Title: Anaphylaxis in an emergency department: a retrospective 10-year study in a tertiary hospital

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ABSTRACT

Background: Anaphylaxis is a potentially fatal medical emergency. The frequency of hospital admissions for anaphylaxis seems to be increasing in the recent decades.

Objective: Characterize the patients admitted for anaphylaxis to the adult emergency department (ED) of a tertiary care hospital over a 10-year period, discriminating aetiologies, clinical features and therapy administered.

Methods: Retrospective, descriptive and inferential study, evaluating age, sex, Manchester triage system, suspected allergen, site of allergen exposure, comorbidities, cofactors, clinical findings and symptoms, treatment and management. Patients admitted between January 2007 and December 2016 were included.

Results: Forty-three patients were enrolled: 23 males, mean age 54.3 ± 16.2 years, n=22 had history of allergic disease. Two patients were triaged as non-urgent. The most frequently suspected causes of anaphylaxis were: drugs (33%, n=14), *Hymenoptera* venoms (23%, n=10), foods (21%, n=9) and iodinated contrast products (12%, n=5). Adrenaline was used in 88% of the episodes (n=38), 55% of which (n=21) intramuscularly. Mortality was registered in one case. At discharge, adrenaline auto-injector was prescribed in 7% (n=3) of the patients, and Allergy & Clinical Immunology consultation (ACIC) was requested in 65% of the episodes (n=28). Statistically significant associations ($p<0.05$) were established: a) anaphylaxis to drugs associated with a low intramuscular adrenaline use and with frequent oxygen therapy; b) anaphylaxis to food associated with intramuscular adrenaline administration; c) anaphylaxis to *Hymenoptera* venom associated with male sex; and d) anaphylaxis to iodinated contrasts associated with referral to ACIC and with shock. All obese patients developed shock.

Conclusions: Anaphylaxis is a life-threatening condition that requires early recognition. Although most patients received adrenaline, administration was not always performed by the recommended route and only a few patients were prescribed adrenaline auto-injector.

INTRODUCTION

Anaphylaxis was first described by Charles Richet and Paul Portier in the 20th century and it is considered the maximal variant of immediate type systemic hypersensitivity[1–3]. Severe anaphylactic reactions are potentially life-threatening and its symptoms can vary depending on the organic systems affected[4]. Anaphylaxis manifestations usually include skin and mucosas but may also involve airway, respiratory, gastrointestinal and/or circulatory disfunction[4–6].

Patients may report to the emergency department (ED) at various stages of the anaphylaxis reaction, with symptoms ranging from urticaria to cardiorespiratory failure[7]. Severe reactions may require evaluation in the emergency department, management in Intensive Care Units or hospitalization[8].

Despite published criteria and guidelines, diagnostic or coding errors are common, as stated in the World Health Organization (WHO) International Classification of Diseases (ICD)[9]. Consequently, the underuse or late administration of adrenaline as first-line treatment remains an issue[10,11].

The prevalence and incidence of hospital admissions for anaphylaxis varies widely between studies[13]. The incidence of anaphylaxis in the United States of America is 10 to 21 per 100,000 person-years and the estimated prevalence is 1.6% [12–14]. In Europe, reported incidence rates vary from 1.5 to 32 per 100 000 person-years and, according to a study of primary healthcare data from the United Kingdom, the annual incidence of anaphylaxis is 8.4 cases per 100 000 individuals in the general population [15,16]. Many studies have shown that the prevalence of anaphylaxis is increasing, particularly in developed countries [16.]

The most frequent aetiologies in adults are drugs and *Hymenoptera* venom[2]. However, the correct identification of the causes is not always easy and often requires referral to specialized consultation for diagnosis and follow-up.

OBJECTIVE OF THE STUDY

The objective of this study was to characterize the aetiologies, the clinical features and the administered treatment in adult patients presenting with anaphylaxis to the ED of the Centro Hospitalar e Universitário de Coimbra (CHUC), Portugal.

METHODS

Type of study

Retrospective, descriptive and inferential study conducted at the Centro Hospitalar e Universitário de Coimbra (CHUC), Portugal, between January 2007 and December 2016 (10 years).

Patient selection

Patients were selected using the electronic medical codifications on ED-CHUC software (ALERT®) to include the *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9 CM) codes: 995.0 ("Other anaphylactic shock") and 995.6 ("Anaphylactic shock due to adverse food reaction")[17].

Patient files were reviewed and the criteria for inclusion in the study were adults patients admitted to ED-CHUC with a diagnosis of anaphylaxis as defined by "Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology"[4] (see below). A total of 45 cases were identified, two of which were excluded after clinical file revision for not fulfilling anaphylaxis criteria.

The following variables were evaluated: sex, age, year of the episode, site of allergen exposure, site of reaction (out-of-hospital or in-hospital), suspected aetiology, time interval between exposure and allergic reaction, profession, history, comorbidities, cofactors, Manchester triage, clinical manifestations, therapy, need for surveillance, need of intensive care, hospitalization, subsequent referral to Allergy & Clinical Immunology consultation (ACIC), and prescription of adrenaline auto-injector at discharge. Data was collected from the ED records of the anaphylaxis episode. The "suspected allergens" are those so considered by the ED doctors at the anaphylaxis episode report.

Definitions

The European Academy of Allergy and Clinical Immunology defines anaphylaxis as "*a severe, life-threatening generalized or systemic hypersensitivity reaction, which is characterized by being rapid in onset with life-threatening airway, breathing or circulatory problems, and is usually associated with skin and mucosal changes"*[4]. The presence of shock is defined as systolic blood pressure of <90 mmHg or >30% decrease of the baseline blood pressure[4].

History of allergic disease was collected from the patients' medical records. We considered the *World Allergy Organization* definition of atopy, a genetic tendency to develop allergic diseases, such as allergic rhinitis, asthma and atopic dermatitis[18]. We also considered history of chronic spontaneous urticarial and history of probable allergic reactions to drugs, foods, *hymenoptera*, or others.

Statistical analysis

Statistics were performed using SPSS Statistics version 20.0®.

Descriptive statistics were analysed as mean and standard deviation for the variables with normal distribution, and median and interquartile range for the variables without normal distribution. The variables were described in absolute number (n).

The nominal variables were compared using Pearson's chi-square test or Fisher's exact test according to Cochran's rules. The normal distribution of the ordinal variables was evaluated using the Kolmogorov-Smirnov test (considering a population sample of more than 30 individuals in both groups). The comparison of these variables was tested using Student's T-tests (parametric test, applied after verifying the homogeneity of variances by the Levene test) or Mann-Whitney test (non-parametric test). A Type I error of 0.05 was considered.

RESULTS

CLINICAL PRESENTATION

Epidemiology, triage and site of allergen exposure (out-of-hospital/in-hospital)

In the 2007-2016 period, 43 cases of anaphylaxis were identified and codified in ED-CHUC, 53% (n=23) were male and 47% (n=20) female, with a mean age of 54.3 ± 16.2 years, and ranging from 23 to 84 years-old. The years of 2014, 2015 and 2016 had the highest number of registries, n=18, accounting for 42% of the total population – Figure 1.

Considering the Manchester triage criteria, n=10 were classified "red/immediate evaluation", and n=22 were classified "orange/very urgent", these two levels accounting for almost ¾ of the cases. The remaining patients were classified "yellow/urgent" (n=9) or "green/standard evaluation" (n=2). Most of the anaphylaxis episodes occurred out-of-hospital (n=31), while the remaining occurred inside the hospital, for example during the administration of iodinated contrast for computed tomography scan.

A history of probable allergic disease was found in n=22 (comorbid allergic pathologies are described on Table 1).

Aetiologies, clinical manifestations and occupational risk

The suspected causes of anaphylaxis are shown in Figure 2. Most anaphylactic reactions (n=32) were described as immediate (defined as onset of symptoms less than 1 hour after exposure to the suspected

allergen) and the time interval recorded was <15 minutes in the majority of these cases (n=30). In 6 patients the time interval for symptom onset was not recorded. The remaining 5 patients showed intervals between exposure and reaction between 90 to 120 minutes, most of them (n=4) corresponding to cases of suspected food aetiology and 1 to suspected *Hymenoptera* venom allergy.

One case of biphasic anaphylaxis caused by drugs (tramadol) was registered, with a second peak occurring 12 hours after the first symptoms. In this patient, the late reaction was more severe than the initial reaction: 30 minutes after drug administration the patient developed urticarial rash and dyspnoea, with no therapy or health care assistance in the first phase of the reaction, whereas the late reaction was more severe and included dyspnoea, oropharyngeal tightening, urticarial rash and syncope.

Anaphylaxis was identified due to combinations of: dermatological, respiratory and cardiovascular symptoms in n=17 patients; dermatological and respiratory symptoms in n=6 patients; respiratory and cardiovascular symptoms in n=4 patients; respiratory, cardiovascular and neurological symptoms in n=4 patients and a combination of dermatological, respiratory, cardiovascular and gastrointestinal in n=4 patients. Anaphylactic shock occurred in 70% (n=30) – Figure 3.

One case of occupational risk was reported in a forest ranger that suffered anaphylaxis after *Hymenoptera* stinging.

Comorbidities, cofactors and mortality

Comorbidities are presented in the Table 2. Possible anaphylaxis co-factors were observed in some patients, namely: medication with angiotensin-converting enzyme inhibitors (ACEI), n=19, with beta-blockers, n=5, and with non-steroidal anti-inflammatory drugs (NSAIDs), n=2; alcohol was a possible cofactor (intake before the anaphylactic episode) in two cases and one patient had a suspected case of food-dependent exercise-induced anaphylaxis (FDEIA) to wheat.

Intensive Care / Rapid-response emergency-team was called in n=18 episodes, n=7 required orotracheal intubation, and n=5 had cardiorespiratory arrest. One patient died from anaphylaxis to *Hymenoptera* venom after multiple stings.

Treatment

We here analyse together the pre-hospital and the in-hospital therapy registered in patients' medical records. Adrenaline was administered in n=38 cases. The route of administration was intramuscular in n=21, subcutaneous in n=13, intravenous in n=5 and inhaled in n=1. All patients that received intravenous adrenaline had developed anaphylactic shock, including a fatal case of *Hymenoptera* venom allergy. The

single patient that received inhaled adrenaline was an obese and hypertensive patient that developed anaphylactic shock with severe bronchospasm attributed to diclofenac, suggesting the hypothesis of anaphylaxis associated with a history of respiratory disease exacerbated by anti-inflammatory drugs (AERD). Among the patients that received adrenaline treatment, n=30 received only one dose (0.5mg), n=5 two doses and n=3 three doses.

Regarding other concurrent therapies: n=42 patients were treated with systemic glucocorticoids (median 250.0mg of methylprednisolone conversion), n=32 received antihistamine H1 therapy (clemastine was the most frequently used); n=5 antihistamine H2 therapy (ranitidine); n=27 received oxygen therapy (median 2.0L/min; IR 10.0L/min); n=35 received fluid therapy (n=25 crystalloids, n=7 combination of crystalloids and colloids and n=3 colloids) and n=2 were given dopamine.

Serum tryptase during the anaphylaxis episode (minimum 1h – maximum 6h after symptom onset) was evaluated in n=4 cases, with values ranging from 32 to 169mcg/mL (normal range < 11.4mcg/mL).

The mean time of permanence in the ED was 7.0 ± 4.0 hours. Most of the patients were referred for follow-up consultations: Allergy & Clinical Immunology consultation in n=28. Hospitalization was decided in n=23 patients (n=19 in the Short-stay Hospital Unit, n=2 in the Allergy & Clinical Immunology Department, n=1 in the Intensive Care Unit, n=1 in the Internal Medicine Department).

CHUC uses an electronic prescription system that allows prescription alerts/limitations. Among the patients with suspected drug allergy (here including drugs, iodinated contrast and fluorescein dye), the Hospital prescription of the suspected drug was blocked in n=9/20 of the anaphylaxis episodes.

Adrenaline auto-injector was prescribed at ED discharge in n=3 of patients.

CHARACTERISTICS OF ANAPHYLAXIS AND RELEVANT CLINICAL ASSOCIATIONS

Location

Regarding the location where anaphylaxis occurred, all suspected food allergies occurred out-of-hospital ($p<0.05$, Fisher's exact test). Conversely, in suspected drug allergy, half of the cases of anaphylaxis occurred inside the hospital, and drug allergy corresponded to 58% (n=7/12) of all in-hospital episodes ($p<0.05$, Fisher's exact test), with the remaining attributable to CT contrasts and fluorescein dye.

Professional occupation

Professions with performance in external environments, such as farmer, mason, forest ranger and fireman were exclusively reported in the group of suspected *Hymenoptera* venom anaphylaxis.

Suspected causes

Possible epidemiological differences were found between suspected etiologic groups: all patients with suspected *Hymenoptera* venom anaphylaxis were male ($p< 0.05$, Fisher's exact test) whereas all patients with suspected iodinated contrast agent anaphylaxis were female ($p <0.05$, Fisher's exact test). One of the patients with drug anaphylaxis, intravenous magnesium metamizole, had a history of previous metamizole anaphylaxis described in the record of the clinical history of the emergency episode. One patient had a likely diagnosis of Food Dependent Exercise Induced Anaphylaxis with wheat ingestion, tolerating the ingestion of wheat in the absence of the cofactor. Regarding the Manchester triage, unlike other aetiologies, patients with suspected food allergy anaphylaxis were all classified as severe ($p< 0.05$, Fisher's exact test).

Shock

The percentage of patients who developed anaphylactic shock was 70% (n=30). The totality of cases with anaphylaxis to iodinated contrast presented with anaphylactic shock were referenced to ACIC ($p< 0.05$, Fisher's exact test). All obese patients developed shock ($p <0.05$, Fisher's exact test). All patients with shock had immediate anaphylaxis and 87.5% of them initiated symptoms less than 15 minutes after allergen exposure (21 out of the 24 patients with shock and reported time of symptom onset) Patients who developed shock had arterial hypertension in 57% (n=17) and were medicated with angiotensin converting enzyme inhibitor in 40% (n=12). The presence of tachyarrhythmia occurred in 60%, n=18 ($p <0.05$, Pearson's chi-square) and fluid therapy was required in 90%, n=27 ($p <0.05$, Fisher's exact test). Half the patients with shock presented comorbid allergic diseases. Almost all patients with shock, n=29, were treated with the first-line therapy adrenaline ($p <0.05$, Fisher's exact test), n=14 by the intramuscular route, and n=5, intravenously. The only patient treated with inhaled adrenaline was included in this group. Rapid-response emergency-team was called in n=16 of anaphylactic shock cases ($p <0.05$, Pearson's chi-square). All patients who presented anaphylaxis due to iodinated contrast agent developed shock.

Treatment

The suspected causes of the two patients that required dopaminergic support were ibuprofen and cefazolin, and one of them received also intravenous adrenaline. Eleven out of 14 patients with suspected

drug related anaphylaxis were treated with oxygen and this group showed significant differences in oxygen flow, with higher flow records.

All patients with suspected food-related anaphylaxis were treated with adrenaline by the recommended IM route, ($p < 0.05$ Fisher's Exact Test), compared with n = 11/14 that received adrenaline in suspected drug allergy, out of which only 3/11 was intramuscularly ($p<0.05$, Pearson Chi-Square).

Mortality

The only fatal case was a patient that developed anaphylactic shock with cardiorespiratory arrest due to multiple *Hymenoptera* stings (three, one of them in the cervical region). This patient had a previous episode of anaphylaxis due to *Hymenoptera* venom, about 2 years before the fatal episode and no specialty consultation was performed after the initial episode. This patient had arterial hypertension treated with ACEI. Clinical manifestations were urticaria, angioedema, glottal edema and dyspnoea, about 10-15 minutes after *Hymenoptera* stingings. In ED, the patient presented with hypotension refractory to fluid therapy and was administered 3 doses of 0.5mg adrenaline IV, with time intervals of 5 minutes, oxygen and corticosteroid therapy. The patient did not respond to resuscitation and died about one hour after admission (approximately two and a half hours after exposure to venom).

DISCUSSION

In this study we characterized the clinical manifestations and treatment of patients admitted for anaphylaxis in the ED of a tertiary hospital. Several clinical associations between anaphylaxis manifestations and patients characteristics were observed.

The male preponderance (54%) in cases of anaphylaxis noted in this study is not consistent with other published studies that cited a slightly higher incidence in females[19–22]. We also observed differences in the gender predisposition of different groups of this study, such as, *Hymenoptera* venom allergy was present only in males, whereas allergy to iodinated contrast agents occurred exclusively in females.

The presence of comorbidities had a clear association with the severity of anaphylaxis in our study. Obesity was strongly associated with severe clinical manifestations and it was present in all patients that developed shock.. This is concordant with several studies that showed an association between obesity and fatal outcomes[23,24].

The attributable causes of anaphylaxis reported in our study were similar to those reported in the literature for this age group[4]: drugs were the main cause, in particular beta-lactam antibiotics. Regarding food allergy,

shellfish, in particular shrimp, was the most frequently suspected trigger, contrarily to what was found in other Portuguese studies, in which nuts were the most frequently cited food [25].

Our study included 5 cases of anaphylaxis with onset >1 hour after allergen contact. In this group of patients, four had suspected food allergies, in agreement with previous observations that type I hypersensitivity reactions to food may take longer to develop, but usually within 2 hours after ingestion[26].

The treatment discrepancies between suspected food anaphylaxis and suspected drug anaphylaxis is possibly related with the non-recognition of the allergic reaction in drug related cases, as some cases may be interpreted as a non-immunological adverse reaction. The high number of patients with suspected drug related anaphylaxis treated with high oxygen flow therapy may be justified by the fact that most of the reactions occurred inside the hospital.

Regarding anaphylaxis due to *Hymenoptera* venom allergy, two patients had a previous history of anaphylactic reaction to the same trigger, none of them had previous follow-up in Allergy & Clinical Immunology consultation (and therefore no previous *Hymenoptera* venom immunotherapy).

An accurate diagnosis of anaphylaxis may be difficult in the emergency department due to the wide spectrum of clinical presentations and the absence of optimal clinical or laboratorial markers[27]. Late diagnosis of anaphylaxis may delay adrenaline administration and result in worse outcomes. Serum tryptase is considered a specific marker of mast cell degranulation, but it is not always elevated during anaphylaxis and laboratorial processing is usually deferred in time [28,29]. However, it is the only available marker that supports the diagnosis of anaphylaxis, especially when compared with patient's baseline values[4]. In this study, serum tryptase during the anaphylaxis episode was collected only in 4 patients, probably because the clinical presentation was easily recognized on the initial approach or due to the inability of some ED doctors to add this specific analysis on our ALERT® system.

Intramuscular adrenaline is considered the treatment of choice for anaphylaxis in most anaphylaxis consensus and guidelines[10,21,30,31]. However, as also observed in other studies[12,25], there is still a gap in the route of administration of first line therapy: only n=21 patients received adrenaline intramuscularly and n=5 received adrenaline IV (all of which in shock situations), whereas a high proportion of patients were administered subcutaneous adrenaline (n=13).

Despite the long period studied (10 years), only 43 patients were included, at least in part due to the absence of a specific coding for anaphylaxis in ICD-9. ICD-9 has diagnostic codes only for "allergy" and "anaphylactic shock", leaving out the rest of the spectre of anaphylactic reactions[17]. This issue is a major concern of allergy scientific societies and is currently being addressed in the forthcoming ICD-11[31]. In addition, it is sometimes difficult for physicians to codify during clinical practice. These reasons may help explain the low number of cases identified and the fact that a large proportion of patients included in our study presented with severe reactions, namely anaphylactic shock.

The limitations of our study include its retrospective nature, the possibility of under-reporting/lack of correct codification, and missing data from incomplete data records. The lack of anaphylaxis codification or incorrect ICD codification has likely limited the number of patients included in the study. Due to the patient selection method, the incidence of anaphylaxis could not be determined.

CONCLUSION

Anaphylaxis is a medical emergency and its early recognition and treatment is paramount to prevent fatal outcomes. In this study we evaluated clinical presentation of anaphylaxis, evaluation of its possible causes, treatment and adequate referral in a tertiary hospital centre. Incomplete medical records were frequent and an investment in their improvement would be necessary to obtain more accurate estimates of the burden of anaphylaxis. Obesity was highlighted as an important factor of poor prognosis, as all obese patients developed shock during the anaphylactic reaction.

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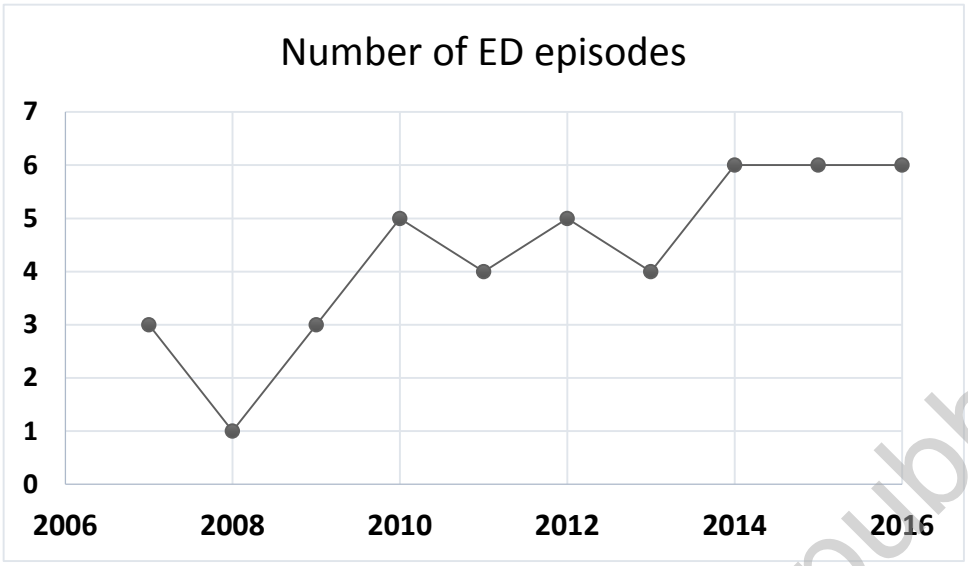

Figure 1 – Number of hospital admissions to ED-CHUC for anaphylaxis per year

COMORBID ALLERGIC DISEASES	n=22
Allergic asthma	n=7
Allergy to beta-lactams	n=6
Allergic rhinitis	n=5
Chronic spontaneous urticaria	n=5
Allergy to non-steroidal anti-inflammatory drugs	n=3
Allergy to cow's milk proteins	n=3
Anaphylaxis to Hymenoptera sting	n=2
Anaphylaxis	n=2
Allergy to corticosteroids	n=1

Table 1 - Comorbid allergic diseases in patients with anaphylaxis admitted to ED-CHUC

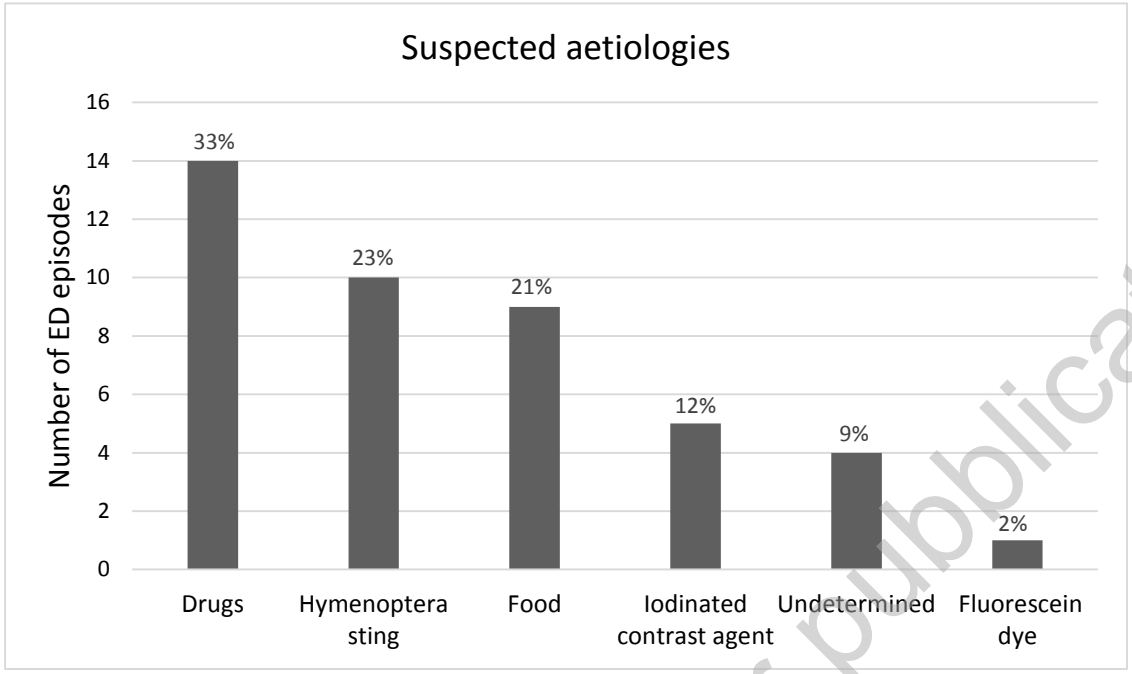

Figure 2 - The most frequent causes of anaphylaxis admitted to ED-CHUC.

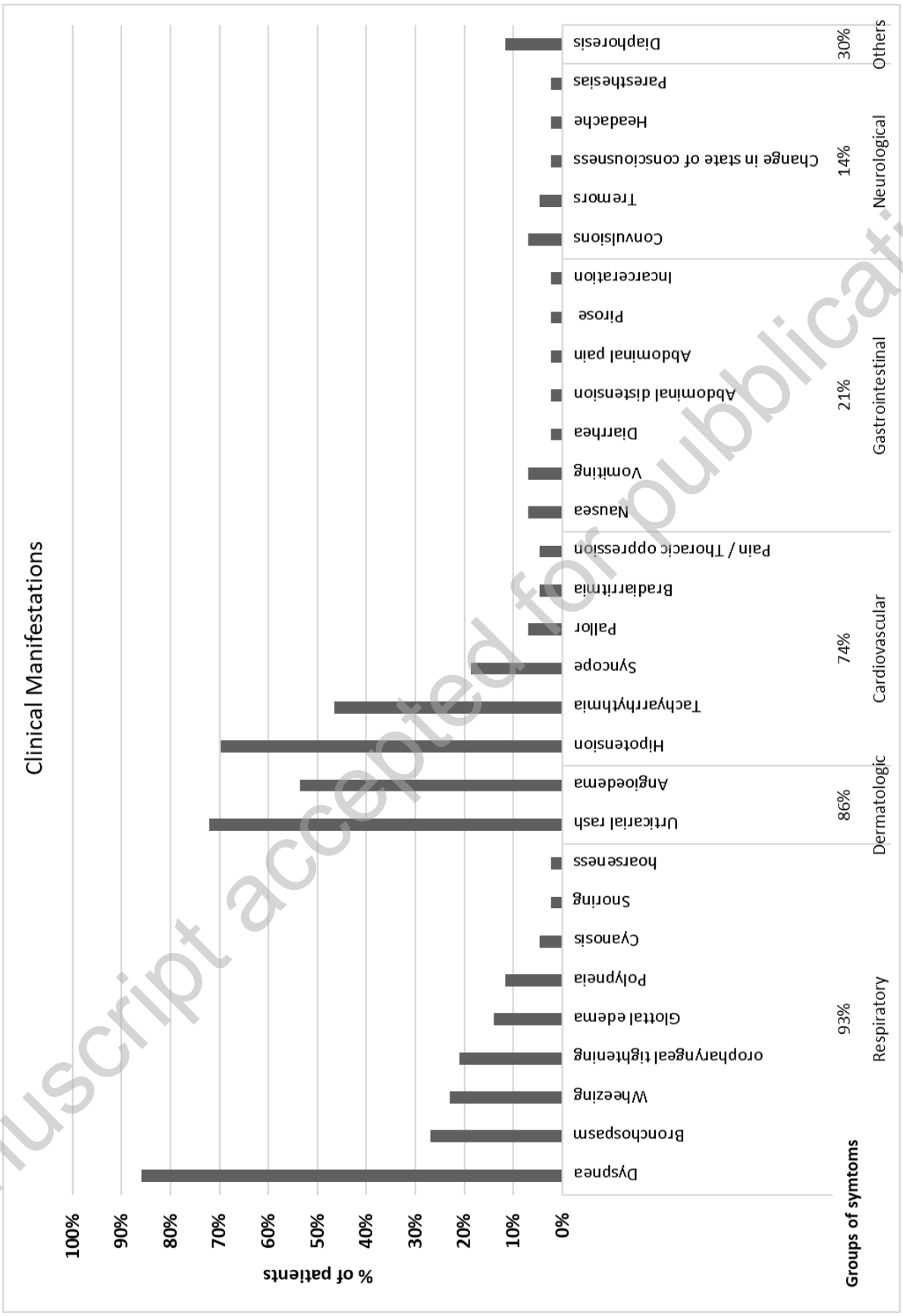

Figure 3 – Signs and symptoms of anaphylaxis in the studied population

COMORBIDITIES	n=35
Arterial hypertension	n=22
Obesity	n=11
Oncological disease	n=10
Alcohol, drug or tobacco abuse	n=9
Depression	n=8
Non-insulin treated diabetes	n=8
Dyslipidaemia	n=8
Thromboembolic disease	n=5
Cardiac arrhythmias	n=3
Sarcoidosis	n=3
Chronic obstructive pulmonary disease	n=3
Thyroid diseases	n=2
Infectious diseases (Acquired Immunodeficiency Syndrome, Tuberculosis and Hepatitis C)	n=1

Table 2 - Comorbidities in the studied population.

Food	n=9
1.1 Shellfish and Molluscs	**n=4**
1.1.1 Shrimp	n=3
1.1.2 Shrimp and squid	n=1
1.2 Dry fruits	**n=2**
1.2.1 Walnut	n=1
1.2.2 Hazelnut	n=1
1.3 Fish	**n=1**
1.3.1 Codfish, hake and tuna	n=1
1.4 Fresh fruits	**n=1**
1.4.1 Peach	n=1
1.5 Legumes	**n=1**
1.5.1 White bean and cabbage	n=1
Drugs	**n=14**
1.1 Antibiotics	**n=4**
1.1.1 Amoxicillin-clavulanic acid	n=1
1.1.2 Cefazolin	n=1
1.1.3 Cefuroxime	n=1
1.1.4 Penicillin	n=1
1.2 Analgesics	**n=3**
1.2.1 Tramadol	n=1
1.2.2 Paracetamol	n=1
1.2.3 Magnesium metamizole	n=1
1.3 Non-steroidal anti-inflammatory drugs	**n=3**
1.3.1 Ibuprofen	n=1
1.3.2 Diclofenac	n=1
1.3.3 Etoricoxib	n=1
1.4 Anesthetics	**n=2**
1.4.1 Lidocaine	n=2
1.5 Benzodiazepines	**n=1**
1.5.1 Diazepam	n=1
1.6 Chemotherapeutic agents	**n=1**
1.6.1 Paclitaxel and carboplatin	n=1

Table 3-Description of the suspected drugs and foods involved in anaphylactic reactions.

SUPPLEMENTARY TABLE 1

Patient	Age (years)	Gender	Shock	Etiology	Atopy	Comor-bidities	Angiotensin Converting Enzyme Inhibitors	Non-steroidal anti-inflammatory drugs	Beta-blockers	Physical exercise	Mortality	Intensive Care	Dermato-logical	Respiratory	Cardiovascular	Neurological
1	63	Male	Yes	Drug	No	Yes	No	No	No	No	No	No	Yes	Yes	Yes	Yes
2	64	Female	No	Drug	No	Yes	Yes	No	Yes	No	No	No	Yes	Yes	No	No
3	54	Male	Yes	Drug	No	Yes	No	No	No	No	No	No	Yes	Yes	Yes	No
4	56	Male	Yes	Drug	No	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes
5	61	Male	Yes	Drug	No	Yes	Yes	No	No	No	No	No	No	Yes	Yes	No
6	71	Female	Yes	Drug	No	Yes	No	No	No	No	No	Yes	Yes	Yes	Yes	No
7	48	Female	No	Drug	No	Yes	No	No	No	No	No	No	Yes	No	No	No
8	58	Female	Yes	Drug	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	No
9	24	Female	Yes	Drug	Yes	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No
10	55	Female	Yes	Drug	Yes	Yes	No	No	No	No	No	Yes	No	Yes	Yes	No
11	57	Male	No	Drug	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	No	Yes
12	56	Male	Yes	Drug	Yes	Yes	No	No	No	No	No	No	Yes	Yes	Yes	Yes
13	79	Female	Yes	Drug	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	Yes	No
14	66	Female	No	Drug	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	No	No
15	73	Male	Yes	Food	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	No
16	27	Male	No	Food	Yes	No	No	No	No	No	No	No	Yes	Yes	No	No
17	82	Female	Yes	Food	Yes	Yes	Yes	No	No	No	No	Yes	No	Yes	Yes	No
18	78	Male	No	Food	Yes	Yes	No	No	No	No	No	No	Yes	Yes	No	No
19	27	Male	No	Food	No	No	No	No	No	Yes	No	No	Yes	Yes	Yes	No
20	43	Female	Yes	Food	Yes	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No
21	84	Female	Yes	Food	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	No
22	60	Female	Yes	Food	Yes	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Yes	No
23	59	Female	No	Food	No	Yes	Yes	No	Yes	No	No	No	Yes	Yes	No	No
24	65	Male	Yes	Dyestuff	No	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	No
25	61	Male	No	Venon	Yes	No	No	No	No	No	No	No	Yes	Yes	No	No
26	52	Male	Yes	Venon	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	No
27	44	Male	No	Venon	No	No	No	No	No	No	No	No	Yes	Yes	No	No
28	23	Male	Yes	Venon	Yes	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No
29	42	Male	Yes	Venon	Yes	Yes	No	No	No	No	No	No	Yes	Yes	Yes	No
30	28	Male	Yes	Venon	No	No	No	No	No	No	No	No	Yes	Yes	Yes	No
31	52	Male	No	Venon	Yes	Yes	Yes	No	Yes	No	No	No	Yes	No	No	Yes
32	38	Male	Yes	Venon	No	Yes	No	No	No	No	No	No	Yes	Yes	Yes	No
33	43	Male	Yes	Venon	No	Yes	No	No	No	No	No	Yes	Yes	Yes	Yes	No
34	55	Male	Yes	Venon	No	Yes	No	No	No	No	No	No	No	Yes	Yes	No
35	38	Female	Yes	Iodinated contrast agent	No	Yes	No	No	No	No	No	Yes	Yes	Yes	Yes	No
36	64	Female	Yes	Iodinated contrast agent	No	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	No
37	62	Female	Yes	Iodinated contrast agent	No	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	No
38	73	Female	Yes	Iodinated contrast agent	No	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	No
39	68	Female	Yes	Iodinated contrast agent	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	No
40	49	Male	No	Undetermined	No	Yes	No	No	No	No	No	No	Yes	Yes	Yes	No
41	23	Female	Yes	Undetermined	Yes	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes
42	49	Female	Yes	Undetermined	Yes	Yes	Yes	No	No	No	No	No	Yes	No	Yes	No
43	61	Male	No	Undetermined	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	No	No

Patient	Oxygen therapy (L/min)	Orotracheal intubation	Cardiorespiratory arrest	Fluid Therapy	Anti-H1	Anti-H2	Salbutamol and/or Ipratropium bromide	Intravenous corticosteroid therapy	Dopaminergic support	ADR	ADR Inhalation	ADR Intravenous	ADR Intra muscular	ADR Sub cutaneous	Allergology and Clinical Immunology consultation
1	No	No	No	Yes	Yes	No	No	Yes	No	No	No	No	No	No	No
2	10	No	No	Yes	Yes	No	Yes	Yes	No	No	No	No	No	No	No
3	3	No	No	Yes	No	No	No	Yes	No	Yes	Yes	No	No	No	No
4	4	No	No	Yes	No	No	No	Yes	No	Yes	No	Yes	No	No	No
5	15	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No
6	4	No	No	Yes	No	No	Yes	Yes	No	Yes	No	No	No	Yes	No
7	No	No	No	No	Yes	No	No	Yes	No	No	No	No	No	No	Yes
8	2	No	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	No	No	Yes
9	15	Yes	No	Yes	No	No	No	Yes	No	Yes	No	No	Yes	No	Yes
10	2	No	Yes	Yes	No	No	No	Yes	No	Yes	No	No	No	Yes	Yes
11	12	No	No	No	Yes	No	Yes	Yes	No	Yes	No	No	No	Yes	Yes
12	3	No	No	Yes	Yes	No	Yes	Yes	No	Yes	No	No	No	Yes	Yes
13	10	No	No	No	Yes	Yes	No	Yes	Yes	Yes	No	No	No	Yes	Yes
14	12	No	No	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes
15	2	No	No	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	No	No
16	No	No	No	No	Yes	No	No	Yes	No	No	No	No	No	No	Yes
17	2	No	Yes	Yes	No	No	No	Yes	No	Yes	No	No	Yes	No	Yes
18	No	No	No	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	No	Yes
19	2	No	No	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	No	Yes
20	4	No	No	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	No	Yes
21	15	No	No	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	No	Yes
22	6	No	No	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No	Yes
23	No	No	No	No	Yes	No	Yes	Yes	No	Yes	No	No	Yes	No	Yes
24	15	Yes	Yes	No	Yes	No	No	Yes	No	Yes	No	No	Yes	No	Yes
25	No	No	No	No	Yes	No	No	Yes	No	No	No	No	No	No	No
26	15	Yes	Yes	Yes	No	No	No	Yes	No	Yes	No	Yes	No	No	No
27	2	No	No	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	No	No
28	3	No	No	Yes	Yes	No	No	Yes	No	Yes	No	Yes	No	No	Yes
29	No	No	No	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	No	Yes
30	No	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No	Yes
31	No	No	No	Yes	No	No	No	Yes	No	Yes	No	No	No	Yes	Yes
32	No	No	No	Yes	Yes	No	No	Yes	No	Yes	No	No	No	Yes	Yes
33	15	Yes	No	Yes	Yes	No	No	Yes	No	Yes	No	No	No	Yes	Yes
34	2	No	No	Yes	No	No	Yes	Yes	No	Yes	No	No	No	Yes	Yes
35	No	No	No	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	No	No
36	3	No	No	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	No	No
37	No	No	No	Yes	No	No	No	Yes	No	Yes	No	No	No	Yes	No
38	15	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	No	Yes	No
39	No	No	No	Yes	Yes	No	No	Yes	No	Yes	No	No	No	Yes	Yes
40	No	No	No	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	No	No
41	No	No	No	No	Yes	No	No	No	No	Yes	No	No	Yes	No	Yes
42	3	No	No	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	No	Yes
43	No	No	No	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No	Yes

Supplementary table 1: Patient characteristics. ADR - adrenaline