Accurate of the diagnosis of allergy reactions at the Emergency Department.

SHORT TITLE: Diagnosis of allergy at the ED

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ABSTRACT

Background: Suspicion of an acute allergic reaction is a common reason for attending Emergency Departments (ED). However, little work has been performed comparing the initial diagnosis made in the ED of patients with suspected allergic reaction, with the definitive diagnosis made subsequently in the allergy department (AD).

Objective: Compare details of the initial diagnoses given in the ED relating to allergy with the final diagnoses performed in the AD.

Methods: Patients attending the ED of two hospitals with suspected allergic reactions were prospectively enrolled based on keywords. A certified allergy specialist revised the ED records of these patients and, if suggestive of an allergic reaction, the patients were scheduled for further evaluation at the allergy clinic.

Results: In total, 2000 patients were enrolled between April 2013-October 2015, of which 1333 passed the initial revision and underwent further evaluation. Of these, 528 underwent allergological study and 206 were confirmed as allergic. Regarding drug allergy, non-steroidal anti-inflammatory drugs were the most common triggers, followed by β-Lactams; in food allergy, plant-based foods were the most common. Only 16.4% of patients confirmed as having anaphylaxis in the AD were initially diagnosed as such in the ED.

Conclusion: Of the 528 patients that finally underwent full allergological study, less than half could be confirmed as allergic. Moreover, there appears to be an underdiagnosis of anaphylaxis in ED. Better communication between ED and AD is necessary to improve this situation and improve the diagnosis and management of these patients.

KEYWORDS

Anaphylaxis, Hypersensitivity drug reactions, Emergency medicine, Food allergy, Follow-up studies

RESUMEN

Antecedentes: La sospecha de una reacción alérgica aguda es un motivo frecuente de consulta en urgencias. Sin embargo, hay pocos trabajos que comparen el diagnóstico inicial realizado en las unidades de urgencias con el diagnóstico definitivo realizado en las unidades de alergia.

Objetivo: Analizar en detalle la sospecha diagnóstica inicial dada en urgencias con el diagnóstico definitivo en las consultas de alergia.

Métodos: Estudio prospectivo, que consistió en las selección, en base a palabras claves, de pacientes con sospecha de reacción alérgica. En la fase de screening, se seleccionaron los pacientes en base a las palabras claves, finalmente aquellos pacientes que presentan reacción sugestiva de alergia se seleccionaron para evaluación final.

Resultados: Se revisaron 2.000 pacientes entre abril de 2013 y octubre de 2015, de los cuales 1333 se seleccionaron para la evaluación. Finalmente, 528 se sometieron a un estudio alergológico y 206 se confirmaron como alérgicos. Con respecto a las reacciones por fármacos, los AINEs y β-Lactams fueron los mayormente implicados; en relación con los alimentos, los de origen vegetal fueron los más frecuentes. Sólo el 16,4% de los pacientes con anafilaxia confirmada tras el estudio de alergia, fueron diagnosticados inicialmente en urgencias.

Conclusión: Sólo la mitad de los pacientes que finalizaron en estudio fueron confirmados como alérgicos. Un dato importante es el infradiagnostico de la anafilaxia en las urgencias. Por ello pensamos que es necesaria una mejor comunicación entre las unidades de urgencias y alergia para mejorar el manejo clínico y terapéutico de estos pacientes.

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INTRODUCTION

Allergic reactions are acute medical events resulting from abnormal immunological hyperreactivity, generally to proteins or drugs. They represent a significant clinical problem in primary care departments. For food allergy, common triggers include cow's milk, egg, wheat, soy, peanut, tree nuts, fish and shellfish, and fruits [1-2] For hypersensitivity drug reactions (HDR), key triggers include non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics [3-4]. The clinical presentation of allergic reactions can be quite variable; however they are usually acute and severe, with urticaria, angioedema and anaphylaxis being the most common symptoms [5-8].

Suspicion of allergic reactions represents an important motive for consultation at the emergency department (ED), and is an economic burden on the healthcare system, with an estimated direct cost of $227 million in the United States for food allergic reactions and anaphylaxis in 2007 [9]. Furthermore, recognition and treatment of anaphylaxis in an ED setting is often undermined by atypical presentation and a lack of adequate formation for primary care physicians [10]. These concerns underline the need for better management of food allergy and HDR by ED physicians.

Few studies have analyzed prospectively the diagnosis of patients presenting at the ED with a suspicion of allergy and subsequently compared those results to a standard outpatient evaluation by an allergist, with most previous studies being focused on anaphylaxis [11-12]. Here, used a multi-step approach to screen ED patients for potential allergic reactions, and compared the ED diagnosis with the final AD results, taking into account clinical characteristics and focusing on the most common triggers.

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METHODS

Study design

We conducted a prospective study of patients over 14 years old who attended the ED of two hospitals in Málaga, Spain between April 2013 and June 2015. As an initial *screening evaluation*, electronic medical records of patients who sought assistance at either of the ED were screened for specific keywords. In the next step (*Primary evaluation*), a certified allergist analyzed the ED electronic medical records of the patients passing the screening evaluation and contacted them by telephone to obtain additional details. Those suspected of having suffered allergic reaction proceeded to the last step *(Final evaluation)* which involved an extensive allergological evaluation in our unit conducted by one of two certified allergists who were not involved in the primary evaluation (Figure 1).

Data collected by the ED physician from patients selected in the *Screening evaluation* were compared to those obtained from patients selected in the *Primary evaluation*. Data from patients selected in the *Primary evaluation* were also compared to those obtained by the allergological work-up in the *Final evaluation*.

The study was conducted according to the principles of the Declaration of Helsinki and approved by the Provincial Investigational Ethics Committee of Malaga. All the participants were informed orally about the allergological study and signed the corresponding informed consent.

Screening evaluation (Keyword Search)

Reason for consultation and final diagnosis for the ED visit were screened for a possible match to a predetermined keyword bank (allergy, hypersensitivity, allergic reaction, urticaria, cutaneous eruption, infection, dermatitis, exanthema, anaphylaxis, reaction, angioedema, adverse event, insect sting, erythema, pruritus, drug intolerance, asthma

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and food intoxication) to search for possible allergic pathologies.

Primary evaluation

A single, certified allergist performed the primary evaluation within 10 days of the ED visit. Those with a suspicion of an allergic reaction (suggestive symptoms and/or suggestive time interval between allergen contact, intake and reaction) were selected. A standardized data abstraction form was used to collect demographical and clinical information, including allergic and asthma history, identification of the number and the type of culprit allergen, timing of the reaction, presenting signs and symptoms and management by an ED physician. Putative patient diagnosis was categorized into one of the following groups: food allergy, HDR, food plus drug allergy, dermatological disease, other allergy, angioedema (without urticaria), idiopathic urticaria and other pathologies.

Final evaluation

An allergological evaluation at the outpatient Allergy Unit was offered to all patients selected in the first evaluation. This formal evaluation was initiated within four weeks of the ED visit and completed by a different allergist to the one that performed the primary evaluation. If necessary, skin prick tests (SPT), intradermal tests (ID), measurement of specific IgE (sIgE) by ImmunoCAP (IDD Thermo Fisher Science, Uppsala, Sweden), basophil activation test (BAT), double-blind placebo-controlled food challenge (DBPCFC) and/or single-blind placebo-controlled drug provocation test (DPT) were performed. Diagnosis of anaphylaxis was based on the European Academy of Allergy and Clinical Immunology (EAACI) guideline criteria [13]. Participants with HDR were classified according to previous described guideliens [14-15]. They were also classified based on the time-interval response as immediate responders (< 1 hour after the drug administration) or non-immediate responders (> 1 hour).

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Skin testing

For food allergy investigation, SPT was performed according to European guidelines [16] using commercialized allergen extracts provided by ALK-Abello (Madrid, Spain). The response was considered positive if the diameter of the wheal area was 3 mm greater than the saline control. For HDR investigation, SPT was performed with the culprit drug and, if negative, by ID as recommended. The dosages for the different drugs were as described previously [17].

In vitro testing

sIgE levels were determined by ImmunoCAP following the manufacturer's recommendations (Thermofisher, Uppsala, Sweden). Results were expressed as kUA/L and considered as positive when > 0.35 kUA/L [18]. BAT was performed as described], including different concentrations of the suspected allergen or drug. Results were presented as the percentage of activated basophils ($CD63^+CD203c^+CCR3^+$).

Provocation test

For food allergy investigation, DBPCFC was performed at the Allergy Unit following EAACI recommendations [20]. Blinded active and placebo meals were randomly administered on separate days, and prepared immediately before the challenge. Up to five doses were administered at 20-min interval until reaching the intended cumulative dose. After the last dose, the patient remained in observation for at least 2 hours.

For HDR investigation, DPT was performed at the Allergy Unit. If negative, a two-day therapeutic ambulatory course with the culprit drug was carried out as described [19, 21)].

Statistical methods

Confidence intervals on descriptive data were calculated using a modified Wald method. The two-tailed Fisher's exact test was used to perform analysis of nominal variables and means between groups were compared using paired student t tests. Quantification of diagnosis agreement between two observers was calculated using Cohen's kappa statistic. All analyses were performed using GraphPad PRISM software version 6.0b (GraphPad, LaJolla, CA).

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RESULTS

This ED department provides care for approximately 450,000 patients each year, of whom the majority are residents of the province of Malaga. Two thousand (0.22% of the total number of patients evaluated in the ED) patients met the inclusion criteria of the screening phase and were analyzed in the *Primary evaluation*. The results of the search for a match between the ED physician diagnosis and predetermined keyword bank is described in Table I. Most of the patients evaluated were females (59.8%) with a median age of 39.2 (IR: 38.2-40.1) years. Of these, 302 patients (15.1%) had a clinical history of atopy, 166 (54.9%) being sensitized to pollen, 124 (41.1%) to dust mite, 62 (20.5%) to pet dander and 8 (2.65%) to mold; 216 (10.8%) patients had a history of asthma. Full demographic and clinical characteristics of the initial 2000 patients are shown in Table II. In order to conduct the primary evaluation, all patients were contacted by phone. A total of 1333 met the inclusion criteria; 199 (9.95%) did not meet the criteria and were discarded as having no suspicion of allergy, and 468 (23.4%) could not be contacted. Of these 1333 patients that passed the primary evaluation, 805 (60.3%) chose not to participate further in the study. The remaining 528 patients (39.6%) patients underwent a complete allergological study (Figure 1).

When comparing these patients who underwent the final allergological studies to those that did not complete the full process for various reasons, differences were found in terms of gender. A higher proportion females undergoing the final studies ($p=0.008$), prior allergy history ($p<0.0001$), specifically to aeroallergens ($p<0.0001$), presumptive diagnosis of HDR ($p<0.0001$), anaphylaxis ($p=0.023$), and specific triggers such as β-Lactam ($p=0.009$), NSAIDs ($p<0.0001$) or contrast media ($p=0.019$). Full details of all comparisons are given in Table III.

Among participants who underwent an allergological study, (40.9%) were diagnosed

with idiopathic urticaria; 86 (16.3%) were confirmed as food allergic, of whom 24 (28.6%) had previously been diagnosed as allergic to the food that caused the ED visit. Among these 86 food allergic patients, 84 (97.6%) participants had reactions only triggered by food, whilst two (2.4%) participants presented a reaction that could be attributed to both food and drug (lipid transfer protein (LTP) and AX). For these 86 participants, diagnosis was achieved by SPT (72.1%) and sIgE (27.9%). Clinical presentation was urticaria and angioedema for 32 individuals (37.2%), anaphylaxis for 26 (30.2%) and upper or lower airway symptoms were present in 16 (18.6%). Fruits and vegetables were the most prevalent triggers, inducing reactions in 34 patients (39.5%) followed by crustaceans in 20 patients (23.2%) and cereals in 16 patients (18.6%).

Comparison of the data after the *final evaluation* with those obtained from the *primary evaluation* showed an increase in the percentage of cases confirmed as anaphylaxis (54.8% vs 28.6%; p=0.026), and in the percentage of reactions induced by fruit and vegetables (39.5% vs 53.5%; p=0.036) and a decrease in the percentage of reactions induced by cereal (18.6% against 0.0%; p=0.005). (More details in Table IV)

Of the patients who underwent an allergological study, 116 (22.0%) were confirmed as having an HDR. Clinical symptoms reported by patients were, in descending order, anaphylaxis 46 (40.4%), urticaria/angioedema 44 (38.6%) and exanthema 18 (15.8%). A total of 94 (81.0%) reported an immediate reaction and 22 (19.0%) a non-immediate reaction. Most patients, 114 (98.3%), reported reactions to only one drug; two patients (1.7%) had a concomitant reaction after the intake of two different drugs: acetaminophen and ibuprofen in both cases. The most frequent triggers were NSAIDs, affecting 72 patients (62.1%) followed by β-Lactams for 26 patients (22.4%), and quinolones and radiocontrast media for 6 patients (5.2%), respectively. The comparison

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of data after the *final evaluation* with those obtained from the *primary evaluation* showed an increase in the percentage of cases reporting only one culprit drug (87.7% vs 98.3%; p=0.032). There was no statistical difference when comparing clinical symptoms, timing of the reaction and identified triggers. Further details in Table V.

Among the 72 patients confirmed with NSAID hypersensitivity after final evaluation, 12 (16.7%) were already known to be NSAID hypersensitive before their ED visit. Seventy patients were diagnosed by DPT; two were diagnosed by SPT to dipyrone. Clinical presentation reported after NSAID intake was urticaria/angioedema 32 (44.4%), followed by anaphylaxis 30 (41.6%), exanthema 4 (5.6%), fixed drug eruption 2 (2.8%) and upper airway symptoms 2 (2.8%). Participant's final diagnoses were confirmed as single NSAID-induced urticaria/angioedema or anaphylaxis 46 (63.9%), NSAID-induced urticaria/angioedema 18 (25.0%), NSAID-induced delayed hypersensitivity reactions 6 (8.3%), or NSAID-exacerbated respiratory disease 2 (2.8%). Dipyrone was the most common trigger, affecting 38 patients (52.8%), followed by propionic acids (namely ibuprofen for 14 (19.4%), naproxen for 6 (8.3%) and dexketoprofen for 4 patients (5.6%), diclofenac for 8 patients (11.1%) and ASA for 2 (2.8%).

Among the 26 patients confirmed as having β-Lactam allergy, four (15.4%) were already known as having β-Lactam hypersensitivity before the ED visit. Diagnosis was established by ID for 14 (53.8%) patients, BAT for 4 (15.4%) and DPT for 8 (30.8%). Clinical presentation after β-Lactam intake reported by patients was anaphylaxis in 10 cases (38.5%), followed by urticaria/angioedema in 8 (30.8%), exanthema in 4 (15.4%), pruritus in 2 (7.7%) and erythema in 2 (7.7%). The culprit drug after the primary evaluation was AX-CLV for all participants. After the allergological evaluation, 12 cases (46.2%) were confirmed as having selective allergy to AX, 10 patients (38.5%)

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selective allergy to CLV and 4 (15.4%) cross-reactive allergy to β-Lactams.

Of the 528 who underwent an allergological workup, 206 (39%) had their suspected allergy trigger confirmed, 96 (18.1%) were actually allergic to a different causal agent, 2 (0.3%) were diagnosed with idiopathic anaphylaxis and mastocitosis and for eight patients (1.5%) no allergic trigger could be found.

Among all patients who underwent an allergological study, 110 (20.8%) met anaphylaxis criteria. Of these, 48 (43.6%) had anaphylaxis caused by food allergy, due to (in descending order) fruits and vegetables for 16 patients (14.5%), crustaceans for 14 (12.7%), tree nuts for 6 (5.5%), anisakis for 4 (3.6%), peanuts for 4 (3.6%), milk for 2 (1.8%) and mustard for 2 (1.8%). Focusing on patients that developed an anaphylactic reaction induced by drugs, 46 (41.8%) of the total 110 anaphylaxis cases, the culprits were (in descending order): NSAIDs for 32 patients (29.1%), β-Lactams for 12 (10.9%) and quinolones for 2 (3.6%). Considering participants with NSAID hypersensitivity, 26 patients (23.6%) were confirmed as having single NSAID-induced urticaria/angioedema or anaphylaxis and 6 (5.5%) as having NSAID-induced urticaria/angioedema. Considering patients with β-Lactam allergy, a total of 4 (3.6%) were diagnosed as having cross allergy to β-Lactams, 4 (3.6%) a selective allergy to AX and 2 (1.8%) a selective allergy to CLV. Eight patients (7.3%) were diagnosed with idiopathic anaphylaxis and anaphylaxis induced by hymenoptera sting, latex allergy, exercise induced allergy and mastocytosis (1.8%, respectively) (Supplementary table I).

Of these 110 patients meeting anaphylaxis criteria, only 18 (3.8%) were diagnosed as such in the ED. Moreover in-patient treatment by ED physicians included epinephrine for 20 (18.8%) of these 110 individuals, anti-histaminics for 82 (74.5%) and systemic corticosteroids for 88 (80%). Upon discharge, prescribed treatment included self-injectable epinephrine for 8 (7.2%) participants, anti-histamines for 90 (81.8%) and

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systemic corticosteroids for 48 (43.2%) (Supplementary table II)

Diagnosis concordance between ED physicians, trained allergists in the primary evaluation and trained allergists in the final evaluation was measured using Cohen's kappa statistic, for all 528 fully evaluated cases. A concordant result was found between the ED physician and the allergist after the final evaluation for 246 of the 528 cases (46.6%: kappa=0.325 [0.254-0.396]); a concordant result was found between the allergist in the primary evaluation and the different allergist in the final evaluation for 282 of the 528 finally evaluated cases (53.41%: kappa=0.413 [0.343-0.482]).

DISCUSSION

We assessed all patients attending the ED over a two-year period using a keyword based screening evaluation, resulting in 2000 patients that presented a possible allergic pathology. After removing patients that were clearly not allergic, could not be contacted or chose not to participate further, we ended up with 528 patients who completed the allergological work-up. These were mainly diagnosed with idiopathic urticaria (40.9%), HDR (22.0%), food allergy (16.3%) or dermatological pathologies (10.2%).

The majority of initial 2000 participants were not assessed; in fact, only 26.4% of 2000 initial participants completed the study. This relatively low rate of completion limits the power of the study, including the identification of statistical difference in characteristics such as allergen type. As well as the 199 patients who were clearly not allergic and thus discarded at the primary evaluation, other patients did not complete the study due to problems in obtaining and maintaing contact, as well as reasons such as lack of interest, work-commitments, and prohibitive distance.

We compared demographical and clinical information between patients who were not studied and those who finally underwent allergological evaluation, finding that female gender participants were more prone to be investigated. This is a well-documented phenomenon for various medical conditions [22-23. Interestingly, many of the patients diagnosed with anaphylaxis in the allergological work-up were diagnosed with urticarial/angioedema in the ED. It may be the case that patients who themselves suspect a more severe reaction being more likely to attend their allergological evaluation. On the other hand, a more mild allergic presentation may discourage the completion of the study, for example, the patients who did not complete the full assessment showed a much higher percentage of dermatological disease than those who underwent the allergological work-up (Table II). Similarly, HDR sufferers, especially

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those reacting to NSAIDs and β-Lactams, were more likely to undergo the final allergological work-up. This phenomenon could be explained by the lack of knowledge regarding these prevalent drug allergies in our population, or perhaps the lack of alternative medicines means patients are more keen to attend their appointments. This is an important point, as for many drugs such as β-Lactams resistance and cost of alternatives is a big issue [24].

Nonetheless, when considering the prevalence of NSAID and β-Lactam allergy in evaluated patients, results were similar to other studies [25]. More studies are necessary in other EDs in different geographical locations in order to extrapolate these findings to the general population.

Furthermore, anaphylaxis was identified in 20.8% of the 528 participants who completed the allergological work-up, diagnosed through analysis of their clinical history based on the EAACI guideline criteria [26]. Food allergy and HDR represented 43.6% and 41.8% respectively of all anaphylaxis cases. The prevalence of food anaphylaxis found here agrees with other studies, ranging from 31.0% to 51% [27-28]. However, the prevalence of drug-induced anaphylaxis appears to be slightly higher in our population, possibly due to higher drug consumption or demographical differences. The most frequent culprits found here were NSAIDs, in agreement with other studies [29-30].

Of the 528 patients finally evaluated in the allergological work-up, 110 were confirmed as suffering anaphylaxis. However, the term anaphylaxis was used in only 3.8% of ED electronic medical records. This tie in with the finding that only 18.1% of the 110 confirmed anaphylaxis sufferers were treated with epinephrine according to guidelines whilst in the ED. Moreover, less of half of these patients were discharged with a prescription for self-injectable epinephrine. In fact, various studies have shown that

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erroneous identification of anaphylaxis is a real issue in ED, and that around 57% of cases may be misdiagnosed and up to 80% undertreated [31-33]. Given that, timely administration of epinephrine is essential for the effective treatment of anaphylaxis and that such treatment is dependent on the correct identification of cases, better training of ED physicians and better collaboration with AD will ensure prompt recognition and better management [10].

Analysis of the agreement in diagnosis between the final allergological evaluation and the primary and the initial ED physician evaluations, showed a moderate and fair correlation respectively, with concordance values of 53.4% and 46.6%. Since primary evaluation depends on data available in electronic medical records, this is likely to explain the discrepancy between the primary and final evaluations, despite both being performed by certified allergists. Interestingly, the trigger was not identified during the ED visit for 19.8% of patients who underwent the allergological workup, however the complexity of identifying the trigger of an acute allergy reaction is well known [34] and this finding should not necessarily be considered a deficiency of the ED.

After the final evaluation, only 69.72% of patients initially diagnosed with drug allergy and 76.24% of those diagnosed with food allergy in ED were confirmed as not allergic. This represents an important percentage of patients being over-diagnosed, leading to them unnecessarily avoiding certain drugs and foods.

In summary, these results highlight the importance of educating primary care physicians about the clinical presentations of allergy, particularly with regards to anaphylaxis and its adequate treatment with epinephrine, and of the subsequent thorough assessment of food allergy and HDR by a trained allergist for the correct identification of triggers.

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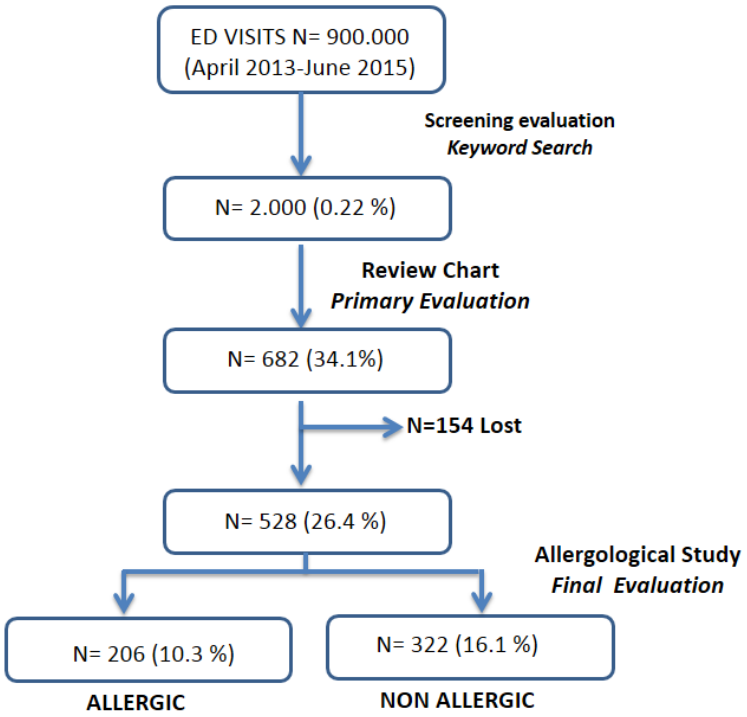
LEGEND OF FIGURE

Figure 1. Flow Chart



LEGEND OF THE TABLES

Table I. Search results using screening keywords during the primary evaluation.

Keywords	N (%)
Allergic reaction	992 (49.6)
Urticaria	496 (24.8)
Cutaneous eruption	156 (7.8)
Infection	78 (3.9)
Dermatitis	44 (2.2)
Exanthema	44 (2.2)
Anaphylaxis	40 (2.2)
Reaction	34 (1.7)
Angioedema	32 (1.6)
Adverse event	24 (1.2)
Insect sting	14 (0.7)
Erythema	12 (0.6)
Pruritus	10 (0.5)
Drug intolerance	8 (0.4)
Asthma	6 (0.3)
Food intoxication	6 (0.3)
Anaphylactic shock	4 (0.2)

Table 2. Demographic characteristics and previous allergic reported of patients selected

Characteristics	n	%
Participants (N)	2000	
Age (mean)	39.2 (38.2-40.1)	
Women (N, %)	1196	59.8
Allergy history	**672**	**33.6**
Aeroallergens	**302**	**15.1**
Pollen	166	54.9
Dust mite	124	41.1
Pet dander	62	20.5
Mold	8	2.6
Unidentified	86	28.5
Food	***126***	***6.3***
Fish	10	7.9
Crustacean	26	20.6
Mollusc	28	22.2
Tree nuts	48	38.1
Fruits and vegetables	70	55.5
Legumes	2	1.58
Milk	4	3.2
Egg	2	1.6
Cereal and soya	6	4.7
Other	4	3.1
Drugs	***340***	***17***
β-Lactam	122	35.8
Quinolone	14	4.1
Macrolide	10	2.9
Sulfamide	24	7.1
Other antibiotics	14	4.1
NSAID	140	41.2
Radiocontrast media	18	5.29
Other drugs	72	21.2

Table 3. Comparison of primary evaluation results between studied and unstudied patients

Characteristics	Not studied (n)	(%- DS)	Selected (n)	(%-DS)	P
Participants	1472	73.5	528	26.4	
Age (mean)	39	(38.1-44.3)	39.5	(39-45)	0.721
Female	844	57.3	352	66.7	**0,008**
Asthma history	144	9.8	72	13.6	0.105
Allergy history	**426**	**28.9**	**246**	**46.6**	**<0.0001**
Aerollergens	**172**	**11.7**	**130**	**24.6**	**<0.0001**
Food	76	5.2	50	9.5	**0.018**
Drug	240	16.3	100	18.9	0.340
Other	18	1.2	*12*	2.3	0.242
Presumptive diagnosis					
HDR	**388**	**26.4**	**218**	**41.3**	**<0.0001**
Food allergy	362	24.6	138	26.1	0.62
Food and drug allergy	38	2.6	18	3.4	0.515
Other allergy	124	8.4	30	5.7	0.179
Dermatology	252	17.1	22	4.2	**<0.0001**
Idiopathic urticaria	240	16.3	96	18.2	0.502
Clinical presentation					
Anaphylaxis	112	7.6	66	12.5	**0.023**
Dermatitis	114	7.7	14	2.7	**0.003**
Erythema	96	6.5	30	5.7	0.768
Exanthema	154	10.5	46	8.7	0.474
Pruritus	28	1.9	8	1.5	0.794
Undefined rash	110	7.5	24	4.5	0.115
Airway symptoms	76	5.2	36	6.8	0.349
Urticaria/angioedema	658	44.7	144	54.5	**0.006**
Vesicles	36	2.4	4	0.8	0.12
Undefined	26	1.8	*6*	1.1	0.581
Suspected triggers					
Drug					
β-Lactam	*126*	8.6	72	14.4	**0.009**
Quinolone	*32*	2.2	14	2.7	0.637
Macrolide	*14*	1.0	6	1.1	0.729
Sulfamid	*6*	0.4	2	0.4	1
Other antibiotics	*42*	2.9	18	3.4	0.675
NSAID	*224*	15.2	138	26.1	**<0.0001**
Radiocontrast media	2	0.1	8	1.5	**0.019**
Food					
Fish	100	6.8	36	6.8	1
Crustacean	64	4.3	30	5.7	0.398
Mollusk	54	3.7	14	2.7	0.554
Tree nut	32	2.2	18	3.4	0.26
Fruit and vegetable	132	9.0	60	11.4	0.273
Legume	12	0.8	2	0.4	0.683
Milk	22	1.5%	8	1.5%	1
Egg	40	2.7%	14	2.7%	1
Cereal and soya	46	3.1%	24	4.5%	0.328
Other food	28	1.9%	16	3.0%	0.327
No food or drug	176	12.0%	22	4.2%	**0.0002**

Table IV. Differences between the primary and final evaluation by a trained allergist among 86 food allergic participants

	Primary evaluation	*Final evaluation*	*P*
Diagnosis N (%)			
Food allergy	62 (72.2)	84 (97.7)	**0.002**
Food and drug allergy	12 (14)	2 (2.3)	0.109
Other allergy	6 (7)	0	0.241
Dermatology	2 (2.3)	0	1
Idiopathic urticaria	4 (4.7)	0	0.494
Clinical presentation			
Anaphylaxis	26 (30.2)	48 (55.8)	**0.023**
Erythema	6 (7)	2 (2.3)	0.616
Undefined rash	4 (4.7)	0	0.494
Upper or lower airways symptoms	16 (18.6)	18 (20.9)	1
Urticaria and/or angioedema	32 (37.2)	18 (20.9)	0.152
Undefined	2 (2.3)	0	1
Triggers			
Fish	8 (9.3)	0	0.116
Crustacean	20 (23.3)	26 (30.2)	0.625
Mollusk	8 (9.3)	6 (7)	1
Tree nut	10 (11.6)	18 (20.9)	0.381
Fruit and vegetables	34 (39.5)	46 (53.5)	**0.076**
Legume	0	6 (7)	0.241
Milk	6 (7)	2 (2.3)	0.616
Egg	6 (7)	0	0.241
Cereal and soya	16 (18.6)	0	**0.005**
Meat	10 (11.6)	0	0.055
Anisakis	0	4 (4.6)	0.056
Other Food	6 (7)	2 (2.3)	0.616
Drug	14 (16.3)	2 (2.3)	0.057
Other	2 (2.3)	0	1

Table 5. Differences between the primary and final evaluation by a trained allergist among 116 drug allergic participants.

	Primary evaluation	*Final Evaluation*	*P*
Diagnosis N (%)			
HDR	106(93)	116 (98.3)	0.206
Food allergy	2 (1.8)	0	1
Food and drug allergy	6 (5.3)	2 (1.7)	0.618
Other allergy	2 (1.8)	0	1
Dermatology	0	0	1
Idiopathic urticaria	0	0	1
Other	0	0	1
Clinical presentation			
Anaphylaxis	26 (22.8)	46	0.070
Erythema	10 (8.8)	2 (1.7)	0.206
Pruritus	2 (1.8)	2 (1.7)	1
Undefined rash	10 (8.8)	2 (1.7)	0.206
Upper or lower airways symptoms	4 (3.5)	2 (1.7)	1
Urticaria and/or angioedema	50 (43.9)	44 (37.9)	0.706
Exanthema	14 (12.3)	18 (15.5)	0.787
Undefined	0	0	1
Mechanism identified			
Immediate reaction	94 (82.5)	94 (81)	1
Non-immediate reaction	20 (17.5)	22 (19)	1
Undefined	2 (1.8)	0	1
Number of drug triggers			
One	100 (87.7)	114 (98.3)	**0.032**
Two	10 (8.8)	2 (1.7)	0.206
Three and more	4 (3.5)	0	0.496
Not identified	2 (1.8)	0	1
Triggers			
β-Lactam	28 (24.6)	26 (22.4)	1
Quinolone	6 (5.3)	6 (5.2)	1
Macrolide	0	0	1
Sulfamid	0	0	1
Other antibiotics	4 (3.5)	0	0.496
NSAID	72 (63.2)	72 (62.1)	1
Raciocontrast media	6 (5.3)	6 (5.2)	1
Other drug	12 (10.5)	6 (5.2)	0.49
Food	8 (7)	2 (1.7)	0.364
No food or drug	0	0	1

Supplementary tables:

Table I: Cause of anaphylaxis reaction.

Table II: Treatment by primary care physician