

Alergológica 2015: A National Survey on Allergic Diseases in the Spanish Pediatric Population

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On behalf of the investigators participating in the National Survey of the Spanish Society of Allergology and Clinical Immunology Alergológica 2015.

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■ Abstract

Background: Allergic diseases are highly prevalent in industrialized populations. In Spain, children suspected of having an allergic disease are usually referred by their primary care pediatrician to an allergy unit at a general hospital or a children's hospital. We report data from a subanalysis of the pediatric population in Alergológica 2015.

Methods: Data were collected from pediatric patients (age, ≤ 14 years) consulting an allergist for the first time in 2014 and the first quarter of 2015 in order to determine variations compared with data reported in Alergológica 2005.

Results: Alergológica 2015 included fewer pediatric patients than Alergológica 2005. The study population comprised 481 patients aged ≤ 14 years from more than 200 centers throughout Spain. Males accounted for 56.5%. Rhinoconjunctivitis was the main reason for consulting an allergist (53.8% vs 46.3% in 2005), followed by asthma (30.2% vs 34.6%), and food allergy (20.0% vs 14.5%).

Conclusions: The findings of Alergológica 2015 show a notable increased frequency of allergic rhinitis, drug allergy, and food allergy. The frequency of other allergic conditions remained unchanged, except for asthma, whose frequency decreased, as in adult patients.

Key words: Alergológica 2015. Epidemiological survey. Allergic diseases. Spain.

■ Resumen

Antecedentes: Las enfermedades alérgicas son muy prevalentes en las poblaciones industrializadas. En España, los niños con sospecha de enfermedad alérgica son habitualmente derivados por su médico de atención primaria a una unidad de alergia de un hospital general o de un hospital infantil. Se notifican los datos del subanálisis de la población pediátrica de Alergológica 2015.

Métodos: Se recogieron los datos de los pacientes pediátricos (edad ≤ 14 años) que acudieron al alergólogo por primera vez en 2014 y el primer trimestre de 2015 con el objetivo de determinar las variaciones con respecto a los datos de Alergológica 2005.

Resultados: Alergológica 2015 incluyó menos pacientes pediátricos que Alergológica 2005. La población estudiada comprendía 481 pacientes de edad ≤ 14 años, de más de 200 centros españoles. Los varones representaron el 56,5%. La rinoconjuntivitis fue el principal motivo de consulta al alergólogo (53,8% frente a 46,3% en 2005), seguida del asma (30,2% frente a 34,6%) y la alergia alimentaria (20,0% frente a 14,5%).

Conclusiones: Los hallazgos de Alergológica 2015 muestran un aumento notable de la frecuencia de la rinitis alérgica, la alergia a fármacos y la alergia alimentaria. La frecuencia de otras afecciones alérgicas permaneció inalterada, excepto para el asma, cuya frecuencia disminuyó, al igual que en los pacientes adultos.

Palabras clave: Alergológica 2015. Encuesta epidemiológica. Enfermedades alérgicas. España.

Introduction

Allergic diseases are prevalent among industrialized populations, particularly in younger individuals, with a reported prevalence of 15%-20% for atopic dermatitis, 7%-10% for asthma, and 15%-20% for rhinoconjunctivitis [1].

In Spain, infants and children suspected of having an allergic condition in the public health care system can be referred by their primary care pediatrician to an allergy unit, either at a general hospital, where they are always attended by a board-certified allergist, or at a children's hospital, where they are attended by a board-certified allergist or a pediatrician.

In order to provide a clear picture of the distribution of allergic diseases at allergy clinics in Spain and how these conditions are handled by allergists, the Spanish Society of Allergy and Clinical Immunology (SEAI) carried out an epidemiological study, *Alergológica*, in 1992 [2]. Two subsequent editions of this survey—*Alergológica* 2005 and *Alergológica* 2015—have been carried out with the same scope and based on the same methodology in order to be able to compare data. The results of *Alergológica* 2015 for the adult population (age >14 years) were recently reported [3,4].

The surveys from 2005 and 2015 included a subanalysis of the data in the pediatric sample. In this publication, the results of *Alergológica* 2015 in the sample of patients aged ≤14 years are reported and compared with those of the corresponding sample in *Alergológica* 2005 [5].

Material and Methods

The main objective of the study was to obtain information on clinical practice in allergy departments in Spain. Data were collected from pediatric patients consulting an allergist for the first time in 2014 and the first quarter of 2015 in order to determine variations compared with data reported in *Alergológica* 2005 [2].

The design of the study and the study procedures can be consulted in the previous publication containing the results of *Alergológica* 2015 for the adult sample [3].

Results

Study Sample

The study sample comprised 481 patients (vs 917 in *Alergológica* 2005). The minimum sample calculated to draw conclusions with a 95% confidence interval (CI) of ±5% was 385 patients. Consequently, the sample size is adequate.

Males accounted for 56.5% (55% in *Alergológica* 2005) and females for 43.5% (vs 45%). The distribution by region was similar to that of the general population. At the time of the interview, most children lived in the Autonomous Community where they were born (87.9% vs 95.9%), and only 9 were born abroad (1.9% vs 3.2%). Mean age was 7.6 (4.4) years, with a range of 4 months to 14 years (vs 7.58 [3.9]).

Patients lived in urban areas (61.5% vs 61.6% in *Alergológica* 2005), rural areas (19.6% vs 20.3%), and suburban areas (19% vs 18.1%). Slightly more than one-third

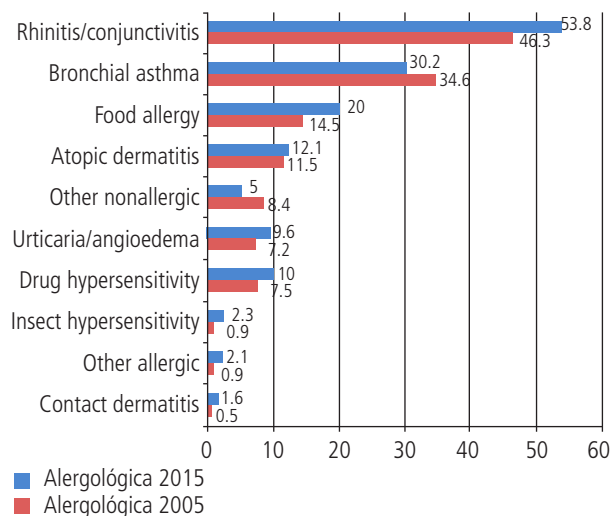


Figure 1. Prevalence of allergic diseases in children diagnosed for the first time in the allergology unit.

lived with a pet (36.2% vs 32%), which was a dog in 24.3% of cases (vs 18%). Almost all of the children went to school (85.9% vs 88%); the remainder (15.1% vs 12%), did not attend school because of their age. Socioeconomic level was low-medium in 34.6% (vs 47%) and medium-high in 50.4% (vs 46%).

Supplementary Tables 1 and 2 of the on-line repository show data on referrals from other physicians and time on the waiting list for the whole pediatric sample and in the different diseases.

The main reasons for seeking medical attention were mostly related to the respiratory system (Supplementary Figure 1). The distribution of the final diagnoses is compared with that of the previous edition of *Alergológica* (Figure 1). Supplementary Figure 2 shows the distribution by age in *Alergológica* 2015.

Rhinoconjunctivitis

Rhinoconjunctivitis was the main reason for consulting an allergist (56.6%); the diagnosis was confirmed in 53.8% (vs 46.3% in *Alergológica* 2005). Most children consulted because of rhinoconjunctivitis (68.6%), 29.6% did so because of rhinitis, and only 1.9% because of conjunctivitis. A large percentage of children with rhinoconjunctivitis (45.2% vs 44.7% in 2005) also had asthma and atopic dermatitis (9.7% vs 8.9% in 2005).

Rhinitis was allergic in 90.3% of cases, infectious in only 3.4% of cases, and intrinsic/eosinophilic in 2.5%. Table 1 shows the distribution of the main groups of allergens responsible for rhinitis and compares them with those of the adult population and *Alergológica* 2005. The individual allergens are shown in Supplementary Table 3.

Most cases of rhinitis manifested in spring (58.4%), and the mean time the patient was attended in the primary care setting before being referred to the allergologist was 26.5 (26.5) months (range, 0-13 years). Rhinitis was severe in

Table 1. Most Frequent Allergens in Children and Adults

Allergen	Alergológica 2015		Alergológica 2005	
	Adults	Children	Adults	Children
Pollens	79.3	68.5 ^a	56.0	47.8
Mites	36.3	37.0	50.0	42.2
Dander	21.0	11.1 ^b	12.0	13.4
Molds	4.3	11.1 ^c	5.0	12.5
Food	0.3	1.2	3.0	2.8

^aP=.017^bP=.021^cP=.004

4.63% of patients, moderate in 53.28%, and mild in 35.14%. Supplementary Figure 3 shows the results of the ESPRINT quality of life questionnaire [6]. Supplementary Table 2 shows the time on the waiting list.

The disease was diagnosed using skin tests in 94.6% of children and specific IgE in 46.6%. The percentage of children who underwent nasal or ocular provocation testing was low (3.3%) and did not differ widely from that of adults (4.2%). Supplementary Table 4 shows the mean time to reach a diagnosis, with a median time of 1 day.

The therapy prescribed for rhinitis was an antihistamine in 92.7% (75.8% in Alergológica 2005); this was oral in 90% (vs 78%). The children were given written norms for avoidance in 73.4% of cases (vs 71.5%). Particularly noteworthy is the increased prescription of nasal topical corticosteroids—in line with clinical practice guidelines [1]—which was 66.8% (49.2% in 2005). Nasal irrigation was prescribed in 47.9% of cases. Immunotherapy was prescribed in 31.7% of cases (34.6% in 2005); this was subcutaneous in 77.78% and sublingual in 18.52%. Immunotherapy was perennial in 37.04%. No data were recorded for this variable in 2005.

Most cases of conjunctivitis were treated with an antihistamine (92.8%) and allergen avoidance (77.2%). Eyewash and artificial tears were prescribed in 35.0%. Immunotherapy in conjunctivitis was subcutaneous in 73.47% of cases, sublingual in 22.45% of cases, and perennial in 36.73%.

Asthma

Bronchial asthma was detected in 145 children (vs 371 in 2005), that is, 30.2% of the sample (vs 34.6%). Therefore, bronchial asthma is the second most common disease after rhinitis in our clinics. This percentage is clearly greater than the 20.3% recorded for adults (vs 28%). Patients consulting for asthma were ≤5 years old in 25.6% of cases (vs 30%).

Boys accounted for 68.6% of cases (vs 54.6% in 2005). Asthma was associated with another disease in 81% of cases, as follows: rhinitis/conjunctivitis, 77.2% (vs 51.6%); atopic dermatitis, 8.3% (12.2%); urticaria/angioedema, 1.4% (vs 3.5%); food allergy, 4.8% (7.6%); and drug allergy, 2.1% (vs 1.1%).

Although most cases manifested in spring (41.7%) and autumn (28.8%), asthma was perennial in 61% of cases (vs

60% in 2005) and seasonal in only 27.3% (vs 40%). Asthma was considered atopic in 82.8% (vs 82%) of cases. The 3 main groups of allergens involved were pollens, house dust mites, and molds (50.8%, 46.1%, and 15.6%, respectively). The distribution of the types of allergen causing asthma is shown in Supplementary Table 3.

Asthma was classified as episodic in most cases (73.4% vs 67.4% in 2005). As for severity, the classification criteria varied between the studies: occasionally episodic, 40.6% vs 62%; frequently episodic, 32.8% vs 36.8%; and persistent-moderate, 26.6% vs 1.1%. The patient had to be admitted to hospital in 7% of cases, and in 71.7% of cases, had had 1-2 exacerbations during the previous year. This led to workplace absenteeism for 27.7% of parents (mean of 10 workdays lost and 12.2 school days lost per year). As for the degree of control, the disease was well controlled in 42% of patients, partially controlled in 29%, and poorly controlled in 9% (in 20% of the cases this item was not recorded).

Data on referrals from other physicians, waiting lists and time to diagnosis are shown in Supplementary Tables 1, 2, and 4.

The most commonly used diagnostic tests, irrespective of the age of the child, were skin tests (88.5% vs 95.4%), spirometry (73.4% vs 46.1%), specific IgE (47.5% vs 50.4%), and total IgE (46.8% vs 52.0%). The tests used did not differ substantially from those used in adults. Fractional exhaled nitric oxide (FeNO) was assessed in 17.3% of cases. Of note, this test was not applied in Alergológica 2005.

As for treatment, 75.8% of children (77% in 2005) reported having adhered to the treatment prescribed by their pediatrician. In 2015, 7.6% had never been treated (vs 3.7%). The specialist made at least 2 changes in the treatment already prescribed in the primary care setting, in 55.6% of cases (54.4% in 2005). Supplementary Figure 4 shows the type of treatment prescribed.

Urticaria and Angioedema

In Alergológica 2015, 14% of patients diagnosed with urticaria were aged ≤14 years (vs 13.4% in Alergológica 2005). Of the 481 children studied, 46 (9.6% vs 7.2%) were diagnosed with urticaria. Boys accounted for 41.9% of the patients affected (52% in 2005). Except for a lower frequency in children aged <3 years, prevalence was equally distributed between the age groups (3-6, 7-10, and 11-14 years). Urticaria was acute in 71.74% of patients and chronic in 23.91%, with no significant differences in the types of presentation between the age groups. The condition was recurrent in 73.9% of patients and presented as urticaria alone (62.2% vs 56.3% in 2005), angioedema (20% vs 7.8%), and urticaria/angioedema (17.8% vs 35.9%).

The parents of children with urticaria were unable to attend work in 8.7% of cases (3.2% in 2005), with a median of 3 days missed in the previous year.

Data on referrals from other physicians, waiting lists and time to diagnosis are shown in Supplementary Tables 1, 2, and 4.

Almost one-third of patients (31% vs 68% in 2005) had visited the emergency department during the previous year (median of 1 visit in 2005 and 2015) and almost three-quarters

of the study population (71.1%) had received treatment during the previous year, as follows: antihistamines, 81.3% vs 80.4% in 2005; corticosteroids, 50% vs 34.8%; and mast cell stabilizers, 3.1% vs 4.3%.

The most frequently used tests for diagnosis of urticaria were the clinical history and examination (93.5% vs 89.5%).

The etiological diagnosis was made using skin tests with foods in 65.2% (vs 63.6% in 2005) and with aeroallergens in 69.6% (vs 51.5%). Allergic serology tests were used in 39.1% (vs 53%) of cases of urticaria in children ≤ 14 years. The cause of urticaria was established in 52.5% of patients (vs 64.4%). This finding contrasts with those of the general sample, in which the cause was established in only 33.6% ($P=.03$, Fisher exact test vs 20% in 2005, $P=.0001$).

The therapeutic approach involved avoidance in 33.3% of cases (vs 43.9% in 2005) and 10.3% were recommended an exclusion diet (24.2%). Antihistamines were recommended in 82.1% of cases (66.7%). Among antihistamines, second-generation and new agents were the most frequently used (84.4% for both vs 28.8% and 27.3% in 2005). First-generation drugs were used in 18.8% (vs 10.6%).

Atopic Dermatitis

In *Alergológica* 2015, a total of 58 children were diagnosed with atopic dermatitis (106 in 2005). This corresponds to a prevalence of 12.1% (vs 11.5%) in the pediatric sample compared with 3.4% (vs 3.4% in 2005) in the whole sample and 1.6% (vs 1.5%) in patients aged >14 years (Fisher exact test, $P<.0001$ in both surveys). Most patients with atopic dermatitis were aged 0–6 years, and prevalence was fairly homogeneously distributed between the age groups and tended to decrease with age (Supplementary Figures 2 and 5). Distribution by sex among adults was 47.3% for men and 52.7% for women. These percentages did not differ significantly from those of the pediatric population. Patients had a personal history of atopy (35.9% in remission, 24.8% active vs 38.2% for both in 2005).

In 58.6% of cases, atopic dermatitis was associated with other allergic diseases especially rhinitis (43%) and asthma (29.6%) (Supplementary Table 5). A considerable percentage of patients did not have active atopic dermatitis when they saw the allergist (38.9%). The disease was very mild or mild in 42.6% and moderate in 18.5%. No cases of severe atopic dermatitis were recorded.

Most patients (79.3% vs 74.5% in 2005) consulted their primary care physician/pediatrician for atopic dermatitis during the previous quarter, with a median of 1 visit (vs 2). Data on referrals, waiting list and time to reach a final diagnosis are shown in Supplementary Tables 1, 2, and 4.

Diagnosis was based on the clinical history and physical examination in 96.5% of cases, with frequent use of skin prick tests (71.9%, 61% foods, 80.5% aeroallergens) and determination of total IgE (22.8%) and specific IgE (19.3%). Patch tests and oral/physical challenge tests were performed in only 5.3% of patients in both cases. The allergology work-up revealed that 62% of cases did not have a recognizable allergic origin (similar to 2005 [61%] and 1992 [57%]).

Anti-allergic treatment had been received in the previous year in 74.1% of cases (77.4% in *Alergológica* 2005). Emollients, antihistamines, and topical corticosteroids are

the most frequently used treatments. Therapy is summarized in Supplementary Table 6.

Contact Dermatitis

In *Alergológica* 2015, a total of 8 patients were diagnosed with contact dermatitis, that is 1.6% of patients aged ≤ 14 years and 6.7% of the total number of patients with contact dermatitis in the general sample (119 patients). Complete data for analysis were only available in 5 children diagnosed with contact dermatitis. Of these, sensitization was only identified in 1 patient with patch tests, and the allergen was thiomersal. In 2005, this allergen was the third most frequent after nickel and cobalt salts. The cause was not identified in the other 4 cases.

Food Allergy

Food allergy is the third most common type of pediatric allergy diagnosed in allergy services; in adults it is the fifth most common type.

Food allergy in childhood is more common in boys (54.6% vs 57% in *Alergológica* 2005); in adults, it is more common in women (60.6% vs 61.8%) ($P=.02$ in *Alergológica* 2015 and $P=.001$ in *Alergológica* 2005).

The distribution by age is shown in Supplementary Figure 3.

Most food-allergic children (72.7% vs 62.8% in *Alergológica* 2005) had been breastfed only during their first months of life. This percentage differs significantly from that of the total population aged ≤ 14 years included in the study (56.3% in both *Alergológica* surveys; $P=.01$ in *Alergológica* 2015 and $P=.41$ in *Alergológica* 2005).

The survey showed that 80.2% of patients (63.2% in *Alergológica* 2005) had an atopic first-degree family member (parents or siblings). In addition, 22.9% of patients (vs 21.8%) simultaneously had atopic dermatitis, 7.2% had asthma (vs 21.8%), and 15.6% had rhinitis. The association with other allergic diseases proved to be much poorer.

Data on referrals, waiting list and time to reach a final diagnosis are shown in Supplementary Tables 1, 2, and 4. During the previous quarter, 74% (vs 75.8%) had visited their family physician or pediatrician, and 29.5% (vs 24.6%) had visited their specialist at some point, with a mean of 1.6 visits (vs 2 visits). In *Alergológica* 2015, 49.5% (vs 48.5%) had to visit the emergency department a mean of 1.3 times (vs 1.7 times). Five patients (5.2%) (13 [9.8%] in *Alergológica* 2005) had to be admitted to hospital once during the previous year, with a mean stay of 2 days (vs 5 days).

The 4 most common culprit foods were milk, fruit, egg, and nuts (Figure 2). Supplementary Table 7 shows the distribution of the foods involved by age group. Most children were allergic to only 1 food, although 33.3% were allergic to more than 1 food (22.6% in *Alergológica* 2005).

As for clinical presentation, 59.4% (73.6% in *Alergológica* 2005) of patients had not previously presented with reactions to food; therefore, they attended the allergy clinic because of a first adverse reaction to a food. Of the patients who had previously had a reaction, 76.3% (vs 78.6%) had the same clinical reaction. Patients had a mean of 2 (2.2) episodes of acute reactions to foods in the previous year (vs 2.45 [2.8] episodes). Cutaneous and digestive symptoms were the most frequent presentation, with anaphylaxis in 7.5% of cases (Figure 3).

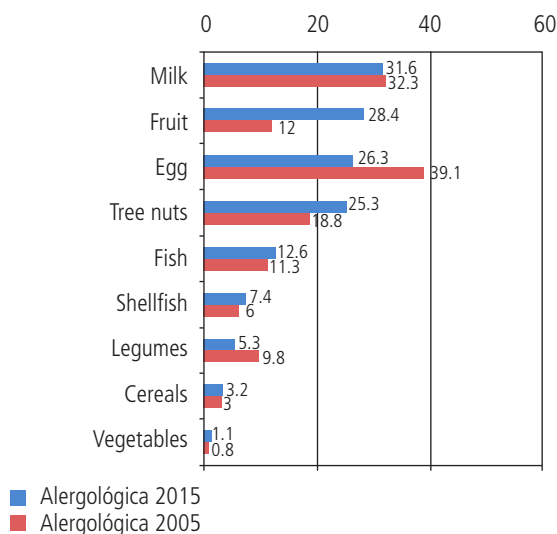


Figure 2. Distribution by frequency of the main groups of foods causing allergy.

Supplementary Figures 7 and 8 show the diagnostic techniques used in pediatric patients. Clinical history, prick testing, and determination of specific IgE were the most widely used approaches.

Avoidance was the most frequent therapeutic approach recommended by specialists. Almost half of the patients (48.8%) were prescribed epinephrine autoinjectors. Antihistamines were prescribed in 87% of cases and topical

Table 2. Drugs Involved in Patients Diagnosed With Drug Allergy

Drug		Confirmed	Sensitization Suspected	Ruled Out	Total
Penicillin	No.	0	0	0	0
	(%)	0.0	0.0	0.0	0.0
Amoxicillin	No.	0	17	10	27
	(%)	0.0	65.4	55.6	57.4
Clavulanic acid	No.	0	6	2	8
	(%)	0.0	23.1	11.1	17.0
Other penicillin derivatives	No.	0	1	0	1
	(%)	0.0	3.8	0.0	2.1
Cephalosporins	No.	0	2	1	3
	(%)	0.0	7.7	5.6	6.4
Macrolides	No.	1	1	1	3
	(%)	33.3	3.8	5.6	6.4
NSAIDs	No.	2	4	1	7
	(%)	66.7	15.4	5.6	14.9
Pyrazolones	No.	0	1	0	1
	(%)	0.0	3.8	0.0	2.1
Local anesthetics	No.	0	1	0	1
	(%)	0.0	3.8	0.0	2.1
Other	No.	0	2	3	5
	(%)	0.0	7.7	16.7	10.6
Total	No.	3	35	18	56
	(%)	100.0	134.6	100.0	119.1
Cases	No.	3	26	18	47

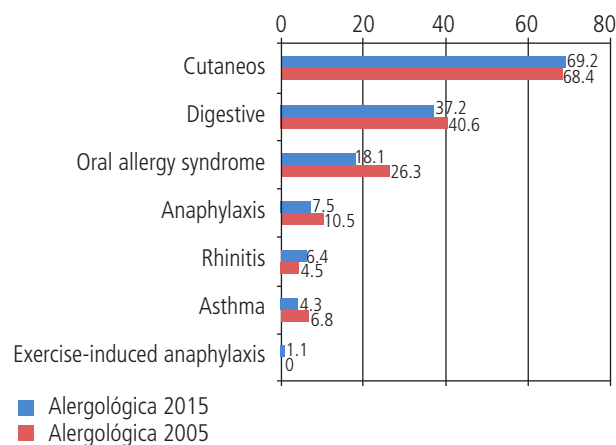


Figure 3. Clinical manifestations of food allergy.

or systemic corticosteroids in 46.4%. Oral immunotherapy with food was prescribed in 9%.

Drug Allergy

A total of 48 children (10%) aged ≤ 14 years (vs 69 [7.5%] in Alergológica 2005) consulted for possible allergy to drugs: 51.1% of them were males (vs 49.2% in 2005). In 77.8% of cases, the reaction occurred concomitantly with infection.

In 29 cases (vs 28 in Alergológica 2005), the diagnosis was hypersensitivity to drugs, that is, a prevalence of 6% (vs 3%) of patients aged ≤ 14 years and 60% (vs 40%) of those

who consulted with suspected drug allergy. Table 2 shows the drugs involved in the reactions studied, with amoxicillin and NSAIDs being the most frequently involved. Most reactions were immediate (47.9% of cases), 35.4% were late, 2.1% delayed, and 14.6% unknown. The drug was administered orally in 85.4% of cases and parenterally in 10.4%.

Flare-ups were more common in winter (35.9%) and fall (32% and 21%, in *Alergológica* 2005) than in spring (20.5%) and summer (10.3%), probably because antibiotics, which are prescribed less in spring and summer, are the drugs that produce the most allergic reactions. As in *Alergológica* 2005, the vast majority of patients (93.5%) only experienced cutaneous manifestations; 4% (2 patients) had anaphylaxis and 2% asthma.

As for health care, mean time from the last reaction was 89 (131) days, with a median of 30 days. Time to reach a final diagnosis is shown in Supplementary Table 4.

As for diagnostic tools, the most widely used were the clinical history (89.4%), prick tests and/or intradermal tests (72.3%), and challenge tests (70.2%).

Three out of 29 patients diagnosed with drug allergy were diagnosed by challenge tests (1 with a macrolide and 2 with NSAIDs) and 26 (54.2%) by suspicion. Drug allergy was ruled out in 18 cases (37.5%). The approaches used were determination of specific IgE in 34% of cases, the basophil activation test in 4.3%, and determination of tryptase in 6.4%. Other nonspecified in vitro tests were used in 2.1% of cases.

Therapy comprised avoidance in 47.9% of cases and desensitization in 2.1% (1 patient). The question remained unanswered in 50% of cases; we imagine that avoidance was indicated.

Hypersensitivity to Insect Venom

Eleven patients (8 in 2005) were diagnosed with hypersensitivity to insect venom, that is a prevalence of 2.3% (vs 0.9% in *Alergológica* 2005) in patients aged ≤ 14 years. Boys accounted for 71.4% and 80% of patients were aged 7-14 years.

Time to diagnosis was 4.1 (5.8) days (vs 16.6 [17.5] in *Alergológica* 2005). The diagnostic techniques used were clinical history and physical examination (90.9% vs 100.0%), type 1 skin tests (90.9% vs 25.0%), determination of IgE (36.4% vs 62.5%), and tryptase testing (18.2% [not used in 2005]).

The insects involved in the reactions were honeybee (9.1% vs 0.0%), *Vespula* species (0.0% vs 25.0%), *Polistes* species (0.0% vs 37.5%), mosquitoes (81.8% vs 37.5%), and other (9.1% vs 0.0%). Only 1 systemic reaction was reported (see Discussion). Antihistamines were prescribed in 90.9% of cases, corticosteroids in 81.8%, autoinjectable epinephrine in 9.1% (1 patient), and no treatment in 9.1% (1 patient). Specific immunotherapy was only indicated in the patient who experienced anaphylaxis after a bee sting.

Other Diagnoses

Eight patients aged ≤ 14 years were diagnosed with an allergic disease not specifically included in the case report form (2 allergic gastrointestinal diseases, 2 allergic kidney-

urinary tract diseases, 1 grade III idiopathic anaphylaxis, 1 exercise-induced anaphylaxis, 1 latex allergy, and 1 unknown). Nonallergic diseases were detected in 19 patients (3 with $\alpha 1$ -antitrypsin deficiency, 2 with respiratory infections, 2 with celiac disease, 1 with upper airway obstruction, 1 with parasitosis, 1 with pulmonary malformation, and 11 with other diagnoses).

The mean time to diagnosis was 2.7 (2.9) days (vs 9 [17.3] in *Alergológica* 2005).

Discussion

Alergológica 2015 included fewer patients aged < 14 years than *Alergológica* 2005, probably because of the low number of pediatrics units that saw allergic patients in 2015. Consequently, there were fewer patients aged 0-5 years than in 2005, although the mean age was very similar in both studies. This observation may indicate a slight bias with respect to the distribution of allergic diseases in the sample studied, with a—possibly—lower proportion than expected of food allergies, especially to early foods, such as milk and egg, and a greater proportion of patients seen with suspicion of drug hypersensitivity.

Rhinoconjunctivitis

As shown in phase I and phase III ISAAC surveys, the prevalence of allergic rhinoconjunctivitis in children is increasing worldwide, and in Spain it is estimated at 7.9% [1]. This is seen clearly in the observation that rhinoconjunctivitis is the main presenting complaint among children in allergy clinics. This prevalence increased considerably with respect to *Alergológica* 2005.

The frequency of pollens as the culprit allergen increased in rhinoconjunctivitis, whereas that of other allergens remained unchanged, except for dog dander, which was not recorded as a culprit allergen in *Alergológica* 2005. Only sensitization to molds was more frequent in children than in adults (11% vs 4.3%). An unexpectedly high frequency of sensitization to *Cladosporium* has been reported in asthmatic children [7], and Nolles et al [8] reported a peak in sensitization to mold allergens in children aged 7-8 years, although this subsequently decreased. This pattern was not seen with house dust mites or pollens.

It is noteworthy that it took an average of 26.5 months (and even as long as 13 years) to refer a patient to a specialist for an allergy work-up, when in most cases, the diagnosis is made on the day of the visit, although in some cases diagnosis took several months (mean, 10.2 [32.4] days vs 12.6 [21] days in *Alergológica* 2005), with a mean time on the waiting list of 34 days (vs 60 days). This delay in referral could lead to a delay in treatment of the cause of the disease and to chronification, with possible progression to asthma, as shown by the fact that 45% of patients with rhinitis already had asthma. Although the mean time to referral has improved slightly compared with 2005 (average of 29 months), improvements in referral criteria and procedures could benefit the allergic child, thus helping to slow the progress of the disease. When analyzing the data of *Alergológica* 2005 in greater depth,

Ibañez et al [9] showed that the association between asthma and rhinitis was significantly higher in children than in adults (44.9% vs 35.5%; $P < .05$) and that it was related to the time since onset of allergic rhinitis. Izquierdo-Dominguez et al [10] also showed that allergic rhinitis tends to be more severe in children than in adults. Consequently, these patients should be referred to allergy units early.

Asthma

Diagnosis of asthma is difficult in children, and in clinical practice, it is mostly based on the presence of compatible symptoms, positive family history, physical examination, and response to previous anti-asthmatic medication. In this study, diagnosis of asthma was based on the clinician's criteria, and there were no specific instructions about when to diagnose asthma in the patients included. However, considering that all study investigators were board-certified specialists, we are confident that the diagnoses made are reliable.

Only 25.6% of children who consulted for asthma (30% in 2005) were under 6 years of age, thus indicating that Spanish pediatricians do not refer preschool children with asthma to a specialist unless—in line with guidelines for diagnosis and treatment of asthma—the children present risk factors for allergy or have refractory asthma. In addition, it took a mean of 24.2 (22.6) months to refer the patients to the allergologist for a work-up (vs 32 [24] months in 2005). As with rhinitis, this delay in referral to a specialist slows up the etiologic diagnosis of asthma, the implementation of specific treatments aimed at the cause, allergen avoidance, and specific immunotherapy, all of which contribute to tertiary prevention of the disease.

Urticaria and Angioedema

Urticaria is one of the most common allergic disorders in the general population. Data from the Spanish Society of Allergy and Clinical Immunology (SEAIC) indicate that approximately 20% of the Spanish population have experienced an episode of urticaria in their lifetime and that urticaria was chronic in 0.65% of cases. The exact incidence of urticaria in children is unknown. Some studies report that 3% of preschool children and 2% of older children have experienced urticaria [11].

When the etiology was identified, the most frequent causes were foods (19.6%), physical causes (13.0%), drugs (10.9%), and infection (10.9%). In *Alergológica* 2015, more cases of urticaria (both chronic and acute) were attributed to infection than in 2005. It is noteworthy that foods were more frequently involved in acute urticaria and physical factors in chronic urticaria, and no significant differences were established according to patient age. Also of note, in the present edition of *Alergológica*, there were no cases of hereditary angioedema, which was the cause in 14.3% of cases of chronic urticaria in the 2005 survey.

Atopic Dermatitis

Atopic dermatitis generally first manifests during childhood. The disease decreases in intensity and frequency with age. Children accounted for 61.1% of cases of atopic dermatitis (63.9% in *Alergológica* 2005) in the whole sample. Despite this tendency to improve with age, data

from *Alergológica* 2015 show that atopic dermatitis is a more disabling disease than other allergic diseases. During the previous year, 48.7% of children had missed school, with a median of 8.7 (12.1) days (vs 13 [22.8] days). Eleven parents (25% vs 16%) had missed work because of their children's disease, with a median of 3 days (3.5 days). In 40 patients (vs 63 patients) for whom data were available, the mean number of days with symptoms in the current outbreak was 11.5 (15.3) days (52.3 [103.7] days). Patients had a mean of 3.9 (4.3) flare-ups (vs 3.6 [3.2] flare-ups) during the previous year, with 0-2 flare-ups per year in 46.4% (vs 43%).

When the diagnostic tests used by allergologists are compared with those used by dermatologists in the DERTA study [12], we see that allergologists apply skin tests and determination of specific IgE much more often. The allergologist investigates potential allergic sensitization as the origin of dermatitis or cause of the exacerbation. However, it is important to remember that determination of total and specific IgE were used much less frequently for the diagnosis of atopic dermatitis than in 2005, thus implying that, at present, allergologists less frequently suspect that the cause of atopic dermatitis is an allergen. In addition, patch testing with aeroallergens and foods is rarely used, perhaps because it has not been validated and its diagnostic utility in dermatitis has yet to be defined.

Food Allergy

Population studies show that the frequency of food allergy is 3 times greater in children than in adults and that the prevalence of food allergy is 6% in children aged <3 years and 2% in adults [13]. The prevalence of food allergy as the initial complaint when consulting the allergologist has continued to grow in the successive editions of *Alergológica*, from 3.6% in 1992 to 7.4% in 2005 and 11.4% in 2015 for the whole sample. Even though the sample of children aged ≤ 14 years was not analyzed separately in *Alergológica* 1992, the increase is more marked in this age group (14.5% in 2005 and 20.0% in 2015).

With respect to the foods involved, the distribution by frequency is fairly similar to that reported in the previous edition of the survey, although the significant increase in allergy to fruits and decrease in egg allergy are worthy of mention. Age may have played a role in this finding, although, given that the mean age of patients in both studies was very similar (7.6 [4.4] years in 2015 and 7.58 [3.9] years in 2005), this does not seem to be the case. Given that an increase in sensitization to pollens has been observed in patients with respiratory allergy and cross-reactivity between pollen allergens and fruits is pronounced [14], the increase in fruit allergy could be caused by this fact.

Compared with data from *Alergológica* 2005, the clinical manifestations of food allergy have not varied significantly, except for a slight decrease in the percentage of cases presenting with anaphylaxis (Figure 3). However, caution is mandatory since several studies have shown an increase in hospital admissions for anaphylaxis in recent decades [15-17].

As for the diagnostic techniques used, the procedures have remained largely unchanged since the first edition of *Alergológica* and are based mainly on the clinical history, prick tests (performed in the vast majority of patients), determination

of specific IgE (performed in a large percentage), and challenge tests in selected cases (performed in approximately a quarter of patients). Although molecular diagnostic techniques have been increasingly used in recent years, the questionnaire was not designed to detect these changes.

In contrast, changes were recorded in the approach to therapy. Prescription of antihistamines and corticosteroids increased considerably, as did that of epinephrine autoinjectors (not recorded in *Alergológica* 2005). These differences may have been due more to methodological changes in the 2005 study with respect to 2015. Furthermore, 9% of children with food allergy were prescribed oral immunotherapy with food, in contrast with *Alergológica* 2005, where oral immunotherapy was not prescribed, even though the approach was already used in several centers at the time. This increase could in fact result from growing implementation of the treatment in Spanish allergy units, as evidenced by participation of many Spanish allergy units in the publication of the first worldwide clinical guidelines on oral immunotherapy with foods [18,19].

Drug Allergy

Drug allergy is clearly less frequent in children than in adults. The reason for this lower prevalence is unknown, although it could simply be due to reduced exposure to drugs among children or differences in the immune system; however, this has not been demonstrated. In any case, the drugs that most frequently cause allergic reactions are the same as in adults, namely, β -lactam antibiotics, especially amoxicillin, followed by NSAIDs. This frequency of presentation seems to remain constant over time and across different series: in *Alergológica* 1992, 79% of patients aged ≤ 14 years experienced reactions to antibiotics (81% of which were to β -lactams) and 16% with NSAIDs. *Alergológica* 2015 revealed a substantial change in the type of β -lactam involved. Penicillin was involved in 35% of reactions to β -lactams in *Alergológica* 1992, 13.6% in 2005, and 0.0% in 2015. The frequency of sensitization to amoxicillin and amoxicillin-clavulanic acid has increased (57.4% and 17% of cases, respectively, in *Alergológica* 2015).

A comparison of the overall sample reveals that reactions to drugs reported by children are generally less severe, manifesting as anaphylaxis in 4.4% of children compared with 8.4% of adults ($P=.024$) (3.8% vs 10% in *Alergológica* 2005), as reported by Le et al [20].

As for therapy, the pediatric sample did not differ from the adult sample, with avoidance being the predominant approach. Desensitization was used in 1 case among children and in 10 adult patients (2.1% and 1.8% of children and adults, respectively, who consulted for drug allergy). Nevertheless, as reported in the review by de Groot et al [21], drug desensitization is rarely used in children in daily clinical practice.

Hypersensitivity to Insect Venom

While the percentage of patients aged ≤ 14 years consulting for insect stings has increased in this edition of *Alergológica* compared with 2005 (2.3% vs 0.9%), the number of patients consulting for this reason is low (11), and it is noteworthy that none were stung by wasps and most were bitten by mosquitoes. The fact that fewer patients were stung by wasps

could account for the lower frequency of determination of specific IgE (36.4% vs 62.5%) in *Alergológica* 2015 than in 2005 and the more frequent performance of skin tests (90.9% vs 25%, respectively). In the only case of a patient who consulted for a grade III systemic reaction to a honeybee sting, the diagnosis was made according to accepted standards (clinical history, tryptase test, determination of total and specific IgE, and molecular techniques), and the patient was prescribed an epinephrine autoinjector and specific immunotherapy [22,23].

In summary, *Alergológica* 2015 is the third edition of the *Alergológica* series, which was started by the Spanish Society of Allergy and Clinical Immunology in 1992. The present publication evaluates several areas of daily clinical practice in the treatment of allergic diseases presented by pediatric patients seen for the first time in allergy clinics. The study included a sample of 481 patients, aged 0-14 years, from more than 200 allergy units in both the public and private health care systems in Spain. As in the adult sample, the results of the current edition in the pediatric population show a notably increased frequency of allergic rhinitis, drug allergy and food allergy, whereas the frequency of other allergic conditions remained practically unchanged, except for asthma, whose frequency decreased, as in adult patients.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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