ORIGINAL ARTICLE

Anaphylaxis: A Decade of a Nationwide Allergy Society Registry

Gaspar A[1], Santos N[2], Faria E[3], Câmara R[4], Rodrigues-Alves R[5], Carrapatoso I[3], Gomes E[6], Pereira AM[7], Carneiro-Leão L[8], Morais-Almeida M[9], Delgado L[7,8,10], Pedro E[11], Branco-Ferreira M[11,12], Portuguese Society of Allergology and Clinical Immunology (SPAIC) Anaphylaxis Interest Group

[1]Immunoallergy Department, Hospital da Luz Lisboa, Portugal
[2]Immunoallergy Department, Centro Hospitalar Universitário Algarve, Portugal
[3]Immunoallergy Department, Centro Hospitalar Universitário Coimbra, Portugal
[4]Immunoallergology Unit, Hospital Dr. Nélio Mendonça, Funchal, Portugal
[5]Immunoallergology Unit, Hospital Divino Espírito Santo, Ponta Delgada, Portugal
[6]Immunoallergy Department, Centro Hospitalar Universitário do Porto, Portugal
[7]Immunoallergology Unit, Hospital CUF Porto and Instituto CUF Porto, Portugal
[8]Immunoallergy Department, Centro Hospitalar São João, Porto, Portugal
[9]Immunoallergy Department, CUF Descobertas Hospital, Lisbon, Portugal
[10]Basic and Clinical Immunology Unit, Department of Pathology, Faculty of Medicine, University of Porto, Portugal
[11]Immunoallergy Department, Hospital Santa Maria, Centro Hospitalar Lisboa Norte, Portugal
[12]Immunoallergology University Clinic, Faculty of Medicine of the University of Lisbon, Portugal

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Abstract

Background: Anaphylaxis is an acute, life-threatening, multiorgan hypersensitivity reaction.
Objective: The aim of this study was to identify the causes of anaphylaxis in Portugal in order to improve our knowledge of epidemiology and management.
Methods: We implemented a nationwide notification system for anaphylaxis over a 10-year period, with voluntary reporting by allergists. Data on 1783 patients with anaphylaxis were included. Etiopathogenesis, manifestations, and clinical management were characterized in detail for both children and adults.
Results: The mean age was 32.7 (20.3) years, and 30% were 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 to 88 years). The main culprits of anaphylaxis were foods (48%), drugs (37%) (main trigger in adults, 48%), and hymenoptera venom (7%). The main culprit foods were shellfish (27%), fresh fruit (17%), cow's milk (16%), tree nuts (15%), fish (8%), egg (7%), and peanut (7%). The main drugs were nonsteroidal anti-inflammatory drugs (43%), antibiotics (39%), and anesthetic agents (6%). Other causes included exercise (3%), latex (2%), cold-induced anaphylaxis (2%), and idiopathic anaphylaxis (2%). Most patients (80%) were admitted to the emergency department; only 43% received adrenaline. Anaphylaxis recurred in 41% of patients (21% with ≥3 anaphylactic episodes); 7% used an adrenaline autoinjector device.
Conclusions: Food is the leading cause of anaphylaxis in Portugal, while drugs were the main elicitors in adults. We emphasize undertreatment with adrenaline and recurrent episodes, highlighting the need to improve diagnostic and therapeutic approaches to anaphylaxis.

Key words: 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.

Introduction

Anaphylaxis is a severe and life-threatening systemic hypersensitivity reaction and, therefore, a clinical emergency [1]. The diagnostic criteria were reviewed and published in 2006, thus enabling the definition of anaphylaxis to be standardized [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].

The prevalence of lifetime anaphylaxis ranges from 0.05% to 2% in the general population [5,6]. A review of European studies points to an estimated prevalence of 0.3%, meaning that 1 out of 300 individuals experience an episode of anaphylaxis during their lifetime [7]. Foods, drugs, and hymenoptera venom were the most commonly identified triggers [1,4,6-9]. In population studies, the incidence rate of anaphylaxis was estimated to be between 8.4 and 50-103 per 100 000 person-years [5,6,10,11], with a mortality rate up to 1 to 3 per million person-years [6,9], accounting for 0.3% to 2% of all cases of anaphylaxis [6].

The prevalence of anaphylaxis has increased over time, especially in children [6,7,9,12,13] and particularly in preschoolers [6,7,9,11]. Food is the most common elicitor in children [7,12-16], and drugs are the main triggers in adults, particularly in the elderly [9,12,13,17]. The incidence of anaphylaxis to foods and drugs is affected by geographical factors, namely, diet and prescription patterns, respectively [1,4,8,13].

In Portugal, the prevalence and incidence of anaphylaxis in the general population are unknown. At national level, the only data available are from case series of outpatient care and hospitalizations. In a study conducted in 2006, a prevalence of 1.3% was reported in a specialized allergy outpatient center in Lisbon [18]. In a subsequent evaluation carried out in 2011, in the same city and based on the same methodology, prevalence had increased to 1.8% [15]. The real population prevalence is unknown owing to the lack of a widely implemented national registry of anaphylaxis; however, the number of cases observed in recent years seems to be increasing.

The aims of this study were to describe elicitors of anaphylaxis in Portugal and to improve our knowledge of epidemiology and management based on proactive reporting by allergists of cases identified in their allergy clinics through a nationwide notification system.

Methods

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

Anaphylaxis was diagnosed according to the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria [2], requiring the presence of at least 1 of 3 clinical criteria, consistent with the EAACI and WAO consensus. The definition of anaphylaxis was included on the form in order to ensure that all the reporters used the same definition.

All allergists who were members of the SPAIC were invited to participate in this registry and were asked to voluntarily report all cases of anaphylaxis identified in their allergy referral centers using the questionnaire designed by the SPAIC. The study population comprised patients attending the allergy clinics with a history of "at least 1 episode of severe systemic reaction" and a diagnosis of anaphylaxis confirmed by an allergist.

Data Collection

The structured questionnaire [17] was designed and validated by the SPAIC Anaphylaxis Interest Group, with a paper and online version available on the SPAIC website. The reporting form could be returned by letter, fax, e-mail, or online (patient data were anonymized). All notifications received were evaluated and validated by the SPAIC Anaphylaxis Interest Group, and, when necessary, the SPAIC asked the notifiers to clarify.

The parameters assessed in the questionnaire were as follows: demographic data, including age, sex, and area of residence; personal history of asthma and other allergic diseases; characterization of the known (confirmed or highly suspected) culprit agent; date of first anaphylaxis episode 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 an adrenaline autoinjector device (AAI).

Population

We included 1783 patients with a history of anaphylaxis reported by 82 allergists from all mainland regions (Northern,

Center, and Southern) and from the Azores and Madeira islands. The allergy work-up to identify the culprit agent was performed by the reporting allergists at their allergy centers. Specific details of the etiology, manifestations, and clinical management were provided.

Statistical Analysis

Categorial variables are presented as frequencies and percentages for the total number of validated responses. Normally distributed continuous variables are expressed as mean (SD); nonnormally distributed variables are expressed as median (minimum-maximum). The χ^2 test was used to test the association between qualitative variables, and results were expressed as the OR with its 95%CI. Statistical significance was set at $P<.05$, and the analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp.).

Results

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

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

The personal history of allergic comorbidities is detailed in Table 1. One-third of the patients had asthma and 1 man had systemic mastocytosis.

Table 1. Description of the 1783 Reported Patients in Relation to Age at Notification, Age at the First Anaphylaxis Episode, and Personal History of Allergic Comorbidities

Mean (SD) age at report, y	32.7 (20.3)
< 12 y, No. (%)	367 (21%)
12-17 y, No. (%)	166 (9%)
18-64 y, No. (%)	1142 (64%)
≥ 65 y, No. (%)	108 (6%)
Mean (SD) age at the first anaphylaxis episode, y	27.5 (20.4)
< 12 y, No. (%)	523 (29%)
12-17 y, No. (%)	140 (8%)
18-64 y, No. (%)	1049 (59%)
≥ 65 y, No. (%)	71 (4%)
Comorbidities, No. (%)	1220 (68%)
Allergic rhinitis, No. (%)	1026 (58%)
Asthma, No. (%)	585 (33%)
Atopic eczema, No. (%)	197 (11%)
Allergic conjuntivitis, No. (%)	146 (8%)
Other, No. (%)[a]	7 (<1%)

[a]Other immunoallergic concomitant diseases include 5 patients (3 adults and 2 children) with eosinophilic esophagitis, 1 man with systemic mastocytosis, and 1 woman with hereditary angioedema.

Clinical Manifestations

Clinical manifestations are detailed in Figure 1. Mucocutaneous symptoms were present in 96% of patients, of whom 78% had respiratory symptoms. Respiratory symptoms were more frequent in those with asthma (90% vs 78% without asthma; OR, 2.6 [95%CI, 1.9-3.6]). Cardiovascular manifestations, laryngeal edema, and loss of consciousness were recorded in 57%. The diagnosis of asthma was not a risk factor for the occurrence of these symptoms. Cardiovascular symptoms, laryngeal edema, and loss of consciousness were more frequents in adults (OR, 2.5 [95%CI, 2.0-3.1]; OR, 1.6 [95%CI, 1.3-2.0]; and OR, 2.2 [95%CI, 1.6-2.9]). Gastrointestinal symptoms were more frequent in children (43% vs 21% in adults; OR, 2.9 [95%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. No fatalities were reported by the allergists. Regarding treatment, only 43% of the patients received adrenaline. The diagnosis of asthma was not a risk factor for an ED visit or for administration of adrenaline.

Prescription and Use of Adrenaline Autoinjector

AAIs were prescribed in 1049 patients (59%) in outpatient care setting; prescription was significantly lower in cases of drug-induced anaphylaxis (DIA) than in cases of anaphylaxis of other causes (11% vs 87%, $P<.01$).

Recurrence of anaphylaxis (>1 episodes of anaphylaxis, most frequently to the same or cross-reactive triggers) was observed in 728 patients (41%): 2 episodes in 360 (20%), 3 episodes in 173 (10%), 4 episodes in 93 (5%), and ≥5 episodes in 102 (6%). An AAI was used in these subsequent

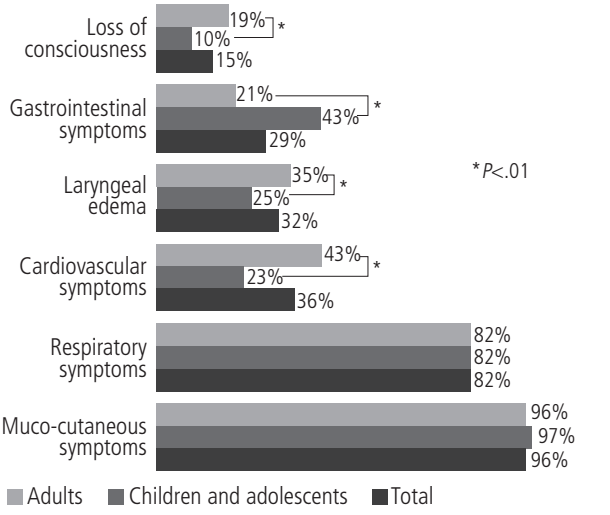

Figure 1. Type of clinical manifestations observed in the first anaphylaxis episode in the 1783 patients and their distribution (%) in children and adolescents (aged <18 years, n=533) and in adults (age ≥18 years, n=1250).

Table 2. Elicitors of Anaphylaxis in the 1783 Patients and Their Distribution[a]

Etiology of anaphylaxis	Mean (SD) age, y Sex, % Asthma, %	All patients n=1783 No. (%)	<18 y n=533 No. (%)	≥18 y n=1250 No. (%)
Food-induced anaphylaxis	23.7 (18.3) Female 54% Asthma 44%	859 (48.2%)	411 * (77.1%)	448 * (35.8%)
Drug-induced anaphylaxis	44.1 (17.4) Female 67% Asthma 22%	659 (36.9%)	57 (10.7%)	602 * (48.2%)
Insect-sting anaphylaxis	39.5 (18.5) Male 65% Asthma 13%	132 (7.4%)	24 * (4.5%)	108 * (8.6%)
Exercise-induced anaphylaxis	26.4 (13.2) Male 62% Asthma 20%	45 (2.5%)	12 (2.3%)	33 (2.6%)
Latex-induced anaphylaxis	36.8 (15.2) Female 88% Asthma 71%	41 (2.3%)	6 ** (1.1%)	35 ** (2.8%)
Cold-induced anaphylaxis	22.7 (16.9) Female 63% Asthma 28%	40 (2.2%)	21 * (3.9%)	19 * (1.5%)
Idiopathic anaphylaxis	34.7 (17.5) Female 53% Asthma 22%	36 (2.0%)	5 ** (0.9%)	31 ** (2.5%)
Other causes	22.9 (14.2) Female 57% Asthma 71%	7 (0.4%)	3 (0.6%)	4 (0.3%)

[a]Numbers do not necessarily reach a total because more than 1 elicitor may be documented for a single patient.
* $P<.01$, ** $P<.05$

reactions by 119 patients (7%). AAIs were more commonly used in patients with asthma (10% vs 6% without asthma, OR, 1.7 [95%CI, 1.2-2.5]).

Etiology

The relative frequency of the known elicitors of anaphylaxis per age group can be seen in Table 2, which shows the etiology in relation to the age at reporting, predominant sex, and asthma comorbidity. Thirty-seven patients had more than 1 known elicitor of anaphylaxis, accounting for a total of 1819 reports of specific causes involved.

The main cause, observed in 48% of patients, was food-induced anaphylaxis (FIA). DIA ranks second (37%), and insect-sting anaphylaxis was the third cause (7%). Other causes were exercise-induced anaphylaxis (3%), latex (2%), cold-induced anaphylaxis (2%), and idiopathic anaphylaxis (2%). In 7 patients, other specific causes identified included subcutaneous allergen-specific immunotherapy (mite immunotherapy in 2 children, pollen immunotherapy in 1 woman, and maintenance bee-venom immunotherapy in 1 man), inhalation of animal allergens in 2 patients (horse dander in both cases), and contamination of raw fish with *Anisakis* in 1 woman.

The 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 first cause of FIA (27%) and occurred more commonly in adults. Crustaceans (especially shrimp) were the main triggers. Regarding mollusks, emphasis should be placed on the geographical particularity of limpet anaphylaxis, which was reported mainly in Madeira Island. Fresh fruits were the second cause (17%) of FIA, especially Rosaceae family fruits (peach, in particular) and kiwi. In many reported cases of anaphylaxis to Rosaceae fruits, notifiers identified sensitization to lipid transfer proteins (LTPs). Cow's milk was the third cause of FIA and the leading cause (32%) in children. Other foods involved included tree nuts, fish, egg, peanut, seeds, and cereals. In relation to rarer causes, we emphasize 3 cases of anaphylaxis to red meat with confirmed sensitization to galactose-α-1,3-galactose (α-gal) and 7 cases of oral mite anaphylaxis ("pancake syndrome") reported in the 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 adulthood.

The drugs implicated in DIA are presented in Table 4, which shows their relative distribution by age group. The main culprits were nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, and anesthetic agents. Other drugs included antineoplastic agents, proton-pump inhibitors, corticosteroids, and radiocontrast media. NSAIDs were the main triggers

Table 3. Elicitors of Food-Induced Anaphylaxis

Food-induced anaphylaxis[a]	All patients n=859 (%)	<18 y n=411 (%)	≥18 y n=448 (%)
SHELLFISH (crustaceans and/or mollusks) – Crustaceans (shrimp - 141, lobster - 4, crab - 4, other) – Gastropod mollusks (snail - 40, limpet - 31, other) – Bivalve mollusks (clam - 18, mussel - 3, other) – Cephalopod mollusks (octopus - 20, squid - 16, other)	230 (26.8%)	53 (12.9%) *	177 (39.5%) *
FRESH FRUITS – Rosaceous (peach - 41, apple - 21, pear - 8, other) – Others (kiwi - 38, banana - 12, grape - 11, other)	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, other)	127 (14.8%)	66 (16.1%)	61 (13.6%)
FISH (codfish - 15, hake - 14, sardine - 6, tuna - 6, other)	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%)
OTHER CAUSES – "Pancake syndrome" – 7[b] – 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%) *

[a]Other crustaceans: edible crab (n=3), barnacles, goose barnacles (n=2). Other mollusks: cockles, whelk (n=2), cuttlefish, oyster (n=1). Other Rosaceae: 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).

[b]"Pancake syndrome": anaphylaxis induced by the ingestion of mite-contaminated flour.

* $P<.01$, ** $P<.05$

of DIA (43%), especially preferential cyclooxygenase-1 inhibitors. We noted paracetamol as the culprit in 12 patients. Antibiotics were the second cause of DIA (39%), especially ß-lactam antibiotics, mainly amoxicillin, 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, which was implicated in 27 adults. One patient developed Kounis syndrome after cefazolin infusion. Among the non–ß-lactam antibiotics, quinolones were the most frequently implicated agents and the elicitor in 19 adults. Anesthetic-induced anaphylaxis was reported in 40 adults. General anesthetics were implicated in 33 patients, especially neuromuscular-blocking agents (elicitors in 66% of cases of intraoperative anaphylaxis); local anesthetics were the culprits in 7 patients.

Insect-sting anaphylaxis occurred in 132 patients. All cases were associated with hymenoptera, except for the case of a child who was bitten by a mosquito. The hymenoptera implicated were *Apis mellifera* (71%), *Vespula* (23%), and *Polistes* (9%).

Exercise-induced anaphylaxis was reported in 45 patients. Food-dependent exercise-induced anaphylaxis (FDEIA) occurred in 44 patients. The foods implicated were cereals (n=14, especially wheat), tree nuts (n=10), Rosaceae fruits (n=8, especially apple), peanut (n=3), cow's milk, grape, legumes and poultry meat (n=2), sesame seed (n=1), and other vegetables (n=4).

Latex-induced anaphylaxis occurred in 41 patients. Five cases involved intraoperative anaphylaxis. Latex-fruit syndrome was the cause in 51% (20 adults and 1 adolescent).

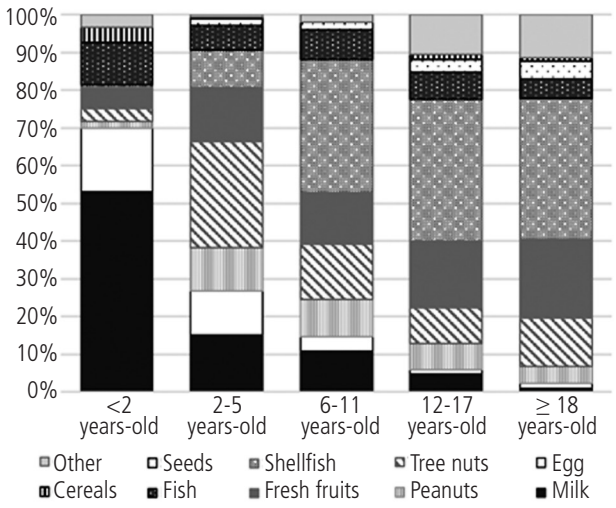

Figure 2. Elicitors of anaphylaxis to food according to age at the first episode in the 859 patients with FIA and their distribution (% within age group) in infants (<2 years, n=149), preschoolers (2 to 5 years, n=148), schoolers (6 to 11 years, n=76), adolescents (12 to 17 years, n=38) and adults (≥18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

The fruits and vegetables implicated were as follows: 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); and papaya, pineapple, sweet pepper, and sweet potato (n=1). We noticed a trend during the study period for latex-induced anaphylaxis: almost all cases were reported during the first 5 years of the study, with only 1 case reported in the last 5 years, thus reflecting a trend toward a decrease in the frequency of latex allergy.

Discussion

Covering a whole decade, this is the first nationwide registry of anaphylaxis in Portugal, which confirms food allergy as the leading cause of anaphylaxis, accounting for three-quarters of all pediatric cases. Other causes identified included drugs (the major elicitor of anaphylaxis in adults), in particular NSAIDs and ß-lactam antibiotics, hymenoptera venom, exercise (almost all cases FDEIA), latex, and cold-induced anaphylaxis. The report was limited to allergists, all of whom used the same diagnostic criteria for anaphylaxis, thus enabling a nationally validated methodology and ensuring the quality of our data.

This study shows that anaphylaxis affects all age groups. As observed in other case-series, anaphylaxis in adults mainly affected females, 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 allergy was the main elicitor of anaphylaxis, as reported in several case series, especially when children are included [8,11,13,15,16,20-23]. Shellfish and cow's milk were the main culprits in adults and in children, respectively. Cow's milk 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 findings differ from those of other authors in other areas [8,14,23-25], thus underlining the importance of detailed local knowledge. The observed frequency varies based on the age group studied, the geographical region, and the associated dietary habits [6,13,14,24,26]. Other main foods in this study were fresh fruits and tree nuts. FIA has important consequences for quality of life, as contact with food allergens, even in minimal amounts, as hidden allergens or cross-reacting allergens may be life-threatening. Education of patients and caregivers, as well as appropriate labeling, is essential for allergen avoidance [4,23].

Tree nut–induced anaphylaxis has been increasingly reported worldwide, in particular in preschoolers [14,23,24,26]. In this case series, tree nuts were an important cause of FIA and the second cause in children; walnut and cashew were the most common. These results differ from those reported in other European studies, where hazelnut was the most frequent tree nut [8,24]. In a case-series reported from a single center in Coimbra, Portugal, tree nuts were the main cause of FIA in adults, especially walnut and hazelnut [27]. By contrast, in a recent study involving preschoolers, also conducted in Portugal, cashew and walnut were the commonest tree nuts [26].

LTPs are 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 is challenging in affected patients [30-32] owing to the presence of these panallergens in many plant foods, such as fresh fruits, vegetables, tree nuts, and seeds. In studies conducted in Italy [28] and Spain [32], LTPs are reported to be the main cause of FIA in adults, especially peach. In this registry, peach is also relevant. In a recent study carried out in Portugal [30] including both children and adults, LTPs were the third cause of FIA, preceded only by shellfish and cow's milk. In the specific approach to FDEIA, it is essential to avoid the implicated foods for at least 4 hours before exercise [30,31], and sports should be played with a partner capable of administering the AAI.

DIA was the leading cause of anaphylaxis in adults, with NSAIDs predominating over antibiotics, as also reported in studies conducted in Spain [11,33]. In this study, a low proportion of DIA was observed in children, as reported elsewhere [8,13,34]. NSAIDs were the main cause of DIA both in our study and 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 the risk of penicillin-induced anaphylaxis is estimated to be high in the general population (0.7% to 10%) [38]. Among NSAIDs, selective cyclooxygenase-1 inhibitors were the most frequently implicated, especially acetylsalicylic acid, ibuprofen, diclofenac, and metamizole, as reported by other authors [8,17,35,36]. Anaphylaxis to selective cyclooxygenase-2 inhibitors was rare, thus reinforcing the role of these agents as alternative drugs [17,35,36].

ß-Lactams were the major elicitors among antibiotics [8,17,25,29,36,38], mainly amoxicillin (including the combination amoxicillin-clavulanic acid) and cephalosporins, and to a lesser extent benzylpenicillins, as observed elsewhere [11,12,29,36,39,40]. This can be explained by changes in the

Table 4. Elicitors of Drug-Induced Anaphylaxis

Drug-induced anaphylaxis[a]	All patients n=659 (%)	<18 y n=57 (%)	≥18 y n=602 (%)
NSAIDs	285 (43.3%)	25 (43.9%)	260 (43.2%)
– Preferential COX-1 inhibitors (ASA - 94, ibuprofen - 81, diclofenac - 67, metamizole - 39, other)	258	21	237
– Preferential/selective COX-2 inhibitors (nimesulide - 12, celecoxib - 1, etoricoxib - 1, parecoxib - 1)	15	0	15
– Paracetamol	12	4	8
ANTIBIOTICS	255 (38.7%)	24 (42.1%)	231 (38.4%)
– ß-Lactam antibiotics	215	23	192
- Penicillins/derivatives (AX - 87, AX-CLV - 37, penicillin - 24, CLV - 7, other)	165	17	148
- Cephalosporins (cefazolin - 27, ceftriaxone - 8, cefuroxime - 6, other)	50	6	44
– Non–ß-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
NMBAs (atracurium - 9, rocuronium - 9, cis-atracurium - 2, other)			
Others (midazolam - 5, propofol - 3)			
– Local anaesthetics (lidocaine - 4, articaine - 2, bupivacaine - 1, ropivacaine - 1)	7	0	7
ANTINEOPLASTIC AGENTS (carboplatin - 7, oxaliplatin - 4, methotrexate - 2, other)	16 (2.4%)	0	16 (2.7%)
PROTON PUMP INHIBITORS (omeprazole - 8, esomeprazole - 3, pantoprazole - 3, lanzoprazole - 1)	14 (2.1%)	0	14 (2.3%)
CORTICOSTEROIDS (hydrocortisone - 7, methylprednisolone - 3, other)	13 (2.0%)	2 (3.5%)	11 (1.8%)
ANALGESICS (clonixin - 5, tramadol - 2, flupirtine - 1)	8 (1.2%)	0	8 (1.3%)
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 (antimeningococcal - 1, MMR - 1, tetanus vaccine - 1)			
– Other drugs			

Abbreviations: ASA, acetylsalicylic acid; AX, amoxicillin; AX-CLV, amoxicillin-clavulanic acid; CLV, clavulanic acid; COX, cyclooxygenase; MMR, measles, mumps, and rubella vaccine; NMBA, neuromuscular-blocking agent; NSAID, nonsteroidal anti-inflammatory drug; RCM, radiocontrast media
[a]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–ß-lactam antibiotics: nitrofurantoine (n=3), vancomycin (n=2), fosfomycin, gentamycin, isoniazid (n=1). Other NMBAs: 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).

prescription pattern of ß-lactams in Europe. Anaphylaxis to cefazolin, especially during surgery, was frequent.

Our findings for anaphylaxis to radiocontrast media (1.2%) were similar to those reported elsewhere [11,25,38]. Severe reactions attributed to radiocontrast media have been decreasing in frequency, given that high-osmolality ionic formulations are no longer used [38].

In this registry, anaphylaxis during allergen-specific immunotherapy was a rare event and less frequent than in other studies [8,16,22,37], thus confirming the safety of this treatment [41,42].

Idiopathic anaphylaxis accounts for up to 20% of all cases of anaphylaxis [1,23,43]; however, this diagnosis of exclusion was rare in our registry (2%) because case reporting was limited to allergists. In fact, given that the etiological study of anaphylaxis should always be detailed, affected patients must be referred to allergy specialists [33,43]. Nevertheless, this low value might also be related

to a reporting bias associated with underreporting when the trigger was unknown.

Our study has a series of limitations, besides the bias related to voluntary reporting and expected underreporting. The cases of anaphylaxis included are limited to those followed at the allergy centers and not all cases managed in the ED. In addition, the questionnaire applied to evaluate severity did not take account of serum tryptase levels or concomitant medication such as ß-blockers and angiotensin-converting enzyme inhibitors, which are known to increase the severity of anaphylaxis [1,23,44].

Gastrointestinal symptoms, although present in 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 in younger patients. Our findings also reinforce the fact that the lack of cutaneous symptoms, as observed in 4% of patients, does not exclude the diagnosis of anaphylaxis.

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

In 80% of the cases reported, patients were admitted to the ED, and 20% required hospitalization. Anaphylaxis is a medical emergency requiring immediate treatment, and intramuscular adrenaline is the first-line drug [1,3,4,23,47,48]. However, although universally recommended in guidelines, it continues to be underused in the ED. Less than half of the patients in the present study received adrenaline, as reported elsewhere [8,16,20,22,25,33,49]. Therefore, medical education concerning management of anaphylaxis in the ED must be improved.

Prescription of AAIs also fell short of expectations. We understand that not all patients with anaphylaxis need an AAI (eg, some patients with DIA). Nevertheless, there are absolute indications for prescription of AAIs according to the EAACI and WAO guidelines [4,23], including previous anaphylaxis triggered by food, latex, or aeroallergens (eg, animal dander) 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 if they have concomitant unstable asthma or experienced a previous reaction to trace levels of food. This is particularly true for hidden allergens such as tree nuts, peanut, cow's milk, and egg [4,23,50].

Physicians commonly underprescribe AAIs worldwide [8,20,25,33,48,49]. Given the risk of recurrence, AAIs should be prescribed, and patients should receive education on when and how to use the device [23,48], as well as training with placebo devices, with emphasis on efficacy and safety. In the present registry, recurrence of anaphylaxis was documented in 41% of patients, and 21% experienced 3 or more episodes. Previous publications regarding the recurrence of anaphylaxis found similar results, with a cumulative incidence ranging from 26.5% to 54% [6,15,16,22]. Underuse of AAIs by patients and caregivers is also reported [8,16,49,50]. It should be noted that in our registry, 7% of patients had successfully used AAIs. 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 the signs of anaphylaxis, correct use of the AAI, early intramuscular adrenaline in the ED, and urgent referral to an allergy specialist should be promoted. An allergy work-up and follow-up are essential to identify triggers, to perform a comprehensive risk assessment, and to prevent recurrence by developing personalized risk reduction strategies [23,33,43]. The role of the allergy specialist is essential for the adoption of preventive measures (allergen avoidance, written emergency action plan, alternative foods and drugs), as well as for the implementation of allergen-specific immunotherapy (hymenoptera, latex, food) or specific desensitization (specific foods and drugs).

Conclusions

This national registry enabled us to obtain a detailed characterization (made by allergists) of patients with anaphylaxis, in whom the main elicitors were foods, drugs, and hymenoptera venom.

We highlight the broad age spectrum, the different sex distribution between children and adults, the relevance of food allergens in both age groups and drugs in adults, the frequent association with comorbid asthma, the high frequency of recurrence of anaphylaxis, and the underuse of adrenaline in the ED.

Nationwide registries are useful tools for improving epidemiological knowledge and outlining local strategies for the prevention and management of anaphylaxis.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Ângela Gaspar

Immunoallergy Department
Hospital da Luz Lisboa
Av. Lusíada 100
1500-650 Lisboa, Portugal
E-mail: angela.gaspar@sapo.pt