ORIGINAL ARTICLE

Anaphylaxis in Adolescent/Adult Patients Treated in the Emergency Department: Differences Between Initial Impressions and the Definitive Diagnosis

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Abstract

Objectives: To contrast the initial suspected etiology of anaphylaxis with the postworkup diagnosis in patients attended at the emergency department (ED) of a tertiary-level hospital in Spain and to investigate the incidence, causes, and management of anaphylaxis.
Methods: We performed an observational study of patients aged more than 15 years who came to the ED with anaphylaxis between 2009 and 2010. All clinical records from the ED were reviewed. We recorded data on clinical management, the etiology proposed by the attending emergency physician, and the cause reported by the patient. The findings were compared with the diagnosis reached after the allergy workup.
Results: The incidence of anaphylaxis was 0.08%. The most common manifestation was skin-mucosal symptoms (98.3%). Anaphylaxis was diagnosed in the ED in only 44% of the cases, regardless of severity. Only 39.7% received epinephrine, which was administered more frequently when the ED physician diagnosed anaphylaxis, regardless of severity. A total of 60 patients were subsequently seen at the allergy department. The final etiology differed from the initial suspicion in the ED in 45% of cases. The frequency of anaphylaxis of uncertain origin decreased from 33.3% to 13.3%. After the allergy workup, drugs (41.7%) were considered the main cause of anaphylaxis, followed by food (25%).
Conclusions: The incidence of anaphylaxis (0.08%) was double that estimated in the ED. Anaphylaxis is underdiagnosed. A correct diagnosis conditions the administration of epinephrine, regardless of the severity of symptoms. The real etiology of anaphylaxis should only be proposed after an allergy workup, which is recommended in all cases, as the real cause can differ considerably from the initial impression in the ED.

Key words: Anaphylaxis. Drug allergy. Emergency department. Epidemiology. Food allergy. Etiology. Allergy study. Comparison.

Resumen

Objetivos: Contrastar la etiología sospechada de la anafilaxia con el diagnóstico tras el estudio alergológico en la población atendida en el Servicio de Urgencias (SU) de un hospital español de tercer nivel, y determinar incidencia, causas y manejo de la anafilaxia.
Métodos: Se realizó un estudio observacional con pacientes mayores de 15 años de edad del SU con anafilaxia, entre 2009 y 2010. Se revisaron las historias clínicas del SU. Se recogieron manejo clínico, impresión etiológica del médico de Urgencias y paciente. Éstos se compararon con el diagnóstico final tras el estudio alergológico.
Resultados: La incidencia de anafilaxia fue 0,08%. La manifestación más frecuente fue la cutáneo-mucosa (98,3%). Sólo se diagnosticó de anafilaxia al 44% de los casos, independientemente de la gravedad. El 39,7% recibió adrenalina, más frecuentemente si se diagnosticaban de anafilaxia, independientemente de la gravedad. Un total de 60 pacientes se atendieron posteriormente en Alergología. La etiología final cambió en un 45% del sospechado en el SU. El origen incierto se redujo de un 33.3% a un 13.3%. Tras el estudio alergológico, la causa más frecuente fueron los fármacos (41,7%), seguidos de los alimentos (25%).
Conclusiones: La incidencia de anafilaxia, 0,08%, dobló la estimada en el SU. La anafilaxia está infradiagnosticada, mientras que el diagnóstico correcto condiciona la administración de adrenalina, independientemente de la gravedad. La verdadera etiología de la anafilaxia debería considerarse tras el estudio alergológico, que se debería recomendar a todos los pacientes, ya que puede ser diferente de la impresión en el SU.

Palabras clave: Anafilaxia. Alergia a fármacos. Urgencias. Epidemiología. Alergia a alimentos. Etiología. Estudio alergológico. Comparación.

Introduction

Anaphylaxis is defined as a severe allergic reaction that is rapid in onset and can be fatal [1]. Although this definition is currently the most widely used, it is not universally accepted. The lack of consensus, together with the severity of the clinical symptoms, hampers diagnosis, appropriate management in the emergency department (ED), and identification of the trigger [2].

There are few data on the incidence of anaphylaxis [3]. Several recent studies have attempted to establish the incidence of anaphylaxis in the ED. The studies are mostly based on database searches, which revealed incidence rates of 0.07% to 0.4% [4-12]. Such large differences may be due in part to the characteristics of the populations analyzed and to methodological factors [13]. Furthermore, there are no complementary tests to confirm or rule out anaphylaxis, although serum tryptase, a marker of mast cell activity, can be elevated during acute episodes [11]. Therefore, it should be measured if possible. Moreover, persistently elevated tryptase levels could enable us to detect patients with indolent mast cell activation syndromes [14].

In the literature, the etiology of anaphylaxis is based mainly on the impression formed in the ED, which may or may not subsequently be confirmed.

The objective of the present study was to determine the concordance between the diagnosis made in the ED and that confirmed after the allergy workup in adolescent and adult patients. We investigated the incidence, clinical management, and etiology of anaphylaxis in a tertiary level hospital in Spain.

Methods

Design

We performed an observational, descriptive study of patients who presented with clinical symptoms of anaphylaxis at the ED of Hospital General Universitario Gregorio Marañón, Madrid, Spain between June 2009 and May 2010. Our hospital is a reference center for a population of 650,000 inhabitants. The emergency department attends patients aged more than 15 years (younger patients are referred to the Pediatrics Department).

The study was approved by the Ethics Committee for Medical Research at our institution (reference number 299/13). As the study was retrospective and observational, the local ethics committee did not require informed consent to be obtained from the patients.

Selection of Participants

An allergy specialist performed a thorough review of the clinical records of patients aged more than 15 years admitted to the Internal Medicine department from the ED. Records from nonmedical emergencies were examined carefully only if the diagnosis was allergy-related.

Patients were considered to have anaphylaxis when their condition met the clinical criteria established by the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) [1], regardless of the initial diagnosis that had been assigned to them in the ED report.

NIAID/FAAN guidelines consider the diagnosis of anaphylaxis to be highly likely when any of the following criteria are fulfilled: *i*) involvement of skin and/or mucosal tissue and with respiratory compromise or signs of cardiovascular dysfunction or hypotension; *ii*) involvement of 2 or more systems (skin and/or mucosal tissue, respiratory, cardiovascular, and gastrointestinal) after recent exposure to a likely allergen; or *iii*) signs of cardiovascular dysfunction after exposure to a known allergen.

Patients who had been admitted for other reasons and presented anaphylactic symptoms during their stay were not included.

Outcomes

Anaphylactic reactions were classified according to severity. An episode was defined as severe if the patient presented arterial oxygen saturation <90%, arterial hypotension (systolic arterial tension <90 mmHg), and/or loss of consciousness [15]. Within this group, patients who experienced arterial hypotension or loss of consciousness were considered to have anaphylactic shock.

We recorded demographic data, clinical symptoms, treatment, factors suspected by the patient and the ED physician to be the anaphylactic trigger, and the final diagnosis. The number of patients admitted daily to the emergency department was also recorded.

As part of our clinical routine, patients were referred to the Allergy Department, where they were reevaluated and the etiology of their reaction was studied. We recorded findings from skin tests and challenge tests, determination of total and specific IgE, complete blood count, biochemistry, catecholamines in urine, and baseline serum tryptase (when indicated).

Statistical Analysis

The statistical analysis was performed using SPSS for Windows, version 16.0 and Microsoft Excel 2003. Qualitative variables are expressed as frequency and percentage, and quantitative variables are expressed as median (IQR).

Categorical variables were compared using the chi-square test, Fisher exact test, and Cochran Q test. Quantitative variables were assessed using the Mann-Whitney test and Kruskal-Wallis 1-way analysis of variance.

The Cohen κ was calculated to assess the reliability of agreement between raters. The κ value was interpreted following the Fleiss grading scale (poor to very good).

P values of <.05 were considered statistically significant.

Results

Incidence of Anaphylaxis and Characteristics of the Study Patients

Of the 145 824 patients who were attended at the ED, we recorded 116 cases of anaphylaxis (cumulative incidence 0.08%). The 116 patients were among the 88 380 patients admitted to the Internal Medicine Department (cumulative incidence, 0.13%). The group included 57 women and 59 men

with a median age of 42.7 (24.5) years. Only 3 were under 20 years old. Twenty-four patients (19.8%) reported a history of atopy (Table 1).

The most common clinical manifestation was skin and/or mucosal symptoms (98.3%), followed by respiratory tract symptoms (79.3%) and gastrointestinal tract symptoms (31%). Severe signs were recorded in 29 patients, 23 of whom developed anaphylactic shock (Table 2).

Table 1. Characteristics of Patients Who Presented With Anaphylaxis in the Emergency Department and Were Subsequently Assessed in the Allergy Department

	Emergency Department (n=116)	Allergy Department (n=60)	*P* Value
Incidence	0.08%	-	-
Sex			.57
- Male	59 (50.9%)	29 (48.3%)	-
- Female	57 (49.1%)	31 (51.7%)	-
Median (IQR) age, y	42.7 (24.5)	49.8 (33.8)	.001
Atopy	24 (19.8%)	11 (18.3%)	.51
- Rhinoconjunctivitis	13 (11.2%)	6 (10%)	.67
- Asthma	17 (14.7%)	7 (11.7%)	.35
- Atopic dermatitis	1 (0.9%)	0	.29
- Food allergy	16 (13.8%)	7 (11.7%)	.49
Diagnosis of anaphylaxis	51 (44%)	28 (46.7%)	.54
Severity	29 (25%)	20 (33.3%)	.09
Administration of epinephrine	46 (39.7%)	24 (40%)	.76

Table 2. Clinical Manifestations of Patients With Anaphylaxis

Signs and symptoms	Number of patients (N=116)
Skin	114 (98.3%)
- Angioedema	62 (53.4%)
- Urticaria	59 (50.9%)
- Pruritus	39 (33.6%)
- Flushing	25 (21.6%)
Respiratory	92 (79.3%)
- Dyspnea	74 (63.8%)
- Laryngeal edema	52 (44.8%)
- Wheezing	17 (14.7%)
- Oxygen arterial saturation < 95%	17 (14.7%)
- Cyanosis	1 (0.9%)
Abdominal	36 (31%)
- Abdominal pain	33 (28.4%)
- Nausea or vomiting	26 (22.4%)
- Diarrhea	4 (3.4%
Cardiovascular	40 (34.5%)
- Tachycardia	20 (17.2%)
- Arterial hypotension	14 (12.1%)
- Instability, dizziness	13 (11.2%)
- Loss of consciousness	13 (11.2%)
- Chest pain	9 (7.8%)

Diagnosis of Anaphylaxis: Half of the Patients Were Not Diagnosed With Anaphylaxis in the ED

Allergy specialists who reviewed ED records made the final diagnosis of anaphylaxis following the NIAID/FAAN guidelines. The ED report reflected a diagnosis of anaphylaxis in only 44% of the cases that fulfilled the diagnostic criteria. Other common terms used instead of anaphylaxis were *allergic reaction* (35.3%), *urticaria* (6.9%), and *angioedema* (5.1%). The diagnosis of anaphylaxis in the report was made regardless of severity (*P*=.09) (Figure 1). Of the 23 patients who developed anaphylactic shock, only 6 were diagnosed as such in the reports; 8 were called anaphylaxis, and the remaining 9 received a different diagnosis.

Treatment of Anaphylaxis: Only 40% of the Patients Received Epinephrine

Epinephrine was administered in 46 episodes (39.7%). The dose was given intramuscularly in 16 cases and subcutaneously in the remaining 30. Other treatments included antihistamines (68.1%), corticosteroids (72.4%), and bronchodilators (6.9%). No treatment was needed in 11 cases. Epinephrine was more commonly administered to patients who had been diagnosed with anaphylaxis by the ED physician (*P*<.001); this factor was independent of the severity of the symptoms (*P*=.11) (Figure 1) or the presence of anaphylactic shock (*P*=.1). The epinephrine autoinjector was only prescribed at discharge in 9 episodes (7.8%).

Etiology in the ED Department: Over 40% of the Patients Were Discharged Without an Etiological Diagnosis

A total of 42 patients (42.2%) were discharged without an etiological diagnosis and, therefore, no instructions on what to do to avoid future anaphylactic episodes. The most frequent triggers were drugs (32.8%), followed by food (18.1%),

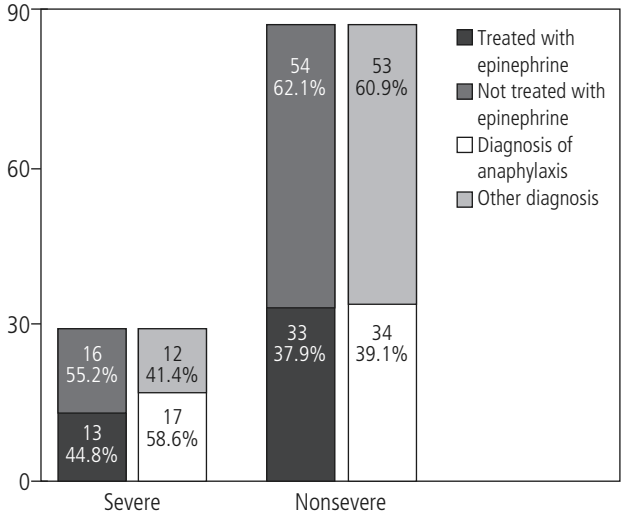

Figure 1. Treatment of anaphylaxis. Less than half of the patients were diagnosed with anaphylaxis, regardless of the severity of symptoms (*P*=.09). The use of epinephrine in anaphylaxis was low, regardless of the severity of symptoms (*P*=.11).

Anisakis simplex (4.3%), and Hymenoptera venom (1.7%). Eighty-three patients (71.6%) were referred to an allergist.

Three patients (2.6%) returned to the ED with a second episode of anaphylaxis. The second episode was at least 1 month later in all 3 cases. These patients had not received an etiological diagnosis at discharge after the first visit. After the allergy workup, they were diagnosed with allergy to nonsteroidal anti-inflammatory drugs (NSAIDs), nut allergy, and idiopathic anaphylaxis.

The Final Etiologic Diagnosis of Anaphylaxis Differed From the Suspicion Recorded in the ED Report

Sixty cases (51.7%) were eventually followed up in the Allergy Department. The patients comprised 29 men and 31 women with a median age of 49.8 (33.8) years, and only 2 were aged less than 20 years. There were no statistically significant differences between patients who came to the unit and those who did not with respect to the following: sex (*P*=.57), severity of the condition (*P*=.09), atopy (*P*=.51), a diagnosis of anaphylaxis in the ED (*P*=.54), and the suspected trigger (*P*=.08). However, patients who attended the allergy unit were older (49.8 years vs 42.7 years; *P*=.001) (Table 1), although there were no differences in distribution by age group (*P*=.57).

No statistically significant differences were observed between the causes of anaphylaxis and age (*P*=.37), sex (*P*=.21), history of atopy (*P*=.89), or severity of symptoms (*P*=.16).

The allergy workup revealed the trigger of the anaphylactic episodes in 52 patients (86.7%). The frequency of the classification *uncertain origin* decreased from 33.3% to 13.3% (60% reduction) (Table 3). Thirty percent of those with a suspected trigger in the ED had received an incorrect diagnosis.

Drugs were the most common cause of anaphylaxis (41.7%), followed by foods (25%). The most commonly involved pharmacological groups were NSAIDs (56%), followed by ß-lactam antibiotics (28%) (Table 3).

The findings recorded after the allergy workup differed from the initial diagnosis made by the ED physician in 45% of cases. A suspected diagnosis of drug allergy in the ED was finally confirmed in 21 of 27 patients (77.8%). In addition, the ED physician detected that a drug was the trigger in 84% of the drug-allergic patients. In 81%, the drug group suspected was correct (Table 3).

Food allergy was suspected in 33.3% of the allergic patients seen in the ED, and the food group suspected was correct in 53.3%, ie, 66.7% more correct diagnoses of food allergy were made after the workup. Nuts were significantly undersuspected (*P*=.04), whereas fish was oversuspected (*P*=.02) (Table 3).

Anaphylaxis caused by the fish parasite *A simplex* was highly underestimated in the ED (3.3% of the cases vs 18.3% after the allergy workup) (Table 3).

Agreement between the ED physician's etiologic impression and the final diagnosis of anaphylaxis was assessed using the Cohen κ. Agreement between the two was poor (κ, 0.40; 95% CI, 0.25-0.56; *P*<.0001).

The patient's suspicion of the trigger was also erroneous in 42.4% of cases. Even though there were no significant differences in percent estimates for any specific group (eg, drugs, food, and Hymenoptera) other than *A simplex*, patients diagnosed with drug allergy were positive to a different drug in 32% of cases (Table 4).

The difference for food-allergic patients was more marked. The suspected food differed from the causative one in 89.7% of cases. Fish was the most oversuspected trigger, while nuts was suggested by 1 of the 7 patients who were finally diagnosed with nut allergy (Table 4).

The number of patients who could not identify a trigger was the same as that of patients who were finally diagnosed with anaphylaxis of unknown origin. However, these were not the same individuals. The etiological agent was finally identified after the allergy workup in 6 out of 8 (75%) patients with no suspected trigger in the ED.

Agreement between the patient's observation and the final diagnosis of anaphylaxis was assessed using the Cohen κ. Agreement between the two was poor (κ, 0.42; 95% CI, 0.26-0.58; *P*<.0001).

Table 3. Triggers of the 60 Cases of Anaphylaxis Followed up in the Allergy Department, According to the Emergency Department Report and the Allergy Workup. Cohen κ, 0.40 (95% CI, 0.25-0.56; *P*<.0001)

Causes	Emergency Report Suspicion	Final Diagnosis	*P* Value
Food	9 (15%)	15 (25%)	.17
- Fish	3 (33.3%)	0 (0%)	.02
- Seafood	1 (11.1%)	2 (13.3%)	.63
- Fruits	3 (33.3%)	4 (26.7%)	0.9
- Nuts	0 (0%)	7 (46.7%)	.04
- Other	2 (22.2%)	2 (13.3%)	.57
Drugs	27 (45%)	25 (41.7%)	.71
- NSAIDs	10 (37%)	14 (56%)	.17
- ß-lactams	9 (33.3%)	7 (28%)	.68
- Other	8 (29.6%)	4 (16%)	.24
Hymenoptera	1 (1.7%)	1 (1.7%)	.48
Anisakis simplex	2 (3.3%)	11 (18.3%)	.008
Unidentified	20 (33.3%)	8 (13.3%)	.009

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug.

Table 4. Triggers of the 60 Cases Followed up in the Allergy Department, as Reported by the Patient and Diagnosed After the Allergy Workup[a]

Causes	Patient Suspicion	Final Diagnosis	*P* Value
Food	21 (35%)	15 (25%)	.23
- Fish	6 (28.6%)	0 (0%)	.02
- Seafood	5 (23.8%)	2 (13.3%)	.72
- Fruits	5 (23.8%)	4 (26.7%)	0.85
- Nuts	1 (4.8%)	7 (46.7%)	.01
- Other	4 (19%)	2 (13.3%)	.65
Drugs	30 (50%)	25 (41.7%)	.36
- NSAIDs	12 (40%)	14 (56%)	.23
- ß-lactams	9 (30%)	7 (28%)	.87
- Other	9 (30%)	4 (16%)	.22
Hymenoptera	1 (1.7%)	1 (1.7%)	.48
Anisakis simplex	0 (0%)	11 (18.3%)	.0005
Unidentified	8 (13.3%)	8 (13.3%)	.79

[a]Cohen κ, 0.42 (95%CI, 0.26-0.58); *P*<.0001.

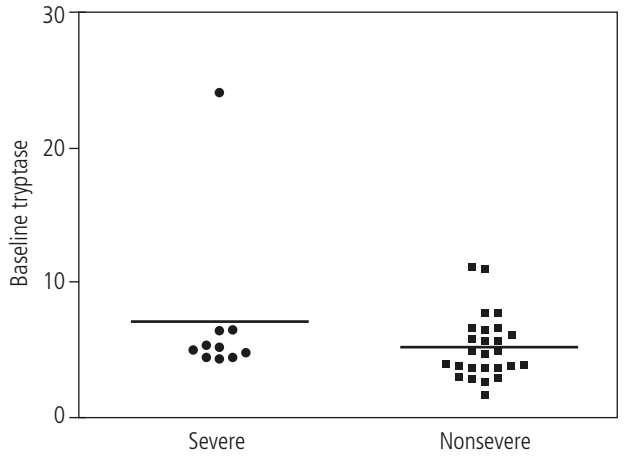

Figure 2. Mean baseline serum tryptase and severity of anaphylaxis. No statistically significant differences in severity were observed (*P*=.13).

The baseline serum tryptase study revealed 1 case of mast cell activation syndrome

Levels of serum tryptase could not be measured during any of the acute episodes owing to unavailability. However, in 36 patients, baseline serum tryptase levels were subsequently measured (15 men and 21 women; median age, 49.2 [32.9] years). Ten patients presented severe symptoms caused by drug allergy (44.4%), food allergy (19.4%), *A simplex* (16.7%), Hymenoptera (2.8%), and unknown allergen in 16.7%. Their distribution was similar to that of the total group of patients.

The median tryptase level was 5.11 (2.46) µg/L, with no differences in severity of the symptoms (Figure 2). Only 1 patient presented a persistently elevated baseline tryptase value (24.3 µg/L) (incidence, 2.7%). She had presented severe anaphylaxis, triggered by allergy to seafood. The patient was finally diagnosed with nonclonal mast cell activation syndrome.

Discussion

Studies on the epidemiology of anaphylaxis are hampered by limited diagnostic criteria and underreporting of the condition by health professionals, which is favored by the lack of a universally accepted clinical definition.

In the present study, the cumulative incidence of anaphylaxis was determined by allergists after analyzing the medical records of all patients attended in the ED. The causes of anaphylaxis were established after a protocol-based allergy workup. The incidence of anaphylaxis was 0.08%, which lies within the range of values for the ED established elsewhere [16]. However, if we only take into account patients from the Internal Medicine Department, the incidence was 0.13%. This could explain differences between studies, since it is not usually stated whether all patients attended in the ED or only real medical emergencies are included. The incidence of anaphylaxis seems to be conditioned by several factors, mainly geographical area and cultural variations, with the result that data vary considerably between studies. If we focus on southern Europe, we find that the incidence we reported is similar to that reported by Cianferoni et al [6] in the region of Florence, Italy (0.074%), but much higher than that reported by Pastorello et al [7] in Milan, Italy (0.03%) or Bellou et al [17] in Nancy, France (0.037%). In Spain, these data are similar to the 0.09% rate that was estimated in Alcorcón (south of Madrid, Spain) [10], although they differ considerably from the 0.39% rate found in Barcelona, Spain [11]. If we broaden our focus, we find that Stewart et al [4] calculated an incidence of 0.066% in Cambridge, United Kingdom, which is lower than that of the present study, as is the 0.001% reported by Poachanukoon et al [9] in Patumthani, Thailand. In Minnesota, USA, Klein et al [18] reported an incidence of 0.09%. However, the highest incidence was reported by Brown et al [5] in Brisbane, Australia (0.22%). The differences in findings may also be due to methodological aspects.

The lack of appropriate codes in the *International Classification of Diseases, Ninth Revision (ICD-9)* makes this classification of little use when attempting to describe anaphylaxis [18,19]. The *ICD-10* update does not seem to be much better [20]. Although large population studies could have better external validity than reports from single institutions, *ICD* codes are limited in terms of sensitivity and specificity [21]. The positive predictive value for *ICD* codes has been reported to range from 52% to 57%, although combination of various codes has provided better results [22]. In 2013, Walsh et al [23] validated an *ICD-9*–based algorithm to identify anaphylaxis in the United States, with a positive predictive value of 75%, although only 66% of cases of anaphylaxis were identified. Consequently, researchers are forced to base their studies on keyword searches [17].

One of the main novelties in the present study is that cases were collected by a thorough review of medical records, and that a significant number of patients were subsequently studied in the allergy department. Since this approach is time-consuming, it cannot be applied to large populations or over many years. Although less cost-effective than other approaches, reviewing medical records avoided the difficulties affecting sensitivity and specificity observed elsewhere [17].

In the ED, patients were diagnosed with anaphylaxis in fewer than half of the cases with diagnostic criteria. Besides, only 8 out of the 23 cases of anaphylactic shock had been properly diagnosed. This problem is related to the rapid progression of the condition and the very nature of emergency work, where the focus is on stabilizing the patient. Furthermore, the excessive caution in using the term anaphylaxis is critical [24]. This phenomenon has been observed elsewhere [3] and is one of the reasons why research based on the diagnosis made in the ED is always significantly biased.

Intramuscular epinephrine is the first-line treatment for anaphylaxis, as recommended in all modern guidelines, including the most recent Cochrane Library review [25]. Accurate recognition of anaphylaxis makes for better management of acute episodes. Patients who had been diagnosed with anaphylaxis in the ED received epinephrine more often, regardless of the severity of their symptoms. Epinephrine was administered to 39.7%, and only in one-third of these patients was the injection intramuscular. Evidence has shown that delayed epinephrine injection is associated with mortality [25]. Nevertheless, and despite the proliferation of guidelines for the

management of anaphylaxis during recent years, epinephrine is still rarely used in clinical practice [26]. In many cases, patients with anaphylaxis do not receive optimal treatment.

Despite the severity of this condition, patients are often reluctant to undergo an allergy workup. Although the workup was proposed to most patients in the ED, only 51.7% agreed to it. Studying all the patients attended would have enabled us to identify the real numbers of etiological factors. This group was representative in all demographic variables except age, which is a key factor in the etiology of anaphylaxis [10]. However, this is mainly evident when comparing children and teenagers to adults. In our study, more than 97% of the patients were over 20 years old. In our opinion, the median difference of 42.7 to 49.8 years between the whole group and the patients studied in the Allergy Department might not predict gross differences. In addition, if our data were applied to a similar population, the exact frequency of triggers might be slightly different.

The most relevant outcome of the present study is the observation that the etiology of anaphylaxis confirmed after a workup differed in many cases from that reported by the patient or proposed by the physician in the ED. Almost half of the patients did not know the cause of their reaction. In many cases, the workup revealed the real trigger. It is important to bear in mind that proposed etiologies based on the first impression in the ED could be erroneous, as there is dissociation between the suspicion and the real cause of anaphylaxis.

Drugs are the causal agent best identified by the ED physician, and it is of interest that once the ED physician predicts drug allergy, the suspect drug is generally correctly identified and appropriate recommendations for avoidance are made. Food is less easily identified in adults. Only one-third of cases are detected in the ED, and the recommendation to avoid the correct food group was made in only half.

In Spain and in other countries, *A simplex* was responsible for one-fifth of cases of anaphylaxis. However, it was considered the causal agent in only 3.3% of cases. Variations in the time between eating fish and the onset of anaphylaxis make it extremely difficult to suspect this allergen.

The etiological data we report differ significantly from those reported elsewhere in Europe [6,7,10], which are based mainly on presumptive diagnoses. In 2 studies, food seemed to be more commonly involved than drugs [7,10].

Three patients required a second visit to the ED for a new episode of anaphylaxis caused by the same trigger. All 3 were discharged without a suspected diagnosis. A specific trigger was identified after the workup in 2 cases. The second episode could have been avoided with a timely allergy workup.

In a follow-up study performed in Barcelona, Spain, patients were further studied in the allergy department [11]. The distribution of confirmed anaphylaxis triggers was similar to that reported in our institution, although no details were provided to clarify the discrepancy between the diagnosis in the ED and the definitive diagnosis.

Mastocytosis or mast cell activation syndrome can manifest with symptoms of anaphylaxis, which are often severe. Apart from the tryptase levels measured in the ED, baseline serum tryptase can help to detect patients whose disease had been silent up to that point [14]. In the cases we report, 1 patient presented elevated baseline tryptase levels after a single anaphylaxis episode. She was finally diagnosed with nonclonal mast cell activation syndrome that would have gone undetected if this marker had not been studied. We found no statistically significant differences in tryptase level with regard to the severity of the symptoms, although such differences have been described in Hymenoptera venom–induced anaphylaxis [27].

Although every effort has been made to overcome the limitations present in previous studies, such as manual review of medical records and collection of allergy workup data, the present study is subject to some limitations. Since the data were collected in an adolescent/adult population of a tertiary-level hospital, our findings may not be extrapolated to other groups of patients or to other healthcare settings. In addition, as only 60 patients underwent an allergy workup, the final percentage of each causative agent could vary in larger populations.

In conclusion, the incidence of anaphylaxis in the ED is low. For many reasons, ED physicians, even in a tertiary-level hospital, tend to underdiagnose this condition, thus leading to erroneous management of the disease. Epinephrine was rarely used, and not all patients were advised to request a workup, which may have helped them to avoid new episodes. Furthermore, studies of the etiology of anaphylaxis must be based on allergy workups, after a careful history is taken by a specialist and, if necessary, after performing additional tests. Considerable differences can be observed between the suspected diagnosis of the ED physician or patient impressions and the definitive diagnosis.

It is necessary to carry out multicenter studies based on reproducible and efficient methods that combine good external validity with diagnostic techniques that provide high sensitivity and positive predictive values. The use of standard definitions of anaphylaxis, validated algorithms, and samples from different populations (eg, primary care and hospital setting) could increase our knowledge of the epidemiology of anaphylaxis.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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