

# Recurrence of Anaphylaxis in a Spanish Series

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## ■ Abstract

*Background:* Anaphylaxis is a potentially fatal condition, and many patients experience recurrence.

*Objective:* We report the incidence of first recurrence of anaphylaxis in our series and examine the risk factors associated with recurrence.

*Methods:* A validated questionnaire was sent to 1512 patients and completed by 887. The chosen definition of anaphylaxis was that of the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network Symposium. We evaluated the incidence of first recurrence of anaphylaxis overall and by subtype (eg, drugs and foods) and attempted to determine associated risk factors.

*Results:* The total incidence rate of the first recurrence of anaphylaxis (same subtype) was 3.2 episodes per 100 person-years (95%CI, 2.83-3.63). Incidence was lower in drug anaphylaxis (2.0 episodes per 100 person-years) than in latex and food anaphylaxis (8.6 and 5.6 episodes per 100 person-years, respectively). Cox and ordinal logistic regression models revealed that a first recurrence was less likely with drug anaphylaxis than with food anaphylaxis. The risk of experiencing 1 or more recurrences was higher for foods, exercise, and idiopathic causes than for the other subtypes.

*Conclusions:* The incidence rate for a first recurrence of the same subtype of anaphylaxis was 2 to 6 times lower than that published by other authors. Recurrence of anaphylaxis is more common in subtypes with an increased prevalence of atopy (food, idiopathic, latex) than in other subtypes (drugs, *Anisakis*). Consequently, particular attention should be paid to prevention and care in this population.

**Key words:** Anaphylaxis. Atopy. Incidence. First. Recurrence. Risk. Factors.

## ■ Resumen

*Antecedentes:* Aunque la anafilaxia es una enfermedad potencialmente fatal, muchos pacientes sufren recurrencias de la misma.

*Objetivo:* Nuestro objetivo fue conocer la incidencia de la primera recurrencia de la anafilaxia en nuestra serie y examinar los factores de riesgo asociados a la misma.

*Métodos:* Un cuestionario validado fue enviado a 1512 pacientes y completado por 887. La definición de anafilaxia elegida fue la del Simposio NIAID-FAAN (National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network). Se evaluó la incidencia de la primera recurrencia de la anafilaxia en general y por subtipo (por ejemplo, medicamentos y alimentos) y se trató de determinar factores de riesgo asociados a la recurrencia.

*Resultados:* La tasa de incidencia total de la primera recurrencia de la anafilaxia (el mismo subtipo) fue de 3,2 episodios por 100 personas-año (95% CI, 2,83 a 3,63). La incidencia fue menor en la anafilaxia por medicamentos (2,0 episodios por 100 personas-año) que en la anafilaxia por látex y alimentos (8,6 y 5,6 episodios por 100 personas-año respectivamente). Los modelos de regresión de Cox y logística ordinal revelaron que la primera recurrencia fue menos probable con anafilaxia por medicamentos que con la anafilaxia alimentaria. El riesgo de sufrir una o más recurrencias fue mayor para los alimentos, el ejercicio, y anafilaxia idiopática que para los otros subtipos.

*Conclusiones:* La tasa de incidencia de una primera recurrencia del mismo subtipo de anafilaxia fue 2-6 veces inferior a la publicada por otros autores. La recurrencia de la anafilaxia es más común en los subtipos con una mayor prevalencia de atopia (alimentos, idiopática, látex) que en los otros subtipos (medicamentos, *Anisakis*). Por lo tanto, se debería prestar especial atención a la prevención y atención de estas poblaciones.

**Palabras clave:** Anafilaxia. Atopia. Incidencia. Primera. Recurrencia. Riesgo. Factores.

## Introduction

Anaphylaxis is a potentially fatal disease, and many patients suffer from recurrences caused by the same or related allergens [1-13]. Recurrence of anaphylaxis affects 26.5% to 54% of patients (follow-up of 1.5-25 years) [4,5,11-13], and its incidence rate has been reported to be 98 episodes per 100 person-years in a pediatric population [12] and 5.5 to 57 episodes per 100 person-years in mixed populations (pediatric and adult) [6,11].

Comparisons of these studies are difficult for the following reasons: differences in the origins of the populations analyzed (general population [3,5,6] or series from allergy outpatient clinics [1,4,12,13]), short follow-up time [12], small number of cases [1,12,13], different age groups [1,5,11-13], unreported order of episodes for which recurrence was studied [4-6,12,13], differences in the prevalence of atopic diseases (41-73%) [11,12], and undeclared atopic status [13].

Likewise, risk factors for recurrence have received little attention. In 3 studies, the authors found that anaphylaxis to food [11-13] was associated with recurrence; in one of these studies, a small pediatric series [13], urticaria, edema, atopic dermatitis, and positive skin prick test results with food were also associated with recurrence.

The objective of the present study was to determine the incidence of the first recurrence of anaphylaxis in a cohort of patients. We also investigated risk factors for recurrence adjusted for demographic and clinical variables.

## Material and Methods

### Patients

Our cohort comprised 1512 individuals of all ages (mean [interquartile range, IQR] age, 34.9 [12-49] years; 57.8% women) diagnosed with anaphylaxis between 1998 and 2005 in different clinical settings of the catchment area of Hospital Universitario Fundación Alcorcón (HUFA), Alcorcón, Spain.

### Data Collection

We retrieved all cases of anaphylaxis in our catchment area during the study period using the following sources: (1) computerized records of hospitalized patients and patients attended at the Emergency Department of HUFA (SELENE, SIEMENS SPAIN); (2) the diagnosis database of the Allergy Unit of HUFA, where all cases of anaphylaxis are recorded; and (3) clinical notes of primary care physicians recorded in the electronic clinical application used at this level (OMI, Stacks).

Cases of anaphylaxis were retrieved from the databases of our emergency department, hospitalized patients, and primary care centers using alphanumeric strings that included characters of words used in Spanish\* to denominate acute allergic syndromes, as follows: *alergi\** allergy, *anafila\** anaphylaxis, *urtica\** urticaria, *hipersensibili\** hypersensitivity, *eritema\** erythema, *picadu\** bite, *advers\** adverse, *edem\** edema, *medica\** drug, *reacc\** reaction, *alimen\** food, *abeja\** honey bee, *avispa\** wasp. The sensitivity of this strategy (91.7%: 95%CI, 61.6%-99.8%) has previously been reported by our group [14].

The presence of atopic disease was investigated in 92.8% of patients; this group formed the cohort attended in the Allergy Outpatient Clinic of HUFA. Diagnosis was confirmed by experienced allergists using different combinations of skin prick tests, serum specific immunoglobulin (Ig) E tests, and controlled challenge tests when indicated, together with a clinical history that correlated with positive results in the allergy tests performed. Atopic patients with food allergy included patients with food allergy but no anaphylaxis (as defined below) before the first anaphylaxis episode.

### Questionnaire

A questionnaire was designed to obtain information on possible recurrences of anaphylaxis. Comprehensibility was tested twice among 6 experienced allergists, who recommended several changes.

We first ascertained the consistency of the questionnaire, which was completed by 52 patients with previous anaphylaxis episodes who had attended the allergy outpatient clinic to continue their clinical follow-up. Two independent allergists determined whether these patients had had a recurrence of anaphylaxis using 2 different approaches: one conducted a standard clinical interview, while the other studied the information obtained from the questionnaire. Each allergist was blind to the information obtained by the other. Concordance between the allergists ( $\kappa$  index) was 0.4 (moderate score,  $P=0.004$ ), with 73.1% agreement (both allergists diagnosed recurrence in 69.2% of patients and absence of recurrence in 84.6%), a positive likelihood ratio of 1.8 (95%CI, 1.2-2.7), and a negative likelihood ratio of 0.1 (95%CI, 0.03-0.6).

The survey was first sent by ordinary mail to all 1512 patients of the cohort from January to April 2008. We tried to contact the patients who did not respond (1082) by telephone (1 call in the morning and 2 calls in the afternoon) from September 2008 to January 2009. Replies were obtained from 887 people (58.7%), 430 by ordinary mail and 457 by telephone.

We analyzed whether there were differences in demographic variables (age and gender) and clinical variables (subtype of anaphylaxis, severity, and previous atopic illnesses) between patients who returned and did not return the questionnaire. The only difference found was that patients who had been attended in the allergy outpatient clinic returned their questionnaires more frequently than those who had not (60.1% vs 44.8%,  $P=0.01$ ). Data for these analyses were obtained from the clinical records of HUFA. A significantly higher proportion of patients who replied to the questionnaire by ordinary mail had recurrences than patients who replied by telephone (64.87% vs 6.56%,  $P=0.001$ ).

### Definitions

We used the definition of anaphylaxis of the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network Symposium [15], which states that anaphylaxis is likely in patients fulfilling 1 of the following 3 criteria: (1) presence of skin signs or symptoms, together with respiratory involvement or signs of organic dysfunction or hypotension; (2) involvement of at least 2 organs or systems after recent exposure to an allergen; and (3) signs of organ dysfunction or hypotension after exposure to a known allergen. Participants

in this symposium believed that that these criteria accurately identify anaphylactic reactions in more than 95% of cases.

Patients identified their first episode of anaphylaxis in the clinical questionnaire by explicitly rejecting the occurrence of previous episodes. Episodes of anaphylaxis occurring after this first episode were considered recurrences. We ascertained whether the recurrence of anaphylaxis was due to the same food or drug, cross-reactive allergens (eg, Rosaceae family or penicillins), or the same subtype (eg, drugs, foods, latex, and exercise). Unless indicated otherwise, recurrence of anaphylaxis involves the same subtype.

According to the answers to the questionnaire, in 229 of 309 patients (74.1%), the recurrence occurred after the first visit to our allergy outpatient clinic. We classified anaphylaxis as severe or moderate according to the criteria of Brown [16], who defined generalized hypersensitivity reactions as mild (only skin and subcutaneous tissues involved), moderate (suspected respiratory, cardiovascular, or gastrointestinal involvement), and severe (hypoxia [ $SpO_2 \leq 92\%$ ], hypotension [systolic blood pressure  $<90$  mmHg in adults], or neurologic involvement). Brown recommended that generalized hypersensitivity reactions including any of the features listed in the moderate and severe grades should be considered as anaphylaxis.

### Design

The study was an observational retrospective cohort study and was approved by the Research Ethics Committee of our institution (number 22/2005). As the study was observational, our Research Ethics Committee did not request informed consent.

### Statistical Analysis

We report crude and standardized incidence rates and cumulative incidence of recurrence (according to the distribution

of ages in the standard European population [17]) with their respective 95%CI based on Poisson estimates. Cox regression and ordinal logistic regression were used to determine which factors were associated with first and subsequent relapses of anaphylaxis, respectively. Assumptions for proportional hazard ratios over time and proportional odds were satisfied in Cox regression and ordinal logistic regression, respectively. In these models, the dependent variable was the first recurrence of anaphylaxis and the number of recurrences (expressed in quartiles), respectively. Independent variables were subtype of anaphylaxis, presence/absence of previous atopic disease, age, and gender.

## Results

### Demographic and Clinical Characteristics of Patients Who Completed the Questionnaire

Table 1 shows the care level, demographic data, severity, and previous atopic disease for patients who returned the questionnaire. Table 2 shows the subtype and cause of the first anaphylactic episode. Mean (IQR) age was 45.3 (30.8-68.1) years, the tenth percentile was 17.1 years, and 57.4% were women. The IQR for follow-up time was 0.5-11.6 years, and the IQR for follow-up time after the first visit to our allergy outpatient clinic was 3-27 months.

### Incidence of Recurrences

The total incidence rate of the first recurrence of anaphylaxis (same subtype) was 3.2 episodes per 100 person-years (95%CI, 2.8-3.6); the total standardized incidence rate of first recurrence was 3.1 episodes per 100 person-years (95%CI, 2.6-3.5). Men and women had similar rates ( $P=.3$ ), although the incidence of recurrence decreased significantly with age (score test for trend of odds,  $P=.01$ ). No differences were observed in the incidence of recurrence according to duration of follow-up (score test for trend of odds,  $P=.8$  [Table 3]) or according to whether patients were attended or not in the allergy outpatient clinic of HUFA ( $P=.9$ ,  $\chi^2$  test [Table 4]). In this comparison, we chose patients whose first anaphylaxis episode occurred during 2004-2005, because this is the only period for which we were able to track patients with anaphylaxis in the different clinical settings of the catchment area of HUFA.

The cumulative incidence of anaphylaxis for the same subtype was 28.2%. If the recurrences of the same subtype are grouped into quartiles, 15.5% of patients had a single recurrence, 19.4% had 2 or 3 recurrences, and 2.9% had 4 or more recurrences.

The incidence rates of recurrence were lower for drug anaphylaxis (2.0

Table 1. Care Level, Severity of First Episode of Anaphylaxis, Sex, and Previous Atopic Disease in Patients Who Returned the Completed Questionnaire

Care Level	Years Data Collected	No.	%
Primary care	2004-5	105	11.8
Allergy outpatient clinic	1998-2005	823	92.8
Emergency department	2004-5	151	17.0
Hospitalization	1999-2005	32	3.6
Severity of anaphylaxis			
Moderate	717	80.9	
Severe	169	19.1	
Sex			
Female	507	57.4	
Male	376	42.7	
Previous atopic disease	242	27.3	
Allergic rhinitis	178	20.1	
Allergic asthma	126	14.2	
Previous food allergy without anaphylaxis	57	6.4	
Atopic dermatitis	25	2.8	

Table 2. Subtypes of the First Episodes of Anaphylaxis and Causative Foods and Drugs<sup>a</sup>

	Subtype		No.	%	
	Drug		407	45.9	
	Food		228	25.7	
	Anisakis simplex		102	11.5	
	Idiopathic		71	8.0	
	Hymenoptera		30	3.4	
	Other causes		28	3.2	
	Exercise		12	1.4	
	Latex		8	0.9	
	Echinococcus		1	0.1	
	Total		887	100	
Causative foods	No.	%	Causative drugs	No.	%
Rosaceae	38	4.3	Penicillins	169	19.1
• Peach	20	2.3	• Amoxicillin	87	9.8
• Apple	12	1.4	• Amoxicillin-clavulanic acid	51	5.9
Crustaceans	33	3.7	• Benzyl-penicillin	25	2.8
• Prawn	10	1.1	Pyrazolones	95	10.7
Fish	23	2.6	• Metamizole	74	8.3
• Whiff ( <i>Lepidorhombus whiffiagonis</i> ) <sup>b</sup>	6	0.7	• Propyphenazone	13	1
Hen egg	22	2.5	Arylpropionic NSAID	33	3.7
Cow milk	16	1.8	• Ibuprofen	28	3.2
Compositae	9	1.0	Arylacetic NSAID	21	2.4
Peanut	7	0.8	• Diclofenac	16	1.8
Kiwi	9	1.0	• Aceclofenac	5	0.6
Banana	6	0.7	Salicylates	18	2.0
			Cephalosporins	15	1.7
			• Cefaclor	6	0.7
			Iodine contrast medium	12	1.4

Abbreviation: NSAID, nonsteroidal anti-inflammatory drugs.

<sup>a</sup>The list is not exhaustive.

<sup>b</sup>See reference 23.

Table 3. Incidence Rate of First Recurrence of Anaphylaxis According to Duration of Follow-Up<sup>a</sup>

Duration of Follow-up	Person-Years	Number of Events	Incidence Rate per 100 Person-Years	95%CI, Lower Limit	95%CI, Upper Limit
3-5 years	817	56	6.9	5.3	8.9
6-7 years	837	40	4.8	3.4	6.5
8-9 years	970.5	45	4.6	3.4	6.2
10-14 years	1587.5	43	2.7	2.0	3.6
>14 years	3217	41	1.3	0.9	1.7

<sup>a</sup>Score test for trend of odds,  $P= .84$ .

Table 4. Incidence Rate of First Recurrence of Anaphylaxis According to Demographic and Clinical Characteristics and Allergens

	Person-Years	Number of Events	Incidence of First Anaphylaxis Recurrence	95%CI, Lower Limit	95%CI, Upper Limit
<b>Sex</b>					
Male	3047.5	93	3.1	2.5	3.8
Female	4367.5	145	3.3	2.8	3.9
<b>Age, y</b>					
0-9	915	31	3.4	2.3	3.9
10-19	913	25	2.7	1.8	4.1
20-29	1270.5	50	3.9	2.9	5.2
30-39	1453.5	43	3.0	2.2	4.0
40-49	1385	32	2.3	1.6	3.3
50-59	975	26	2.7	1.7	3.9
60-69	332	16	4.8	2.8	7.8
70-79	51	1	2.0	0.05	10.9
≥80	18	0	0	0	0
<b>Clinical settings<sup>a</sup></b>					
Attended in the outpatient allergy clinic	563	25	4.4	2.9	6.6
Not attended in the outpatient allergy clinic	201	9	4.5	2.1	8.5
<b>Anaphylaxis subtype</b>					
Food	1549.5	86	5.6	4.4	6.9
Drugs	4234.5	85	2.0	1.6	2.5
Exercise	61	1	1.6	0.04	9.1
<i>Anisakis</i>	639.5	20	3.1	1.9	4.8
Latex	70	6	8.6	3.2	18.7
Hymenoptera venom	237	8	3.4	1.5	6.7
Idiopathic	430	21	4.9	3.0	7.5
<b>Previous atopic disease</b>					
Atopic	1848.50	76	4.1	3.3	5.2
Nonatopic	5580.50	162	2.9	2.5	3.4
<b>Drugs</b>					
Aminopenicillins	1119	35	3.1	2.2	4.4
Cephalosporins	123	1	0.8	0.02	4.5
Salicylates	156.5	8	5.1	2.2	10.1
Arylacetic NSAID	194	2	1.0	0.1	3.7
Arylpropionic NSAID	191	6	3.1	1.2	6.9
Pyrazolones	895	23	2.6	1.6	3.9
Iodine contrast medium	134	1	0.8	0.02	4.2
<b>Foods</b>					
Rosaceae family	277	12	4.3	2.2	7.6
Compositae family	93	4	4.3	1.2	11.0
Legumes	188	11	5.9	2.9	10.5
Hen egg	85	8	9.4	4.1	18.5
Cow milk	45.5	3	6.6	1.4	19.3
Fish	133	6	4.5	1.7	9.8
Crustaceans	188	11	5.9	2.9	10.5

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

<sup>a</sup>In this comparison, we chose patients whose first anaphylaxis episode was in 2004-2005, because these were the only years during which we were able to track patients in the different clinical settings of the catchment area of our institution.

episodes per 100 patient-years) and higher for latex anaphylaxis and food anaphylaxis (8.6 and 5.7 episodes per 100 patient-years, respectively), with no overlapping 95% CIs between drugs and food/latex. The rates for anaphylaxis caused by hymenoptera venom had an intermediate value and overlapped with those of food and latex anaphylaxis, whereas those for atopic and nonatopic disease were similar, with overlapping confidence intervals (Table 4).

Recurrence rates were higher for nonsteroidal anti-inflammatory drugs than for antibiotics, although the confidence intervals overlapped. Recurrence rates were higher, although not significantly, in patients with anaphylaxis by hen egg (9.4 episodes per 100 persons-years) and cow milk (6.6 episodes per 100 person-years) (Table 4).

Only 3 (3.6%) patients with recurrences of drug anaphylaxis reported having a new episode with a different drug or one that did not cross-react with the agent that caused the first episode. Among recurrences of food anaphylaxis, only 10 cases were with different foods (12.1%) or foods that did not cross-react with the food responsible for the first episode (8.6%). When the same allergen was investigated, a significant percentage of patients did not give enough information to confirm that it caused the recurrence. Therefore, based on the information provided by the patients, we found that 95.3% of recurrences were due to the same main cause (eg, exercise, food, idiopathic), 97.2% to the same allergen, and 98.2% by a cross-reactive allergen or the same allergen.

#### Clinical Characteristics of Recurrences

We also found that when patients had a severe first episode of anaphylaxis, they more frequently had respiratory symptoms in the recurrences than patients who had nonsevere anaphylaxis in their first episode (severe, 48.9%; nonsevere, 40.5%;  $P=.03$ ).

However, these differences were not observed in the case of circulatory symptoms or signs (severe, 18.4%; nonsevere, 14.1%;  $P=.4$ ), although the number of patients with a severe first episode of anaphylaxis and circulatory involvement in the recurrences was low (9 patients). No patient died of anaphylaxis, while 21 (1.4%) died of other nonallergic causes.

Cutaneous involvement was recorded always or almost always in 76.8% of patients, respiratory symptoms always or almost always in 42.1%, cardio-circulatory signs or symptoms always or almost always in 15.3%, and involvement of other organs or systems always or almost always in 35.5%.

#### Multivariate Analysis

The Cox regression model revealed that the probability of a first recurrence was lower for drug and *Anisakis* anaphylaxis than for food anaphylaxis, which was the subtype chosen as a reference (Table 5).

We used an ordinal logistic regression model to study factors associated with the number of recurrences. We chose patients with a similar duration of follow-up and a sufficient number of cases to justify the power of the study. A total of 222 patients who were followed for 4-5 years and had data for all cells of the matrix fulfilled these conditions. In this model, the dependent variable was the number of recurrences (quartiles) reported by patients. As in the above models, recurrences were less likely in patients with drug anaphylaxis than in patients with food anaphylaxis (Table 6). The postestimation analysis revealed that the anaphylaxis subtypes with the highest mean probability of not having recurrences were drugs and *Anisakis*, although the risk of experiencing 1 or more recurrences was higher for foods, exercise, and idiopathic anaphylaxis than for the remaining subtypes (Figure). An  $\alpha$  error of 0.05 was considered significant.

Table 5. First Recurrence of Anaphylaxis by Cox Regression<sup>a</sup>

N=844	Nonadjusted Hazard Ratio	$P>Z$	Adjusted Hazard Ratio	$P>Z$	95% CI, Lower Limit	95% CI, Upper Limit
Age 0 to 9 y	1					
Age 10 to 19 y	0.8	0.7	1.2	0.8	0.3	4.3
Age 20 to 39 y	1.0	1.0	1.7	0.3	0.6	4.9
Age 40 to 59 y	0.6	0.2	1.1	0.9	0.4	3.3
Age $\geq 60$ y	0.3	0.0	0.5	0.3	0.1	2.0
Male	0.8	0.4	0.1	0.3	1.1	
Atopy	2.2	0.01	0.1	0.8	3.4	
Food anaphylaxis	1					
Drug anaphylaxis	0.4	0.01	0.4	0.02	0.1	0.9
Exercise anaphylaxis	1.4	0.7	1.1	0.9	0.2	6.7
<i>Anisakis</i> anaphylaxis	0.5	0.1	0.5	0.3	0.2	1.6
Latex anaphylaxis	1.9	1.0	2.7	1.0	0.0	.
Hymenoptera anaphylaxis	0.8	0.8	1.1	0.9	0.2	8.4
Idiopathic anaphylaxis	0.9	0.8	0.7	0.5	0.3	2.0

<sup>a</sup>This model included all patients who returned the questionnaire.

Table 6. Recurrence of Anaphylaxis in Quartiles by Ordinal Logistic Regression<sup>a</sup>

N=222	Nonadjusted Odds Ratio	P>z	Adjusted Odds Ratio	P>z	95% CI, Lower Limit	95%CI, Upper Limit
Age 0 to 9 y	1					
Age 10 to 19 y	0.8	0.7	1.2	0.8	0.3	4.3
Age 20 to 39 y	1.0	1.0	1.7	0.3	0.6	4.9
Age 40 to 59 y	0.6	0.2	1.1	0.9	0.4	3.3
Age ≥60 y	0.3	0.0	0.5	0.3	0.1	2.0
Male	0.8	0.4	0.6	0.1	0.3	1.1
Atopy	2.2	0.01	1.7	0.1	0.8	3.4
Food anaphylaxis	1					
Drug anaphylaxis	0.4	0.01	0.4	0.02	0.1	0.9
Exercise anaphylaxis	1.4	0.7	1.1	0.9	0.2	6.7
<i>Anisakis</i> anaphylaxis	0.5	0.1	0.5	0.3	0.2	1.6
Latex anaphylaxis	1.9	1.0	2.7	1.0	0.0	–
Hymenoptera anaphylaxis	0.8	0.8	1.1	0.9	0.2	8.4
Idiopathic anaphylaxis	0.9	0.8	0.7	0.5	0.3	2.0

<sup>a</sup>In this model, we chose only patients who were followed for 4-5 years in order to obtain a similar duration of follow-up and a sufficient number of cases to justify the power of the study. The dependent variable was the number of recurrences (quartiles) reported by patients.

### Discussion

The most remarkable findings in our study were as follows: (1) The incidence of a first recurrence of the same subtype was 3.2 episodes per 100 person-years; (2) The cumulative incidence of anaphylaxis for the same subtype was 28.2%; and (3) In the 2 multivariate analyses, which were adjusted for age and presence of atopic disease, drug anaphylaxis and anaphylaxis by *Anisakis* had less risk of recurrence than other subtypes of anaphylaxis.

The incidence of first recurrence was 3.2 episodes per 100 person-years. In other studies, the incidence of recurrence of anaphylaxis was estimated differently. Mullins [11] found overall recurrence (all recurrences, not only the first) to be 57 episodes per 100 person-years in a mixed population, and Gold and Sainsbury [12] found the overall rate to be 98 episodes per 100 person-years in a pediatric series. Gonzalez-Pérez et al [6] reported a first recurrence rate of 5.5 and 10.7 episodes per 100 person-years in patients with nonsevere and severe asthma, respectively. Mullins found a first recurrence rate of 19.2 per 100 person-years (data calculated by authors based on data from Mullins).

Our incidence rate was lower than that of Mullins [11], whose study design, nevertheless, was very similar to ours (patients seen at an allergy outpatient clinic, questionnaire answered by ordinary mail and telephone call). This discrepancy can be explained, at least partially, by the lower percentage of atopic disease in our study (27.3 vs. 73%) and a younger population in the series by Mullins (45.3 vs. 27.4 years). Given the increased frequency of atopic illnesses (food allergy) in younger patients [18], an association between the differences is likely. These

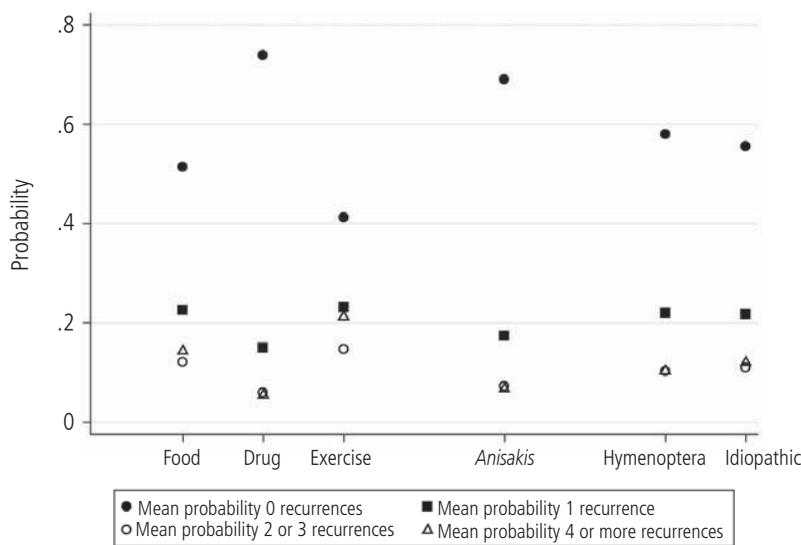


Figure. Probability of experiencing a recurrence of anaphylaxis (ordered logistic regression).

findings are confirmed in our study, where the bivariate analysis showed that age was associated with recurrence of anaphylaxis, although this association disappeared when the subtypes of anaphylaxis and age were used as covariates in the multivariate analysis.

Despite the fact that the results of Gonzalez-Perez et al [6] were very similar to ours, their study was different in several ways: samples were from primary care (allergy outpatient clinic in our series), the incidence rates corresponded to asthmatic patients with a predictable higher prevalence of atopic disease, and a slightly higher presence of atopy was recorded (24% in the nonasthma cohort and 48% in the asthma cohort). Nevertheless, our patients were also frequently attended in primary care; in a previous study [18], we found that 59% of patients with

anaphylaxis were attended first in primary care and then in the allergy outpatient clinic. In our series, patients with asthma did not experience more recurrences of anaphylaxis than patients without asthma (data not shown).

We made several estimates using a definition of recurrent anaphylaxis according to which recurrence was due to the same major cause (eg, foods, drugs, hymenoptera venom). Recurrence of anaphylaxis by any other cause, regardless of the associated risk, could most likely have been due to chance. Other authors report the number of recurrences caused by new sensitizations [11-13] and show that almost all new cases were caused by the same major allergen (especially food). We found that 97.2% of recurrences were produced by the same allergen; Mullins [11] reported that 97.7% of recurrences were caused by the same allergen. Therefore, our results for recurrence can be compared with those of other authors.

Atopic patients are predisposed to certain subtypes of anaphylaxis, as described in the literature [4,5,13,19,20], and food, latex, and idiopathic anaphylaxis have all been reported to be associated with atopic disease [4,11-13]. Our analyses revealed that the recurrence rate of anaphylaxis associated with atopic disease (food, latex, and exercise) [4,11-13] was 2-3 times greater than anaphylaxis not associated with atopic disease (drugs [21], *Anisakis* [22]).

Our findings are consistent with those of previous studies, which also associated atopic disease with recurrence. Mullins [11] found that idiopathic anaphylaxis and exercise anaphylaxis caused by wheat had higher recurrences rates. In a small pediatric series, Cianferoni et al [13] reported that atopic dermatitis and the presence of a positive skin prick result to food were risk factors for recurrence, and that food anaphylaxis recurred 4.5 times more than the remaining subtypes (exercise, idiopathic, and drugs). Gold and Sainsbury [12] found that children with food anaphylaxis were 4 times more likely to experience a recurrence than children with hymenoptera venom anaphylaxis.

Atopic patients are more likely to experience recurrence than nonatopic patients, probably because of a greater predisposition to sensitization to new allergens or because of cross-reactivity between different food allergens or between food allergens and latex.

The incidence of recurrence of hymenoptera venom anaphylaxis was low in our study. Mullins [11] found this rate to be high (>100 recurrences per 100 person-years). Anaphylaxis series from Australia show a high incidence of episodes due to hymenoptera venom [16,20], probably because of the high degree of exposure to this allergen. As our study was performed in an urban setting, exposure to hymenoptera venom was low, and few recurrences were recorded. Therefore, differences in the degree of exposure to hymenoptera venom account for the differences in incidence and recurrence rates.

We analyzed the consistency of the questionnaire used in the study. Although our response percentage was approximately 10% smaller than that recorded by other groups [11,12], our strategy of a sequentially administered questionnaire (ordinary mail followed by telephone call) achieved a balanced incidence of anaphylaxis by enabling us to collect data from patients with and without recurrences. An acceptable  $\kappa$  index and a large negative likelihood ratio were found for questionnaire data and the standard clinical interview. In the ordinal logistic regression

model based on patients followed for 4-5 years (first episode in 2004 or 2005) and who, consequently, were less likely to be affected by recall bias, we observed similar results to those of the Cox regression model obtained over a longer follow-up period. Therefore, we believe our questionnaire is a reasonable tool for self-reporting of recurrences in patients with anaphylaxis.

Nevertheless, recall bias remains possible, as many patients had to remember their first and subsequent episodes several years after they had occurred. This bias is common to all studies of recurrence of anaphylaxis [4,11,13] and may undermine their validity.

The survey was returned by 58.6% of patients. We did not observe demographic or clinical differences between patients who answered and those who did not, except that patients who had been attended in the allergy outpatient clinic returned their questionnaires more frequently than those who had not. This observation may not be relevant, as only 7.2% of the patients in our cohort were not attended in our allergy outpatient clinic. The low participation in our survey could lead us to overestimate the true incidence of recurrence if the patients who did not participate in the study were similar to those who answered by phone. However, as we do not know the characteristics of these patients, we cannot automatically include them with those who answered by phone. Finally, we cannot rule out unknown reasons leading patients with some subtypes of anaphylaxis to reply less frequently than patients with other subtypes, thus preventing us from obtaining the true incidence of recurrence of different subtypes of anaphylaxis in our population. Our results show that sequential administration (ordinary mail followed by telephone call) enables us to include patients with few and many recurrences.

Our study is also limited by its retrospective design. A prospective study would be the best way to measure the incidence of recurrence, although it would be much more time-consuming and expensive and probably impractical. Other authors report the same limitation [6,11-13]. We think the measures used to ensure the consistency of the questionnaire warranted a compromise between efficiency and internal validity.

In conclusion, the incidence rate for the same subtype was 3.2 recurrences per 100 person-years, a somewhat lower rate than that published by other authors. Finally, anaphylaxis related to atopic disease had a higher risk of recurrence than other anaphylaxis subtypes; consequently, particular attention should be paid to prevention and care in this population.

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### Conflicts of Interest

The authors declare that they have no conflicts of interest.

### Previous Presentation

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