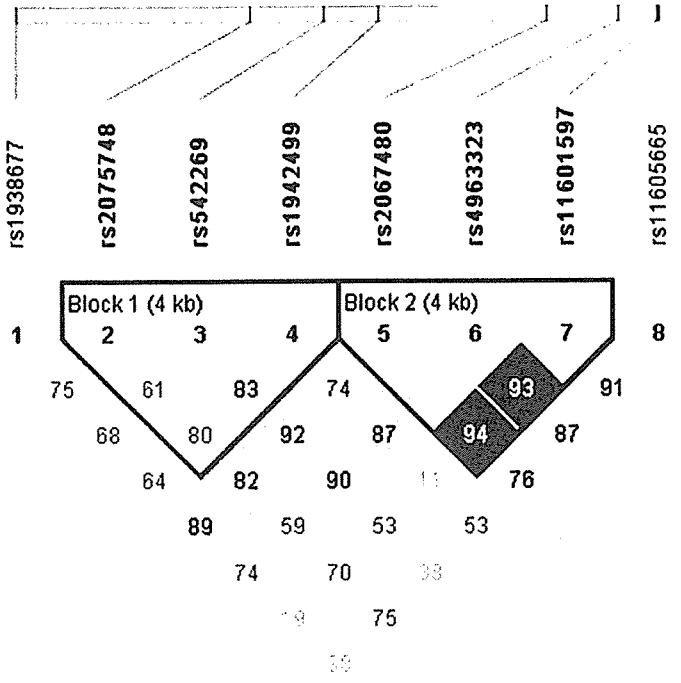

Figure 1. Locations and linkage disequilibrium (LD) map structure of single-nucleotide polymorphisms (SNPs) in and around the *CHRM1* Haploview plot shows pairwise LD (D' values) for 8 SNPs based on genotypes of 659 individuals of the case-control study. The eight SNPs include −18379G > A [rs1938677], −9697C > T [rs2075748], −6965T > C [rs542269], −4953A > G [rs1942499], +1353C > T [rs2067480], +3970C > G [rs4963323], +5418C > G [rs11601597], and +5455G > T [rs11605665]. LD blocks are framed in *black* and were classified according to the "solid spine" option (25). Each *square* plots the level of LD (D' values) between a pair of SNPs.

This difference in transcriptional activity was consistent in eight independent experiments.

EMSA failed to show a robust difference in binding affinity of NF-κB to the −9697T or the −9697C allele, or in binding affinity of USF-1 to the −4953A or the −4953G allele (data not shown).

DISCUSSION

Given a high *a priori* biological plausibility for asthma, we tested the hypothesis that the allelic variants at the regulatory region of the *CHRM1* confer susceptibility to asthma by conducting a case-control study in a relatively large population of unrelated Japanese subjects. In accordance with our primary hypothesis, we found that the presence of the −9697CC genotype, −4953GG genotype, or the −9697C/−4953G haplotype at the regulatory region was significantly associated with a diagnosis of asthma. Our genetic association study had several strengths: first, muscarinic receptors, including M1, have been biologically implicated in the pathogenesis of asthma; second, the gene encoding the CHRM1 is located on chromosome 11q13, a genomic region

TABLE 4. ESTIMATED HAPLOTYPE FREQUENCIES OF THE *CHRM1* GENE POLYMORPHISMS

				Haplotype Frequency			
				Control (*n* = 333)	Asthma (*n* = 326)	Haplotype-specific Score	p Value* (*Empirical*)
Block I							
Haplotype	−9697/−6965/−4953						
1	T	T	A	0.207	0.158	−3.03	0.00055
2	C	C	A	0.239	0.234	−0.23	0.827
3	C	T	A	0.250	0.254	0.057	0.959
4	C	T	G	0.268	0.303	2.15	0.020
Block II							
Haplotype	+1353/+3970/+5418						
1	T	C	C	0.371	0.391	0.120	0.131
2	C	C	C	0.353	0.349	0.808	0.814
3	C	G	C	0.192	0.179	0.926	0.918
4	C	C	G	0.371	0.391	0.454	0.481

Haplotype frequencies were estimated using the Haplo.Stats program. In Block I (regulatory region of the gene), haplotype analyses showed that the −9697T/−6965T/−4953A haplotype was associated with a significantly lower risk of asthma ($p = 0.00055$) and the −9697C/−6965T/−4953G haplotype was associated with a significantly increased risk of asthma ($p = 0.020$). In contrast, in Block II, none of haplotypes showed a significant association with asthma. Note that haplotype-specific scores give effect estimates; negative haplotype-specific scores are associated with a protective effect, and positive haplotype-specific scores are associated with an increased risk. Haplotypes with frequencies less than 0.05 were excluded from the analyses.

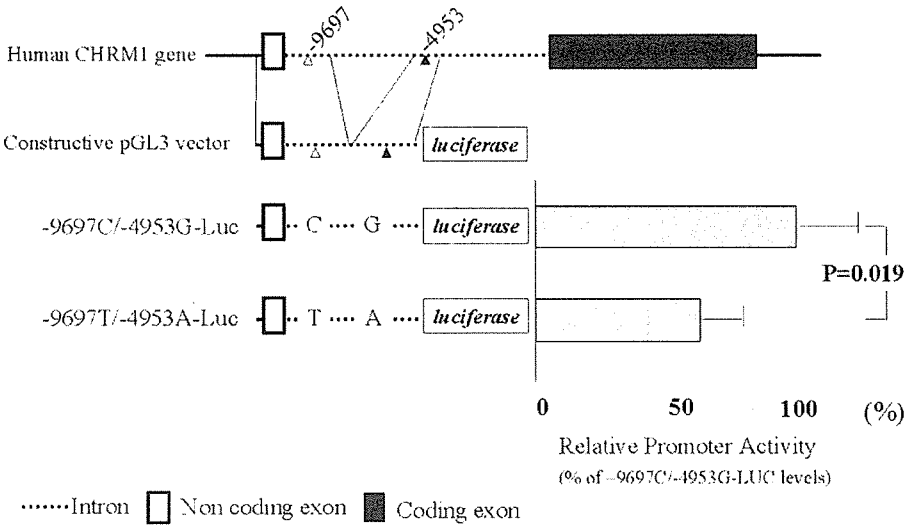

Figure 2. Transcription activity analysis of the promoter region of *CHRM1* IMR32 cells were transiently transfected with 9.5 μg of *CHRM1* luciferase reporter constructs (schematically depicted to the *left*) plus 0.5 μg of pRL-TK vector. Luciferase activities were normalized against the internal control Renilla values. The data represent means ± SD for the entire dataset (four independent experiments, each in duplicate), and are expressed as a percentage of the −9697C/−4953G LUC activity. The difference between these constructs was significant at $p = 0.019$ (paired *t* test; $n = 8$).

linked to the diagnosis of asthma and atopy in several genome-wide scans (14–17); third, *in vitro* functional analyses have shown that the haplotype at the regulatory region has an effect on a basal promoter function in IMR32 cells, with the −9697T/4953A haplotype associated with 37% decreased promoter activity compared with the −9697C/−4953G haplotype. Accordingly, our data suggest that the −9697/−4953 haplotype may influence the affinity of a particular nuclear protein to the regulatory region of the *CHRM1* gene, resulting in altered transcriptional activity and ultimately leading to a higher or lower risk of asthma.

Although the exact mechanisms underlying the involvement of the *CHRM1* gene in the pathogenesis of asthma remain to be identified, several reports indicate that the cholinergic pathway has an important role in the pathogenesis of asthma, in particular in the regulation of bronchoconstriction, airway inflammation, and airway remodeling. An M1 receptor–dependent pathway counteracts cholinergic bronchoconstriction, possibly via the release of a relaxing agent (8); both respiratory epithelia and sympathetic nerve terminals within bronchial smooth muscle are equipped with M1 receptors (7, 26) and releasable bronchodilating agents, such as nitric oxide and prostaglandin E_2 (27). Studies with the M1 receptor–preferring antagonist, pirenzepine, have also suggested the existence of pulmonary M1 receptors modulating airway diameter (28). Furthermore, Jones and colleagues (29) demonstrated that stable expression in RBL-2H3 mast cells of the M1 muscarinic acetylcholine receptor leads to carbachol-stimulated mast cell degranulation. An animal model of asthma showed that anticholinergic agents protect against allergen-induced airway remodeling (30). Together with these *in vivo* and *in vitro* findings, our findings support the contention that CHRM1 plays an important role in the pathogenesis of asthma. Our findings may be of considerable relevance to asthma treatment, providing an important basis for identification of individuals for whom the cholinergic pathway could be targeted.

Sequence analysis indicated that the T allele at the −9697C > T polymorphism creates a potential NF-κB binding site and that the A allele at the −4953A > G polymorphism creates a potential USF-1 transcription factor binding site by reference to the MatInspector or TFSEARCH database (31). We, however, failed to see any difference in binding intensities of these nuclear factors to the −9697C > T or −4953A > G polymorphism. Therefore, we cannot exclude the possibility that these SNPs might not be causative in nature, but are in LD with a true susceptibility allele in the regulatory region of the *CHRM1* gene. Population stratification may influence the observed associations (32). However, our population is racially homogeneous, as all subjects recruited in the study were from the Japanese population, which is considered monoracial; thus, our subjects had a relatively low risk of population stratification effects. Furthermore, we recruited all participants in the current study from a single institute to minimize the chance of mixing populations with inherently diverse allele frequencies of a susceptibility gene. In addition, all SNPs were in HWE in a set of unrelated healthy subjects. Therefore, we believe that the usual problems associated with population stratification may be of limited importance in the present study. Nevertheless, we acknowledge that population stratification may have influenced the present findings, and that the findings of the current study are preliminary and do not, by themselves, conclusively confirm an etiologic relationship. A more comprehensive approach that examines the functional consequences of the *CHRM1* promoter polymorphisms and identifies the possible promoter-dependent mechanism for an association between *CHRM1* and asthma is required.

In conclusion, given the important role of muscarinic cholinergic mechanisms in pulmonary disease, this case–control study, together with an *in vitro* functional analysis, suggests that the *CHRM1* gene is an important susceptibility locus for asthma at chromosome 11q13. The −9697/−4953 haplotype at the regulatory region of the gene may contribute to the development of asthma by altering the human lung muscarinic receptor system in ways that could account for the increased *in vivo* lung cholinergic hyperresponsiveness found in patients with asthma.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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천식 및 알레르기 제26권 제3호
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□ Review Article □

Management of Food Allergy: "Food Allergy Management Guideline 2005" by National Food Allergy Research Group Supported by the Ministry of Health, Welfare, and Labor

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In October 2005, we released "Food Allergy Management Guideline 2005". To cover food allergy from infancy to adulthood, the project committee included not only pediatric researchers, but also internists, dermatologists, and otolaryngologists. The guideline concept was to utilize the data accumulated by the National Food Allergy Research Group, to be plain and as short as a pamphlet, and to be released on internet. The most glowing argument was about relation between infantile atopic dermatitis and food allergy, and how it should be treated in the guideline. To avoid neither overvaluation nor undervaluation, fastidious care was given to the denotation. With the definition of "infantile atopic dermatitis associated with food allergy", both dermatologic and pediatric members of the project committee finally came to agreement, which was a landmark between dermatologists and pediatricians in Japan. The guideline explains fundamentals with the least paragraphs and with tables and figures as many as possible. Flowcharts are made largely as a composition in the parts of diagnosis and treatment. I really hope that this guideline is useful for Korean doctors involved in food allergy and that quality of life of food allergy patients and their parents are improved. **(Korean J Asthma Allergy Clin Immunol 2006;26:177-185)**

Key words: Anaphylaxis, Food allergy, Food provocation test, Referral relationship

INTRODUCTION

In October 2005, we released on internet "Food Allergy Management Guideline 2005",[1] the most important subject we had worked on in the course of "the research on determination of causative agent (allergen) for anaphylaxis caused by food and other factors, and on establishment of its prevention and prognosis" (principal investigator: Motohiro Ebisawa, M.D., Ph.D., 3 years project since 2003), which is the national research project on prevention and treatment of immunological and allergic diseases, supported by the Ministry of Health, Welfare, and Labor by Japanese government.

The guideline was created for general physicians to improve diagnosis and treatment of food allergy and for food-allergy patients to improve their quality of life. Its concept was decided in 2003 that it should utilize the data accumulated by the Food Allergy Research Group supported by the Ministry of Health, Welfare, and Labor, that it should be plain and as short as a pamphlet, and that it should be released on internet so that anyone is free to download it. In 2004 the draft was written by staffs of the Department of Pediatric Allergy, National Hospital Organization, Sagamihara National Hospital, and then in January 2005 it was discussed for three hours in the public symposium held at the 5th Workshop on Food Allergy, (which was combined with the meeting of the Food Allergy Research Group supported by the Ministry of Health, Welfare, and Labor.) To cover food allergy from infancy to adulthood, the project committee included not only pediatric researchers, but also internists, dermatologists, and otolaryngologists (Table 1). The guideline finally came to completion through three times tough arguments for about 10 hours altogether in June, July and September 2005, and through further communication by e-mail.

The most glowing argument was about relation between infantile atopic dermatitis and food allergy, and how it should be

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Table 1. "Food Allergy Management Guideline 2005" Project Committee

(Principal investigator)	
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Akira Akasawa	General Medical Care Department, National Center for Child Health and Development, Childhood Care Service
Setsuko Ito	Department of Food Studies and Nutrition, Doshisha Women's College of Liberal Arts
Atsuo Urisu	Department of Pediatrics, Fujita Health University Banbuntane Hotokukai Hospital
Naomi Kondo	Department of Pediatrics, Gifu University School of Medicine
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Mitsuhumi Mayumi	Department of Pediatrics, Fukui University School of Medicine
Hiroshi Tachimoto	Department of Pediatrics, National Hospital Organization, Sagamihara National Hospital
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Kimihiro Okubo	Department of Otolaryngology, Nippon Medical School
(Internists)	
Kazuo Akiyama	Clinical Research Center for Allergoloy and Rheumatology, National Hospital Organization, Sagamihara National Hospital
Naohito Suzuki	Department of Allergy and Respiratory Disease, Fraternity Memorial Hospital,
Takemasa Nakagawa	Department of Internal Medicine, St. Mariannna University School of Medicine
(Dermatologists)	
Zenro Ikezawa	Department of EnvironmentalImmunopathology and Dermatology, Yokohama City University School of Medicine
Masutaka Furue	Department of Dermatology, Kyushu University Graduate School of Medicine
(Collaborator for document preparation)	
Chizuko Sugizaki	Department of Allergym, Clinical Research Center for Allergoloy and Rheumatology, National Hospital Organization, Sagamihara National Hospital,

treated in the guideline. The point whether to admit dermatitis as a symptom of food allergy or not, was on focus. The committee members of dermatologists insisted that generally eczema can not be developed by the allergic stimuli absorbed through digestive system. In contrast, the committee members of pediatricians insisted that infantile food allergy can be diagnosed in the subjects among infantile atopic dermatitis. The committee members from pediatrics explained the onset situation of infantile food allergy to the members from dermatology in order to achieve agreement.[2] The guideline tried to include clinical classifications of types of food allergy as it was thought out to place emphasis basically on comprehensibility.

Another big argument was about definition of "complicated cases of infant atopic dermatitis and food allergy." To avoid neither overvaluation nor undervaluation, fastidious care was given to the denotation. With the definition of "infantile atopic dermatitis associated with food allergy", both dermatologic and pediatric members of the project committee finally came to agreement, which was a landmark between dermatologists and pediatricians in Japan.

The guideline explains fundamentals with the least paragraphs and with tables and figures as many as possible. Flowcharts are made the most of as a composition in the parts of diagnosis and treatment. In the following sections, I explain summary of the guideline using actual tables, figures and flowcharts.

THE GENERAL

1. Definition

It is based on food allergy committee report from the Japanese Pediatric Allergy Society.[3] In that report, food allergy is defined as "Phenomenon of harmful symptoms (on skin, in the mucosa, in the digestive system, in the respiratory system or anaphylaxis) triggered by immunologic mechanisms after consuming a causative food. (not including food poisoning, nor response to toxic foods, nor food intolerance; pseudo-allergen, enzyme disorders)."

Table 2. 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	Neonatal peroid	Milk (powdered milk for infant)	(+)	(−)	IgE-dependent
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. (−) to (+/−) Most of others	(++)	IgE-dependent
Subtype					
Food-dependent, exercise-induced, anaphylaxis (FEIAn/FDEIA)	Later childhood to adulthood	Wheat, shrimp, calamari, etc.	(−) to (+/−)	(+++)	IgE-dependent
Oral allergy syndrome (OAS)	Early childhood to adulthood	Fruit, vegetables, etc.	(−) to (+/−)	(+−) to (+)	IgE-dependent

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

Table 3. Symptoms triggered by food allergy

Symptoms on skin and in mucosa:
- Skin symptoms: pruritus, urticaria, angioedema, flushing, eczema
- Eye symptoms: Hyperemia in conjunctiva, edema, pruritus, watery eyes, blepharedema
- Oral and throat symptoms: Sense of discomfort and edema on oral cavity, lips and tongue, strangalesthesia in throat, laryngeal edema, hoarseness, itchy throat, tickle in throat

Symptoms in the digestive system:
- Abdominal pain, nausea, vomiting, diarrhea, bloody stool

Symptoms in the respiratory system:
- Upper-airway symptom: Sneezing, rhinorrhea, nasal obstruction
- Lower-airway symptom: Dyspnea, cough, wheezing

Generalized symptoms:
- Anaphylaxis: Symptoms in multiple organs
- Anaphylactic shock: Tachycardia, collapse (limpness), loss of consciousness, drop in blood pressure

2. Classifications of clinical types in food allergy

There are many types from infancy to adulthood in food allergy. Table 2 summarizes the clinical types, age of onset, high frequency causative food, possibility of tolerance acquisition, possibility of anaphylactic shock and food-allergy mechanisms. The denotation of "infantile atopic dermatitis associated with food allergy" decided in above-mentioned course, is quite significant.

3. Symptoms

The symptoms triggered by food allergy are various but can be mainly classified into four categories; symptoms on skin, in the mucosa, those in the digestive system, those in the respiratory system, and generalized symptoms, as shown in Table 3. It was unexpectedly the first time for specialists from the concerned services to get together and to arrange and classify the symptoms.

4. Epidemiology

According to various researches on the food allergy prevalence rate, it is considered that prevalence of infants is around 5～10% and that in school children approximately 1～2%.[1] No data exist on the prevalence of food allergy in adulthood in Japan. Across all generations the prevalence rate is therefore considered 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 shows that 6% of children three years old have medical histories of food allergy.[6]

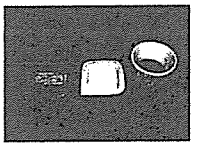
In the guideline, we presented the data from the nationwide food allergy monitoring investigation which a contributing investigator, deceased Prof. Y. Iikura and a current committee member Dr. Imai had made in 2000 and 2001, and showed causative allergens specific to ages.[1] Within those two years, 3,882 cases of the doctor-diagnosed immediate type of food allergic response were accumulated by more than two thousands volunteer doctors' contribution. The investigation of monitoring adverse events by food allergy was carried out by the using postcards with return cards every 3 months for 2 years. Frequency of causative foods in 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%), peanut (2.8%). The ranking of hen's eggs, cow's milk products and wheat did not change from age 0 up to 3. As for the group of age 4 to 6, the ranking from the 3rd position downward was shellfish, fruits and peanut. From age 7 to adulthood, the first position of frequency of causative food was shellfish, and wheat, fruits and buckwheat were at higher positions. Causes were different between the types in which onset appears in infancy and in which it appears in adulthood. The most frequent among induced symptoms was skin symptom by 88.6%, then followed symptom in the respiratory system by 26.8%. Anaphylactic Shock came to 10.9%.

DIAGNOSIS

Although we surveyed a variety of examinations for food allergy such as measurement of antigen-specific IgE or skin prick test or histamine release test and its characteristics in the guideline, we stated that final diagnosis should be upon food challenge test. Food

Table 4. Methods and results of Food challenge test

[Medical check by doctor]
Physical checkup
Consulting patient's parents (regarding blood-test result and their request)
After the explanation, let them sign the acceptance form.
[Challenging foods]
Powder from dried food (not for sale)
[Schedule]



	Food challenge										
Time (min.)	Start	15	30	45	60	90	2 h	3 h	4 h	6 h	24 h
Evaluation	●	●	●	●	●	●	●	●	●	●	●
Doses	1/20	1/10	1/5	3/10	Rest						

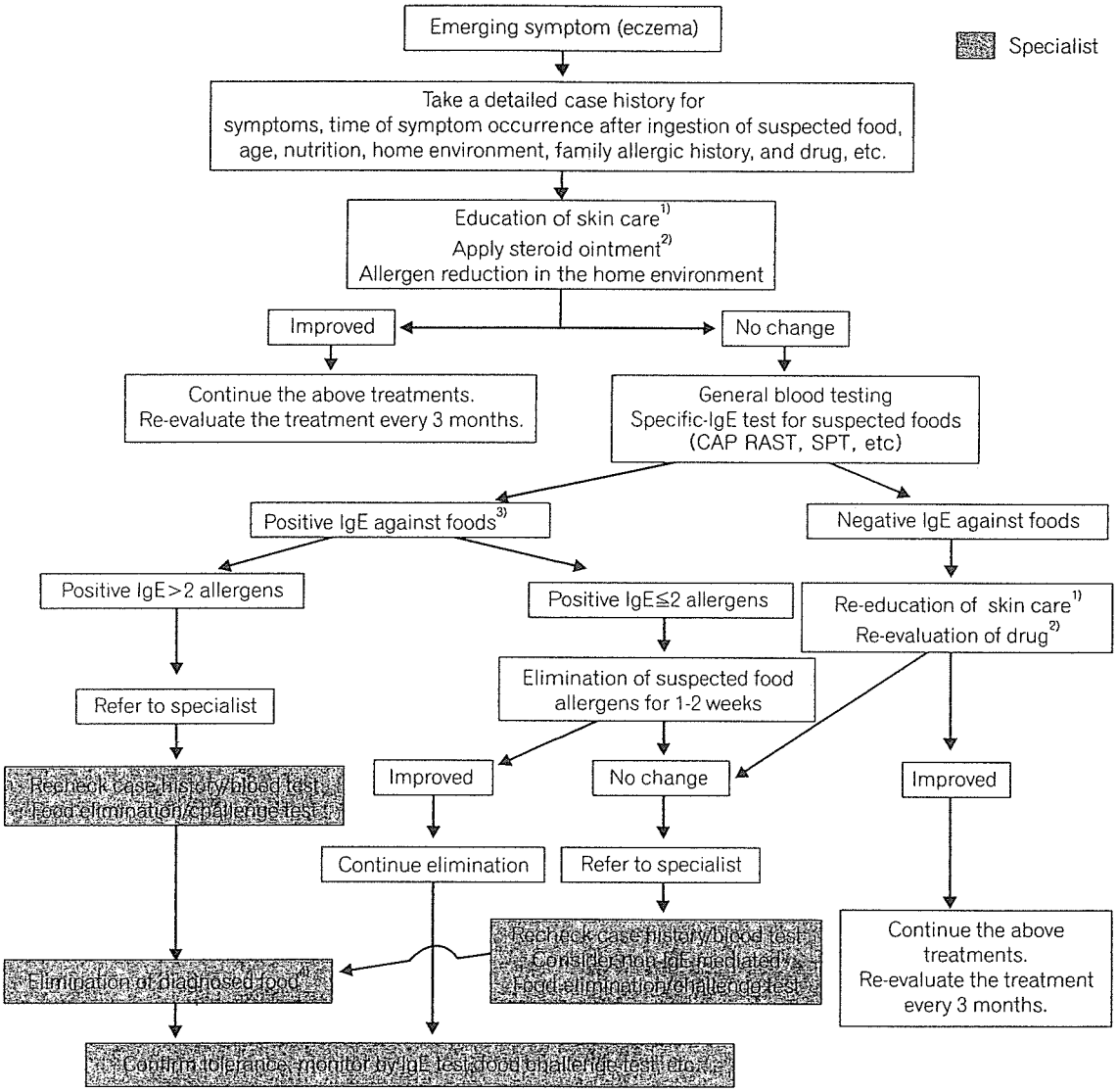
[When doctor confirms the symptom]
Stop the challenge and provide a care to the symptom.

Result of blinded-food challenge tests

	Food-challenge test	IgE CAP RAST	Skin Prick Test
Hen's egg (whole)	229/379 (60%)	309/369 (84%)	189/213 (89%)
Hen's egg (yolk)	20/82 (24%)	66/81 (81%)	53/57 (93%)
Cow's milk	115/263 (44%)	194/259 (75%)	116/146 (79%)
Wheat	47/140 (34%)	117/140 (84%)	59/77 (77%)
Soybean	12/81 (15%)	62/78 (79%)	24/43 (56%)
Total	423/945 (45%)	748/927 (81%)	441/536 (82%)

Food Provocation Network System in Japan by the National Food Allergy Research Group

challenge test has significance in two ways, of diagnosis of causative allergen and of judging acquisition of tolerance. Table 4 shows the results of food tolerance test on 945 cases which was done with a common protocol (blinded challenge, increasing the doses of food every 15 min) among "Food Provocation Network System in Japan" by the National Food Allergy Research Group supplying powdered-challenge foods (whole egg and egg yolk, cow's milk, wheat, and soy) co-developed by Q.P. Corporation and myself[1,7] The result indicates dissociation from positive rate of IgE CAPRAST with class 2 and up to be positive, and it proves the significance of food challenge test. Food challenge test should be carried out at a hospital with admission facilities under the direction of a well-trained doctor (specialist) with a lot of skill, and so promotion of alliance between general physician and specialists is desirable. In order to support it, it is indispensable for food challenge test to be acknowledged as medical care by



Note 1: Skin care
Cleaning with soap and moisturizing is essential for skin care.

Note 2: Drug treatment
Steroid ointment is the essential treatment for infantile atopic dermatitis.

Note 3: When providing the food sensitized via maternal milk to child, it is necessary to confirm by the food challenge test.

Note 4: 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").

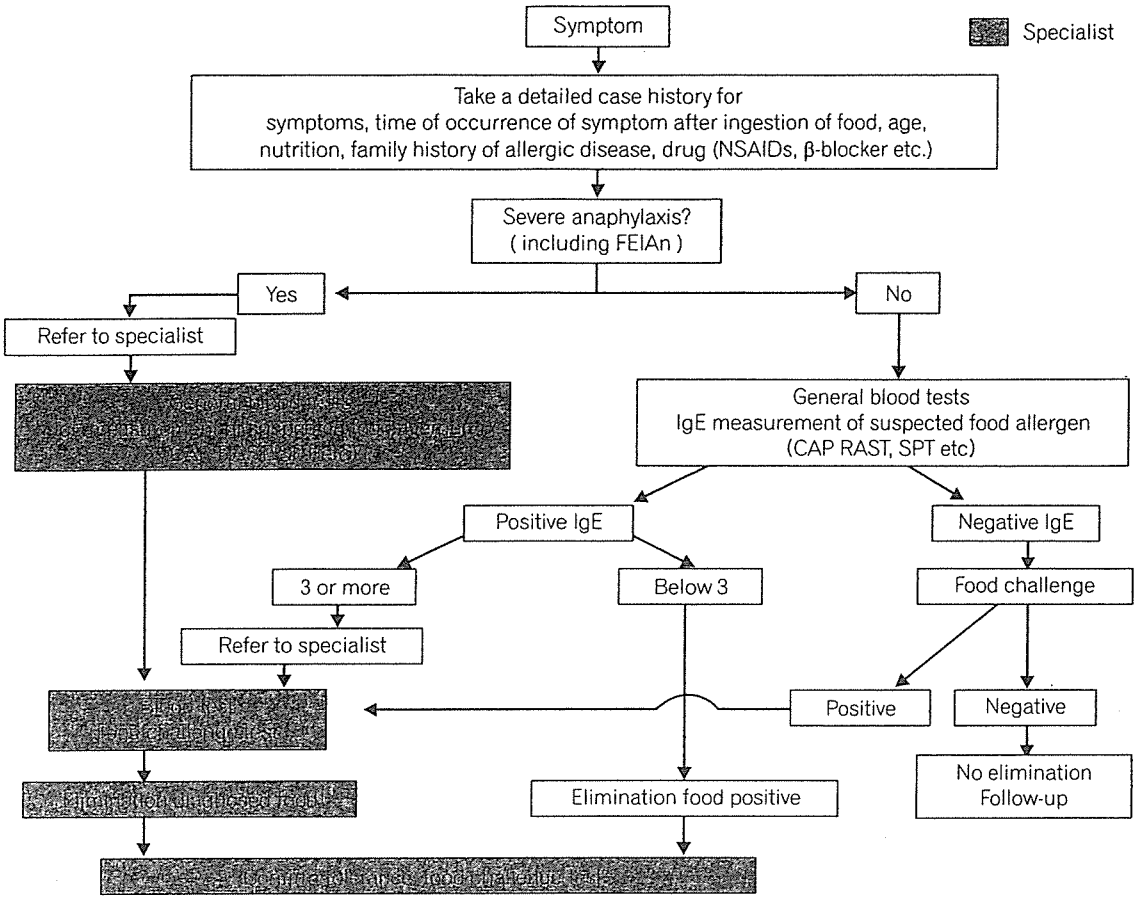


Fig. 2. Procedure for diagnosis of food allergy (for immediate type reaction). *Generally, patients who demonstrate immediate type reaction in later childhood are less likely to acquire tolerance.

health insurance system. In April 2006, Japanese government permit specialized allergists to perform food challenge tests as medical care covered by health insurance system, finally. We made out two types of flowcharts showing procedure for diagnosis of food allergy for infantile atopic dermatitis associated with food allergy (Fig. 1) and for immediate type reaction (Fig. 2), since diagnostic procedure is different in the two types of food allergy.

TREATMENT AND PREVENTION

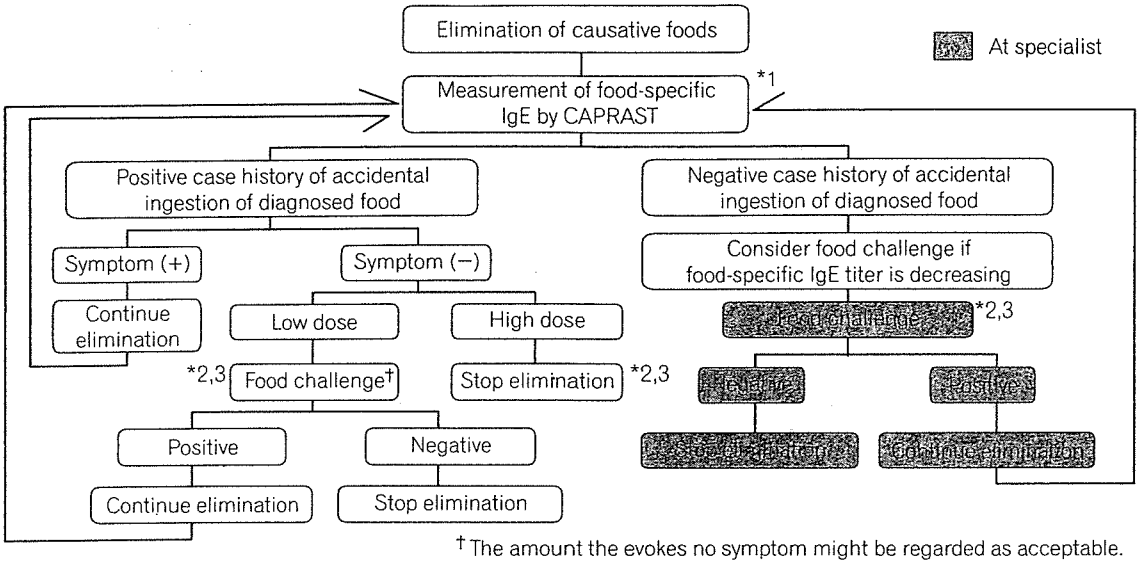
We clearly indicated that the fundamentals of treatment of food allergy are "minimal elimination of causative food (s)" based on correct diagnosis made by food challenge tests, and that medication is only subordinate.

According to the project committee's consensus on primary prevention related to foods in the case of high risk infant, no particular prevention of food is to be done during pregnancy and lactation of mother.

Follow up after determination of causative food allergens is very important for treatment of food allergy patients, so we showed the follow-up flowchart in Fig. 3. Though judgment of tolerance acquisition should be fundamentally based on results of food challenge tests,[7] sometimes history of accidental intake is unexpectedly significant information in routine clinical situation. We also summarized information of contraindicated drugs for food allergy patients which is important in pharmacotherapy in the guideline.

CARE FOR FOOD-INDUCED ANAPHYLAXIS

With regard to care for anaphylaxis, Japan has come into a new stage with the approval of EPIPEN (auto-injector of epinephrine) to be used for food allergy in April 2005. As the word "anaphylaxis" is comprehensive and can be interpreted in various ways, we showed the grading of food-induced anaphylaxis according toclinical symptoms suggested by Sampson in Table 5.[8] For care for anaphylaxis, we presented flowcharts of procedure both pre-



〈 Timing of examinations〉

	Below 3 yrs.	3–5 yrs.	Over 6 yrs.
*1: Food-specific IgE	Every 6 months	0.5–1 yr.	1 yr. or more
2: Food challenge test	0.5–1 yr.	1–2 yrs.	2–3 yrs.
*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 for the patient who has had anaphylaxis. However, in small infants, some become tolerant in regard to foods with which a child would have anaphylaxis.

Fig. 3. Follow up after determination of causative foods.

Table 5. 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 "pending 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

(Sampson H. Pediatrics 2003;111:1601-8)

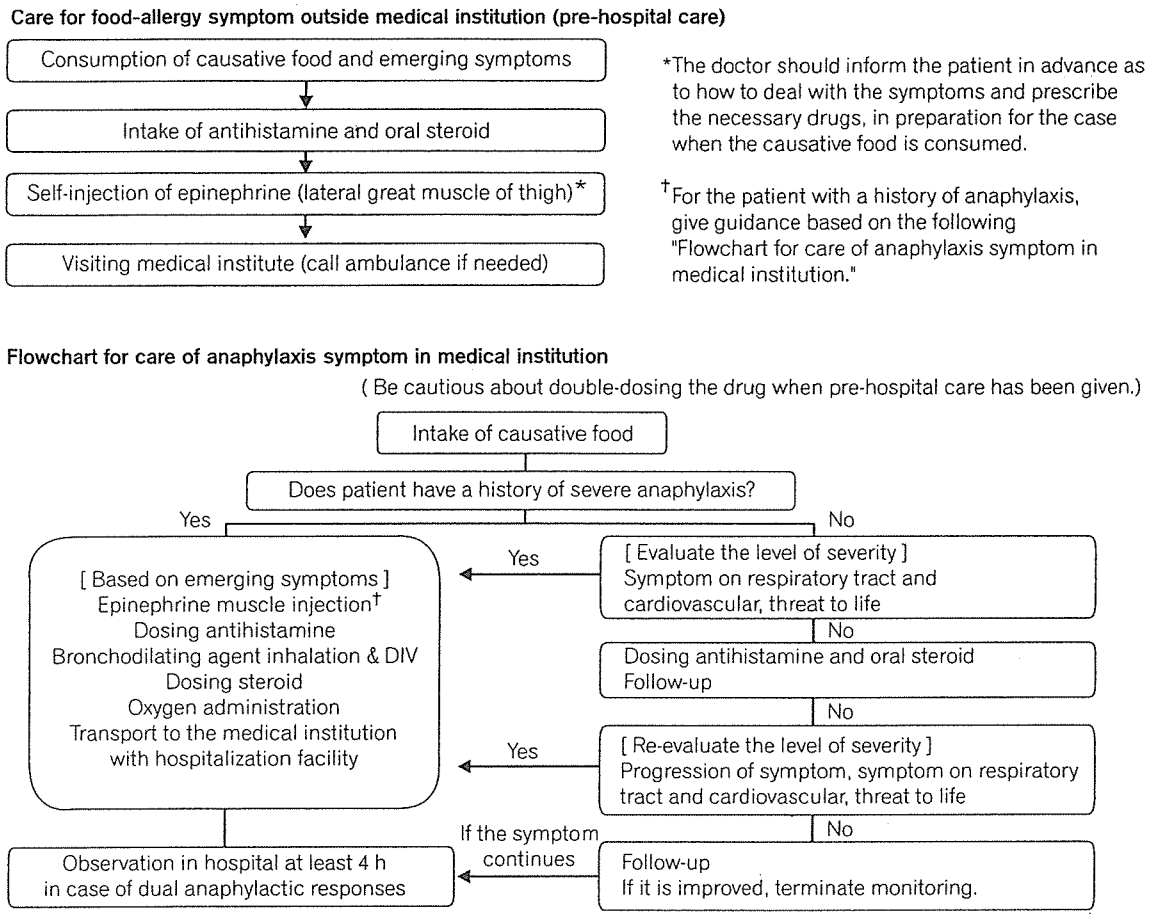


Fig. 4. Treatment of food-induced anaphylaxis in pre-hospital and hospital settings.

hospital and in medical institution (Fig. 4). In the flowchart of pre-hospital care, we explained the necessity of oral administration of anti-histamine and steroid drug, self-injection of epinephrine (EPIPEN), the timing of its use, and so on.

NUTRITION AND SOCIAL MANAGEMENT

In the guideline, the importance of careful observation of infants' growth and nutritional education by dieticians are clearly stated when doctors recommend elimination of multiple causative foods from infantile diets. Japanese food allergen labeling system (five food items; hen's egg, cow's milk, wheat, buckwheat and peanuts, mandated by ministerial ordinance and 20 food items recommended by notice) amended by food sanitary law in 2002 was also explained (Labeling for allergy Q&A http://www.mhlw.go.jp/topics/0103/tp0329-2b.html).

In most of kindergartens or elementary schools in Japan, they provide lunch for children. Management of food allergic children relevant to school lunch in kindergarten or school is not well established. In the guideline, we proposed basic rules for the management of food allergic children (minimum complete elimination) and a sample of Instruction (certificate) for elimination diet (Fig. 5).

CONCLUDING REMARKS

The content and making process of "Food Allergy Management Guideline 2005" are introduced in this article. "Food Allergy Management Guideline 2005" can be downloaded as a PDF file from the following home page without charge: Clinical Research Center for Allergology and Rheumatology, National Hospital Organization, Sagamihara National Hospital: http://www.hosp.go.jp/%7Esagami/rinken/crc/index. html (English version will be available soon).

ACKNOLEDGEMENT

I would like to express my appreciation to Dr. Jae-Won Oh for encouraging me to write this review article for the members

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 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 by 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 6 months/ 12 months later.
Date (Month/Day/Year) _____
Name of medical institution:_____
Phone number: _____ – _____
Doctor's name: _____

*Please make a copy of this page and use.

Fig. 5. Instruction (medical certificate) for elimination diet.

of Korean Academy of Asthma, Allergy and Clinical Immunology. I also appreciate immeasurable cooperation of the committee members shown in Table 1 and staff at Department of Pediatrics, Sagamihara National Hospital for the creation of "Food Allergy Management Guideline 2005". The establishment of "Food Allergy Management Guideline 2005" is fully supported by the Health and Labor Sciences Research Grants of the Research on Allergic disease and Immunology from the Ministry of Health, Labor and Welfare.

Finally, I would like to dedicate this review article to deceased Prof. Yoji Iikura who introduced me to the field of Allergy, to Prof. Hugh A. Sampson who introduced me to the field of food allergy during my fellowship at Johns Hopkins University, and to my family who always supports my academic activity.

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アレルギー 55(2),
107-114, 2006(平18)

〔綜 説〕

食物アレルギーへの対応について

—厚生労働科学研究班による「食物アレルギーの診療の手引き 2005」—

国立病院機構相模原病院臨床研究センター
アレルギー性疾患研究部
海老澤元宏

Key words：anaphylaxis —— food allergy —— food provocation test

1. はじめに

厚生労働科学研究の免疫・アレルギー疾患予防・治療研究事業「食物等によるアナフィラキシー反応の原因物質（アレルゲン）の確定，予防・予知法の確立に関する研究」(主任研究者：海老澤元宏，平成15年から3年計画）において最重要研究課題として取り組んできた「食物アレルギーの診療の手引き 2005」を2005年10月インターネット上で公開した[1]．この手引きは一般医を対象に「食物アレルギーの診断と治療の向上」と「食物アレルギー患者の生活の質の改善」を図るため作成した．平成15年度に「厚生労働省研究班のデータの活用」「わかりやすい小冊子程度のボリューム」「インターネットで公開しダウンロードできるように」というコンセプトの確定，平成16年度に国立病院機構相模原病院小児アレルギーのスタッフによるドラフトの作成，さらに2005年の1月の第5回食物アレルギー研究会（厚生労働科学研究班班会議も兼ねる）での3時間の公開シンポジウム形式の討議を行った．小児から成人までの食物アレルギーをカバーするために検討委員には小児科系の分担研究者に加え，内科，皮膚科，耳鼻咽喉科の委員にも加わっていただいた（表1）．2005年6月，7月，9月の計3回10時間弱の検討会での討議とメールによる連絡で完成することができた．討議で最も白熱したのは「食物アレルギー」と「乳児アトピー性皮膚炎」の関係とその取り扱いであった．食物アレルギーの症状として“湿疹”を「認める」か「認めないか」という議論になり皮膚科の委員に小児科の委員が湿疹の発症状況を説明し納得していただいた[2]．この手引きの特徴はわかりやすさを基本としているので，手引きの中で食物アレルギーの病型分類も行った．“乳児のアトピー性皮膚炎に食物アレルギーが合併しているケース”の定義も大問題となった．食物アレルギーの過剰評価も過小評価も避けるため，その呼称に対して細心の注意を払ったのである．その結果「食物アレルギーの関与するアトピー性皮膚炎」と定義することで皮膚科と小児科の委員の合意が得られたことは画期的であった．この手引きは文章を最小限にし基本原則を可能な限り表・図を用いて解読している．診断・治療のパートではフローチャートを活用した構成になっている．実際に図や表を示しながらそれぞれの要点の解説をする．

2. 総論

1) 定義

日本小児アレルギー学会の食物アレルギー委員会報告に基づいている[3]．

2) 食物アレルギーの臨床分類

食物アレルギーは小児期から成人期まで様々なタイプが存在するので表2に臨床型・発症年齢・頻度の高い食品・耐性の獲得・アナフィラキシーの可能性・機序に関してまとめた．ここでは「食物アレルギーの関与する乳児アトピー性皮膚炎」という分類名を前述のように決定したことが極めて重要な点である．

3) 症状

MANAGEMENT OF FOOD ALLERGY
(FOOD ALLERGY MANAGEMENT 2005 BY NATIONAL FOOD ALLERGY RESEARCH GROUP)

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表1 「食物アレルギーの診療の手引き 2005」検討委員会

(主任研究者)	
海老澤元宏	国立病院機構相模原病院臨床研究センターアレルギー性疾患研究部
〈小児科〉	
相原 雄幸	横浜市立大学附属市民総合医療センター小児総合医療センター
赤澤 晃	国立成育医療センター総合診療部小児期診療科
伊藤 節子	同志社女子大学生活科学部食物栄養科学科
宇理須厚雄	藤田保健衛生大学坂文種報徳會病院小児科
近藤 直実	岐阜大学大学院医学研究科小児病態学
柴田瑠美子	国立病院機構福岡病院小児科
眞弓 光文	福井大学医学部病態制御医学講座小児科
田知本 寛	国立病院機構相模原病院小児科
今井 孝成	国立病院機構相模原病院小児科
〈耳鼻咽喉科〉	
大久保公裕	日本医科大学耳鼻咽喉科
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〈皮膚科〉	
池澤 善郎	横浜市立大学大学院医学研究科環境免疫病態皮膚科
古江 増隆	九州大学大学院医学研究院皮膚科
(作成協力者)	
杉崎千鶴子	国立病院機構相模原病院臨床研究センターアレルギー性疾患研究部

表2 臨床型分類

臨床型		発症年齢	頻度の高い食品	耐性の獲得（寛解）	アナフィラキシーショックの可能性	食物アレルギーの機序
新生児消化器症状		新生児期	牛乳（育児用粉乳）	(+)	(−)	IgE 非依存型
食物アレルギーの関与する乳児アトピー性皮膚炎*		乳児期	鶏卵，牛乳，小麦，大豆など	多くは (+)	(−)〜(+)	主に IgE 依存型
即時型症状（じんましん，アナフィラキシーなど）		乳児期〜成人期	乳児〜幼児：鶏卵，牛乳，小麦，そば，魚類など 学童〜成人：甲殻類，魚類，小麦，果物類，そば，ピーナッツなど	鶏卵，牛乳，小麦，大豆など (+) その他の多く (−) 〜(±)	(++)	IgE 依存型
特殊型	食物依存性運動誘発アナフィラキシー (FEIAn/FDEIA)	学童期〜成人期	小麦，エビ，イカなど	(−)〜(±)	(+++)	IgE 依存型
特殊型	口腔アレルギー症候群 (OAS)	幼児期〜成人期	果物・野菜など	(−)〜(±)	(±)〜(+)	IgE 依存型

*慢性の下痢などの消化器症状，低タンパク血症を合併する例もある．全ての乳児アトピー性皮膚炎に食物が関与しているわけではない．

食物アレルギーによる症状は多彩であり，表3に示すように大きく皮膚粘膜症状・消化器症状・呼吸器症状・全身症状に分類されるが，意外なことに各科の専門医が一堂に会して症状の整理・分類をしたのは初めての試みであった．

4) 疫学

平成13年・14年に分担研究者の故飯倉教授と今井委員が行った全国食物アレルギーモニタリング調査のデータを掲載し年齢別の原因抗原を示した[4]．2年間に3882例の即時型食物アレルギー反応の症例が集め

表3　食物アレルギーにより引き起こされる症状

皮膚粘膜症状：
　皮膚症状　　：瘙痒感，じんましん，血管運動性浮腫，発赤，湿疹
　眼症状　　：結膜充血・浮腫，瘙痒感，流涙，眼瞼浮腫
　口腔咽喉頭症状：口腔・口唇・舌の違和感・腫張，喉頭絞扼感，喉頭浮腫，嗄声，喉の痒み・イガイガ感
消化器症状：
　腹痛，悪心，嘔吐，下痢，血便
呼吸器症状：
　上気道症状　　：くしゃみ，鼻汁，鼻閉
　下気道症状　　：呼吸困難，咳嗽，喘鳴
全身性症状：
　アナフィラキシー　　：多臓器の症状
　アナフィラキシーショック：頻脈、虚脱状態（ぐったり）・意識障害・血圧低下

表4　厚生労働科学研究班による食物負荷試験の結果

《プロトコール》
【医師による診療】
　体調のチェック
　親との相談（血液検査結果や家族の希望など）・説明の上，承諾書をとる
【負荷食品】
　乾燥食品粉末（非売品）
【スケジュール】

	食物負荷										
時間(分)	開始時	15	30	45	60	90	2h	3h	4h	6h	24h
症状観察	●	●	●	●	●	●	●	●	●	●	●
負荷量	1/20	1/10	1/5	3/10	残り						

【症状が認められた場合】
　負荷を中止し，症状に応じて対応．

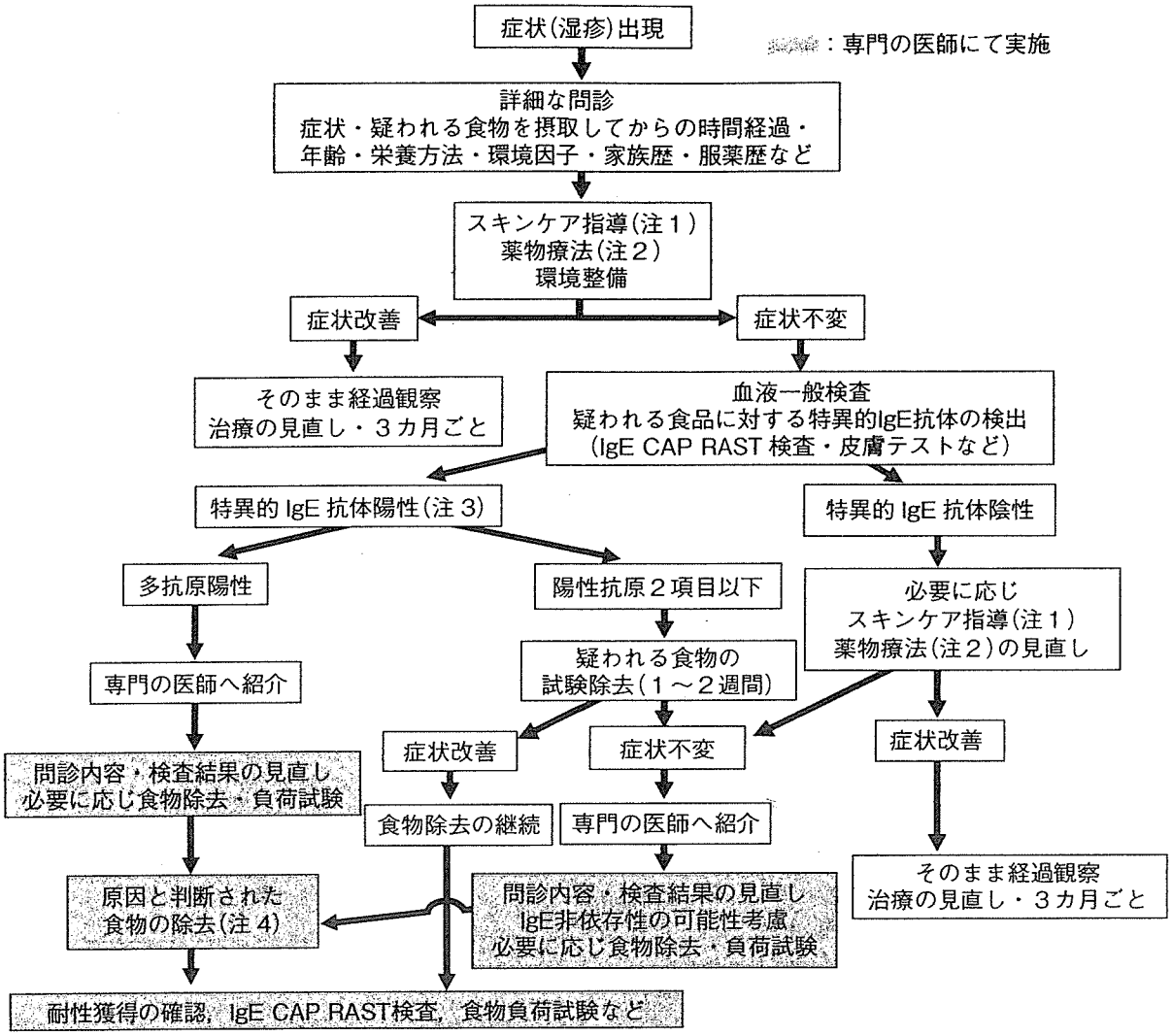
	食物負荷試験	IgE CAP RAST	皮膚テスト
鶏卵（全卵）	229/379（60%）	309/369（84%）	189/213（89%）
鶏卵（卵黄）	20/82（24%）	66/81（81%）	53/57（93%）
牛乳	115/263（44%）	194/259（75%）	116/146（79%）
小麦	47/140（34%）	117/140（84%）	59/77（77%）
大豆	12/81（15%）	62/78（79%）	24/43（56%）
合計	423/945（45%）	748/927（81%）	441/536（82%）

海老澤元宏　平成16年度厚生労働科学研究班報告より引用．

られ，全体では原因食品の頻度は鶏卵（38.3%），牛乳（15.9%），小麦(8.0%)，甲殻類(6.2%)，果物類(6.0%)，ソバ(4.6%)，魚類(4.4%)，ピーナッツ(2.8%)であった．3歳までは鶏卵・乳製品・小麦の順は変わらないが，4歳から6歳のグループでは3位以下に甲殻類，果物類，ピーナッツとなり，7歳以上成人ではいずれも甲殻類が原因食品の1位となり，小麦・果物・ソバなどが上位を占めていた．乳児期に発症するタイプと幼児期から成人期に発症するタイプで原因が異なっていた．誘発された症状の頻度は皮膚症状が88.6%と最も高く呼吸器症状が26.8%と続き，ショック症状も10.9%認めた．

3．診断

食物アレルギーに関する各種検査の説明と特徴を概説したが，確定診断は食物負荷試験によることを明記した．負荷試験には原因抗原診断と耐性の獲得の判断と2通りの意味がある．表4に厚生科学研究の食物負荷試験ネットワークにおける共通のプロトコール（ブラインド法・15分漸増法）にてキューピー研究所と共



注1：スキンケアに関して
スキンケアは皮膚の清潔と保湿が基本であり，詳細は厚生労働科学研究「アトピー性皮膚炎治療ガイドライン2002」などを参照.

注2：薬物療法に関して
薬物療法の中心はステロイド外用薬であり，その使用方法については厚生労働科学研究「アトピー性皮膚炎治療ガイドライン2002」などを参照.
乳児に汎用されている非ステロイド系外用薬は接触性皮膚炎を惹起することがあるので注意する.

注3：経母乳感作が成立している食物を児に直接与えるときには，食物負荷試験に準じる注意が必要である.

注4：除去食実施上の注意
成長発達をモニターしていくこと.
除去食を中止できる可能性を常に考える.

図1. 食物アレルギー診断のアプローチ（食物アレルギーの関与する乳児アトピー性皮膚炎).

同開発した負荷試験食（卵【全卵・卵黄】・牛乳・小麦・大豆）を提供して行った計945例の負荷試験成績を示した[5)6)]. クラス2以上を陽性とした場合のIgECAPRASTの陽性率と解離を示しており負荷試験の重要性が証明された. 負荷試験は入院施設のある専門の医師のもと行うべく病診連携の推進が望まれる. それをサポートするためには負荷試験が保険診療として認められることが必須である.

食物アレルギーの診断のフローチャートとして対応方法が異なるので「食物アレルギーの関与する乳児アトピー性皮膚炎」(図1) と「即時型症状」(図2) の2タイプを作成した.

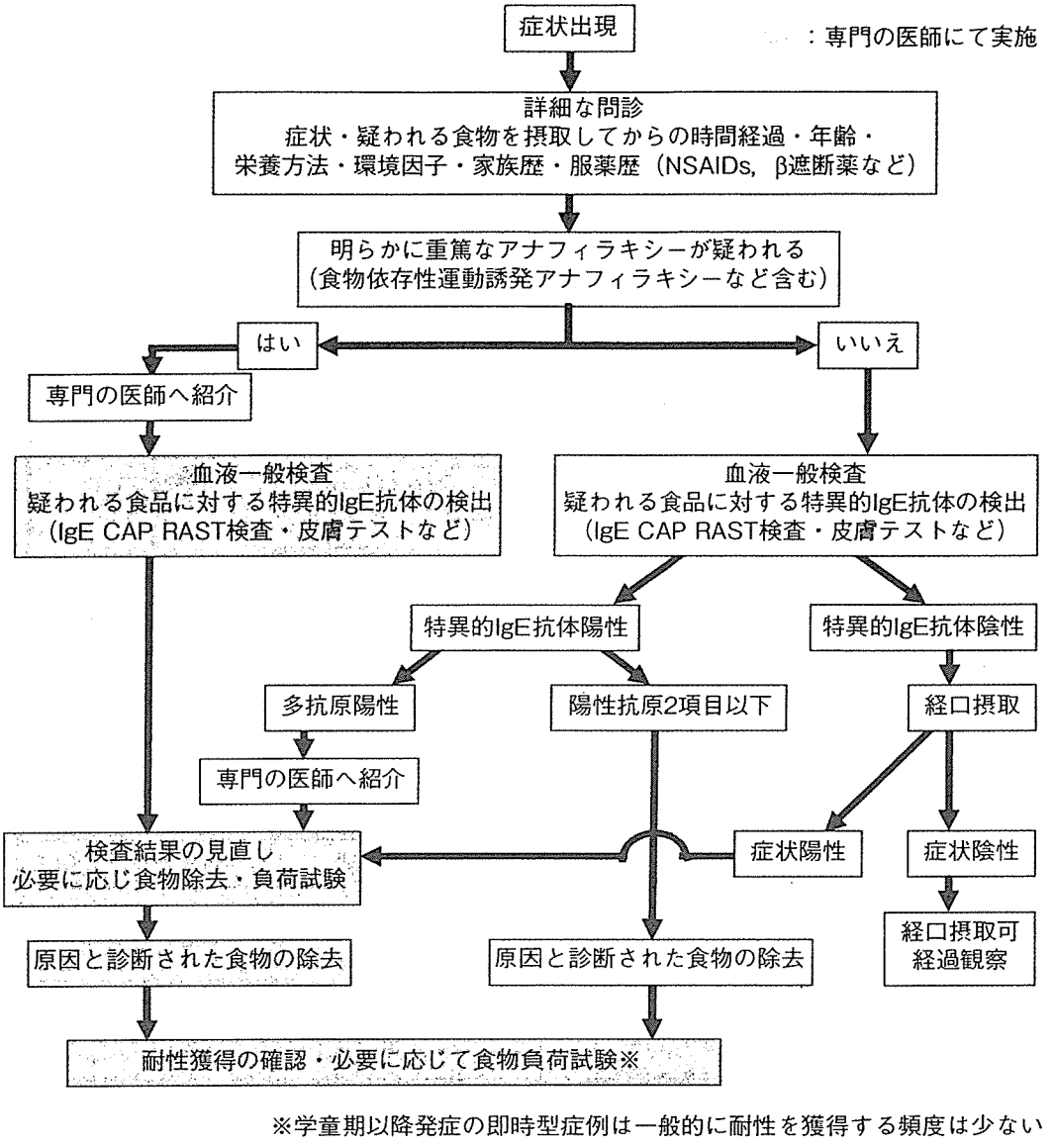


図2.　食物アレルギー診断のアプローチ（即時型症状）.

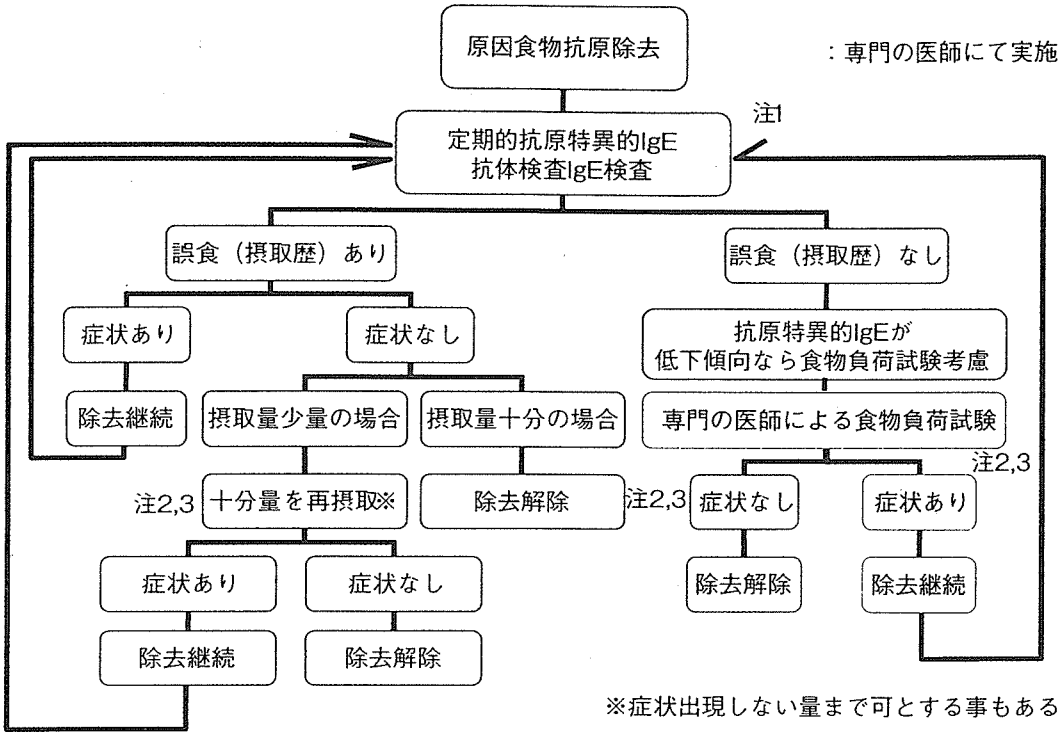
4. 治療・予防

治療の原則は「正しい診断に基づいた必要最小限の原因食物の除去」であり，薬物療法はあくまで補助的療法であることを明記した.

検討委員会のハイリスク児に対する食物に関連した一次予防のコンセンサスとして，食物に関して妊娠中・授乳中に特殊なことは行わないこととした．原因食物抗原決定後の経過観察は食物アレルギー患者の治療上重要であるのでその対応方法のフローチャートを図3に示した．耐性の獲得の判断は負荷試験に基づくべきであるが[7]，実際の臨床では誤食（摂取）歴が意外と重要な情報でもある．卵・牛乳アレルギーの患者において薬物治療を行う上で大切な投与禁忌薬物の情報もまとめた.

5. アナフィラキシーへの対応

食物によるアナフィラキシーへの対応もエピペンが2005年の4月に食物アレルギーに対して承認されわが国も新しい段階に入ってきた.「アナフィラキシー」という意味は大変幅が広く捉え方が多様であるが，表5にSampsonが提唱するアナフィラキシーの臨床的重症度を示した[8]．アナフィラキシーへの対応としてプレホスピタルケアと医療機関における対応（図4）に関してチャートを呈示した．プレホスピタルケアにおいては抗ヒスタミン薬・ステロイド薬の内服，そしてエピネフリンの自己注射の適応，使うタイミング等に



《定期的検査のスケジュールの目安》

	3歳未満	3歳以上6才未満	6歳以上
注1 抗原特異的IgE抗体価	6カ月毎	6カ月～1年毎	1年毎またはそれ以上
注2 食物負荷試験考慮※（専門の医師において，体調の良いときに行う）	6カ月～1年毎	1～2年毎	2～3年毎またはそれ以上
注3 食物負荷試験方法	オープンチャレンジ	オープン・シングルブラインド・ダブルブラインドチャレンジ	オープン・シングルブラインド・ダブルブラインドチャレンジ

※アナフィラキシー例では原則的には食物負荷試験は行わない．
ただし，乳幼児期発症例の中には耐性獲得することがあるため，時期を見て実施することがある．

図3.　原因食物抗原決定後の経過観察

表5　食物によるアナフィラキシーの臨床的重症度

Grade	皮膚	消化器	呼吸器	循環器	神経
1	限局性瘙痒感，発赤，じんましん，血管性浮腫	口腔内瘙痒感，違和感，軽度口唇腫脹	—	—	—
2	全身性瘙痒感，発赤，じんましん，血管性浮腫	上記に加え，悪心，嘔吐	鼻閉，くしゃみ	—	活動性変化
3	上記症状	上記に加え，繰り返す嘔吐	鼻汁，明らかな鼻閉，咽頭喉頭の瘙痒感／絞扼感	頻脈（＋15/分）	上記に加え，不安
4	上記症状	上記に加え，下痢	嗄声，犬吠様咳嗽，嚥下困難，呼吸困難，喘鳴，チアノーゼ	上記に加え，不整脈，軽度血圧低下	軽度頭痛，死の恐怖感
5	上記症状	上記に加え，腸管機能不全	呼吸停止	重度徐脈，血圧低下，心拍停止	意識消失

H. Sampson：Pediatrics. 2003；111：1601－8. より引用

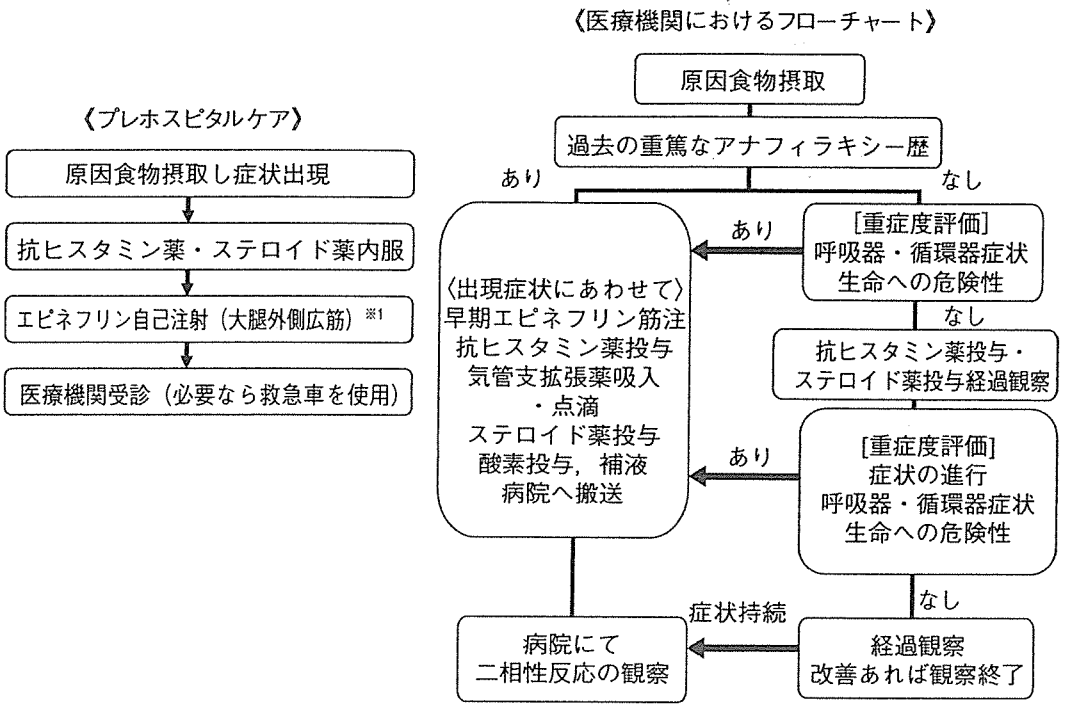


図4.　アナフィラキシー発症時のプレホスピタルケアと医療機関におけるフローチャート.

関して解説した.

6. 栄養と社会的対応

乳幼児に複数食品除去を指導する場合に栄養士の協力のもと成長発達に注意して行うことを明記した. 平成14年4月から始まったアレルギー物質を含む食品表示(義務5品目, 推奨20品目)に関しても解説した. 保育園・幼稚園・学校などの給食への対応方法に関して問題点と基本方針を示し（細かい複雑な指示は事故のもとであり, 必要最小限の完全除去を基本とする), 食品除去の指示書（診断書）に関して雛形を作成し添付した.

最後に

「食物アレルギーの診療の手引き 2005」の作成の過程と内容に関して紹介させていただいた. この手引きが食物アレルギーの診療に携わる医師に役立ち, その結果食物アレルギーの患者さんの生活の質の向上に繋がることを祈念してやまない.

なお「食物アレルギー診療の手引き 2005」は, 下記のホームページよりPDFファイルをダウンロードできます.

●国立病院機構相模原病院臨床研究センター
http://www.hosp.go.jp/%7Esagami/rinken/crc/index.html

●財団法人　日本アレルギー協会
http://www.jaanet.org/medical/guide.html

●リウマチ・アレルギー情報センター
http://www.allergy.go.jp/allergy/guideline/index.html

本論文は第17回日本アレルギー学会春季臨床大会（岡山)の教育講演「食物アレルギーによるアナフィラキシーとその対応」の発表内容が「食物アレルギーの診療の手引き2005」のドラフトをもとにしていましたので, その内容を紹介させていただきました. この手引きは表1の検討委員の先生方の絶大なる協力により作成することができましたことをここに記し深謝致します. 厚生労働科学研究の食物負荷試験ネットワークご参加の先生方, ドラフトの作成から最終版完成まで協力してくれた国立病院機構相模原病院小児アレルギーのスタッフに感謝致します.

最後に私をアレルギーの世界に導いてくださった恩師の故飯倉洋治先生, 食物アレルギーの世界に導いてくれた恩師Hugh A Sampson教授, いつもサポートしてくれている家族にこの論文を捧げたいと思います.

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