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REVIEW ARTICLE

Management of Food Allergy in Japan "Food Allergy Management Guideline 2008 (Revision from 2005) " and "Guidelines for the Treatment of Allergic Diseases in Schools"

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ABSTRACT
In 2005, the "Food Allergy Management Guideline 2005" was published. In order to encompass food allergy from infancy to adulthood, the project committee included not only pediatricians, but also internists, dermatologists, and otolaryngologists. After the release of the guideline, oral food challenge tests were approved as a medical examination on hospital admission by the national health insurance system in 2006, and the tests at outpatient clinics were also approved in 2008. As clearly stated in the guideline, it is essential for general practitioners to refer food allergy patients to specialists to receive accurate diagnosis. A specialist is needed because the oral food challenge test, which is sometimes required for accurate diagnosis, carries the potential risk of developing an adverse reaction. In 2008, the "Food Allergy Management Guideline 2008" was revised to update recent advances, such as the appropriate conditions needed to perform oral food challenge tests and probability curves for hen's egg and cow's milk developed in Japan. In the same year, "The Guidelines for the Treatment of Allergic Diseases in Schools" was published by the Japanese Society of School Health. In addition to the guideline, "School Life Management Certificate (for Allergic Diseases) " was developed in order to allow the verification of the diagnosis and encourage the discussion of countermeasures by parents/guardians and school teachers for students requiring special care. It is hoped that this review article will be useful for doctors treating food allergy and that the quality of life of food allergy patients and their parents will be improved.

KEY WORDS
anaphylaxis, food allergy, oral food challenge test, referral relationship, school

INTRODUCTION

In October 2005, as a result of research activity supported by grants from the Ministry of Health, Labour and Welfare, we posted the "Food Allergy Management Guideline 2005"[1] on the internet. This guideline was created in order to help general practitioners improve their diagnosis and treatment of food allergy and to improve the quality of life of food-allergy patients. The guideline utilized data accumulated by the National Food Allergy Research Group and was conceptualized as a simple, brief pamphlet to be made available on the internet. The most important section concerned the relation between infantile atopic dermatitis and food allergy and its proper method of treatment.

To avoid both overvaluation and undervaluation, fastidious care was given to this topic. Flowcharts also outlined the diagnosis and treatment. With the definition of "infantile atopic dermatitis associated with food allergy", both dermatologic and pediatric members of the project committee finally came to an agreement, which constituted a landmark decision among dermatologists and pediatric allergists in Ja-

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Table 1 Classifications of clinical types

Clinical type		Age of onset	High frequency food	Tolerance acquisition (Remission)	Possibility of anaphylactic shock	Food-allergy mechanism
Newborn infant's digestive symptom		Neonatal period	Milk (powdered milk for infant)	(+)	(+/-)	IgE-independent
Infantile atopic dermatitis associated with food allergy †		Infancy	Hen's eggs, cow's milk, wheat, soybean, etc.	Mostly (+)	(-) to (+)	Mainly IgE-dependent
Immediate type reaction (hives, anaphylaxis, etc.)		Infancy to adulthood	Infancy to early childhood: hen's eggs, cow's milk, wheat, buckwheat, fish, etc. Later childhood to adulthood: Shellfish, fish, wheat, fruit, buckwheat, peanut, etc.	(+) Hen's egg, cow's milk, wheat, etc. (+/-) Most of others	(++)	IgE-dependent
Sub type	Food-dependent, exercise-induced, anaphylaxis (FEIAn/FDEIA)	Later childhood to adulthood	Wheat, shrimp, calamari, etc.	(+/-)	(+++)	IgE-dependent
Sub type	Oral Allergy Syndrome (OAS)	Early childhood to adulthood	Fruit, vegetables, etc.	(+/-)	(+/-) to (+)	IgE-dependent

† There are cases that might develop complications with digestive symptoms, such as chronic diarrhea and hypoproteinemia. Not all cases of infantile atopic dermatitis are associated with food allergy.

pan. This agreement resolved a long term controversy, similar to other countries, concerning the association of atopic dermatitis and food allergy.[2]

In November 2008, the guideline was updated with recent advances such as the conditions needed to perform oral food challenge tests and the probability curves for hen's egg and cow's milk developed in Japan.[3] In order to encompass food allergy from infancy to adulthood, the project committee again included not only pediatric researchers, but also internists, dermatologists, and otolaryngologists. The guideline also included the various types of food allergy so as to place emphasis on basic concepts. The importance of the referral relationship between general practitioners and specialists was also emphasized throughout the guideline.

Since the number of school children with food allergy and anaphylaxis is increasing, various safeguards are necessary to secure their health. Although the fundamental policy regarding social countermeasures against food allergy is also described in the guideline,[1] "The Guidelines for the Treatment of Allergic Diseases in Schools" was published by the Japanese Society of School Health in 2008. In addition to the guideline, "School Life Management Certificate (for Allergic Diseases) " was developed in order to allow the verification of the diagnosis and encourage the discussion of countermeasures by parents/guardians and school teachers for students requiring special care. In the following sections, I summarize these two guidelines using tables, figures and flowcharts.

FOOD ALLERGY MANAGEMENT GUIDELINE 2008

GENERAL

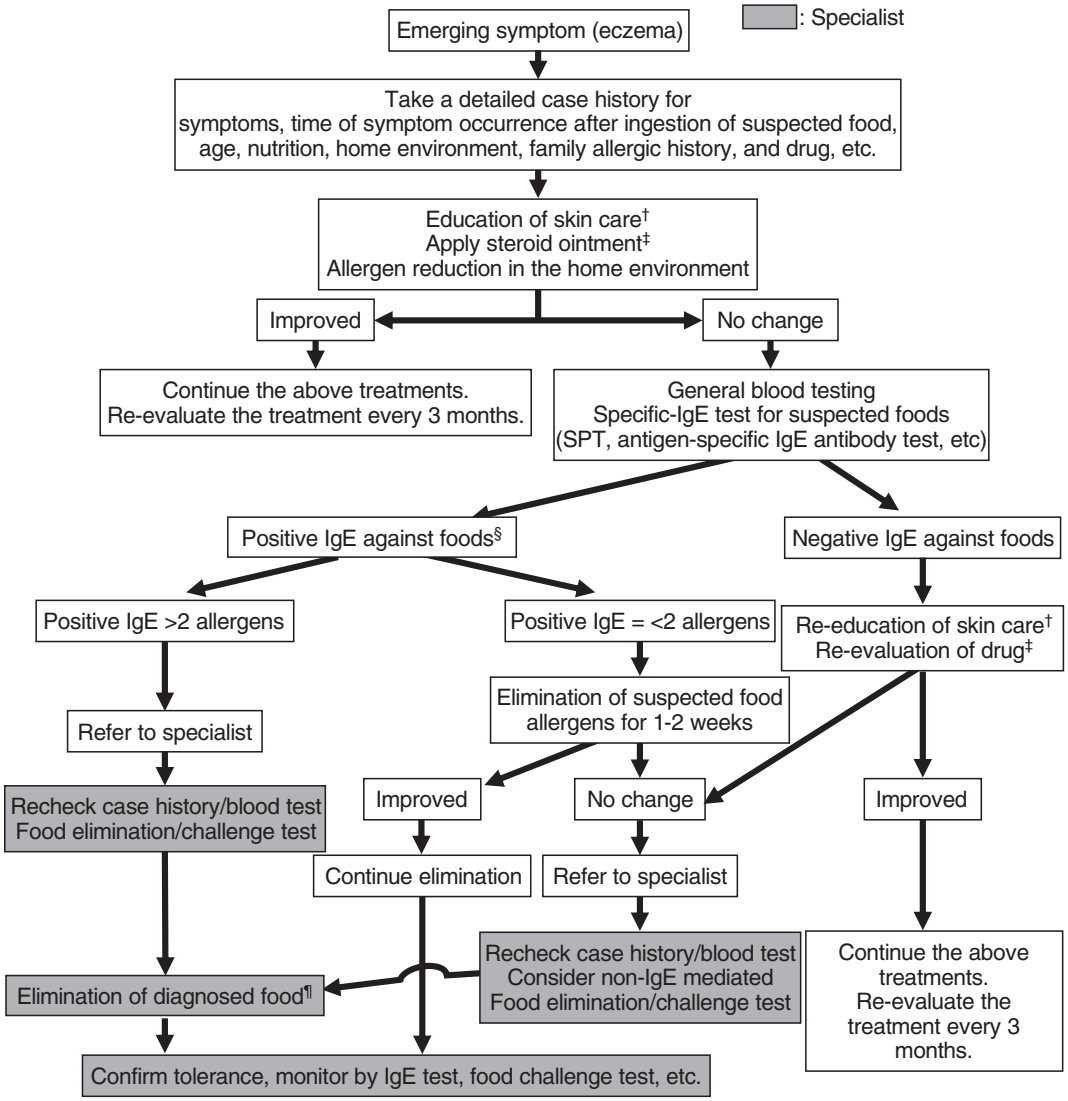
Classification of Food Allergies

There are several clinical types of food allergy that occur from infancy to adulthood. Table 1 summarizes the clinical types, age of onset, high frequency causative foods, possibility of tolerance acquisition, possibility of anaphylactic shock and food-allergy mechanisms. The definition of "infantile atopic dermatitis associated with food allergy", described above, is quite significant since most pediatric food allergies start in infancy.

Epidemiology

According to research on food allergy prevalence rate, the prevalence of food allergies in infants is approximately 5-10% and approximately 2% in school children.[1] However, no data exists on the prevalence of food allergy in adults in Japan. Across all generations, the prevalence rate is estimated to be approximately 2% in Japan. The rate is reported to be 3-5% in France[4] and 3.5-4% in the USA.[5] One report showed that 6% of three-year-old children have a medical history of food allergy.[6]

The guideline presents data from the nationwide food allergy monitoring investigation conducted by a contributing investigator, the late Prof. Y. Iikura and a current committee member Dr. Imai in 2000 and 2001. This research demonstrated causative allergens that were specific to age.[1] During this two-year period, 3882 cases of doctor-diagnosed immediate type food allergic response were accumulated by more than two-thousand volunteer doctors. Adverse events



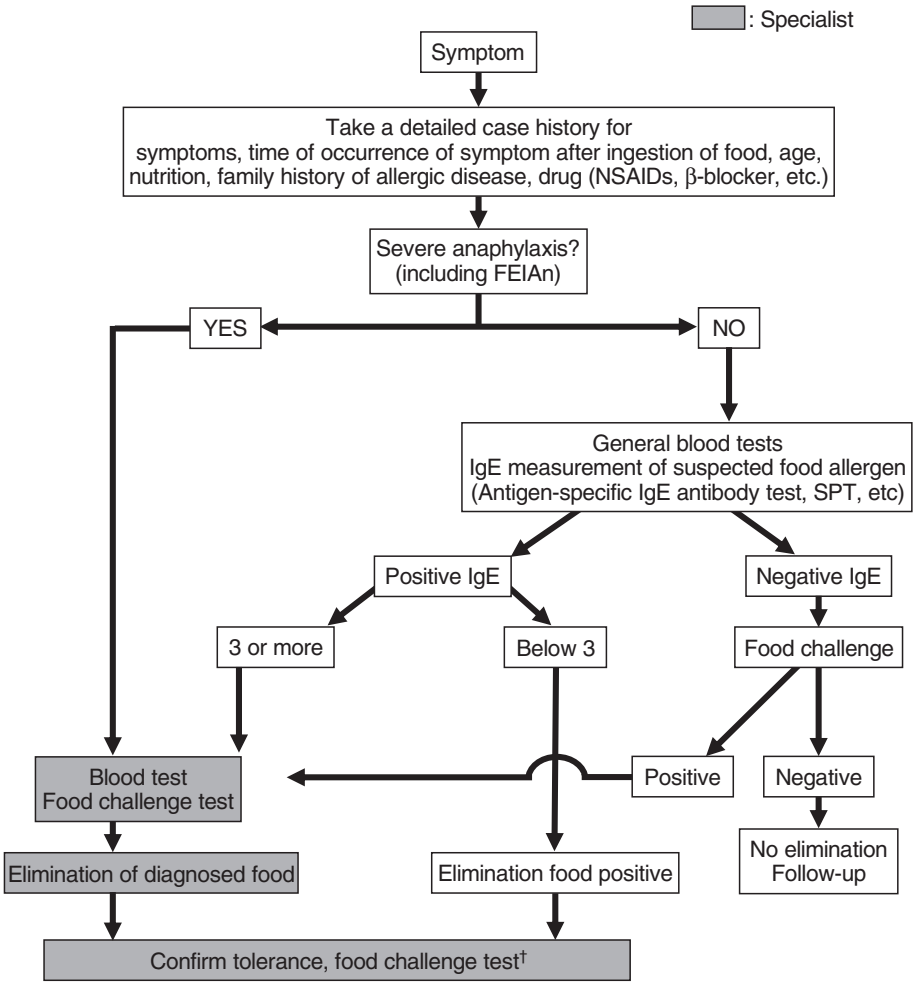
†Skin care.
Cleaning with soap and moisturizing is essential for skin care.
‡Drug treatment.
Steroid ointment is the essential treatment for infantile atopic dermatitis.
§SPT is useful for a baby under six months of age because an IgE antibody tends to become negative.
¶Precautions for practicing the elimination diet.
Monitor child's growth and development.
Always look for the possibility of ceasing the elimination diet.

Fig. 1 Procedure for Diagnosis of Food Allergy (for "Infantile Atopic Dermatitis associated with Food Allergy").

secondary to food allergy were monitored using postcards with update cards returned every 3 months for 2 years. Causative foods for all ages were hen's eggs (38.3%), cow's milk products (15.9%), wheat (8.0%), shellfish (6.2%), fruits (6.0%), buckwheat (4.6%), fish (4.4%), and peanut (2.8%). The ranking of hen's eggs, cow's milk products and wheat did not change from age 0 up to age 3. For ages 4 to 6, the ranking from the 3rd position downward was shellfish, fruits and peanut. From age 7 to adulthood, the highest frequency of allergic reaction was due to shellfish, and wheat, fruits and buckwheat were at higher frequencies. Depending on whether the allergic onset occurred in infancy or adulthood, the cause of the reaction was different. The most frequently induced symptom was skin eruption (88.6%), followed by respiratory symptoms in 26.8%. Anaphylactic shock occurred in 10.9%.

DIAGNOSIS AND TREATMENT

Although we surveyed a variety of examinations that could be used to determine food allergy, such as



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

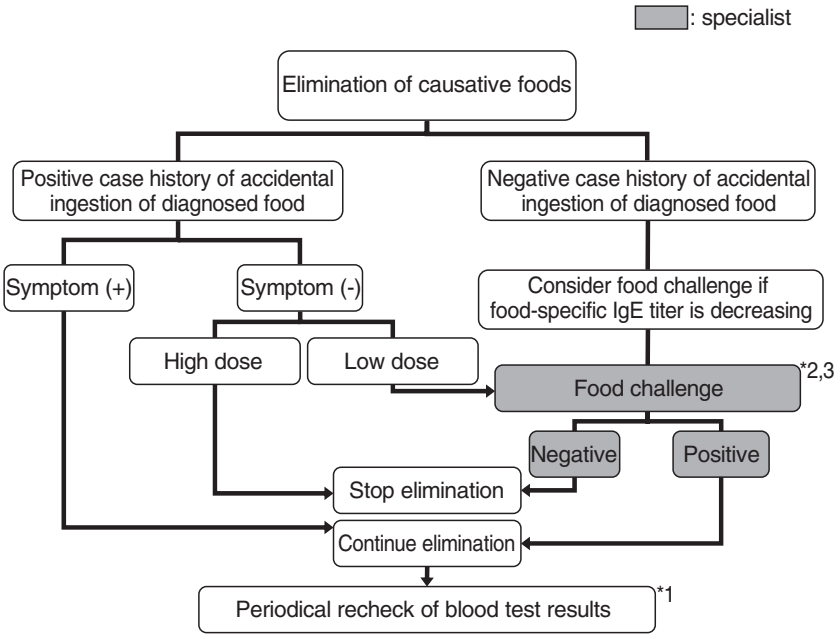
Fig. 2 Procedure for Diagnosis of Food Allergy (for "Immediate Type Reaction").

measurement of antigen-specific IgE, skin prick test or histamine release test and its characteristics in the guideline, we stated that final diagnosis should be based upon oral food challenge tests. Oral food challenge tests are significant because they not only provide a diagnosis of the causative allergen, but also judge acquisition of tolerance. Oral food challenge test should be carried out in a hospital setting with admission facilities under the direction of a well-trained specialist. Cooperation between general practitioners and specialists is also desirable.

In 2006, the Japanese government permitted allergy specialists to perform oral food challenge tests as a medical examination covered by the health insurance system, and the government also approved oral food challenge tests at outpatient clinics in 2008. We are very proud that these two advances were based on the "Food Allergy Management Guideline 2005". We produced two types of flowcharts demonstrating the steps in the diagnosis of food allergy for infantile atopic dermatitis associated with food allergy (Fig. 1) and for immediate type reaction (Fig. 2), since the diagnosis differs between the two types of food allergy.

We have stressed that the fundamentals of the treatment of food allergy include "minimal elimination of causative food(s) based on accurate diagnosis made primarily by oral food challenge tests, and that medication is subordinate".

After the determination of causative food allergens it is very important to conduct follow up for the treatment of pediatric food allergy patients, since most pediatric food allergy patients outgrow their food allergy. The follow up flowchart and timing of examinations is shown in Figure 3. In the procedure, the probability curves developed on hen's egg and cow's milk are used to indicate appropriate application of oral food challenge tests (Fig. 4). We found different threshold values depending on the age of the child, indicating that for a young child there was a higher probability of a reaction to a low level of egg and/or



《Timing of examinations》

	Below 3 yrs	3-5 yrs	Over 6 yrs
*1: Food-specific IgE	Every 0.5 yr	Every 0.5-1 yr	Every 1 yr or more
*2: Food challenge test †	Every 0.5-1 yr	Every 1-2 yrs	Every 2-3 yrs or more
*3: Methods of food challenge test	Open	Open, single-blind, double-blind	Open, single-blind, double-blind

†Generally, the food challenge test should not be performed in a patient who has had a previous anaphylaxis. However, in small infants, some may become tolerant to foods which, in a child, would cause anaphylaxis.

Fig. 3 Follow up after determination of causative foods.

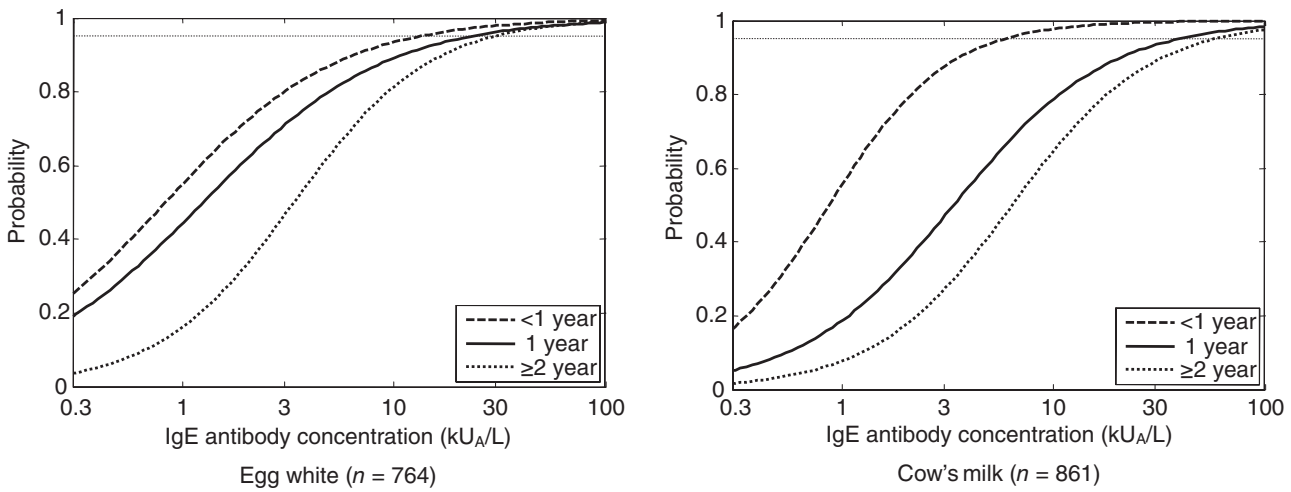


Fig. 4 Probability curves for hen's egg and cow's milk. **A**: 374 Positive reactions (Skin: 368, Mucosa: 7, Lower respiratory tract: 21, Digestive: 34, Anaphylaxis: 8, Others: 1). **B**: 215 Positive reactions (Skin: 213, Mucosa: 9, Lower respiratory tract: 15, Digestive: 14, Anaphylaxis: 8, Others: 2).

Table 2 Grading of food-induced anaphylaxis according to clinical symptoms

Grade	Skin	GI Tract	Respiratory Tract	Cardiovascular	Neurological
1	Localized pruritus, flushing, urticaria, angioedema	Oral pruritus, oral "tingling", mild lip swelling	-	-	-
2	Generalized pruritus, flushing, urticaria, angioedema	Any of the above, nausea and/or emesis x's 1	Nasal congestion and/or sneezing	-	Change in activity level
3	Any of the above	Any of the above plus Repetitive vomiting	Rhinorrhea, marked congestion, sensation of throat pruritus or tightness	Tachycardia (increase >15 beats/min)	Change in activity level plus anxiety
4	Any of the above	Any of the above plus diarrhea	Any of the above, hoarseness, "barky" cough, difficulty swallowing, dyspnea, wheezing, cyanosis	Any of the above, dysrhythmia and/or mild hypotension	"Light headedness" feeling of "impending doom"
5	Any of the above	Any of the above loss of bowel control	Asphyxia	Severe bradycardia, and/or hypotension or cardiac arrest	Loss of consciousness

Adapted from Sampson.[8]

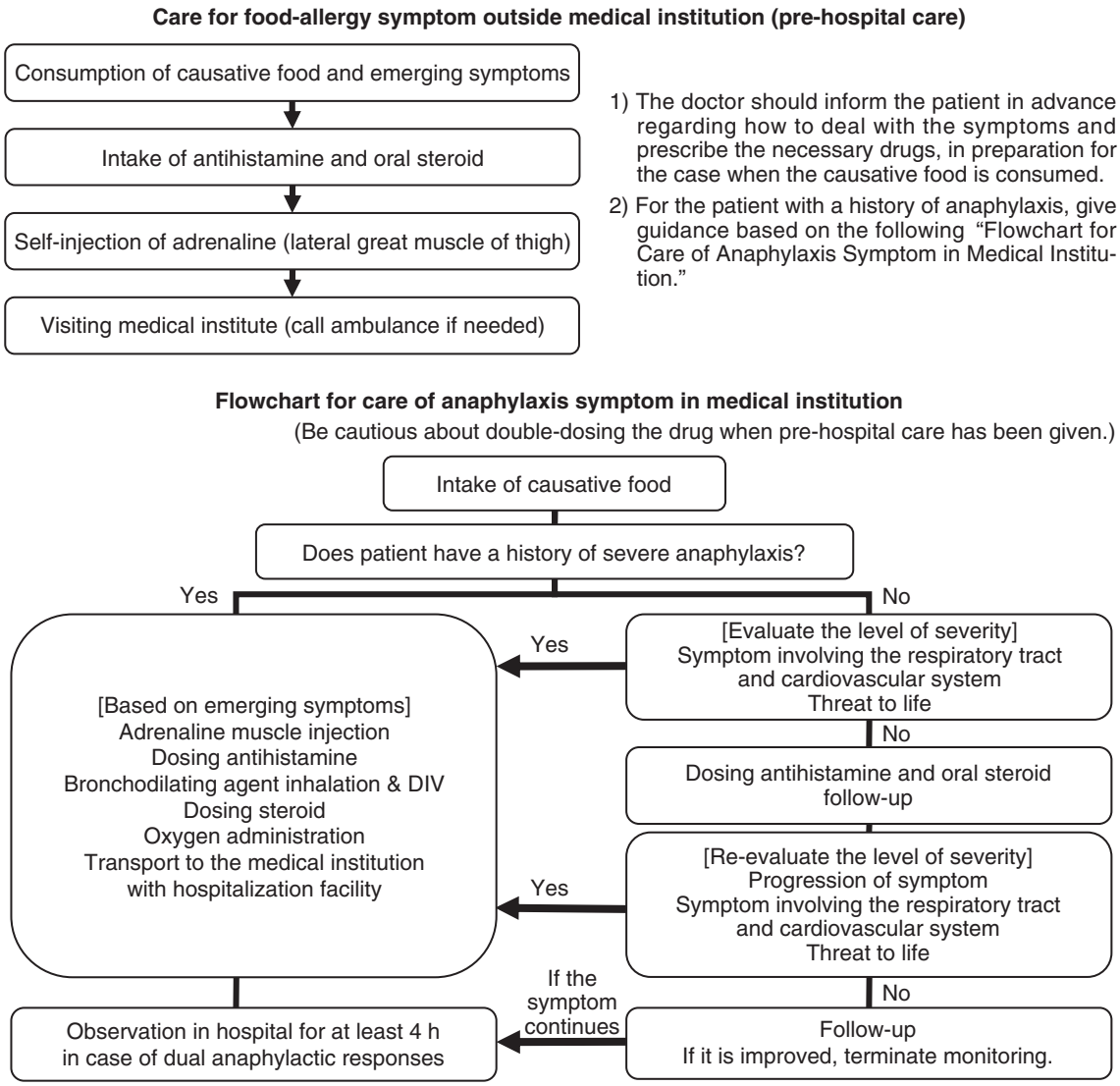


Fig. 5 Treatment of food-induced anaphylaxis in pre-hospital and hospital settings.

Table 3 Instruction (medical certificate) for elimination diet

Name_____(Male/Female)
Date of birth (Month/Date/Year)_____
Diagnosis #1 Food allergy_____
#2_____
#3_____

1) Please eliminate the following foods completely. (Circle all that apply)
1. Egg 4. Buckwheat
2. Milk 5. Peanut
3. Wheat 6. Others (_____)
Remarks: Use of infant formula for allergy
Yes (name of article_____)/No
Use of soy sauce Yes/No

2) Previous anaphylactic symptom (Circle that apply)
Yes No
If yes: Causative food (Allergen)_____
Date (Month/Day/Year)_____

3) How to deal with the symptom from taking the causative food (Circle all that apply)
1. Medication ( )
2. Self-injection (EPIPEN® 0.3 mg/0.15 mg)
3. Medical institution to be referred
Name of medical institution_____
Phone number_____-_____-_____

4) The content of this instruction needs to be revised in 6 months/in 12 months.
Date (Month/Day/Year)_____
Name of medical institution:_____
Phone number: _____-_____-_____
Doctor's name:_____

milk specific IgE antibody levels, than for an older child.[3] Though the decision regarding tolerance acquisition should be based fundamentally on the results of oral food challenge tests,[7] sometimes a history of accidental intake provides significant information unexpectedly in a routine clinical setting.

CARE FOR FOOD-INDUCED ANAPHYLAXIS

With regard to the treatment of anaphylaxis, Japan has entered a new stage with the approval, in 2005, of EPIPEN® (auto-injector of adrenaline) for the treatment of food allergy. As the word "anaphylaxis" is comprehensive and can be interpreted in a variety of ways, we outline the grading of food-induced anaphylaxis according to clinical symptoms, as suggested by Sampson, in Table 2.[8] For the treatment of anaphylaxis, we present flowcharts of both pre-hospital care and care in the hospital setting (Fig. 5). In the flowchart outlining pre-hospital care, we explain such factors as the necessity of oral administration of antihistamine and corticosteroids, self-injection of adrenaline (EPIPEN®), and the timing of its use.

SOCIAL COUNTERMEASURES FOR FOOD ALLERGY

FUNDAMENTAL RULES

In most kindergartens and elementary schools in Japan, lunch is provided for children. The management of food allergic children that participate in the school lunch program in nursery schools, kindergartens or schools is not well established. In the Food Allergy Management Guideline 2008, we proposed fundamental rules for the management of food allergic children (minimum complete elimination) and a sample of Instruction (certificate) for elimination diet (Table 3) to avoid accidental intake of a causative food.

GUIDELINES FOR THE TREATMENT OF ALLERGIC DISEASES IN SCHOOLS

The Research Study Committee on Allergic Diseases of the Ministry of Education, Culture, Sports, Science and Technology reported on the prevalence rates of food allergy and anaphylaxis among approximately 12 million school children at elementary, junior high, and senior high schools throughout Japan in 2004. According to this report, the prevalence was 2.6% for food allergies, and 0.14% for anaphylaxis, and the report revealed that countermeasures against allergic diseases such as food allergy and anaphylaxis were insufficient in most schools in Japan. Therefore, "The Guidelines for the Treatment of Allergic Diseases in Schools" with "School Life Management Certificate (for Allergic Diseases) " (Table 4) was developed by medical specialists and school officials, and the guideline and certificate were distributed to education boards nationwide by the Japanese Society of School Health in 2008. It is expected that the major strategy, "School Life Management Certificate (for Allergic Diseases) " will be widely utilized as a tool facilitating communication between physicians in charge and schools when cases requiring special care have been identified.

Most cases of food allergy in school-aged children are the immediate type, and food allergies rarely lead to worsening of atopic dermatitis. Types of food allergy among school-aged children are classified as follows: 1) immediate-type, 2) oral allergy syndrome, and 3) food-dependent exercise-induced anaphylaxis. School-aged children's food allergy should be diagnosed on the basis of objective symptoms or results of oral food challenge tests. As shown in Table 4, it is the doctor's responsibility to care for the patient and the doctor is required to clarify the diagnostic evidence in the certificate.

As shown in Table 4, several issues for food allergy and anaphylaxis need to be addressed in school life. The most fundamental concern is the school lunch service. The presence or absence of specific changes in the school-provided lunch for children with food allergies is basically dependent on the local govern-

Table 4 "School Life Management Certificate (for Allergic Diseases)"

Name _____ Male/Female Birthday MM/DD/YY (age: y)
Name of school _____ Grade _____ Class _____ Date of submission MM/DD/YY

Food Allergy (with or without)
Anaphylaxis (with or without)

Type of Disease/Treatment	Attention of the school life	Emergency contact number
A. Type of Food Allergy 1. Immediate type 2. Oral Allergy Syndrome (OAS) 3. Food-dependent, exercise-induced, anaphylaxis (FEIAn/FDEIA)	A. Type of Food Allergy 1. Consideration-free 2. Consultation with parents	*Parents* Phone number:
B. Type of Anaphylaxis 1. Food (causes) 2. Food-dependent, exercise-induced, anaphylaxis (FEIAn/FDEIA) 3.Exercise-induced, anaphylaxis (EIAn/EIA) 4. Insect 5. Drug 6. Others ( )	B. Activity to treat food 1. Consideration-free 2. Consultation with parents C. Exercise (gymnastics/club activities) 1. Consideration-free 2. Consultation with parents	*Medical agency* Name: Phone number:
C. Causative foods/basis of the diagnosis **Check all that apply and fill out the basis of the diagnosis* ***The basis of the diagnosis: a) history of apparent symptom, b) positive reaction by food challenge test, c) positive reaction by blood antigen-specific test* 1. Chicken egg ( ) 2. Cow's milk products ( ) 3. Wheat ( ) 4. Buckwheat ( ) 5. Peanut ( ) 6. Nut ( ) 7. Shellfish (shrimp, crab) ( ) 8. Fruit ( ) 9. Fish ( ) 10. Meat ( ) 11. Other 1 ( ) 12. Other 2 ( )	D. School activity with the lodging 1. Consideration-free 2. Consideration is necessary at the time of meals and events E. Other consideration (free text)	Date of written MM/DD/YY Written by (name of doctor) *signature* Medical agency
D. Prescribed medicine of the emergency 1. Medicines for internal use 2. Self-injection of adrenaline 3. Others ( )		

ment. It is not rare in schools for a child in a class to bring a bag lunch due to his or her food allergy, while others in the class have the lunch provided by the school. Improvement in the response to food allergies should begin with the promotion of an understanding of food allergies among school teachers. With this background, the range of available responses to food allergies should be decided according to the actual circumstance of each school lunch center and kitchen. Health hazards in children with food allergies during school life can be caused by even handling foodstuffs or recycling milk cartons. Finally, some children with food allergies may not be able to participate in school trips, which can be once-in-a-lifetime events. Such cases have actually been found by our surveys, regardless of whether the surveys reflected the patient's viewpoint or the school's viewpoint.

Thus, although many problems remain to be solved, it is expected that improvements will be achieved at the level of diagnosis and treatment of food allergies, and that accurate knowledge of food allergies will spread among parents and school teachers, thereby improving the current situation.

Anaphylaxis is a critical type of allergic reaction that may be life-threatening and require emergency response. The most common cause of anaphylaxis is food allergy.[9] In addition, other causes include bee stings, exercise, and food plus exercise (food-dependent exercise-induced anaphylaxis). The most dangerous sign of anaphylaxis is difficulty breathing (laryngeal edema, wheezing, etc.). The first and most important thing school teachers must do is to recognize the patient's symptoms and evaluate the severity. Emergency response plans (where to transfer the patient, making contact with a parent/guardian, etc.) should be determined with the parents/guardians in advance.[9] The most effective therapy for anaphylaxis is self-injection of adrenaline (EpiPen®). However, the efficacy of this therapy is not yet fully recognized by healthcare providers; therefore, it is necessary to disseminate reliable information. Although the use of EpiPen® by the patient as well as by the parent/guardian is permitted, it is also recommended that

the drug should be used by a third person only in an emergency.

CONCLUDING REMARKS

This review article introduced the content of the "Food Allergy Management Guideline 2008" and "The Guidelines for the Treatment of Allergic Diseases in Schools". It is hoped that the introduction of these guidelines will be useful for doctors who treat food allergy patients, and that the quality of life of food allergy patients and their parents/guardians will be improved.

ACKNOWLEDGEMENTS

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