powder can be kneaded into cookie dough or hamburger.

The shortcomings of these test methods are (1) that dose adjustment is difficult when the challenge food powder is used in the form of a capsule, and (2) that the risk of anaphylaxis is high. It is difficult to determine the amount of dried food powder corresponding to that of the original daily food. If a blind test is negative, an open-label test needs to be performed to verify safety.²²

In Japan, Ebisawa *et al.* and other physicians have started performing blind challenge tests at numerous institutions and more accurate standards for challenge tests are being established.²⁵ This test method is easy to apply to infants because the allergen food powder is mixed with strawberry puree (masking) to mask the original flavor. Detailed procedures for the challenge test are provided in Figure 6. The test usually starts with 1/20 of the challenge dose, then doubles the dose in increments. For a patient who is likely to develop hypersensitivity, the test should start with a minimal amount. The interval between challenges is 10–15 minutes, and the dose is increased in six steps.^{25,26}

PREDICTION AND PREVENTION OF ALLERGIC EPISODES

Prevention of allergic episodes is considered important to derail the progress of the course of an allergy. Although food allergy tends to decline with age, early

treatment, such as an allergen elimination diet, improves the prognosis. Based on this, the necessity of earlier treatment, including intervention in a pregnant woman's diet, has been discussed.

Regarding the relationship between the development of allergic diseases in infants and their mothers' diet during pregnancy, some researchers reported no significant difference in the development of allergic diseases between babies whose mothers completely avoided eggs and milk during late pregnancy and babies whose mothers had no food restrictions.²⁷ Likewise, another study found no difference in total IgE levels in cord blood and specific IgE levels between babies whose mothers had an elimination diet in late pregnancy and babies whose mothers did not.²⁸

Dietary restrictions during pregnancy are not advisable because there is no evidence that exclusion of an allergen during pregnancy reduces the incidence of allergy diseases in infants.

Furthermore, avoidance of a food allergen in the diet of a breast-feeding mother is not recommended as a prophylactic for the development of a food allergy in the infant because a number of studies demonstrated that an elimination diet during lactation is not associated with the incidence of allergy diseases in children.

COURSE

The following is a description of how symptoms of a food allergy occur and the allergens responsible vary as the child grows. Allergic diseases tend to change with age starting from atopic dermatitis to bronchial asthma and allergic rhinitis with different causes and affected organs. This phenomenon is called “allergy march.”²⁹

Food allergy develops in the early years of the allergy march, and reducing food allergen-induced sensitization in infancy helps derail it. Most food allergy

that develops in infancy diminishes with age. Approximately 70% of children with food allergy that developed in infancy acquire resistance by age 3.³⁰

On the other hand, food allergy that develops in older childhood or adulthood or allergy accompanied by a severe anaphylactic reaction to buckwheat or peanuts tends to persist for a longer period and requires a long-term elimination diet.³¹

It is essential to monitor the clinical course of a food allergy, especially the acquisition of resistance, and provide guidance for the discontinuation of the elimination diet to improve the child's and the family's quality of life.

TREATMENT

Treatment is broadly divided into two types. One treatment is to prevent the allergic symptoms that may occur upon ingestion of the offending food and the other treatment is to alleviate or terminate the symptoms induced by a food allergy. The former is represented by diet therapy to eliminate the responsible allergen, and the latter by drug therapy.

DIET THERAPY

In the treatment of food allergies, preventive measures are based on diet therapy to eliminate the offending food from the patient's diet. Merely avoiding the food responsible is not sufficient; however, the physician must search for alternative food to meet nutritive requirements and closely monitor the child's growth and any signs of nutritional problems.

The determination of the time and method for stopping the elimination diet is also an important issue in the everyday life of the child. Counseling and advice is required to address the variety of social problems and psychological stress caused by the elimination diet and the problems associated with meals provided by nurseries, kindergartens, or schools.

Important Points in Diet Therapy

The physician needs to pay particular attention to the following when providing diet therapy for a food allergy:

① The food allergen should be identified based on the correct diagnosis. (A positive specific IgE test alone is not sufficient for determination of the specifics of an elimination diet.)

② Guidance for food exclusion should correspond to how the food allergen is cooked or processed, ingestion, and the severity of hypersensitivity (e.g., some children may have symptoms when eating the offending food raw but not when eating the same food when well cooked or processed).

③ Alternative food (e.g., allergy free food, replacing food) should meet nutritional requirements.

④ Symptomatic therapy, or antiallergic agents in some cases, should be used to relieve symptoms and keep the elimination diet to the minimum required

level.

⑤ The elimination diet should be phased out as time passes because allergic reactions to specific foods that developed in infancy are likely to decline with age (guidance and supervision should continue until the child can lead a near-normal daily life).

⑥ Since allergy that induces severe anaphylactic symptoms tends to continue for a longer period, strict avoidance of the allergen, even in a minimal amount, should be observed. Instructions should be provided on how to review food labels.

Food Labeling System in Japan

In April 2002 under the Food Sanitation Law, the government started requiring that the names of substances likely to induce an allergic reaction be indicated on food labels with the objective of preventing foods with known allergens from endangering the health of people.

From the perspective of eliminating potential health hazards for people predisposed to a specific allergy, five foods—eggs, milk, wheat, buckwheat, and peanuts, which all rank high both in the incidence of allergic reactions and in the severity of symptoms—were selected from among a variety of known foods that cause an allergic reaction as ingredients that must be indicated on food labels. The law now requires these five items to be indicated through all distribution levels up to finished products even if the amount of carryover or the amount of any of those foods used as a processing material is minimal (e.g., a concentration of a few $\mu\text{g}/\text{mL}$ and a level of a few $\mu\text{g}/\text{g}$).

Aside from the above, the law also recommends indications for abalone, cuttlefish, salmon caviar, prawns, oranges, crabs, kiwi fruit, beef, walnuts, salmon, mackerel, soybeans, chicken, pork, *matsutake* mushrooms, peaches, glutinous yams, apples, bananas, and gelatin, based on the fact that these foods have relatively small numbers of clinical cases of allergic reactions and need further research (Table 4). Because serious health hazards involving these foods have occurred consistently, indication of processed food products containing any of those ingredients are also encouraged whenever possible. The range of specified raw materials indicated on labels was based on the Japan Standard Commodity Classification. The physician should give the patient with a food allergy, in particular the patient with a history of anaphylaxis, guidance on how to review food labels.

When and How to Discontinue an Elimination Diet

Most food allergies that first occur in infancy or early childhood declines with age. Elimination diet therapy places a considerable burden on the child as well as the mother. Once an elimination diet starts, the physician should, instead of continuing it needlessly,

Table 4 Specified raw materials required or encouraged to be indicated on food labels

Regulations	Specified Raw Materials	Reasons
Indication required by ministerial ordinances	Eggs, milk, wheat	These materials are the most common allergens. Milk and cheese belong to the category of food made from milk (milk and dairy products).
	Buckwheat, peanuts	These materials can induce serious, life-threatening symptoms, warranting special attention.
Indication encouraged by notifications	Abalone, cuttlefish, salmon caviar, prawns, oranges, crabs, kiwi fruit, beef, walnuts, salmon, mackerel, soybeans, chicken, pork, <i>matsutake</i> mushrooms, peaches, glutinous yams, apples, bananas	These materials are less common allergens. Further research is necessary for coverage under specific ordinances.
	Gelatin	Often derived from beef or pork, gelatin is handled in the same way as specified raw materials, and the indication of "beef- or pork-derived" are already required for food labels. However, in light of numerous requests for an indication as "gelatin" only from the public, as well as from specialists, gelatin is categorized separately.

Source: Shokuki Notification No. 2 and Shokukan Notification No 46 dated March 21, 2001 by Director, Planning Division and Director, Supervision and Safety Division, Department of Food Safety, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labour and Welfare. Revised in July 2004.

phase it out according to the child's age and the degree of hypersensitivity so that the child can return to as normal a diet as possible.

For immediate allergic reactions that first occur in infancy, the indicators for reintroduction of the food allergen include the patient's age, changes in specific IgE levels, and a histamine release test. Age-related changes in sensitivity also depend on the kind of food allergen. When using a food challenge test as an indicator for re-exposure of the allergen, the physician should be aware that reactions may vary depending on whether the allergen is cooked and how much of the allergen is consumed. Particularly in an older child, psychological factors can induce subjective symptoms. Such cases require a double blind test.

For a mild food allergy in infancy, 12 to 18 months of age is a rough standard for stopping an elimination diet. Well-cooked food containing the allergen should be given to the infant in incremental amounts and frequency because a food challenge test with a large dose may induce symptoms. Discontinuation of the elimination diet should therefore be considered based on an overall evaluation of age and changes in hypersensitive reactions, as well as allergic symptoms monitored every 3–6 months and results of blood examinations.

In contrast, an elimination diet must be carefully continued for a child with a history of anaphylactic shock or severe symptoms because acquisition of resistance to the allergen with age is unlikely.

Guidance on Weaning Food for Infants Predisposed to Atopy

An infant, whose parents or any of the siblings have

atopic disease or who has an atopic predisposition to eczema, diarrhea, or vomiting, has a higher risk of being sensitized to food. Weaning food should be carefully introduced to such babies.

It is not necessary to delay the introduction of weaning food. As for normal infants, solid food may be introduced when the baby is 5 months old and weighs about 7 kg.

It is appropriate to start weaning with starch-rich food, such as rice porridge and mashed potatoes, which rarely induce an allergy. Once the baby is accustomed to them, vegetables are introduced. Introduction of protein-rich food should start with bean curd or whitefish.

Eggs have a high risk of inducing allergic reactions. It appears safe to avoid egg white until the atopic predisposed infant turns 1 year of age. Egg yolks are less allergenic and can be used earlier starting with a small portion of hard-boiled yolks.

The meat of fat-rich bluefish, such as mackerel, sardines, and saury readily goes stale and contains histamines. Bluefish meat should therefore be introduced in the late weaning period.

When giving a new food to the allergy prone infant, introduction should be limited to one new food at a time. Another new food should be tried only after 3–4 days of problem-free ingestion of the new food. Food should be fresh and well cooked. Introduce new food in the morning because the mother can observe the child's condition more easily and if an abnormal reaction occurs, medical attention can be sought during office hours.

Other allergenic food including buckwheat, cuttlefish, octopus, prawns, crab, salmon caviar, and shell-

fish should be avoided in the initial and middle weaning periods.

DRUG THERAPY

Drug therapy has two purposes. One is to prevent allergic symptoms from occurring when the offending food is ingested and the other is to alleviate ongoing symptoms. Drug therapy curbs the manifestation of symptoms to a degree, but not completely, and does not cure the food allergy. The type and severity of symptoms determine the treatment, ranging from administration of histamine H₁ antagonists, anti-allergic agents, adrenocorticosteroids or sympathomimetic agents to fluid replacement, oxygenation, endotracheal intubation, and management of assisted respiration.

Oral disodium cromoglycate (DSCG) is a standard prophylactic treatment for food allergy-related atopic dermatitis. Some researchers reported that oral DSCG is effective to a certain degree in treating atopic dermatitis,³² whereas others noted that the drug had no beneficial effect.³³

Symptoms of anaphylactic shock, which can result in death due to respiratory or circulatory failure or both, require immediate treatment. Many of the children who survived such severe episodes received intramuscular adrenaline (epinephrine) soon after onset. In contrast, the drug was not used in most fatal cases. These findings demonstrate that intramuscular adrenaline administered soon after the onset of anaphylactic shock helps save the patient's life.^{34,35}

On the other hand, a researcher found that some fatal anaphylactic shock-related cases were associated with overdoses of adrenaline.³⁶

Self-injectable adrenaline is available as an emergency treatment for anaphylaxis caused by a food allergy. Early intramuscular administration of adrenaline is absolutely essential in the treatment of anaphylactic shock. It is ideal to self-inject the drug upon manifestation of the initial symptoms (numbness or discomfort in the mouth, edema of the lips, discomfort, nausea, vomiting, abdominal pain, urticaria, and/or coughing after ingestion of the offending food) before the shock symptoms progress. Only authorized physicians can prescribe adrenaline. The physician should advise when to use the drug because the appropriate timing of the injection differs according to the type and severity of food allergy symptoms in individual patients.^{34,37}

Collaboration with Communities (particularly with nurseries, kindergartens, and schools)

The physician needs to prepare a written order describing the allergen and the symptoms experienced by the child and hand it to the nursery, kindergarten, or school so that the child will be accepted and receive allergen-free meals.

Table 5 presents an example of a written order for

an elimination diet to be followed by the kindergarten staff.³⁸ Major information includes (1) the name of the food to be avoided, (2) possible symptoms after ingestion of the offending food, (3) emergency treatment, and (4) the reevaluation period. If necessary, the names of specific foods to be excluded from the child's meals should be listed as well.

Accidental exposure to the allergen is not rare during elimination diet therapy. It is important to give the child's parents guidance on necessary oral drugs and the proper time to seek medical care in the event of unexpected reactions and seek as much assistance as possible from childcare workers.

In addition to oral ingestion, a child who is highly sensitive to the allergen may have symptoms upon physical contact with the allergen. Attention may also be paid to the child's activities at the nursery or kindergarten, including splashing of dairy products, and touching cookie dough made from eggs and flour, touching nuts and soybeans during the bean-throwing ceremony, and playing with flour-based clay. Necessary information should be given to childcare workers or teachers so that they understand that special attention must be paid to the child's daily activities.

Many infants with food allergies naturally acquire resistance with childhood development, and a written order should be reissued in 3, 6, or 12 months in compliance with the discontinuation of an elimination diet.

Most of the food allergies affecting school children seem to result from the failure of reintroducing the allergen. Most patients who had severe food allergy symptoms in early childhood or later often had a history of anaphylaxis.

In Japan, 99% of elementary schools and 82% of junior high schools provide lunch services, and 76% of those schools are reported to have children with food allergies. According to research by Imai *et al.*, 54% of 10,190 schools implement some measures for children with food allergy. About 60% of those schools only provide children with allergies with allergen-free meals (by excluding the allergen from the standard meals), while 40% prepare allergen-free, alternative meals.³⁹ Measures taken by schools for children with allergies vary according to region. Although these differences largely depend on the number of pupils, cooking equipment, and manpower, whether meal problems are successfully addressed or not in schools primarily hinges on a correct understanding of food allergy by the board of education, teaching staff, and school nutritionists.

As at home, safe meals should be served in a pleasant atmosphere in nurseries, kindergartens, and schools. It is important to attach a high value to food education (teaching children about a healthy diet) and to create a school environment that accepts children with allergies.

Table 5 Example of a medical certificate (written order by the physician in charge) for an allergen elimination diet in a kindergartener

Child name _____ (Male, female) Birth date _____

Diagnosis: _____

As a result of diagnosis and examinations, this child should avoid the following foods in his/her diet.

1. The following food must be eliminated.

Food to be eliminated (_____)

(_____)

Milk that can be used when the child is allergic to milk (_____)

* A detailed list of food to be eliminated is provided on a separate sheet.

2. The following symptoms may develop if the child eats the food specified above.

Food	Symptoms
Eggs: (_____)	:Unknown because the child has never been exposed to this allergen
Milk: (_____)	:Unknown because the child has never been exposed to this allergen
Wheat: (_____)	:Unknown because the child has never been exposed to this allergen
(_____): (_____)	:Unknown because the child has never been exposed to this allergen
(_____): (_____)	:Unknown because the child has never been exposed to this allergen
(_____): (_____)	:Unknown because the child has never been exposed to this allergen

Immediate reactions: (1) shock; (2) coughing; (3) difficulty breathing; (4) vomiting, abdominal pain; (5) facial flushing; (6) hives; (7) itching sensation

Non-immediate reactions: (8) eczema; (9) itching sensation; (10) diarrhea

3. If any symptoms should develop after eating the food, provide the child with the following emergency treatment.

(1) Oral drugs:

(2) Other:

This medical certificate (written order) needs to be reevaluated in (3, 6, 12) months.

Date: _____

Clinic/hospital
Phone No.
Physician

Sealed

CONCLUSION

Allergy has a wide variety of clinical manifestations. Not only individual predisposition but also food and other environmental factors play a role in the manifestation of allergic diseases. Food allergy is a personal daily diet problem, but it also requires collaboration with communities. In particular, children with allergy during the growth period need diet therapy suited to their developmental level. The basic law on nutritional education was established in 2005 with the aim of helping children grow with a healthy body and mind and nourishing their humanity at school and in the nursery. In line with this, a food allergy handbook for parents and co-medicals is now being prepared for implementing the guidelines on the diagnosis and management of pediatric food allergy in an attempt to promote food education for children with allergy.

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