Anaphylaxis: a decade of a nationwide allergy society registry

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Abstract

Background: Anaphylaxis is an acute, life-threatening, multi-organ hypersensitivity reaction.

Objective: The aim of this study was to identify the causes of anaphylaxis in Portugal, contributing to a better knowledge of the anaphylaxis epidemiology and management.

Methods: During a 10-year period a nationwide notification system for anaphylaxis was implemented, with voluntary reporting by allergists. Data on 1783 patients with anaphylaxis were included. Detailed characterization of etiopathogenesis, manifestations and clinical management was obtainedfrom pediatric and adult ages.

Results: The mean age was 32.7±20.3 years, 30% under 18 years of age; 58% were female. The mean age at the first anaphylaxis episode was 27.5±20.4 years (ranging from 1-month-old to 88years). The main culprits of anaphylaxis were foods (48%), drugs (37%) (main trigger in adults, 48%) and hymenoptera-venoms (7%). The main culprit foods were shellfish (27%), fresh fruits (17%), cow's milk (16%), treenuts (15%), fish (8%), egg (7%) and peanut (7%). The main drugs were nonsteroidal anti-inflammatory drugs(43%), antibiotics (39%) and anaesthetic agents (6%). Other causes were exercise (3%), latex (2%), cold-induced (2%) and idiopathic anaphylaxis (2%). Most patients (80%) were admitted to the emergency department; only 43% received adrenaline treatment. Recurrence of anaphylaxis occurred in 41% of patients (21% with ≥3 anaphylactic episodes); 7% used an adrenaline autoinjector device.

Conclusions: Food has been the leading cause of anaphylaxis in Portugal, while drugs were the main elicitors in adults. We highlight the undertreatment with adrenaline and recurrent episodes, pointing for the need to improve diagnostic and therapeutic approaches of anaphylaxis.

Keywords: Adrenaline. Anaphylaxis. Drug allergy. Epidemiology. Epinephrine. Food allergy. Nationwide registry.

Resumen

Antecedentes: La anafilaxia es una reacción de hipersensibilidad sistémica potencialmente mortal.

Objetivo: El objetivo de este estudio fue el identificar las causas de la anafilaxia en Portugal para mejorar el conocimiento de la epidemiología y del manejo de la enfermedad.

Métodos: Durante un período de 10 años, se implementó un sistema nacional de notificación de anafilaxia, por parte de los alergólogos, mediante la emisión de informes voluntarios. Se recogieron datos de 1.783 pacientes con anafilaxia, pediátricos y adultos, relativos a la etiopatogenia, las manifestaciones clínicas y el manejo clínico de la misma.

Resultados: La edad media fue de 32,7 ± 20,3 años, siendo el 30% de los pacientes menores de 18 años. El 58% fueron mujeres. La edad media del primer episodio de anafilaxia fue de 27,5 ± 20,4 años (desde 1 mes hasta 88 años). Los principales agentes responsables de anafilaxia fueron los alimentos (48%), los medicamentos (37%), que fue el principal desencadenante en los pacientes adultos, y los venenos de himenópteros (7%). Los principales alimentos responsables fueron: mariscos (27%), frutas frescas (17%), leche de vaca (16%), nueces (15%), pescado (8%), huevo (7%) y cacahuete (7%). Los principales fármacos, fueron los antiinflamatorios no esteroideos (43%), antibióticos (39%) y anestésicos (6%). Entre otras causas implicadas se incluyó: ejercicio físico (3%), látex (2%), frío (2%) e idiopática (2%). La mayoría de los pacientes fueron atendidos en el servicio de urgencias (80%), y solo el 43% recibió tratamiento con adrenalina. La recurrencia de la anafilaxia ocurrió en el 41% de los pacientes (21% con ≥3 episodios anafilácticos). El 7% utilizó un dispositivo autoinyector de adrenalina.

Conclusiones: Los alimentos son la principal causa de anafilaxia en Portugal y en el subgrupo de pacientes adultos, lo son los medicamentos. Se constata la infrautilización del tratamiento con adrenalina y la elevada recurrencia de los episodios. Se pone de manifiesto la necesidad de mejorar los enfoques diagnósticos y terapéuticos de la anafilaxia.

Palabras clave: Adrenalina. Anafilaxia. Alergia A Medicamentos. Epidemiología. Epinefrina. Alergia Alimentaria. Registro Nacional.

Background

Anaphylaxis isa clinical emergency, as it is a severe and life-threatening systemic hypersensitivity reaction [1].The diagnostic criteria were reviewed and published in 2006, allowing standardization of the anaphylaxis definition [2]. These clinical criteria were subsequently adopted by the European Academy of Allergy and Clinical Immunology (EAACI) [3] and the World Allergy Organization (WAO)[1,4].

Prevalence of lifetime anaphylaxis ranges from 0.05to2% of the general population[5,6].A review of European studies points to an estimated prevalence of 0.3%, meaningthat 1 out of 300 subjects have anepisode of anaphylaxis in their lifetime[7].Foods, drugs and hymenoptera-venoms were the most commonly identified triggers[1,4,6-9]. In populationstudies, the incidence rate of anaphylaxis was estimated between 8.4 to 50-103per 100,000 person-years[5,6,10,11],with a mortality rateup to1 to 3 per million person-years[6,9], accounting for 0.3 to 2% of all cases of anaphylaxis[6].

There has been an increase in anaphylaxis prevalence over time, especially in children [6,7,9,12,13]andparticularly in preschoolers [6,7,9,11]. Foodis the most common elicitor of anaphylaxis in children [7,12-16]. Drugs are the main triggersinadult age, particularly in the elderly [9,12,13,17]. There are geographical factors influencing the incidence of anaphylaxis to the different foods and drugs, that are related to diet habits and prescription patterns, respectively [1,4,8,13].

In Portugal, the prevalence and incidence rates of anaphylaxis in the general populationare unknown. At national level, only case-series data of outpatient care and hospitalizations are available. In a study conducted in 2006, an anaphylaxis prevalence of 1.3% was reportedin a specialized allergy outpatient center in Lisbon [18].In a subsequent evaluationcarried out in 2011, in the same city and with the same methodology,anaphylaxis prevalence raised to 1.8%[15].The real population prevalence isunknown, due to the lack of a widely implementednational registry of anaphylaxis;however,the perception of an increasing number of cases observed in the last years is commonly reported.

Aims

The aims of this studywere to describe the elicitors of anaphylaxis in Portugal, and to contribute to a better knowledge of anaphylaxis epidemiology and management, basedon theproactive reporting by allergistsof cases of anaphylaxis identified in their allergy consultations in a nationwide notification system.

Methods

During a 10-year period (2007-2017) a nationwide notification system for anaphylaxis has been implemented by the Portuguese Society of Allergology and Clinical Immunology (SPAIC).

Anaphylaxis was diagnosed according to the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria[2], in the presence of at least one of three clinical criteria,consistent with the EAACI and WAOconsensus. Thedefinition of anaphylaxiswas included in the form in order to ensure that all the reporters used the same definition.

All allergists' members of SPAIC were invited to participate in this registry, and were asked to voluntarily report all cases of anaphylaxis identified in their allergy referral centers, by completing the questionnaire designed by SPAIC. All patients observed in

the allergy consultations with an history of "at least 1 episode of severe systemic reaction" and the diagnosis of anaphylaxis confirmed by an allergist were included in the study.

Data collection

Thestructured questionnaire,previously published[17], was designed and validated by SPAIC Anaphylaxis Interest Group, with a paper and online version available at SPAIC's website. The reporting formcould be returned by letter, fax,e-mail or online(anonymous individual patient data).All notifications received were evaluated and validated by the SPAIC Anaphylaxis Interest Group and, when necessary, clarificationsof data were requested to the notifiers.

The following parameters were assessed in the questionnaire: demographic data, including age, gender and residence area; personal history of asthma and other allergic diseases; characterization of the known (confirmed or highly suspected)culprit agent; first anaphylaxis episode´s date and detailed description of clinical manifestations; number of anaphylaxis episodes and implicated agents; emergency treatment received, information on adrenaline use, emergency department (ED) visits and hospital admissions; and prescription and use of adrenaline autoinjector device (AAI).

Population

We included1783 patients with history of anaphylaxis, reported by 82 allergists from all mainland regions (Northern, Centre and Southern) and from Azores and Madeira islands.The allergy workup carried out on these patients in order to identify the culprit agent was performed by the reporting allergists in their allergy centers. Detailed characterization of etiology, manifestations and clinical management was obtained.

Statistical analysis

Categorial variablesare presented as frequencies and percentages for the total number of validated responses. Continuous variables with normal distribution are expressed as mean±standard deviation and those not normally distributed as median (minimum-maximum). The chi-square test and odds-ratio (OR) with 95% confidence interval (CI)were used to test association between qualitative variables, considering significant a p-value<0.05 (IBM® SPSS® *Statistics version* 23).

Results

We analyzed 1783 case-reports of patients with anaphylaxis (Table 1), agedfrom 3 months-old to 90 years; 30% were under 18 years. The female-male ratio was 1.4:1.0; male gender predominated in children (1.0:1.6), while in adults female were predominant (1.9:1.0).

The age at the first anaphylaxis episode ranged from 1 month, in an infant with cow's milk (CM) anaphylaxis, to 88 years, in an elderly with acetylsalicylic acid (ASA) induced anaphylaxis. The first anaphylaxisepisode occurred under the age of 18 years in 37%,and in 20% at preschool age.

Personal history of allergic comorbidities is detailed in Table 1. One-third of the patients have asthma and one man hadsystemic mastocytosis.

Clinical manifestations

Clinical manifestationsare detailed in Figure 1. Mucocutaneous symptoms were present in 96% of patients, of which 78% had respiratory symptoms.The proportion of respiratory symptoms was higher in those with asthma (90% *vs.* 78% without asthma, OR=2.6, CI=1.9-3.6). Cardiovascular manifestations, laryngeal oedema or loss of consciousness were present in 57%. The diagnosis of asthma was not a risk factor for the occurrence of these symptoms.Cardiovascular symptoms, laryngeal oedema and loss of consciousness were more frequents in adults, OR=2.5 (IC=2.0-3.1), OR=1.6 (IC=1.3-2.0) and OR=2.2 (IC=1.6-2.9). Gastrointestinal symptoms were more frequentat pediatric age (43% *vs.* 21% in adults, OR=2.9, CI=2.3-3.6), being higher (51%) in preschoolers.

Emergency care

A visit to the ED was required in 1426 patients(80%), and hospitalization was required in 20% of patients.There were no fatalities reported by the allergists.Regardingtreatment, only 43% of the patients received adrenaline.The diagnosis of asthma was not a risk factor for ED visit neither foradrenaline administration.

Prescription and use ofadrenaline autoinjector

AAIs were prescribed in 1049 patients (59%) in ambulatory care setting; prescription was significantly lower in cases of drug-inducedanaphylaxis (DIA), compared to anaphylaxis of other causes(11% *vs.*87%, $p<0.01$).

Recurrence of anaphylaxis (>1 episodes of anaphylaxis, most frequently to the same or cross-reactive triggers) was observed in728patients (41%): 2 episodesin 360 (20%), 3 episodesin 173 (10%), 4 episodes in 93 (5%) and ≥5 episodes in 102 patients (6%). AAI was used, in these subsequent reactions, in 119 patients (7%).The use of AAI was more common in patients with asthma (10% *vs.* 6% without asthma, OR=1.7,CI=1.2-2.5).

Etiology

The relative frequency of the known elicitors of anaphylaxis per age group is shown in Table 2, also including the description of patients within different culprits in relation to the age at the report, gender predominance and asthma comorbidity. Thirtyseven patients had more than one known elicitor of anaphylaxis, accounting for a total of1819reports of distinct causes involved.

The main cause, observed in 48% of patients, was food-induced anaphylaxis (FIA). DIA ranks in second (37%), and insect-sting anaphylaxis was the third cause (7%). Other causes were exercise-induced anaphylaxis (3%), latex (2%), cold-induced (2%) and idiopathic anaphylaxis (2%). In seven patients, other specific causes were identified, such as subcutaneous allergen-specific immunotherapy (mite immunotherapy in 2 children, pollen immunotherapy in one woman and maintenance bee-venom immunotherapy in one man), inhalation of animal allergens, such as horse dander, in two patients, and contamination of raw fish with *Anisakis* in one woman.

Foods implicated in FIA are presented in Table 3, which shows their relative distribution in children and adults. Shellfish (crustaceans and/or mollusks) was the firstcause of FIA(27%), and occurred most commonly in adults. Crustaceans (especially shrimp) were the main triggers; regarding mollusks, emphasis should be made on the geographical particularity of limpet anaphylaxis, which has been mainly reported in MadeiraIsland. Fresh fruits were the second cause(17%) of FIA, especially*Rosacea* family fruits(peach, in particular) and kiwi. In manyreported cases of anaphylaxis to *Rosacea* fruits, notifiers have identified sensitization to lipid transfer proteins(LTP).CM

was the third cause of FIA, being, however, the leading cause (32%) in children. Other foods were treenuts (TNs), fish, egg, peanut, seeds andcereals, among others. In relation to rarer causes, we emphasize three cases of red meat anaphylaxis with confirmed galactose-alpha-1,3-galactose (alpha-gal) sensitization, and seven cases of oral mite anaphylaxis ("pancake syndrome") reported in Azores Islands.The foods implicated in FIA according to the age at the first anaphylaxis episode are specified in Figure 2, which shows their relative distribution from infancy to adult age.

Drugs implicated in DIAare presented in Table4, which shows their relative distribution by age groups. The main culprits werethe nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics and anaesthetic agents. Other drugs wereantineoplastic agents, proton-pump inhibitors, corticosteroidsand radiocontrast media (RCM), among others.NSAIDs were the main triggers of DIA (43%), especially preferential cyclooxygenase-1 inhibitors. We noted paracetamol asthe culprit in 12 patients. Antibioticswere the second cause of DIA (39%), especially beta-lactam antibiotics, main lyamoxicillin, which was the culprit in 49% of these cases, compared to 9% for penicillin. Cephalosporins were the second cause of antibiotic-induced anaphylaxis (20%), especially cefazolin, implicated in 27 adults. One patient developed Kounis syndrome after cefazolin infusion.Among the nonbeta-lactam antibiotics, quinolones were the main implicated, being the elicitor in 19 adults. Anaesthetics-induced anaphylaxis was reported in 40 adults.General anaesthetics were implicated in 33 patients, especially neuromuscular-blocking agents (elicitors in 66% of intraoperative anaphylaxis); local anesthetics were the culprits in 7 patients.

Insect-stinganaphylaxis occurred in 132 patients. All cases were associated tohymenopterasting, except for one child related to mosquito sting. The *Hymenoptera*implicated were *Apismellifera*(71%), *Vespula*(23%) and *Polistes* (9%).

Exercise-induced anaphylaxis was reported in 45 patients.Food-dependent exercise-induced anaphylaxis (FDEIA) occurred in 44 patients. Foods implicated were: cereals (n=14, especially wheat), TNs (n=10), *Rosacea* fruits (n=8, especially apple), peanut (n=3), CM, grape, legumes andpoultry meat (n=2), sesame seed (n=1) and other vegetables (n=4).

Latex-induced anaphylaxis occurred in 41patients.Five cases were intraoperative anaphylaxis. Latex-fruit syndrome was the cause in 51% (20 adults and one adolescent).Fruits and other vegetables implicated were: chestnut (n=15), banana (n=7), passion fruit (n=6), kiwi and peach (n=3), avocado, fig, manioc, mango, melon, spinach and tomato (n=2), papaya, pineapple, sweet pepper and sweet potato (n=1).We noticeda trend during these 10-years forlatex-induced anaphylaxis: almost all cases have been reported during the first five years of the study, with only one case reported in the last five years, reflecting a trend to a decrease in latex allergy.

Discussion

Covering a whole decade, this is the first nationwide registry of anaphylaxis in Portugal, whichconfirms food allergy as the leading cause of anaphylaxis, accounting for three-quarter ofcasesat pediatric age. Other causes identified were drugs, the major elicitor of anaphylaxis in adults, in particular NSAIDs and beta-lactam antibiotics, hymenoptera-venoms, exercise (almost all cases FDEIA), latex and cold-induced anaphylaxis.The report was limited to allergists, and all used the same anaphylaxis diagnostic criteria, allowing nationally validated methodology which assured the quality of presented data.

This study shows that anaphylaxisoccurs across all age groups. As observed in other case-series,a predominance of anaphylaxis was found in female gender in adults, whereas in children there was a male predominance[5,13,15,16,19,20].It has been suggested that endocrine factors might be involved in the pathogenesis of this disease, as with other immune-based diseases[5,19].

Food allergywas the main elicitor of anaphylaxis, as it has been described in several case-series, especially when children are included [8,11,13,15,16,20-23].Shellfish and CM were the main culprits, in adults and in children, respectively. CM was the leading cause in children, as reported by others [6,15,16,18,21],especially in the first years of life[6,15].These findingsdiverge from those of other authors[8,14,23-25],underlining the importance of having a detailed knowledge of each country's reality.The observed frequency has variations, based on the studied age group, the geographical region and the associated food habits [6,13,14,24,26].Other main foods in this study were fresh fruits and TNs. FIAhas important quality of life repercussions, as contact with food allergens, even in minimal amounts, ashidden allergens or cross-reacting allergens, may be life-threatening. Labeling and education of patients and caregivers areessential for allergen avoidance [4,23].

TNs-induced anaphylaxis has been increasingly reportedworldwide, in particular in preschoolers[14,23,24,26].In this case-series, TNswere an importantcause of FIA,being the second cause inchildren; walnut and cashewwere the most commonreportedTNs. These results diverge from other European studies,where hazelnut was the most frequent TN[8,24].In a case-series reported from a single center in our country, in Coimbra, TNs were the main cause of FIA in adults, especially walnut and hazelnut[27].By contrast, in arecent study also conducted in our country, involving preschoolers, cashew and walnut were the commonestTNs[26].

LTPsare a common cause of FIA in the Mediterranean area[9,28-30],and have been pointed out as the main elicitor of FDEIA[28,30,31].Food management in these patients is challenging [30-32],due to the presence of these panallergens in a great number of plant foods,like fresh fruits, vegetables, TNs and seeds.In studies conducted in Italy[28] and Spain[32], LTPs are reported as the main cause of FIA in adults, especially peach. In this registry, peach is also of particular relevance. In a recent study carried out in our country[30],including both children and adults, LTPswerethe third cause of FIA, only preceded by shellfishand CM. In the specific approach to FDEIA, avoidance of the implicated foods for at least 4 hours before exerciseis essential [30,31] and sports should be practiced with a partner capable of administering AAI.

DIAwas theleadingcause of anaphylaxis in adults, with NSAIDs predominating over antibiotics, as it has been also reported in studies conducted in Spain[11,33].In this study, a low proportion of DIA was noticed in children, asdescribed by others[8,13,34].NSAIDs were the main cause of DIA, as found in other case-series of nonhospitalized patients[33,35,36];however, in several studies,antibiotics are the first cause of DIA [10,25,34,37,38],and a high risk of penicillin anaphylaxis is estimated in the general population(0.7 to10%)[38].Among NSAIDs, preferential cyclooxygenase-1 inhibitors were the main implicated, especially ASA, ibuprofen, diclofenac

andmetamizole, as found in other case-series [8,17,35,36].Anaphylaxisto selective cyclooxygenase-2 inhibitors NSAIDswas rare, reinforcing these as alternative drugs [17,35,36].

Among antibiotics, beta-lactams were the major elicitors[8,17,25,29,36,38],mainly to amoxicillin, including the combination amoxicillin-clavulanic acid, and cephalosporins,in detriment of benzylpenicillins, as observed in other case-series[11,12,29,36,39,40].This can be explained by changes in the prescription pattern ofbeta-lactams in Europe.Anaphylaxis to cefazolin, especially inperioperative anaphylaxis, was of particular relevance.

Anaphylaxis to RCM occurred in 1.2% of our patients, percentage similar to that observed by others [11,25,38].Severe reactions attributed to RCM have been decreasing due to the fact that, currently, high osmolality ionic formulations are no longer used[38].

In this registry, anaphylaxis during allergen-specific immunotherapy was a rare event, lower than in other case-series [8,16,22,37], confirming the current safety of this treatment [41,42].

Idiopathic anaphylaxis may account for up to 20% of all cases of anaphylaxis [1,23,43];however, this diagnosis of exclusion was rare (2%) in our registry. This can be explained by the fact that case reporting was limited to allergists. In fact, the etiological study of anaphylaxis should always be detailed, and therefore it is extremely important the referral of all anaphylaxis cases to allergy specialists[33,43]. Nevertheless, this might also be relatedto a reporting bias associated to an underreporting when the trigger was unknown.

Our study has a series of limitations, besides the bias related to the voluntarily report, and expected underreporting. One limitation of this study, is the fact that the cases of anaphylaxis included are only the ones that were followed at the allergy centers and not the global cases that were observed at EDs. Other limitation of this study is that reactions were not categorized according to the degree of severity. Moreover, other limitations also related to the severity evaluation, are the fact that the serum tryptase levels were not included in the questionnaire, nor the concurrent medications such as beta-blockers and angiotensin-converting enzyme inhibitors, which are known to increase the severity of anaphylaxis [1,23,44].

Gastrointestinal symptoms, although present across all age groups, were more common in children, especially in preschoolers, as described by others [16,45]. This finding reinforces the importance of including gastrointestinal symptoms in the diagnostic criteria of anaphylaxis [2], especially at younger age. Our findings also reinforce that the lack of cutaneous symptoms, as observed in 4% of patients, does not exclude the diagnosis of anaphylaxis.

Several studies suggest that asthma diagnosis is a risk factor for severity of anaphylaxis [1,3,5,10,46].Although, as stated, one of the limitations of this studywas the absence of a classification of the degree of severity, patients with asthma did not show a higher frequency of more severe symptoms, such as laryngeal oedema, cardiovascular symptoms or loss of consciousness, and no differences were observed in terms of ED visits or adrenaline administration.

In 80% of the reported cases patients were admittedtothe ED, and 20% required hospitalization. Anaphylaxis is a medical emergency requiring immediate treatment, and intramuscular adrenaline is the first-line drug treatment[1,3,4,23,47,48].However, although recommended by all guidelines, it continues to be underused at the ED. Less than half of our patients received adrenaline treatment, asreported by others[8,16,20,22,25,33,49].Therefore, improving medical education concerning anaphylaxis management in the EDis crucial.

The prescription of AAI also fell short of the expectations. We understand that not all patients with anaphylaxis need to have an AAI, namely some patients with DIA. Nevertheless, there are absolute indications for prescription of AAI according to EAACI and WAO guidelines [4,23] including previous anaphylaxis triggered by food, latex, or aeroallergens such as animals or other unavoidable triggers, as well as exercise-induced anaphylaxis or idiopathic anaphylaxis. Regarding food allergy, which is the leading culprit in this registry, some patients should carry an AAI namely if concomitant unstable asthma, or previous reaction to only traces of food, specially hidden allergens like TNs, peanut, CM or egg[4,23,50].

AAIunderprescriptionbyphysiciansforanaphylaxistreatmentiswellknownworldwide[8,20,25,33,48,49].AAI should be prescribed,due to the risk of recurrences,and education on when and how to use the device should be provided[23,48], training with placebo devices, insisting on AAI efficacy and safety. In the present registry, recurrence of anaphylaxisoccurred in 41% of the patients, and 21% experienced three or more episodes of anaphylaxis.Previous publications regarding recurrence of anaphylaxis found similar results, with a cumulative incidence ranging from 26.5 to 54%[6,15,16,22].Underutilization of AAI by patients and caregivers is also known [8,16,49,50]. It should be noted that in our registry 7% of patients had successfully used AAI. A similar result was found in a recent study conducted in Spain [50], as well as in the European anaphylaxis registry[8,16,49], showing that anaphylaxis in the community remains undertreated.

As anaphylaxis is an unpredictable and life-threatening reaction, prevention is fundamental.Early recognition of anaphylaxis signs, correct use of AAI, early intramuscular adrenaline at the ED,and urgent referral to an allergy specialistshould bepromoted. The allergy workup and follow-upis essential to investigate triggers, to perform a comprehensive risk assessement and to prevent recurrence by developing personalized risk reduction strategies[23,33,43]. The key role of the allergy specialist is essential for the adoption of preventive measures (allergen avoidance, written emergency action plan, proposal of food and drug alternatives), as well as the implementation of allergen-specific immunotherapy (hymenoptera, latex, food) or specific desensitization (specific foods and drugs).

Conclusions

This nationalregistry allowed us to obtaina detailed characterization (made by allergists) of patients with anaphylaxis, in whom the main elicitors were foods, drugs and hymenoptera-venoms.

We highlight thebroad age spectrum, the different gender distribution in childrenand adults, the relevance of food allergens in both age groups and drugs in adults, the frequent association to asthma comorbidity, the high frequency of anaphylaxis recurrence, and the underuse of adrenalineat the ED.

Nationwide anaphylaxis registries are usefull toolsfor the improvementof epidemiological knowledge and to outline local strategies for the prevention and management of anaphylaxis.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Table 1. Description of the 1783 reported patients in relation to age at the notification, age at the first anaphylaxis episode, and personal history of allergic comorbidities

Age at report, mean±SD	32.7±20.3 years
<12 years-old, n (%)	367 (21%)
12 to 17 years-old, n (%)	166 (9%)
18 to 64 years-old, n (%)	1142 (64%)
≥65 years-old, n (%)	108 (6%)
Age at the first anaphylaxis episode, mean ± SD	27.5±20.4 years
<12 years-old, n (%)	523 (29%)
12 to 17 years-old, n (%)	140 (8%)
18 to 64 years-old, n (%)	1049 (59%)
≥65 years-old, n (%)	71 (4%)
Comorbidities, n (%)	1220 (68%)
Allergic rhinitis, n (%)	1026 (58%)
Asthma, n (%)	585 (33%)
Atopic eczema, n (%)	197 (11%)
Allergicconjuntivitis, n (%)	146 (8%)
Other*, n (%)	7 (<1%)

SD: standard deviation; %: valid percent
* Other immunoallergicconcomitant diseases include five patients (3 adults and 2 children) with eosinophilic esophagitis, one man with systemic mastocytosis and one woman with hereditary angioedema.

Table 2. Elicitors of anaphylaxis in the 1783 patients, and their distribution (n, % within age group) in children and adolescents (aged <18 years-old) and in adults (aged ≥18-years old). Description in relation to age at the report, gender predominance and asthma comorbidity is characterized within different elicitors of anaphylaxis.

Etiology of anaphylaxis	**Age,mean±SD Gender (%) Asthma (%)**	**All patients n=1783 (%)**	**< 18 yrs n=533 (%)**	**≥ 18 yrs n=1250 (%)**
Food-induced anaphylaxis	23.7 ± 18.3 yrs Female 54% Asthma 44%	**859 (48.2%)**	411 * (77.1%)	448 * (35.8%)
Drug-induced anaphylaxis	44.1 ± 17.4 yrs Female 67% Asthma 22%	**659 (36.9%)**	57 * (10.7%)	602 * (48.2%)
Insect-sting anaphylaxis	39.5 ± 18.5 yrs Male 65% Asthma 13%	**132 (7.4%)**	24 * (4.5%)	108 * (8.6%)
Exercise-induced anaphylaxis	26.4 ± 13.2 yrs Male 62% Asthma 20%	**45 (2.5%)**	12 (2.3%)	33 (2.6%)
Latex-induced anaphylaxis	36.8 ± 15.2 yrs Female 88% Asthma 71%	**41 (2.3%)**	6 ** (1.1%)	35 ** (2.8%)
Cold-induced anaphylaxis	22.7 ± 16.9 yrs Female 63% Asthma 28%	**40 (2.2%)**	21 * (3.9%)	19 * (1.5%)
Idiopathic anaphylaxis	34.7 ± 17.5 yrs Female 53% Asthma 22%	**36 (2.0%)**	5 ** (0.9%)	31 ** (2.5%)
Other causes	22.9 ± 14.2 yrs Female 57% Asthma 71%	**7 (0.4%)**	3 (0.6%)	4 (0.3%)

Numbers do not need to sum up because more than one elicitor may be documented for a single patient.
SD: standard deviation; %: valid percent
* p<0.01, ** p<0.05

Table 3. Food elicitors of anaphylaxisin the 859 patients with FIA, and their distribution (n, % within age group) in children and adolescents (aged <18 years-old) and in adults (aged ≥18 years-old)

Food-induced anaphylaxis	All patients n=859 (%)	< 18 yrs n=411 (%)	≥ 18 yrs n=448 (%)
SHELLFISH (crustaceans and/or mollusks) - **Crustaceans**(shrimp - 141, lobster - 4, crab - 4, others) - **Gastropod mollusks** (snail - 40, limpet - 31, others) - **Bivalve mollusks** (clam - 18, mussel - 3, others) - **Cephalopod mollusks** (octopus - 20, squid - 16, others)	**230 (26.8%)**	53 (12.9%) *	177 (39.5%) *
FRESH FRUITS - **Rosaceous**(peach - 41, apple - 21, pear - 8, others) - **Others** (kiwi - 38, banana - 12, grape - 11, others)	**145(16.9%)**	45 (10.9%)*	100(22.3%)*
MILK (cow's milk - 136, goat's milk - 4, sheep's milk - 1)	**139(16.2%)**	130(31.6%)*	9 (2.0%)*
TREE NUTS (walnut - 43, cashew - 21, hazelnut - 16, others)	**127 (14.8%)**	66 (16.1%)	61 (13.6%)
FISH (codfish - 15, hake - 14, sardine - 6, tuna - 6, others)	**65 (7.6%)**	33 (8.0%)	32 (7.1%)
EGG	**60 (7.0%)**	50 (12.2%)*	10 (2.2%)*
PEANUT	**56 (6.5%)**	32 (7.8%)	24 (5.4%)
SEEDS (sesame - 13, sunflower - 10, flaxseed - 2, pumpkin - 1)	**26 (3.0%)**	7 (1.7%)**	19 (4.2%)**
CEREALS (wheat - 7, corn - 3, rice - 2, barley - 1)	**13 (1.5%)**	9 (2.2%)	4 (0.9%)
MEATS (poultry - 4, pork - 3, cow - 2, rabbit - 2)	**10 (1.2%)**	4 (0.9%)	6 (1.3%)
OTHERS - **"Pancake syndrome"** - 7 - **Legumes** (soya - 4, lupin - 3, green bean - 1, pea - 1) - **Spices** (pepper - 3, cumin - 2, mustard - 2, others) - **Other vegetables** (garlic - 3, corn - 2, onion - 2, others) - **Other foods**	**52 (6.1%)**	12 (2.9%)*	40 (8.9%)*

"Pancake syndrome": anaphylaxis induced by the ingestion of mite-contaminated flour; %: valid percent
* p<0.01, ** p<0.05

Othercrustaceans: edible crab (n=3), barnacles, goose barnacles (n=2); Other mollusks: cockles, whelk (n=2), cuttlefish, oyster (n=1); Otherrosaceous: plum (n=7), cherry(n=3), sour cherry (n=2), apricot, raspberry, strawberry (n=1); Other fresh fruits: mango, melon (n=6), passion fruit, pineapple (n=5), fig, papaya (n=4), avocado, coconut(n=3), lychee (n=2), date, sweet melon (n=1); Other tree nuts: almond, pine nut (n=16), pistachio (n=7); Other fish: cutlassfish(n=4), conger, porgy, salmon, sea bream, skipjack, sole (n=3), vermilion snapper, wrasse (n=2), forkbeard, mackerel, monkfish, perch, plaice, skate, wreckfish (n=1); Other spices: peppermint (n=2), basil, cinnamon, cocoa, curry, ginger, nutmeg (n=1); Other vegetables: bell pepper, broccoli, courgette, goji berry, lettuce, radish, spinach, tomato (n=1); Other foods: mushroom, sulphites(n=2), honey, royal jelly (n=1).

Table 4. Drug elicitors of anaphylaxisin the 659 patients with DIA, and their distribution (n, % within age group) in children and adolescents (aged <18 years-old) and in adults (aged ≥18 years-old)

Drug-induced anaphylaxis	All patients n=659 (%)	< 18 yrsn=57 (%)	≥ 18 yrsn=602 (%)
NSAIDs	**285(43.3%)**	25(43.9%)	260(43.2%)
- Preferential COX-1 inhibitors	258	21	237
(ASA - 94, ibuprofen - 81, diclofenac - 67, metamizole - 39, others)			
- Preferential / selective COX-2 inhibitors	15	0	15
(nimesulide - 12, celecoxib - 1, etoricoxib - 1, parecoxib - 1)			
- Paracetamol	12	4	8
ANTIBIOTICS	**255(38.7%)**	24(42.1%)	231(38.4%)
- Beta-lactam antibiotics	215	23	192
- Penicillins / Derivatives	165	17	148
(AX - 87, AX-CLV - 37, penicillin - 24, CLV - 7, others)			
- Cephalosporins	50	6	44
(cefazolin - 27, ceftriaxone - 8, cefuroxime - 6, others)			
- Non Beta-lactam antibiotics	40	1	39
- Quinolones (ciprofloxacin - 11, moxifloxacin - 5, levofloxacin - 3)			
- Macrolides (clarithromycin - 5, spiramycin - 1)			
- Sulphonamides(cotrimoxazole - 6)			
- Others			
ANESTHETICS	**40 (6.1%)**	0	40 (6.6%)
- General anaesthetics	33	0	33
NMB (atracurium - 9, rocuronium - 9, cis-atracurium - 2, others)			
Others(midazolam - 5, propofol - 3)			
- Local anaesthetics	7	0	7
(lidocaine - 4, articaine - 2, bupivacaine - 1, ropivacaine - 1)			
ANTINEOPLASTIC AGENTS	**16 (2.4%)**	0	16 (2.7%)
(carboplatin - 7, oxaliplatin - 4, methotrexate - 2, others)			
PPI	**14 (2.1%)**	0	14 (2.3%)
(omeprazole - 8, esomeprazole - 3, pantoprazole - 3, lanzoprazole - 1)			
CORTICOSTEROIDS	**13 (2.0%)**	2 (3.5%)	11 (1.8%)
(hydrocortisone - 7, methylprednisolone - 3, others)			
ANALGESICS	**8 (1.2%)**	0	8 (1.3%)
(clonixin - 5, tramadol - 2, flupirtine - 1)			
RCM	**8 (1.2%)**	0	8 (1.3%)
OTHERS	**29 (4.4%)**	2 (3.5%)	27 (4.5%)
- Vitamins (vitamin B12 - 3, vitamin D3 - 1)			
- Vaccines (anti-meningococcal - 1, MMR - 1, tetanus vaccine- 1)			
- Other drugs			

ASA: acetylsalicylic acid; AX: amoxicillin; AX-CLV: amoxicillin-clavulanic acid; CLV: clavulanic acid; COX: cyclooxygenase;MMR: measles, mumps and rubella vaccine; NMB: Neuromuscular-blocking agents; NSAID: nonsteroidal anti-inflammatory drugs; PPI: proton-pump inhibitors; RCM: radiocontrast media

Other NSAIDs: naproxen (n=4), flurbiprofen(n=3), fentiazac, ketoprofen, ketorolac, propyphenazone(n=2), aceclofenac, dexibuprofen, etodolac(n=1); Other penicillin derivatives: flucloxacillin (n=7), ampicillin (n=2); Other cephalosporins: cefoxitin(n=3), cephradine(n=2), cefadroxil, cefalexin, cefatrizine, ceftazidime(n=1); Other non beta-lactam antibiotics: nitrofurantoine(n=3), vancomycin (n=2), fosfomycin, gentamycin, isoniazid (n=1); Other NMBs: succinylcholine, vecuronium (n=2); Other antineoplastic agents: docetaxel, paclitaxel, tamoxifen (n=1); Other corticosteroids: betamethasone, deflazacort, prednisolone (n=1); Other drugs: ranitidine (n=6), atropine (n=3),metoclopramide,patent blue dye (n=2),atovaquone,calcitonin,colloidal solution,diosmin,hydroxyzine,sulfasalazine,terbinafine, venlafaxine(n=1).

Figure 1. Type of clinical manifestations observed in the first anaphylaxis episode in the 1783 patients, and their distribution (%) in children and adolescents(aged <18 years-old, n=533) and in adults (aged ≥18 years-old, n=1250).

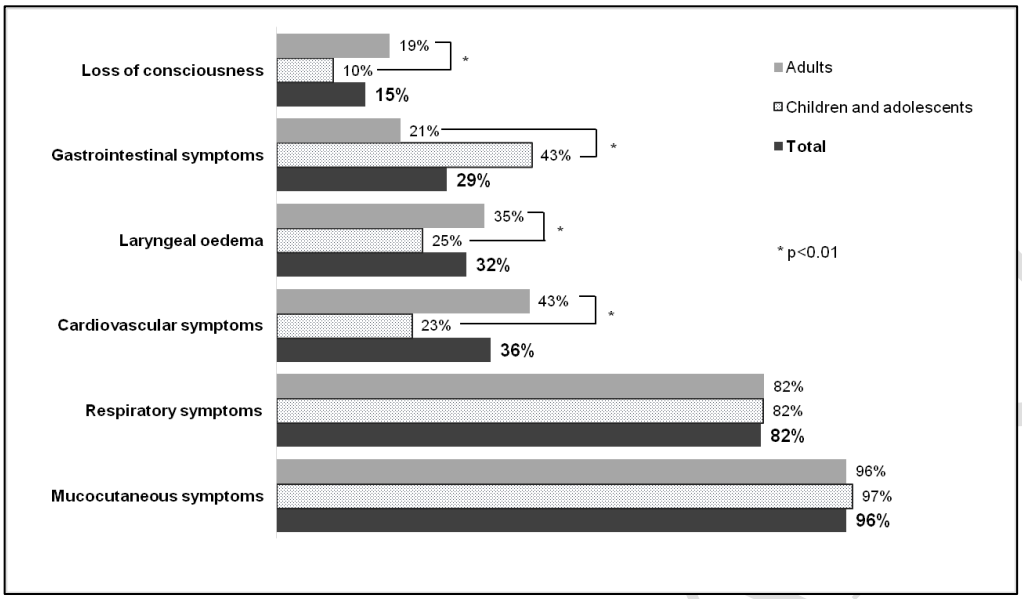

Figure 2. Food elicitors of anaphylaxisaccording to the age at the first anaphylaxis episode in the 859 patients with FIA, and their distribution (% within age group) in infants (<2years-old, n=149), preschoolers (2 to 5 years-old, n=148), schoolers (6 to 11 years-old, n=76), adolescents (12 to 17 years-old, n=38) and adults (≥18 years-old, n=448)