# Questionnaire-based Study of the Doctor's Guidance for Patients with Atopic Dermatitis

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Atopic dermatitis is a chronic and relapsing disease that requires long-term treatment in addition to doctor's guidance based on patients' life styles. We previously reported the results of a questionnaire-based survey of physicians with respect to the doctor's guidance for atopic dermatitis. In the present study, 435 patients with atopic dermatitis participated in a similar questionnaire-based survey. The results were analyzed by cross tabulation to compare the responses by physicians with those by the patients. Issues in the doctor's guidance which both the physicians and the patients considered to be necessary were "instructions about topical application of steroid ointment" and "instructions about how to apply moisturizing agents". The patients rated an explanation of the pathogenesis of atopic dermatitis as more important than did the physicians, whereas the physicians considered an explanation about how to avoid inappropriate treatment and a discussion to dispel anxiety toward steroid therapy as more important. In the cross tabulation analysis of the questionnaire-based survey of the patients,those patients who were familiar with the guidelines for the treatment of atopic dermatitis were reported to have received advice from their doctors, suggesting that some patients have enough knowledge about the management of atopic dermatitis.

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**Key words:** Atopic dermatitis, Guidance, Questionnaire-based study

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**TABLE I.** Sensitivity, specificity, and positive and negative predictive values of BATs with *D pteronyssinus* in the AR and LAR groups

| | Positive BAT result (%) | Sensitivity | Specificity | PPV | NPV | κ Index |
|---|---|---|---|---|---|---|
| AR (n = 14)* | 11/13 (85%) | 85% | 93% | 92% | 87% | 0.78† |
| LAR (n = 16) | 8/16 (50%) | 50% | 93% | 89% | 62% | NA |
| CG (n = 15)* | 1/14 (7%) | NA | NA | NA | NA | NA |
| NAR (n = 10) | 1/10 (10%) | NA | NA | NA | NA | NA |

*CG*, Control group; *NA*, not applicable; *NPV*, negative predictive value; *PPV*, positive predictive value.
*One subject from the AR group and 1 subject from the healthy control group were excluded from the analysis (nonresponders in the BAT assay).
†$P = .0001$.

performing BATs with wortmannin pretreatment in 4 randomly selected patients with LAR, showing negativization of results with the IgE-mediated positive control and persistence of positivity with N-formyl-methionine-leucine-phenylalanine (fMLP) (non–IgE-mediated positive control). Also, positive responses to *D pteronyssinus* became negative in all patients with LAR when wortmannin was added to the assay (see Fig E1 in this article's Online Repository at www.jacionline.org).

Since the first study of Huggins and Brostoff,[8] several investigators have reported local production of IgE antibodies in patients with NAR.[2,3] Others have shown that a percentage of patients with NAR respond to NPTs with allergens, being defined as having "local allergic rhinitis" or "entopy."[2-4] The current investigation represents the first evidence of detection of specific basophil activation in peripheral blood in patients with LAR who did not have positive responses to conventional tests, such as skin testing and serum specific IgE measurement. Our results show that at least 50% of the patients with LAR to *D pteronyssinus* can receive a correct diagnosis by using this approach in contrast with the low sensitivity of other determinations, such as measurement of specific IgE levels in nasal lavage fluid (22% of positive responses to *D pteronyssinus*),[2] and it is less time-consuming than the NPT. Moreover, BAT wortmannin assays demonstrated that the activation of basophils in these patients was IgE mediated. In a recent review Dullaers et al[9] stated that the mucosa might be the primary site of allergen-specific IgE production and suggested that some nonatopic subjects are in fact atopic but that there is a lack of spillover of the mucosally produced allergen-specific IgE into the circulation. In our study we detected allergen-specific IgE on the surfaces of peripheral basophils of patients with LAR, suggesting that after local production of specific IgE, basophils might be the first or only target cells for specific IgE before the detection of free serum specific IgE and skin mast cell sensitization. It is possible that BAT might be a useful tool for supporting the diagnosis of LAR.

In conclusion, BAT was able to diagnose at least 50% of cases of LAR to *D pteronyssinus* and was more sensitive than detection of nasal specific IgE and less time-consuming than NPTs. IgE-specific activation of basophils was demonstrated by using BAT wortmannin assays. The allergen concentration range for proper basophil stimulation in patients with LAR has to be defined because the low amount of specific IgE in these patients might require the use of higher doses of allergen stimulation to achieve better sensitivity. Although this pilot study is promising, future studies with larger populations and replication of these results with other allergens are needed to fully assess the diagnostic performance of BAT in patients with LAR.

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## Gly m 2S albumin is a major allergen with a high diagnostic value in soybean-allergic children

*To the Editor:*

Several soybean proteins have been suggested to have IgE reactivity but only 6 of them have so far been recognized by the WHO/IUIS Allergen Nomenclature Subcommittee.[1] Gly m 4, a pollen-related allergen, and the storage proteins Gly m 5 and Gly m 6 have been found to be associated with food allergy.[2,3] The storage protein 2S albumin has not yet been recognized as

**TABLE I.** Demographic, serologic, and clinical characterization of 55 soybean-sensitized Japanese children with or without symptoms

| Patient characteristics | Symptomatic (n = 19) | Nonsymptomatic (n = 36) | *P* value* | AUC† |
|---|---|---|---|---|
| Sex, male/female | 12/7 | 28/8 | | |
| Age (y), median (range) | 2.4 (0.7-9.8) | 1.9 (0.6-10.3) | | |
| Specific IgE to ($kU_A/L$), median (range) | | | | |
| Soybean | 23.7 (0.4-92.0) | 4.1 (0.5-77.3) | .0258 | 0.69 |
| 2S albumin | 6.8 (0.1-120.0) | 0.5 (0.0-46.6) | .0024 | 0.75 |
| Gly m 5 | 20.4 (0.1-58.3) | 1.7 (0.1-81.9) | .0521 | 0.69 |
| Gly m 6 | 15.5 (0.3-70.8) | 2.5 (0.4-93.5) | .1016 | 0.64 |
| Diagnosis of soybean allergy | | | | |
| OFC | 16 | 19 | | |
| History | 3 | 17 | | |
| Symptoms | | | | |
| Skin | 16 | — | | |
| Oral | 5 | — | | |
| Respiratory | 6 | — | | |
| Gastrointestinal | 1 | — | | |
| Anaphylaxis | 1 | — | | |

*Comparison between the study groups regarding IgE level to Gly m 2S albumin, soybean, Gly m 5, and Gly m 6 using the Mann-Whitney *U* test ($P < .05$ was considered significant).
†Area under the curve (AUC) from receiver operating characteristic (ROC) curve analysis comparing children in the symptomatic and nonsymptomatic groups.

an important allergen for soybean (Gly m 2S albumin), and its association with clinical symptoms is not clearly established.[4] Biochemically, the 2S albumins are characterized by a conserved 3-dimensional structure, high stability to the gastrointestinal tract environment, and high resistance to thermal processing.[5] The amino acid sequence identity between 2S albumins from different species is low, often less than 40%. Altogether these properties may explain the generally high diagnostic value of IgE measurements.[6] In this study, the diagnostic value of Gly m 2S albumin was investigated and compared with Gly m 5 and Gly m 6, by analysis of IgE in sera from soybean-allergic children.

Sera from 55 soybean-sensitized Japanese children were collected (Table I). Nineteen were diagnosed with soybean allergy by positive oral food challenge (OFC) (n = 16) or a definitive history (n = 3) of urticaria within 1 hour after intake. The remaining 36 children were nonsymptomatic and were either diagnosed by negative OFC (n = 17) or a regular consumption in their daily life (n = 19). Ethical approvals were obtained through the institutional review boards at Sagamihara National Hospital and Aichi Children's Health and Medical Center. Among the symptomatic children, 16 had skin symptoms, 5 oral symptoms, 6 respiratory symptoms (coughing and wheeze), 1 gastrointestinal symptom (diarrhea), and 1 neurologic symptom (sleep). Intramuscular adrenaline injection was used in 1 case, which was considered as an anaphylaxis. No allergies to nuts were documented among the children in the study. OFCs were conducted in accordance with Japanese guidelines.[7]

Gly m 2S albumin was purified from soybeans by anion exchange chromatography followed by gel filtration. Purity and identity of Gly m 2S albumin were determined by SDS-PAGE, analytical gel filtration, matrix-assisted laser desorption/ionization mass spectrometry with time-of-flight ion separation (positive linear mode and peptide mass fingerprinting), and N-terminal protein sequencing (10 cycles). Experimental ImmunoCAP with Gly m 2S albumin was developed by Phadia AB (Uppsala, Sweden).[8] Soybean, Gly m 5, and Gly m 6 are commercially available ImmunoCAP products. The detection limit of the test was 0.1 $kU_A/L$. The Methods are described more fully in this article's Online Repository at www.jacionline.org.

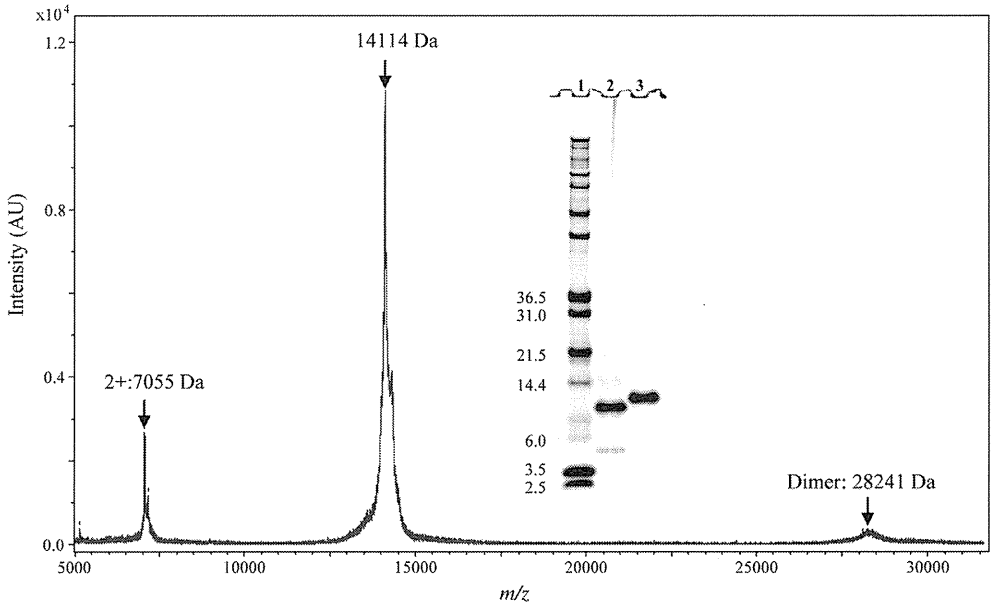


**FIG 1.** Gly m 2S albumin analyzed with MALDI-TOF MS in the positive linear mode showing a pure protein, and SDS-PAGE on NuPAGE 4% to 12% Bis-Tris Gel from Invitrogen (Carlsbad, Calif) under reduced conditions (lane 2, protein divided into 2 subunits 8 kDa and ~5 kDa) and nonreduced conditions (lane 3, 10 kDa), and molecular weight markers (lane 1). *AU*, Arbitrary unit; *MALDI-TOF MS*, matrix-assisted laser desorption/ionization mass spectrometry with time-of-flight ion separation.

The recovery of pure Gly m 2S albumin was 1.1 mg/g of soybeans. Analytical gel filtration showed a homogenous dimer with a molecular size of 28 kDa (see Fig E1 in the Online Repository at www.jacionline.org). Matrix-assisted laser desorption/ionization mass spectrometry with time-of-flight ion separation revealed the mass 14 kDa (*m/z*) (Fig 1). Peptide mass fingerprinting and N-terminal sequencing showed agreement with UniProt accession no. P19594, and 80 amino acids of 120 (75%) were identified (see Fig E2 in the Online Repository at www.jacionline.org). The N-terminal protein sequencing did not indicate the presence of any impurities. No evidence of the presence of carbohydrate chains was found. The allergenicity of Gly m 2S albumin was investigated by analysis of IgE antibody in sera (Table I). Seventeen out of 19 children with soybean allergy and 31 out of 36 nonsymptomatic children had IgE levels of more than 0.1 $kU_A/L$ to Gly m 2S albumin. A significant differentiation between IgE levels in the symptomatic and the nonsymptomatic children was found ($P < .01$). Of the 2 sera with IgE levels of less than 0.1 kUA/L in the symptomatic children, both had IgE to Gly m 5 and 6, and of the 5 sera with IgE levels of less than 0.1 kUA/L in the nonsymptomatic children, all had IgE to Gly m 6 and 4 to Gly m 5. No significant differences in IgE levels between those who were OFC negative and history negative could be seen. Receiver operating characteristic analysis showed that Gly m 2S albumin had an area under the curve of 0.75, followed by soybean and Gly m 5 (0.69 for both) and Gly m 6 (0.64) (see Fig E3 in the Online Repository at www.jacionline.org). Receiver operating characteristic analysis by combining the 3 components, 2 or all 3, did not improve the area under the curve.

Gly m 2S albumin, Gly m 5, and Gly m 6 were found to be major allergens in the study group. Gly m 5 and Gly m 6 have in earlier studies been classified as major allergens in children and have also been correlated with severe symptoms from soybean.[3,9] In this study, IgE to Gly m 2S albumin was significantly higher in the symptomatic group, while IgE to Gly m 5 and Gly m 6 was not, although a trend toward a significant differentiation was seen. IgE reactivity to Gly m 2S albumin has been investigated earlier.[4] Lin et al[4] reported no IgE to 2S albumin in the soybean-allergic patients. This discrepancy between the study of Lin et al[4] and this study may, for example, depend on the study population, geographical reasons, and different 2S albumin preparations, and is further discussed in the Online Repository at www.jacionline.org. Soybean allergy in adults and adolescents may be pollen-related, caused by IgE cross-reactivity between the PR-10 allergen component Bet v 1 from *Betulaceae* pollen and its homologue in soybean, Gly m 4.[2] The Gly m 2S albumin in this study has proved to be pure and homogeneous, and the identity correlates best with the reviewed 2S albumin from soybean with accession no. P19594. Proteins from the lipid transfer protein (LTP) group and the 2S albumin group generally have similar molecular weights, and it is therefore important to eliminate cross-contamination. Extensive efforts have been made to prove that LTP and other contaminating proteins are not present in Gly m 2S albumin. In addition, efforts to purify LTP from soybean have failed (data not shown). Others have shown that soybean LTP is present in the hull of the soybean, and it is therefore not considered a food allergen.[1]

Soybean is 1 of 8 foods thought to cause more than 90% of food allergy reactions in children. Nevertheless, knowledge about specific soybean allergens associated with clinical symptoms is in large part uninvestigated. Earlier studies have shown that analysis of IgE to both Gly m 5 and Gly m 6 will facilitate the diagnosis of soybean allergy in children.[3,9] In this study, we show that 2S albumin from soybean is a major allergen in Japanese children with soybean allergy. The biochemical features of 2S albumin allergens with generally low cross-reactivity between species may be advantageous in the differentiation between clinical soybean allergy and allergies caused by other legumes, for example, peanut. We put forward that analysis of IgE to Gly m 2S albumin will provide a high diagnostic value and will even further facilitate the diagnosis of soybean allergy.

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## METHODS

### Food challenge

Oral soy challenges were conducted in accordance with Japanese guidelines by using an increasing amount of tofu (traditional soy paste containing 6.6% of soy protein) or boiled soybeans (16% protein). Increasing amount in 5 to 6 doses was given every 15 to 20 minutes, up to the cumulative dose of more than 3 g soy protein. Challenge results were considered as positive when obvious objective symptoms were observed. Negative challenge was confirmed after follow-up visits to ensure the absence of any symptoms after the ingestion of soy products.

### Preparation of 2S albumin

Preparation of Gly m 2S albumin was performed from defatted and freeze-dried soybeans, *Glycine max* (Allergon, Ängelholm, Sweden). Extract of soybeans was applied to anion exchange chromatography (Q Sepharose HP; GE Healthcare, Uppsala, Sweden), and adsorbed material containing Gly m 2S albumin was eluted by a linear sodium chloride gradient. Further purification was performed by gel filtration on Superdex 75 pg (GE Healthcare). Fractions containing purified Gly m 2S albumin were pooled and concentrated by using an Amicon cell with regenerated cellulose (5 kDa) membrane filter (Millipore, Billerica, Mass). The protein concentration was determined by using the bicinochroninic acid (BCA) method (BCA protein assay kit, Thermo Scientific, Rockford, Ill). The prepared Gly m 2S albumin solution was frozen at −20°C until use.

### Electrophoresis

SDS-PAGE was performed on NuPAGE 4% to 12% Bis-Tris Gel from Invitrogen (Carlsbad, Calif). Prepared Gly m 2S albumin was treated with NuPAGE lithium dodecyl sulfate sample buffer, and for the reducing condition dithiothreitol was added followed by alkylation with iodoacetamide, and heated at 97°C for 5 minutes. The gel was loaded with 0.5 μg Gly m 2S albumin (reduced and nonreduced). The molecular weight calibration of the gel was achieved by using Mark 12 unstained standard (Invitrogen). Electrophoresis was performed in 2-(N-morpholino) ethanesulfonic acid running buffer following the manufacturer's instruction. The gel was silver stained according to Blum et al[E1] in a Hoefer Processor Plus (GE Healthcare).

### Glycosylation analysis

The glycosylation status of 2S albumin was investigated by enzymatic deglycosylation of the protein with several glycosidases (PNGase F, Neuraminidase, GPase A, 3 *O*-glycosidases) followed by SDS-PAGE, where 5 and 10 μg of treated and untreated Gly m 2S albumin and 5 μg fetuin (positive control) were run on the gel under reducing and nonreducing conditions. The gel was stained by using a glycoprotein detection kit (Sigma-Aldrich, St Louis, Mo) based on the periodic acid-Schiff method.

### Mass spectrometry analysis

Matrix-assisted laser desorption/ionization mass spectrometry with time-of-flight ion separation (MALDI-TOF MS) in the positive linear mode and peptide mass fingerprinting (PMF) were performed by using a Autoflex, II system (Bruker Daltonic, Bremen, Germany) from prepared Gly m 2S albumin in solution. For the PMF analysis, the Gly m 2S albumin solution was reduced with dithiothreitol and alkylated with iodoacetamide before it was digested with trypsin. Salt was removed by reversed phase chromatography on a $C_{18}$ column (Millipore, Billerica, Mass). When the whole Gly m 2S albumin protein was analyzed in the linear mode, salt was removed directly on a $C_{18}$ column.

### Analytical gel filtration

The molecular weight of Gly m 2S albumin was estimated by using a calibrated Superdex 75 PC 3.2/30 column (GE Healthcare) on an Ettan LC system (GE Healthcare). Twenty microliters was applied to the column, and the Unicorn analysis module 5.0 (GE Healthcare) was used to estimate molecular size.

### Amino acid sequencing

Five micrograms of Gly m 2S albumin was diluted in 1 mL 6 M guanidine-HCl, 0.1 M Tris, pH 8, and incubated with 5 μL 0.5 M dithiothreitol for 2 hours at 37°C. After cooling the solution to room temperature, 20 μL 0.5 M iodoacetamide was added and the solution was incubated in the dark for 15 minutes. N-terminal protein sequencing (10 cycles) was then performed by using the Edman degradation method in a G1000A sequencer (Hewlett-Packard, Palo Alto, Calif). The obtained sequence was compared with other known 2S albumins in UniProtKB[E2] by using the BLAST function.

## RESULTS

### Purity of prepared Gly m 2S albumin

Analytical gel filtration of Gly m 2S albumin confirms that the preparation is homogeneous, but it also shows that it acts as a dimer with a molecular size of 28 kDa in the native state (Fig E1) in contrast to the analysis with MALDI-TOF MS in the positive linear mode, which reveals the mass determination, *m/z*, to be 14 kDa. The N-terminal protein sequencing was originally performed to obtain identity of the Gly m 2S albumin. By using the peak area from the internal standard, it was possible to calculate the mole content reflected by the obtained peak areas from the first 10 amino acids from the 2 subunits of Gly m 2S albumin. In this way, it could be shown that the total obtained amount mole corresponds to the amount mole of Gly m 2S albumin used in the analysis given an indirect proof of its purity.

### Verification of the identity of Gly m 2S albumin

The identity of the prepared material was verified by N-terminal protein sequencing and PMF using MALDI-TOF MS. The N-terminal protein sequencing showed that the first 10 amino acids from the 2 subunits corresponded to 100% with 2S albumin (*Glycine max*) with accession no. P19594,[E2] amino acid 22 to 31 and 82 to 91, respectively. Using PMF, peptides containing amino acids 24 to 50, 97 to 105, and 117 to 158, corresponding to accession no. P19594, could be shown, and together with the N-terminal sequences, a total identification of 80 amino acids of a total of 120 (75%) was obtained (Fig E2).

## DISCUSSION

IgE reactivity to Gly m 2S albumin has been investigated earlier.[E3] In the study by Lin et al,[E3] none of the soybean-allergic patients including both children and adults from Europe was found to have IgE to 2S albumin. This discrepancy may depend on several factors, one being the different study group compositions. In the study by Lin et al,[E3] the patients are a mixture of both children and adults, while the patients in this study are composed of children only. Soybean allergy in adults and adolescents has in several studies been shown to be pollen-related, caused by IgE cross-reactivity between the PR-10 allergen component Bet v 1 from Betulaceae pollen (birch) and its homologue in soybean, Gly m 4.[E4-E6] The disagreement may also depend on geographic reasons, with different dietary habits regarding soybean products, and different prevalences regarding Betulaceae pollen–related allergies. Japan is one of the largest soybean-consuming populations in the world but has a low prevalence of Betulaceae pollen–related allergies, while the soybean consumption in Europe is low but with a high prevalence of Betulaceae pollen–related allergies, especially in central and northern parts. However, the reason may also be that different isoforms of 2S albumin have

been used in the 2 studies. In the study by Lin et al,[E3] both native and recombinantly produced 2S albumin from soybean have been used for IgE measurements, while the Gly m 2S albumin used in this study was purified from soybeans.

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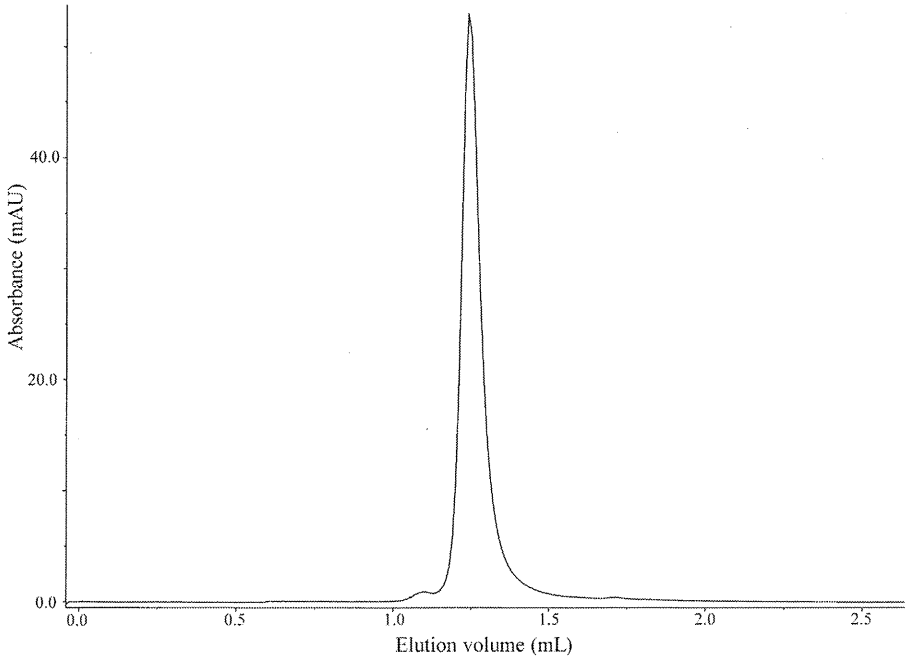


**FIG E1.** Analytical gel filtration of Gly m 2S albumin on Superdex 75 given the molecular size in native state. *AU*, Absorbance unit.

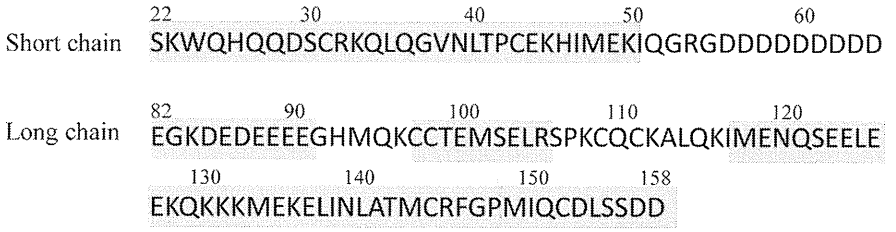


**FIG E2.** The short and long chains from the amino acid sequence of the soybean 2S albumin accession no. P19594. The *gray boxes* indicate identified amino acid residues from N-terminal sequencing and PMF of the prepared Gly m 2S albumin.

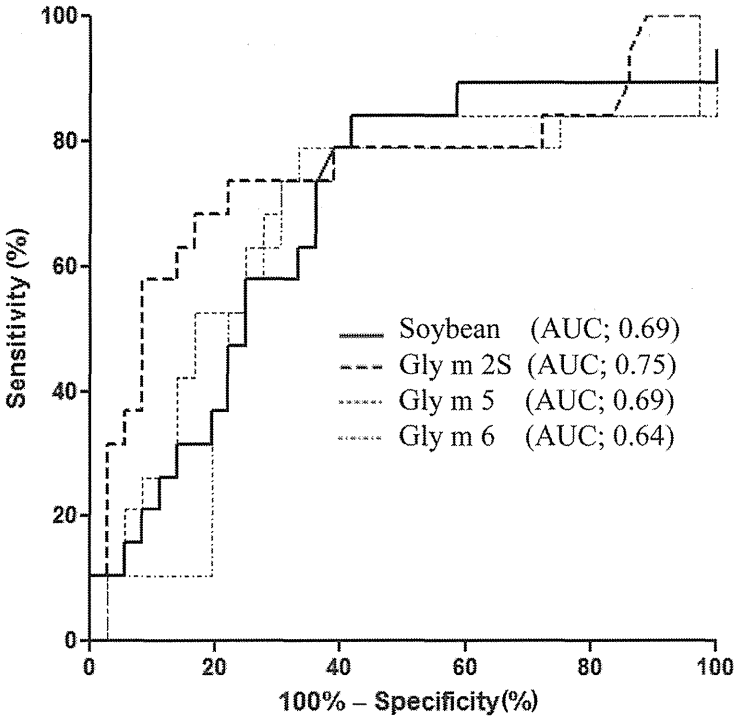


**FIG E3.** Comparison of ROC curves for soybean, Gly m 2S albumin (Gly m 2S), Gly m 5, and Gly m 6 in symptomatic versus nonsymptomatic children. *AUC,* Area under the curve; ROC, receiver operating characteristic.

REVIEW

# Pediatric allergy and immunology in Japan

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## Abstract

The Japanese Society of Pediatric Allergy and Clinical Immunology (JSPACI) was started in 1966 and currently has 3613 members as of August 1, 2012. The number of pediatricians specializing in allergies who have been certified by the Japanese Society of Allergology is 817. Among these, there are 125 training directors and training facilities for allergy and clinical immunology. The JSPACI first published an asthma guideline specific for children in 2000, and this has been revised every 3 yrs, contributing to better control of pediatric asthma. Food allergy management guidelines were first developed in 2005, which have helped to improve the care of food allergy patients. Among 514 pediatric training programs by the Japanese Society of Pediatrics, there are 312 facilities routinely performing oral food challenges. Among these, there were already 53 facilities performing oral immunotherapy at the end of 2011, treating 1400 cases of food allergy. The prevalence of pediatric allergic diseases has increased in Japan over the past 50 yrs. A number of International Study of Asthma and Allergies in Childhood surveys have been conducted in the past at specific times. The prevalence of wheezing among children aged 13–14 yrs in 2002 was 13.0%. Multi-year surveys found a 1.5- to 2-fold increase every 10 yrs until 2002. However, according to the latest data in 2012, asthma prevalence seems to have slightly decreased in Japan. Food allergy mainly associated with infantile atopic eczema among infants younger than 1 yr of age is the most common form as with other developed countries. The estimated food allergy prevalence based on data from several surveys is 5–10% among infants (0–6 yrs) and 1–2% among schoolchildren (6–15 yrs). A variety of patients suffering from primary deficiency syndrome have been actively analyzed. Previously, antibody defects and well-defined syndromes with immunodeficiency were analyzed, but recent research is focusing on not only acquired immune disorders but also on innate immune disorders. In contrast to the widespread use of oral immunotherapy, one immediate issue is to develop and reassess subcutaneous and sublingual immunotherapies for mite and Japanese cedar pollen antigens that have been disused in Japan since the 1990s.

## Historical background of the Japanese Society of Pediatric Allergy and Clinical Immunology

The Japanese Society of Pediatric Allergy and Clinical Immunology (JSPACI) was started in 1966 under the name of 'Pediatric Allergy Meeting' as a sectional meeting of the Japanese Society of Pediatrics (Table 1). It was renamed JSPACI in 1986 and commenced biannual publication of a domestic journal in 1987. The journal was published four times a year from 1991 and then subsequently increased to five times a year in 2001. 'Japanese Pediatric Guideline for the Treatment and Management of Asthma (JPGL)' was published in 2000; it has been revised nearly every 3 yrs (1) and the latest version is JPGL2012. 'Japanese Pediatric Guideline for Food Allergy' was first published in 2005 (2) and revised in 2011. 'The General Guideline for Pediatric Allergic Diseases', a synthesized guideline for bronchial asthma, allergic rhinitis, atopic dermatitis, and food allergy, was published in 2011.

The first academic meeting was held in 1966 in Tokyo, and the 50th anniversary meeting will be in Yokohama in October 2013. The sixth and present JSPACI President is Professor N. Kondo (Gifu University); the first president was T. Matsumura, followed in succession by Y. Nakayama, M. Baba, S. Nishima, and A. Morikawa.

**Table 1** Japanese Society of Pediatric Allergy and Clinical Immunology chronology

| | | | Journal | | Annual meeting | |
|---|---|---|---|---|---|---|
| Year | Events | President | JSPACI journal | Guideline, etc. | | Place |
| 1966 | Pediatric Allergy Association was founded | Matsumura T | | | 1st | Tokyo |
| 1975 | | Nakayama Y | | | 12th | Fukuoka |
| 1981 | | Baba M | | | 18th | Yokohama |
| 1986 | Renamed as JSPACI | | | | 23rd | Kitakyushu |
| 1987 | | | 2 Journals/yr | | 24th | Tokyo |
| 1991 | | | 4 Journals/yr | | 28th | Saitama |
| 1994 | Otsuka academic article award started | | | | 31st | Utsunomiya |
| 1997 | | Nishima S | | | 34th | Tokyo |
| 1998 | *Office relocation* (Tokyo to Fukuoka) | | | | 35th | Osaka |
| 2000 | | | | JPGL2000 | 37th | Maebashi |
| 2001 | | | 5 Journals/yr | | 38th | Kitakyushu |
| 2002 | The Web site of JSPACI was established | | | JPGL2002 | 39th | Morioka |
| 2004 | The best article award of JSPACI started | | | | 41st | Tokyo |
| 2005 | The clinical research encouraging award was established | Morikawa A | | JPGL2005<br>JPG for Food Allergy 2005 | 42nd | Fukui |
| 2006 | Office relocation (Fukuoka to Gunma) | | | | 43rd | Chiba |
| 2008 | | Kondo N | | JPGL2008 | 45th | Yokohama |
| 2009 | Office relocation (Gunma to Gifu) | | | JPG for OFC in Food Allergy 2009 | 46th | Fukuoka |
| 2011 | Office relocation (Gifu to Tokyo)<br>Joint congress with 16th APAPARI | | | Pediatric Allergy Guideline 2011<br>JPGL2012<br>JPG for Food Allergy 2012<br>Brochure for Allergic children during disaster | 48th | Fukuoka |
| 2013 | | | | | 50th | Yokohama |

JSPACI: Japanese Society of Pediatric Allergy and Clinical Immunology; JPGL: Japanese Pediatric Guideline for the Treatment and Management of Asthma; APAPARI: Asia Pacific Association of Pediatric Allergy, Respirology & Immunology; JPG: Japanese Pediatric Guideline.

## Overview of JSPACI

JSPACI aims to help the science and medicine of pediatric allergy and related areas to advance and to disseminate information. The society also aims to promote pediatric health. Studies are conducted in a wide variety of areas: allergic diseases such as bronchial asthma, atopic dermatitis, food allergy, drug allergy, allergic rhinitis, and anaphylaxis, as well as immune disorders such as autoimmune disease, hereditary immunodeficiency disease, infectious disease, and respiratory disease. Its constituent members are general practitioners interested in the area of pediatric allergy, clinical doctors specializing in pediatric allergy, clinical and basic researchers, and paramedical staff. Through basic research, clinical research, and epidemiologic studies, the society makes efforts to explicate the causes and states of diseases; to develop systems of diagnosis, therapeutic management, and prognostic factors, as well as precautions; to cooperate with nurses, pharmacists, and dieticians; and to communicate with patients. It also takes part in preventive medicine such as vaccinations, in maternal and child health, and in school health.

To achieve its goals, the society performs the following activities:

1 Holding an academic meeting once a year,
2 Publishing journals (five times a year),
3 Holding research meetings, short courses, and lectures,
4 Facilitating communication between members,
5 Coordinating with related organizations, both domestic and abroad, and
6 Performing other tasks necessary to achieve its goals.

The society had 3613 members as of August 1, 2012, and the number of members has been increasing annually. The organization consists of a board of directors, a board of councilors, and the general assembly. To promote its tasks efficiently, ten committees have been established: the Editorial Committee, Rules and Regulations committee, Epidemiology Committee,

Health Insurance Committee, Food Allergy Committee, Pharmaceutical Affairs Committee, Guideline Committee for Therapeutic Management of Asthma, Research Promotion Committee, International Exchange Committee, and Conflict of Interest Committee. In addition, the society has set up formal working groups to correspond quickly and appropriately to occasional situations, such as a working group to cope with the new influenza strain in 2009, another group responsible for drawing up 'The General Guidelines for Pediatric Allergic Diseases' in 2010, and another for coping with the Great East Japan Earthquake in 2011. This last working group not only provided support for the victims of the earthquake but also created a pamphlet titled 'The Treatment of Pediatric Allergic Diseases in Times of Disasters (Japanese and English version)' (JSPACI: http://www.jspaci.jp/). The editor in chief at PAI (Prof. U Wahn) also generously expressed sympathy over this tragedy, and we were deeply impressed by his message (3). The secretariat moved from Gifu to Tokyo, and at present, there are only a few staff members.

The number of pediatricians specializing in allergies who have been certified by the Japanese Society of Allergology (JSA) is 817 in Japan, and among these, there are 125 training directors in allergy. There are 126 training facilities in Japan, and the distribution of these training facilities and specialists in pediatric allergy is shown in Fig. 1. The present population of Japan is about 127 million. The figure shows that specialists and training facilities are centered around large cities, and the distribution of allergy training programs is closely related to population distribution. Pediatric board-certified doctors become eligible to be allergy specialists after 3 yrs' training at allergy training facilities. JSA also requires a board examination qualification after the training. JSA board-certified pediatric allergy specialists are required to renew their certification every 5 yrs by collecting continuing medical education credits.

## Allergy practice in Japan

### The Japanese medical system and the position of allergists

The system of public health insurance for the whole nation has been maintained in Japan for 50 yrs and is effective in the restraint of medical expenses. The ratio of medical expenses to the total gross domestic product in Japan is low in rank among member nations of the Organization for Economic Cooperation and Development. The fee a doctor receives is fixed regardless of doctor's length of experience. Thus, doctors are being unfairly compensated to achieve control of medical costs. Although private practice is customary in Europe and the United States, it is seldom found in Japan except in the field of cosmetic surgery. While 4000 or more allergy specialists are authorized by JSA, insurance institutional financial incentives to medical specialists do not exist in Japan. Even without a referral from a primary physician, a patient is able to consult an allergist freely; this is called a free-access system. It enables quite recently medical specialists to advertise the possession of specialist medical qualifications. In Japan, when doctors start their own clinic, they are allowed to advertise freely their practice in any field of medicine other than anesthesiology. Some practitioners advertise as allergists, and patients are consulting these doctors without realizing that they lack specialty training and proper qualification. Because JSA and JSCAPI have prepared guidelines for the treatment of a variety of allergic diseases,

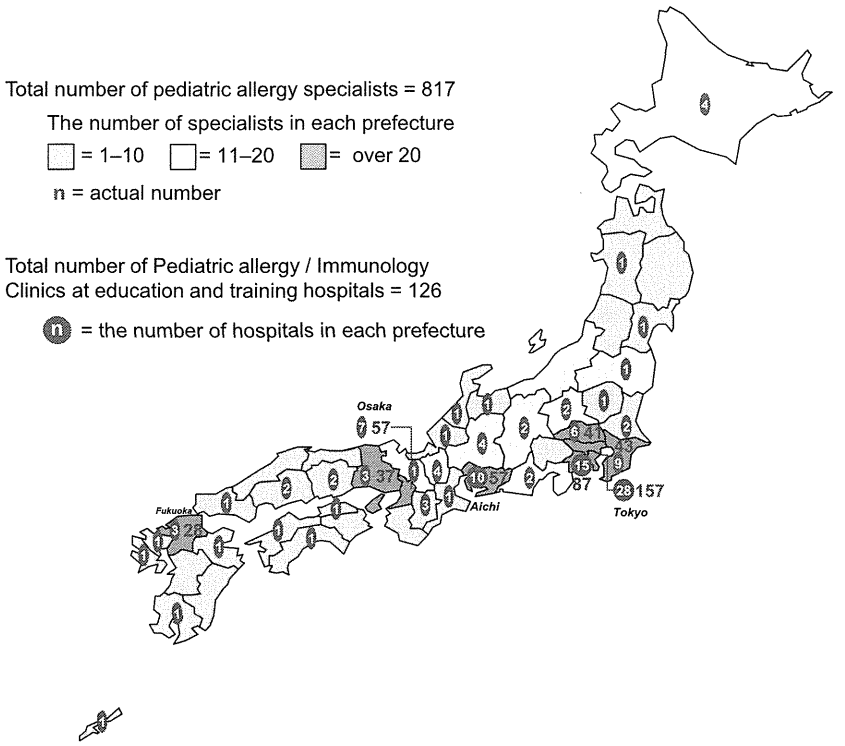


**Figure 1** Number of training programs and specialists. The number of pediatricians specializing in allergies in Japan who have been certified by the Japanese Society of Allergology is 817. There are 126 training facilities in the whole country. The distribution of training facilities and specialists in pediatric allergy in Japan is shown.

over the past 10 yrs, general practitioners have been able to treat allergic diseases to some extent.

### Allergy diagnosis and allergen-specific immunotherapy

By global standards, a doctor who diagnoses allergic disease correctly and performs allergen-specific immunotherapy is usually regarded as an allergist, but not necessarily in Japan. In Japan, allergenic extracts for diagnostic and treatment purposes have been manufactured and sold since 1963 by only one company (TORII Pharmaceutical Co., Ltd. Tokyo, Japan) in the domestic supply system. Because a wide range of antigen-specific IgE antibody tests is covered by health insurance, these tests are more commonly conducted than skin prick tests. The targets of antigen-specific subcutaneous immunotherapy (SCIT) are atopic asthma (caused by house dust mites) and allergic rhinitis (caused by house dust mites and Japanese cedar pollen) in Japan, and immunotherapy has been widely used from the 1960s to the middle of the 1980s. The development of oral anti-allergic drugs prospered in the 1980s in Japan, led by disodium cromoglycate to treat bronchial asthma. Allergen-specific immunotherapy gradually went out of use in the mid-1980s, although the medical cost of the therapy remained low for many years and the therapy required regular injections. After the 1990s, topical steroids such as inhaled corticosteroids (ICS), second-generation antihistamine drugs, and leukotriene receptor antagonists (LTRA) were recommended by professional society guidelines and the use of SCIT waned. Although oral immunotherapy (OIT) for food allergies is widely performed in Japan (see section 'Current Treatment Approaches'), the efficacy of SCIT for aeroallergens should be re-evaluated; furthermore, sublingual immunotherapy (SLIT) is still emerging.

## History

### Bronchial asthma

From a historical point of view, the treatment for pediatric bronchial asthma in Japan has greatly changed over time. In the 1960s, asthma prevalence began to rise, and its causes were mainly attributed to its relationship with air pollution or psychosocial aspects. Treatment was mostly directed at alleviating symptoms with the inhalation of a short-acting β-agonist or oral administration, injection, or intravenous infusion of aminophylline. Subcutaneous immunotherapy (SCIT) at low doses for house dust was used as a long-term treatment for bronchial asthma. At that time, there was the first epidemic of asthma deaths in developed countries, including Japan.

In the 1970s and 1980s, long-term hospitalization treatment expanded throughout the country for patients with severe asthma for whom treatment at outpatient clinics was difficult. Over 3000 schoolchildren received such treatment in hospitals. The mainstream treatment was SCIT at low doses for house dust, inhalation of disodium cromoglycate, slow release of theophylline, and oral administration of an anti-allergic drug that is unique to our country. After the second epidemic of asthmatic deaths around 1990 (4), ICS began to be used. After publication of JPGL in 2000 (5), ICS became established as the first-choice treatment. As a result, the number of hospitalizations due to asthma attack and the number of asthmatic deaths decreased dramatically, coupled with the appearance of LTRA on the market and its increased use.

### Food allergy

In addition to pediatric asthma, issues related to food allergy were also taken up at the Pediatric Allergy Meetings from the beginning of its establishment in 1966. However, bronchial asthma was the central subject of this society from those days until the early 2000s, and food allergy remained in the background with only a small number of doctors seeing patients in their own way. Antigen-specific IgE antibody measurements came to be covered by insurance in the 1980s. Because this test was positive for various food antigens, many doctors advised avoiding these foods without confirmation of efficacy. The turning point in food allergy practice in our country occurred at the beginning of the 21st century. This was the result of many activities such as a nationwide survey of immediate types of food allergy, the start of food allergy labeling in 2001 (6), the establishment of an oral food challenge (OFC) network supported by a research grant from the Ministry of Health, Labor, and Welfare (MHLW), the publication of food allergy management guideline in 2005 by a research grant from MHLW (7), and the approval of OFC by the national health insurance system. Since the 2000s, the practice, but not research on food allergy diagnosis and treatment in our country, has become one of the most advanced in the world.

### Pediatric clinical immunology

Primary immunodeficiency syndromes (PID) are now classified into eight disease categories by the International Union of Immunological Societies (IUIS) (8). A variety of patients suffering from primary deficiency syndrome have been actively analyzed in Japan. In the past, antibody defects and well-defined syndromes with immunodeficiency such as Bloom syndrome and ataxia-telangiectasia syndrome were analyzed (9–11). However, recent research is focusing not only acquired immune disorders but also innate immune disorders such as IRAK4 deficiency, anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID), and autoinflammatory disorders.

## Epidemiology

### Bronchial asthma

*Prevalence*

Asthma prevalence has been rapidly increasing in recent years. The International Study of Asthma and Allergies in Childhood survey was conducted in Fukuoka City and Tochigi Prefecture and across Japan to examine the prevalence of asthma at specific times (12). The prevalence in Japan was comparable with or slightly lower than the prevalence in the United Kingdom, Australia, New Zealand, Canada, and USA (e.g., Fukuoka City, 13%; Tochigi Prefecture, 19%). According to a survey conducted over several years, in which the same

physicians used the same protocol in subjects with the same background, a 1.5- to 2-fold increase was reported every 10 yrs (Fig. 2) (12). However, according to the latest data, asthma prevalence seems to be decreasing, as shown in Fig. 2. Regarding other allergic diseases, the prevalence of atopic dermatitis is also decreasing among school children. Conversely, the prevalence of allergic rhinitis and allergic conjunctivitis is increasing, and the reason for the increase can be attributed to a sharp increase in pollinosis prevalence.

*Asthma death*

The incidence of childhood death due to asthma has decreased dramatically in the past 10 yrs (Fig. 3). In 2012, there were only three deaths of about 16.7 million children (aged 0–14 yrs) (the death rate was 0.02 per 100,000). The main reasons for the phenomenon are thought to be as follows: (i) the regularly published JPGL contributes to equal accessibility of medical treatment; (ii) the use of controllers, mainly ICS and LTRA, has become widespread, especially as early treatment; (iii) an emergency medical treatment system during nighttime and holidays has been provided throughout the country; (iv) medical expenses for children are free or reduced.

## Food allergy

*Prevalence*

Food allergy is common among infants younger than 1 yr of age and decreases with aging, which indicates that tolerance develops with aging. The estimated prevalence in Japan is 5–10% among infants and 1–2% among schoolchildren (7).

*Causative food allergens*

We prospectively investigated the immediate-type food allergy cases in collaboration with more than 2000 doctors between 2001 and 2002 (6). The contributing doctors included those working in hospitals with more than 200 beds as well as allergy specialists working in clinics. Contributing doctors were asked to respond to a questionnaire every 3 months for 2 yrs from 2001 to 2002 and report immediate-type food allergy cases by mail. By only focusing on the immediate-type food allergy, cases were restricted to those in which symptoms occurred within 60 min after ingestion of the suspected food. A total of 3882 cases were reported within the 2-yr period (Table 2). The patients ranged in age from 0 to 80 yrs, with 50% (1969) of them <2 yrs of age. The most common cause of food allergy was hens' eggs (38.3%), followed by cows' milk (15.9%), wheat (8%), shellfish (6.2%), fruits (6%), buckwheat (4.6%), fish (4.4%), and peanuts (2.8%). Notably, the cause of food allergy differed greatly among age groups.

Food-induced anaphylaxis was seen in 10.9% of the reported cases. Hens' eggs, cows' milk and dairy products, wheat, buckwheat, and peanuts were the major causes of food-induced anaphylaxis in Japan. This prospective investigation into immediate-type food allergies has been repeated every 3 yrs as a means of monitoring the condition of food allergies in Japan.

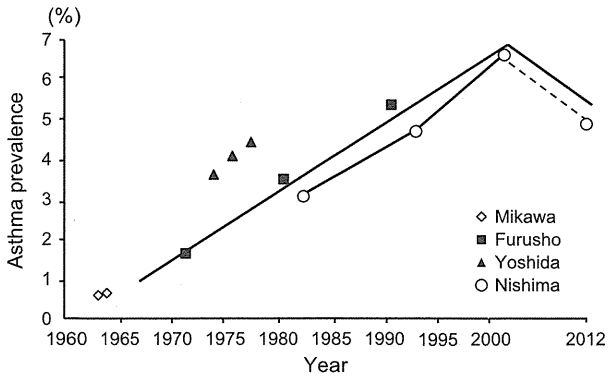


**Figure 2** Changes over years in the prevalence of bronchial asthma in Japanese elementary school children reported by four investigators. According to a multi-year survey in which the same physicians used the same protocol in subjects with the same background, a 1.5- to 2-fold increase was reported every 10 yrs. According to the latest data in 2012, asthma prevalence seems to be decreasing.

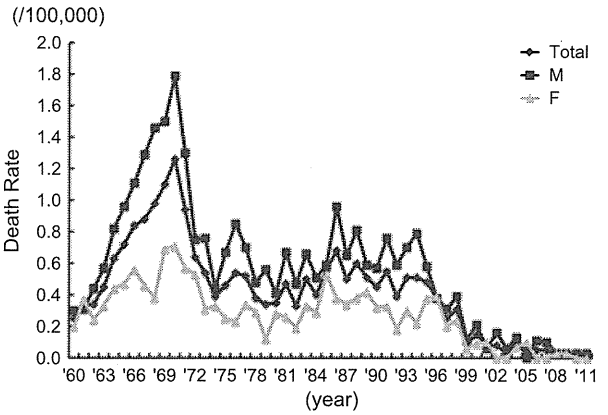


**Figure 3** Mortality from asthma in children of 10–14 yrs of age from 1960 to 2011. The incidence of childhood death due to asthma has decreased dramatically in the past 10 yrs. In 2012, there were only three deaths of about 16.7 million children (age 0–14 yrs) (the death rate was 0.02 per 100,000).

## The prevalence of other allergic diseases in elementary school

Total population questionnaire surveys were conducted 15 times from 1975 to 2006 for all children attending public elementary schools in Japan, with the number of subjects ranging from 460,000 to 900,000. The lifetime prevalence of atopic dermatitis increased to 24% by 1993 and then decreased. The prevalence of rhinitis increased to 25% by 2003, whereas the prevalence of non-seasonal symptoms plateaued from 1993 onwards at 11% and vernal symptoms increased. The prevalence of itchy eyes continued to increase to 21% in 2006, and vernal symptoms increased sharply (13). The most common cause of seasonal rhinitis is Japanese cedar pollen (vernal), and its prevalence exceeds 30% of total population.

**Table 2** Causative food allergens in each age group in 2001 and 2002 survey

| Causative foods | Total cases (%) | 0 year | 1 year | –3 year | –6 year | –19 year | ≥20 year |
|---|---|---|---|---|---|---|---|
| Eggs | 1486 (38.3) | 789 (62.1) | 312 (44.6) | 179 (30.1) | 106 (23.3) | 76 (15.2) | 24 (6.6) |
| Milk products | 616 (15.9) | 255 (20.1) | 111 (15.9) | 117 (19.7) | 84 (18.5) | 41 (8.2) | 8 (2.2) |
| Wheat | 311 (8.0) | 90 (7.1) | 49 (7.0) | 46 (7.7) | 24 (5.3) | 48 (9.6) | 54 (14.8) |
| Fruits | 232 (6.0) | 40 (3.1) | 30 (4.3) | 30 (5.1) | 40 (8.8) | 45 (9.0) | 47 (12.8) |
| Buckwheat | 179 (4.6) | 4 (0.3) | 23 (3.3) | 45 (7.6) | 27 (5.9) | 54 (10.8) | 26 (7.1) |
| Fish | 171 (4.4) | 21 (1.7) | 32 (4.6) | 22 (3.7) | 18 (4.0) | 37 (7.4) | 41 (11.2) |
| Shrimp | 161 (4.1) | 4 (0.3) | 10 (1.4) | 20 (3.4) | 29 (6.4) | 59 (11.8) | 39 (10.7) |
| Peanuts | 110 (2.8) | 4 (0.3) | 22 (3.1) | 31 (5.2) | 28 (6.2) | 22 (4.4) | 3 (0.8) |
| Soybean | 76 (2.0) | 22 (1.7) | 16 (2.3) | 9 (1.5) | 8 (1.8) | 9 (1.8) | 12 (3.3) |
| Meat | 71 (1.8) | 13 (1.0) | 6 (0.9) | 7 (1.2) | 7 (1.5) | 19 (3.8) | 19 (5.2) |
| Others | 469 (12.1) | 28 (2.2) | 88 (12.6) | 88 (14.8) | 83 (18.3) | 89 (17.8) | 93 (25.4) |
| Total | 3882 | 1270 | 699 | 594 | 454 | 499 | 366 |

## Current treatment approaches

### Japanese pediatric guidelines for the treatment and management of asthma (JPGL)

JPGL was published in 2000 and revised in 2002, 2005, 2008, and 2012. A summary of the 2008 edition of the guidelines can be read in English in 'Japanese Guideline for Allergic Disease' (1). Compared with the severity classifications of adults and of foreign countries, the JPGL version has differed by one rank since 2002 (1, 5, 14): For example, the mild persistent type of asthma in Japanese children is equivalent to the intermittent type of asthma in the GINA guidelines, and the moderate persistent type in Japan is equivalent to the mild persistent type. This is because the goal of treatment for achieving a level of control is relatively high in Japan and treatment with a long-term controller is commenced earlier than other countries.

In Japan, for a severe asthma attack in which hospitalization management is needed, continuous inhalation of isoproterenol is given under the monitoring of heart rate and SpO2, together with systemic steroid and inhaled oxygen (15, 16). This common treatment contributes to the remarkable decrease in the number of cases of tracheal intubation with mechanical ventilation.

Treatment plans involving a long-term controller are not so different from the guidelines around the world. Some minor differences are related to the frequency of medication of LTRA for asthma exacerbations induced by viral infection. Anti-IgE antibody treatment is not available yet, but it will be released soon upon the completion of clinical trials.

### Food allergy

*Guidelines for food allergy*

In 2005, as a result of research activity supported by grants from the MHLW, the 'Food Allergy Management Guidelines 2005' was posted on the Internet (7). These guidelines were created to help general practitioners improve their diagnosis and treatment of food allergies and to improve the quality of life of patients with food allergies. 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 guidelines, OFC tests were approved as a medical examination on hospital admission by the national health insurance system. In 2008 and 2011, the 'Food Allergy Management Guideline' was revised to include recent advances (7).

'The Japanese Pediatric Guideline for Food Allergy' was also published in 2005 (2) and then fully revised in 2011 (Japanese Pediatric Guideline for Food Allergy 2012) to have partial unification with 'Food Allergy Management Guideline 2011'. JSPACI also published guidelines for conducting oral food challenges in 2009.

*Oral food challenges and oral immunotherapy*

The MHLW research group and JSPACI together play an important role in the progression of food allergy practice. As shown in Fig. 4, among 514 pediatric training programs approved by the Japanese Society of Pediatrics, there are 312 facilities (58.3%) performing OFC, which means that OFC is already part of the routine diagnostic procedure for food allergy in our country. Based on another survey on OIT by the MHLW research group, there were already 53 facilities performing OIT either in an inpatient setting or in an outpatient setting by the end of 2011, treating 1400 cases of food allergy (mostly hens' eggs, cows' milk, wheat, and peanuts). There are a variety of protocols for OIT. The target subjects' age is usually above 3 yrs, and a majority are 5 yrs and older. We have realized that most of the food allergy patients can be 'desensitized' as far as they can ingest causative foods periodically and that OIT for cows-milk allergy is the most difficult among them.

### Other allergic diseases

*Atopic dermatitis guidelines*

Given the importance of appropriate diagnosis and appropriate assessment of cutaneous symptoms in treatment of atopic dermatitis, the basics of treatment in these guidelines are composed of (i) investigation and countermeasures of causes and exacerbating factors, (ii) correction of skin dys-

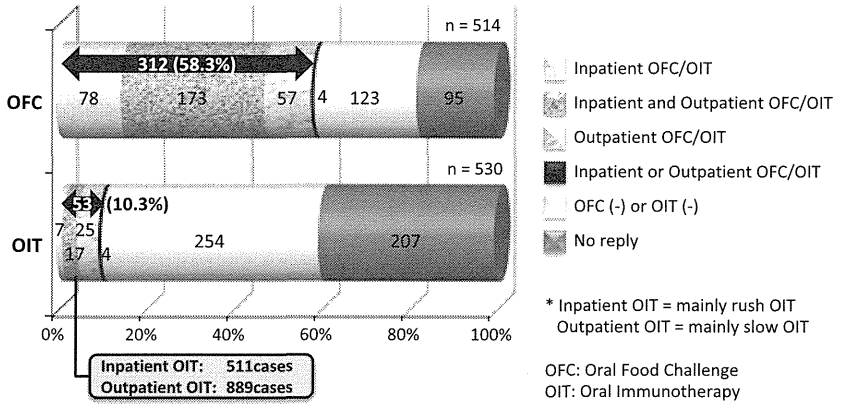


**Figure 4** Number of facilities performing OFC and OIT. Among 514 pediatric training programs by the Japanese Society of Pediatrics, there are 312 facilities (58.3%) performing OFC. Based on another survey on OIT, there were already 53 facilities performing OIT either in an inpatient setting or in an outpatient setting by the end of 2011, treating 1400 cases of food allergy (mostly hens' eggs, cows' milk, wheat, and peanuts).

functions (skin care), and (iii) pharmacotherapy, as three mainstays (17).

*Allergic rhinitis guidelines*

The most common pharmacotherapy is non-sedative antihistamine with nasal spray steroids. Allergen avoidance is recommended, but sometimes impossible. Subcutaneous allergen immunotherapy for Japanese cedar is available, but not so widely used (18).

### Pediatric clinical immunology

First, several diagnostic approach methods were established in Japan. Recently, rapid screening methods were developed for severe combined immunodeficiency (SCID), hyper-IgE syndrome (HIES), familial hemophagocytic lymphohistiocytosis (FHL), chronic granulomatous disease (CGD), innate immune defects, and cryopyrin-associated periodic syndrome (CAPS) using real-time PCR or flow cytometer. The measurements of T-cell receptor excision circles (TREC) and immunoglobulin k-deleting recombination excision circles (KREC) are used as screening method for antibody deficiency syndromes (19). The cytokine production measurement from mitogen-stimulated blood cells is useful for diagnosis of HIES, AD-CMC, and innate immune defects such as IRAK4 deficiency and EDA-ID (20–23). The detection of LPS-induced monocyte cell death is useful for rapid diagnosis of CAPS (24). Intracellular staining is a useful tool for rapid diagnosis of FHL and CGD (25, 26).

Secondly, for the suspected patients of PID and the common physician treating PID patients, PID Japan (PIDJ) was organized, and a genetic analysis center for pathogenic genes of PID was started in 2008 in collaboration with RIKEN Research Center for Allergy and Immunology (http://pidj.rcai.riken.jp/). Precise diagnosis and the accumulation of disease phenotypes may contribute to the developments of future novel treatments for each specific disease. For example, in innate immune defects, because IRAK4 deficiency and MyD88 deficiency showed the immune-deficient tendency against narrow species of pyogenic bacteria only in infancy, defense against bacterial infection is important only in infancy, but not in adulthood. On the other hand, EDA-ID has more severe phenotypes than IRAK4 deficiency, and hematopoietic stem cell transplants have been tried. Now, in Japan, many disease groups for rare diseases have been investigated in conjunction with the MHLW. The results of these research studies have been or will be published elsewhere (27, 28).

## Internationally reported research results from Japan in the field of pediatric allergy and immunology

This section presents the internationally reported human research results in pediatric allergy and immunology field over the past 5 yrs. As many other research results from Japan have been reported in the international journal of JSA (Allergol Int), please refer to the journal Web site (http://ai.jsaweb.jp/).

In the rapidly progressing area of genome research, genetic polymorphisms relevant to allergy or asthma are reported by genomewide association studies and functional analysis research (29–33). In basic research, the pathogenesis of virus infections of the respiratory tract epithelium cells (34) and eosinophil activation by *Staphylococcus aureus* (35) have been studied. The molecules of innate immune system, pathogenesis of autoinflammatory reactions, and molecular mechanisms of MyD88 in TLR4 signaling have been clarified (36). Five Japanese patients with four kinds of gene variations in NLRP3 were given a diagnosis of cryopyrin-associated periodic syndrome or juvenile idiopathic arthritis (37). A rapid screening method to detect autosomal-dominant ectodermal dysplasia with immune deficiency syndrome was reported (23). It should be noted that several pathogenic genes were first identified in Japan, such as IgG2 selective deficiency (CΓ2), hyper-IgE syndrome (STAT3 and Tyk2), autosomal-dominant chronic mucocutaneous candidiasis (STAT1), and autoinflammatory disorder with lipodystrophy (PSMB8) (38–41). Furthermore, the existence of somatic gene mosaicism of NEMO and NLRP3 has been established (24, 42). Kanegane et al. (27) described the clinical characteristics and outcomes of Japanese patients with X-linked lymphoproliferative syndrome (XLP) type 1 and suggested rapid and accurate diagnosis of XLP with the combination of flow cytometric assay and genetic analysis was important.

Research results on the pathogenesis of infantile asthma (43) and respiratory syncytial virus-associated lung diseases have

been reported (44), including the possibility of early intervention for asthma by suplatast tosilate (45). Concerning the management of asthma, the results of a survey of 34,699 children were published by Okabe et al. (46), showing that obesity was associated with asthma in preschool children. A nighttime sleep diary was a useful instrument to monitor daily asthma status in infants and young children with asthma (47). The pandemic H1N1 influenza viral infection can easily induce a severe asthma attack in atopic children without any history of either an asthma attack or an asthma treatment (48). A study showing the close association between rhinitis and nocturnal cough in young children has also been published by Higuchi et al. (49).

Regarding research on atopic dermatitis, the importance of TARC (thymus and activation-regulated chemokine)/CCL17 was reported (50), and coenzyme A contained in breast milk was reported to be associated with its pathogenesis (51).

In Japan, research on the pathogenesis of food allergy, its diagnosis, and treatment has been undertaken by many organizations and facilities for research, and the results have been reported worldwide. The mechanisms of neonatal and infantile non-IgE-mediated digestive food allergies have been reported (52, 53). Regarding the diagnosis of food allergy, using the advantage of OFC as a routine procedure, the probability and component-resolved diagnosis for hens' eggs (54), cows' milk (54), wheat (55–57), soybeans (55, 58), and peanuts (59) have been reported. In addition, studies have also shown the usefulness of basophil activation tests such as the histamine-releasing test and measurement of CD203c (60, 61).

Aside from these reports, there have been many other papers from Japan. Determination of risk factors for the development of allergic sensitization, asthma, and atopic dermatitis is in progress (62–67), and studies have shown the prevalence rates of allergic symptoms in Japanese children (13).

## Social countermeasures for pediatric allergy

### Japanese regulations for the labeling of food allergenic ingredients

According to a national survey of food allergy cases, the food-labeling system for specific allergenic ingredients (i.e., eggs, milk, wheat, buckwheat, and peanuts) in Japan was mandated under law in 2002 (6). In addition, the ministerial notification recommends the labeling of any food that contains the following 18 ingredients: abalone, squid, salmon roe, orange, kiwifruit, beef, walnut, salmon, mackerel, soybean, chicken, banana, pork, matsutake mushroom, peach, yam, apple, and gelatin. To the best of our knowledge, Japan is the first country to set up mandatory food allergy labeling and regulate it under national law. Additional labeling of shrimp/prawn and crab has also been mandatory since 2008. To monitor the validity of the labeling system, the Japanese government announced official methods for the detection of allergens in a 2002 ministry notification. The details of Japanese food allergen labeling are described in the review article (6).

### Countermeasures for allergy in schools

The Research Study Committee on Allergic Diseases of the Ministry of Education, Culture, Sports, Science, and Technology reported the prevalence rates of various allergic diseases among approximately 12 million schoolchildren in elementary, junior high, and senior high schools throughout Japan in 2004. According to this report, the prevalence was 5.7% for bronchial asthma, 5.5% for atopic dermatitis, 2.6% for food allergies, 0.14% for anaphylaxis, 9.2% for allergic rhinitis, and 3.5% for allergic conjunctivitis (7).

Although it is presumed that these prevalence rates failed to cover mild cases of atopic dermatitis and allergic rhinitis or conjunctivitis, children who have some type of allergic disease seem to account for more than 20% of all schoolchildren, even when overlapping cases of multiple allergic diseases are discounted. The number of schoolchildren with allergic diseases is increasing, and various considerations are necessary to secure the safe school lives of such children. Medical specialists and school officials have developed a school life management certificate for children with allergic diseases, which can serve as a tool for communication between medical facilities and schools in cases where such children need special care (7). Children with asthma require special attention during exercise, in dusty environments, when in contact with animals, and during out-of-school activities involving overnight stay. Concerns for children with atopic dermatitis include stimulants that worsen skin eczema, such as perspiration, chlorine in swimming pools, and ultraviolet rays. School lunches are the most serious concern for children with food allergies. Even classes involving the handling of foodstuffs may cause health hazards, thus necessitating caution in this arena. Food allergies are the most frequent cause of anaphylaxis, but it should be noted that anaphylaxis may also occur after a combination of food and exercise or even after exercise alone. It is important that schools are aware of children needing reliever drugs for anaphylaxis and asthmatic attacks.

## Future issues of pediatric allergy immunology in Japan

Regarding asthma, the curative effect is increased by the recent development of long-term controllers and the publication of the guidelines for therapeutic management, which have brought about sharp decreases in asthma deaths, serious cases, and emergency room visits. While long-term controllers control asthma symptoms, the prevention of onset, early correspondence (diagnosis and treatment), and the derivation of remission have not yet been controlled. One immediate issue is to develop and reassess subcutaneous and sublingual immunotherapies for mite antigen that have been disused in our country. We also need to reassess the efficacy of SCIT for Japanese cedar pollen and to develop SLIT for the allergen. Although our standards of medical practice for food allergy are thought to be advanced compared with the world standards, all of the expectations from patients with food allergies have not yet been met. Another urgent issue is to fill the gap on allergy practice between advanced medical institutions and less progressive ones. Countermeasures against anaphylaxis and the enhancement of

correspondence for allergies in nursery schools and grade schools will be important as well. JSPACI will make every effort to continue taking responsibility for public health measures.

Future issues in pediatric allergy are the prevention of onset, early correspondence (diagnosis and treatment), the prevention of aggravation, and the derivation of remission. It is necessary to further improve medical services and promote research. The standards by which a doctor is determined to be an allergy specialist are important because allergies are very common. The Japanese system of allergy specialists is currently at a turning point. JSPACI, in cooperation not only with Japanese professionals but also with international organizations and practitioners, will work on these issues for patients with allergies all over the world.

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