

Incidence of anaphylaxis in the city of Alcorcon (Spain): a population-based study

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Summary

Background Relatively few studies have examined the incidence of anaphylaxis in the general population.

Objective To report the incidence of anaphylaxis among the general population of the city of Alcorcon, Spain, using various public health care databases.

Methods Episodes of anaphylaxis were recovered using validated alphanumeric strings in different fields of electronic clinical records used in the different public health settings in the city of Alcorcon (primary care, Emergency Department, hospitalized patients and Allergy Outpatient Clinic). Patients with anaphylaxis were tracked across the different clinical settings in Alcorcon.

Results The incidence of anaphylaxis in Alcorcon was 103.37 episodes per 100 000 person-years (total standardized incidence rate of 112.2). There was a peak of 313.58 episodes in the 0–4 years age group and a different distribution of incidence rates (although non-significant) among different age groups between male patients and female patients. In most age groups, incidence tended to be higher for female patients aged over 10 years. Patients were attended at two or more levels in 76.78% of episodes, and a new evaluation was often made at a primary care centre (71.43%), Allergy Outpatient Clinic (75.6%), or both after the episode (58.93%).

Conclusion and Clinical Relevance This study revealed a higher rate of anaphylaxis than that in previous studies, although this incidence rate is probably lower than the real incidence rate. Studies exploring potential methodological, genetic and environmental factors accounting for these higher rates of anaphylaxis are required.

Keywords ages, anaphylaxis, clinical settings, gender, incidence, tracks

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Introduction

The epidemiology of anaphylaxis is based mainly on the experience of settings where patients with anaphylaxis have been attended or the cause of their reaction has been assessed [1–12]. Few population-based studies have been performed: only six examine anaphylaxis in the general population [13–18] and five in selected populations (four in paediatric patients [19–22] and one in patients with anaphylactic shock [23]).

Published population-based studies have followed several strategies, the most common being to recover

episodes of anaphylaxis from the clinical records of large primary care databases [16, 17, 19], from regional databases shared by a large number of health carers [13, 14], or from health maintenance organizations [16]. These databases comprise coded diagnoses of health maintenance organizations [18] or clinically relevant data recorded by family physicians [16, 17, 19]. The studies mentioned above show the incidence of anaphylaxis to range from 8 to 68.4 cases per 100 000 person-years. However, many studies are based on a simple database for a specific geographic area [15–17, 19–22] and only a few studies have

collected data from several practice settings [13, 14, 18, 23].

Our primary objective was to know the incidence of anaphylaxis among patients attended at a tertiary institution in Alcorcon, Spain, by collecting data from various clinical settings with possibly different epidemiological contexts.

Methods

Setting

Alcorcon is a city of 150 000 inhabitants in the south-west metropolitan area of the Autonomous Community of Madrid. The demographic distribution of both genders in Alcorcon is similar to that of the rest of Spain (<http://www.ine.es>).

In Spain, the organization and provision of health care is very similar throughout the National Health System. The initial contact with the system in our catchment area is through family physicians working in primary care. Patients also have access to medical and surgical specialties through outpatient clinics of Hospital Universitario Fundación Alcorcon (HUFA), a 450-bed tertiary centre belonging to the National Health System. Patients can also be admitted to HUFA. Our hospital is the reference emergency care centre for its health care district; although less severe emergencies can be treated at the emergency departments of primary care centres and by ambulances supplied with medical equipment and trained staff (nurse and physician). Nevertheless, many mild conditions are also treated at the Emergency Department of HUFA. Our catchment area also has one private hospital and family doctors in private practice, as well as specialist offices for patients with private health insurance. In Spain, health care is universal, and only 0.6% of Spanish population does not have the right to receive free care under the National Health System and, therefore, does not have a social security number [24]. However, all health services assume the obligation of providing health care to the whole population. In the Autonomous Community of Madrid, private health insurance is used by 20% of the population (14.4% in the rest of Spain) [25].

Data collection

We retrieved all possible cases of anaphylaxis from the computerized clinical records of our catchment area at the time of study. Between 1 January 2004 and 31 December 2005, the clinical records of patients attended by health staff in the city of Alcorcon were computerized in primary care centres, specialist outpatient clinics, and in HUFA. The records of patients attended at the emergency departments of primary care centres and

those attended by ambulances had not yet been computerized at the time of the study and were not used in this study. Therefore, data were obtained from the following databases: (1) computerized records of hospitalized patients and patients attended at the Emergency Department of HUFA (SELENE[®], SIEMENS SPAIN, Madrid, Spain); (2) the diagnosis database of the Allergy Unit of HUFA, where all cases of anaphylaxis are recorded together with all other diagnoses of allergic diseases; and (3) clinical notes of primary care physicians recorded in the electronic clinical application used at this level (OMI; Stacks, Barcelona, Spain).

Cases of anaphylaxis were retrieved from the databases using alphanumeric strings that included characters of words used in Spanish* to denominate acute allergic syndromes, as follows: *alergi** allergy, *anafil** anaphylaxis, *urtica** urticaria, *hipersensibili** hypersensitivity, *eritema** erythema, *picadu** bite, *advers** adverse, *edem** edema, *medica** drug, *reacc** reaction, *alimen** food, *abeja** honeybee, *avispa** wasp. This strategy was tested in a pilot study. All emergency episodes between March and April 2004 were reviewed by one of the researchers. Only 1 case out of 12 was not detected using alphanumeric strings, with the result that 91.7% (95% confidence interval [CI], 61.6–99.8%) of all episodes of anaphylaxis during this period were identified using our strategy. All cases of anaphylaxis from the Allergy Outpatient Clinic of HUFA were obtained from the diagnosis database, where anaphylaxis is specifically coded.

As the databases were not linked, we used the Spanish patients' social security numbers (personal identification code and affiliation number) and national identification number to ensure correct identification. These numbers are recorded in hospital and primary care databases.

In order not to duplicate episodes of anaphylaxis from different databases, we assessed the presence of similar or identical organ or system involvement and the same cause. Two or more anaphylaxis episodes in the same patient with a similar clinical profile and the same cause recorded in two or more places were considered the same episode if the interval between them was less than 3 months, except when the attending physician had explicitly recorded in the clinical history that several anaphylaxis episodes had appeared in this time interval. The reporting date was the date of the episode. This was correct when directly collected from a clinical setting where the patient was attended immediately for the episode (emergency departments and hospital wards). In the remaining anaphylaxis episodes, gaps between episodes and attending dates are predictable. In the case of primary care, this interval is probably short, because, in this setting, appointments are very fast (within a maximum of 2 days of the episode). We chose 3 months as the interval to consider two

episodes as different, since, in our health district, this is usually the length of time between episodes of anaphylaxis and receipt by the general practitioner of the clinical report made at the Allergy Outpatient Clinic.

We also analysed data from primary care and the Allergy Outpatient Clinic to determine whether a second or subsequent episode (order of appearance for the same patient) had been recorded in only one of these settings. We found only four from 70 s or further episodes that had been recorded in only one of these settings. In other words, 66/70 s or further episodes of anaphylaxis were recorded as the same episode in several settings, and only four were recorded in a single setting. Therefore, except for very few cases, it is unlikely that the same episode had been counted two or more times.

Design

This observational retrospective cohort study was approved by the Ethics Committee for Medical Research of Hospital Universitario Fundación Alcorcon. As the study was observational, informed consent was not requested by the Ethics Committee for our Medical Research.

Definition of anaphylaxis

We used the definition of anaphylaxis of the NIAID-FAAN Symposium [26], which states that anaphylaxis is probable when several criteria are satisfied. These criteria are as follows: (1) presence of skin signs or symptoms together with respiratory involvement or signs of organ dysfunction or hypotension, or (2) involvement of at least two organs or systems after recent exposure to an allergen, or (3) signs of organ dysfunction or hypotension after exposure to a known allergen. Although participants in this symposium believed that that these criteria accurately identify anaphylactic reactions in more than 95% of cases, it was agreed that the criteria should be reviewed in a prospective multicentre clinical survey to establish their utility and determine whether or not furthermore refinement is necessary.

Any signs and symptoms mentioned were documented as being present and assumed absent if they were not reported or reported as not present. We classified anaphylaxis as severe or moderate according to the criteria of Brown [27], who defined generalized hypersensitivity reactions as mild (only skin and subcutaneous tissues involved), moderate (suspected respiratory, cardiovascular, or gastrointestinal involvement), and severe (hypoxia [$\text{SpO}_2 \leq 92\%$], hypotension [$\text{SBP} < 90$ mm Hg in adults], or neurological involvement). Brown recommended that generalized hypersensitivity reactions including any of the features listed in the moderate and severe grades should be considered as anaphylaxis.

Forty-two patients in our series with moderate anaphylaxis had skin or subcutaneous tissue involvement and various mild symptoms (dysphagia, hoarseness, difficulty speaking, cough, or weakness) that were not explicitly included in the Brown definition [27]. In any case, the definition of the NIAID-FAAN Symposium [28] does allow them to be included.

As it was not possible to carry out an allergy workup of all cases in the Allergy Outpatient Clinic, the individual aetiological agent was evaluated using only records and the experience and criteria of two experienced allergists who assessed cases independently, and reached a consensus upon the final diagnosis in cases of initial disagreement.

Statistics

We report crude and standardized incidence rates (according to the distribution of ages in the standard European population [29]) and incidence rates of anaphylaxis and principal subtypes, with their respective 95% CI using Poisson estimates. For calculations of incidence rates, we used data from the Spanish National Institute of Statistics (<http://www.ine.es>) on population distributions according to age and gender in the city of Alcorcon as on 31 December 2004. The Kappa index was used to measure inter-observer agreement. Statistical significance was set at a *P*-value less than 0.05

Results

In our study, the crude incidence rate of anaphylaxis in the city of Alcorcon was 103.37 episodes per 100 000 person-years (95% CI, 92.62–115.03). There were 336 episodes overall. The interquartile range for age was 19.11–51.46 years. The total standardized incidence rate was slightly higher, 112.2 episodes per 100 000 person-years (95% CI, 99.45–125) (Table 1). Incidence was higher among women than among men (107.81 [95% CI, 92.52–124.91] vs. 98.84 [95% CI, 84.08–115.44]), although the difference was not statistically significant (incidence rate ratio [IRR] for men and women, 0.92 (0.74–1.14), *P* = 0.43) (Table 1).

The distribution of incidence rates varied according to the age group (Table 2). A non-adjusted Poisson regression model showed that the highest incidence, with considerable differences, was observed in patients aged 0–4 years (with 313.58 episodes per 100 000 person-years) compared with the remaining age groups (Table 3). Male patients tended to have higher incidence rates until 10 years, although female patients aged 10 years and older (except 30–45 and 70–74 years) had higher incidence rates than men. However, the same Poisson regression model adjusted for gender showed

Table 1. Total and subtotal incidence rates of anaphylaxis episodes

Year group	Number of episodes	%	Incidence rate (Number of episodes of anaphylaxis per 100 000 person-years)	95% CI lower limit	95% CI upper limit
Crude incidence rate	336		103.37	92.62	115.03
Total standardized incidence rate			112.2	99.45	125
Women	177	52.68	107.81	92.52	124.91
Men	159	47.32	98.84	84.08	115.44
Year 2004	180	53.57	110.75	95.17	128.16
Year 2005	156	46.43	95.99	81.52	112.28
Foods	115	34.23	35.38	29.21	42.47
Drugs	104	30.95	32	26.14	38.77
Idiopathic	73	21.73	22.46	17.6	28.24
<i>Anisakis</i>	38	11.31	11.69	8.27	16.05
Exercise	9	2.68	2.77	1.27	5.26
Latex	2	0.60	0.615	0.0745	2.22
Hymenoptera	1	0.30	0.308	0.008	1.71

Table 2. Distribution of incidence rates of anaphylaxis according to age group and gender

Age group	Total			Women			Men		
	Incidence rate: Number of anaphylaxis episodes per 100 000 person-years	95% CI lower limit	95% CI upper limit	Incidence rate: Number of anaphylaxis episodes per 100 000 person-years	95% CI lower limit	95% CI upper limit	Incidence rate: Number of anaphylaxis episodes per 100 000 person-years	95% CI lower limit	95% CI upper limit
0–4	313.58	230.5	416.78	301.45	189.01	456.05	325.1	210.49	479.54
05–09	74.43	35.7	136.83	31.06	3.76	112.14	114.35	49.38	225.19
10–14	112.52	61.53	188.72	115.4	46.41	237.62	109.79	44.15	226.07
15–19	124.5	73.8	196.69	157.64	78.72	281.88	93.58	37.63	192.72
20–24	124.54	83.42	178.81	133.83	74.92	220.64	115.91	63.38	194.41
25–29	84.12	57.16	119.38	106.07	63.88	165.6	63.36	32.74	110.65
30–34	72.87	48.02	106	61	30.45	109.11	84.12	48.09	136.57
35–39	94.16	62.06	136.96	57.79	24.95	113.83	128.1	77.14	199.97
40–44	153.36	105.59	215.31	104.25	52.05	186.45	200.62	125.77	303.58
45–49	53.13	24.3	100.83	89.55	38.67	176.36	12.49	0.316	69.57
50–54	86.06	50.14	137.75	110.11	56.91	192.26	56.46	18.33	131.71
55–59	65.49	38.16	104.84	64.36	29.43	122.14	66.81	28.85	131.6
60–64	104.85	66.48	157.29	136.86	76.62	225.63	72.89	31.47	143.56
65–69	91.59	47.33	159.93	169.91	84.85	303.81	15.09	0.382	84.03
70–74	71.81	28.88	147.9	38.77	4.7	140	108.93	35.38	254.03
75–79	77.95	25.32	181.83	135.21	43.92	315.25	0	0	135.73
80–84	87.6	23.87	224.15	102.46	21.13	299.13	61.05	1.55	339.67
> 85	153.06	56.19	332.85	213.52	78.4	464.17	0	0	331.78

an almost identical IRR for every age group – the only differences were found in the fourth decimal place – thus ruling out an interaction between age and gender (Table 3).

A previous diagnosis of atopic disease was recorded for 73 (21.73%) patients (allergic asthma, 8.63%; allergic rhinitis, 13.69%; atopic dermatitis, 4.76%; and food allergy, 6.25%). The diagnosis of atopic illnesses was

made using data from computerized records, although 75.6% of diagnoses were made in the Allergy Outpatient Clinic.

Anaphylaxis subtypes and severity

The most frequent cause of anaphylaxis was foods (34.23% of all cases), followed by drugs (30.95%), idio-

Table 3. Risk of suffering anaphylaxis episodes according to a Poisson model adjusted and non-adjusted for gender. IRR incidence rate ratio

Variables	Non-adjusted Poisson regression				Adjusted Poisson regression for gender			
	IRR Incidence rate ratio	P-value	95% CI lower limit	95% CI upper limit	IRR Incidence rate ratio	P-value	95% CI lower limit	95% CI upper limit
Age groups								
<4								
05–09	0.24	< 0.001	0.12	0.47	0.24	0.000	0.12	0.47
10–14	0.36	0.001	0.20	0.65	0.36	0.001	0.20	0.65
15–19	0.40	0.001	0.23	0.68	0.40	0.001	0.23	0.68
20–24	0.40	< 0.001	0.25	0.63	0.40	< 0.001	0.25	0.63
25–29	0.27	< 0.001	0.17	0.42	0.27	< 0.001	0.17	0.42
30–34	0.23	< 0.001	0.14	0.37	0.23	< 0.001	0.14	0.37
35–39	0.30	< 0.001	0.19	0.48	0.30	< 0.001	0.19	0.48
40–44	0.49	0.0020	0.31	0.76	0.49	0.002	0.31	0.76
45–49	0.17	< 0.001	0.08	0.35	0.17	< 0.001	0.08	0.35
50–54	0.27	< 0.001	0.16	0.48	0.27	< 0.001	0.16	0.48
55–59	0.21	< 0.001	0.12	0.36	0.21	< 0.001	0.12	0.36
60–64	0.33	< 0.001	0.20	0.55	0.33	< 0.001	0.20	0.55
65–69	0.29	< 0.001	0.15	0.55	0.29	< 0.001	0.15	0.55
70–74	0.23	< 0.001	0.10	0.51	0.23	< 0.001	0.10	0.51
75–79	0.25	0.003	0.10	0.63	0.25	0.003	0.10	0.63
80–84	0.28	0.014	0.10	0.78	0.28	0.014	0.10	0.78
>85	0.49	0.098	0.21	1.14	0.49	0.098	0.21	1.14
Males					0.91	0.366	0.73	1.12

pathic anaphylaxis (21.73%) and *Anisakis* (11.31%) (Table 1). Crude incidence rates higher than 30 episodes per 100 000 person-years were recorded for anaphylaxis by foods and drugs and rates higher than 10 episodes per 100 000 person-years were recorded for idiopathic anaphylaxis and *Anisakis* anaphylaxis.

For 254 patients evaluated in the Allergy Outpatient Clinic, we observed an excellent kappa index between diagnosis of anaphylaxis subtypes made by the two researchers using computerized data from the study and the final diagnosis made in the Allergy Outpatient Clinic after evaluation (food anaphylaxis 0.83, drug 0.8, *Anisakis* 0.91 and idiopathic 0.84, the same drug 0.98, and the same food 0.94, $P < 0.0001$). The diagnoses based on computerized data were made with no knowledge of the diagnoses made in the Allergy Outpatient Clinic. Likewise, the concordance between the two researchers in the diagnosis of anaphylaxis made based on the clinical notes selected by the alphanumeric strings was very high (kappa index 0.97, $P < 0.0001$).

A confirmatory test was carried out in 165 of 254 patients evaluated in the Allergy Outpatient Clinic. A positive skin test result was found in 43.08% of the 165 patients, a positive specific IgE result in 33.6%, a positive challenge result in 14.55% and a positive result (any test) in 43.64%. In our cohort, patients had moderate and severe anaphylaxis, which precluded challenges in many cases. For *Anisakis* anaphylaxis, a subtype that is very common in Spanish series, diagnosis was made with a suggestive history and presence of positive

skin test and specific IgE results, as recommended by authors who have studied the epidemiology of *Anisakis* anaphylaxis in Spain [30].

Among foods, percentages greater than 10% were observed for fish (17.5%), shellfish (15.83%), nuts and seeds (14.17%), complex foods (13.33%), cow milk (10.93%), fruits (10.83%) and hen's egg (10.08%). Complex foods are defined as foods containing many different and sometimes unknown components or meals cooked with several foods where it was not possible to discover the culprit allergen. Among drugs, most cases of anaphylaxis were caused by nonsteroidal anti-inflammatory drugs and antibiotics; the most frequent triggers were pyrazolones (30.95%), aminopenicillins (26.19%) and arylacetic acid derivatives (15.48%) (Table 4). It was not possible to conclude that a single cause or allergen was responsible for the episode of anaphylaxis in all cases. When two triggers were observed, they were not included in the category of complex food. This is the reason why there are more causes of food and drug anaphylaxis than episodes.

Food anaphylaxis was the most common type in the 0–34 year age group, particularly in the 0–4 year age group. In the 35–39 year age group, drug and idiopathic anaphylaxis were the main causes, and in the 40–70 year age group, *Anisakis* was the main culprit (Fig. 1).

We did not find any peak in the summer months, and only 2 months (September and November) had fewer episodes of anaphylaxis than the remaining

Table 4. Foods and drugs implied in anaphylaxis episodes of the study series. For all cases it was not possible to conclude that a single cause or allergen was responsible for an episode of anaphylaxis. This is the reason why there are more causes of food and drug anaphylaxis than episodes

Foods responsible for anaphylaxis episodes (assessment before allergy outpatient clinic)			Drugs responsible for anaphylaxis episodes (assessment before allergy outpatient clinic)		
	N	%		N	%
Fish	21	17.50	Metamizole	25	22.73
Shellfish	19	15.83	Amoxicillin-clavulanic acid	12	10.91
Crustaceans	10		Ibuprofen	10	9.09
Shellfish	5		Amoxicillin	9	8.18
Molluscs	4		Acetylsalicylic Acid	8	7.27
Nuts and seeds	17	14.17	Ciprofloxacin	3	2.73
Peanut	9		Naproxen	3	2.73
Almond	3		Piroxicam	3	2.73
Hazelnut	2		Carboplatin	2	1.82
Chestnut	1		Iodixanol	2	1.82
Sunflower seeds	1		Cotrimoxazole	2	1.82
Almond	1		Diclofenac	2	1.82
Complex food	16	13.33	Doxazosin	2	1.82
Cow milk	13	10.83	Acetaminophen	2	1.82
Fruits	13	10.83	Acetoclofenac	1	0.91
Apple	3		Acetylcysteine	1	0.91
Peach	3		Codeine + acetaminophen + ascorbic acid	1	0.91
Kiwi	2		Diclofenac + misoprostol	1	0.91
Banana	2		Atorvastatin	1	0.91
Cherry	1		Captopril	1	0.91
Apricot	1		Ceftriaxone	1	0.91
Pitaya fruit	1		Cyanocobalamin-lysozyme	1	0.91
Hen egg	12	10.00	Clarithromycin	1	0.91
Cereals	4	3.33	Cloxacillin	1	0.91
Pollen	2	1.67	Codeine	1	0.91
Meat chicken	1	0.83	Iodinated contrast medium	1	0.91
Mustard	1	0.83	Dextromethorphan	1	0.91
Quail egg	1	0.83	Ketorolac	1	0.91
			Midazolam	1	0.91
			Ibuprofen + misoprostol	1	0.91
			Pyrazinamide	1	0.91
			Pyrazolones	1	0.91
			Albuterol	1	0.91
			Tetrazepam	1	0.91
			Propyphenazone + dihydroergotamine	1	0.91
			Platelet transfusion and frozen fresh plasma	1	0.91
			Cefazolin	1	0.91
			Moxifloxacin	1	0.91
			Bupivacaine	1	0.91
Total	120	100.00	Total	110	100.00

months of the year (Poisson regression, $P = 0.016$) (Fig. 2). We found that patients in September and November were younger (Mann–Whitney $P = 0.022$) and, for the four main causes of anaphylaxis (food, drug, idiopathic and *Anisakis*), the percentages of the subtypes of anaphylaxis differed from those recorded during the rest of the year. In the case of food, the frequency of anaphylaxis was higher during September and November (64.71% vs. 31.23%). In the case of drugs, the monthly average of episodes due to NSAIDs and betalactams was lower in September and November

(1.0 and 0.5, respectively) than during the rest of the year (2.5 and 1.1, respectively).

Only 17.86% of episodes were severe, and 67.58% of episodes were a first episode (Table 5). None of the patients died. We only present data on epinephrine use in the emergency department and hospital wards: clinical records are more accurate because they are collected immediately after the episodes. We observed more extensive use of epinephrine in severe anaphylaxis (moderate 10.76% and severe 37.78%), with two or more epinephrine doses in only two patients with moderate

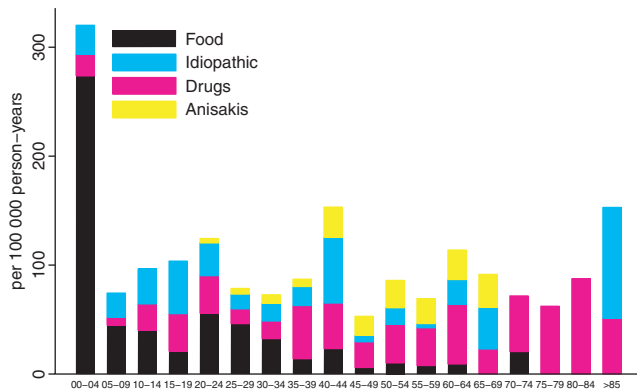


Fig. 1. Incidence rates of anaphylaxis subtypes according to age.

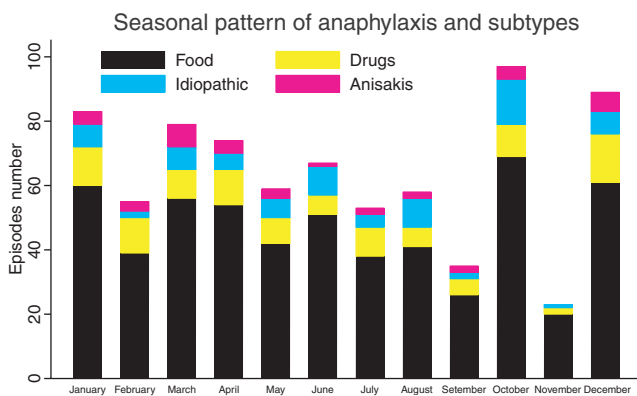


Fig. 2. Distribution of incidence rate according to the month of anaphylaxis episode.

anaphylaxis (2/17), but in six patients (6/17) with severe anaphylaxis ($P < 0.0001$).

Anaphylaxis according to care level

Comparison of the different care levels revealed that 75.6% of the patients were assessed at the Allergy Outpatient Clinic, 71.43% at a primary care centre, and 55.95% at the Emergency Department (Table 6). Patients in our series were generally attended in two or more places (76.78%), with the Allergy Outpatient Clinic and a primary care centre being the most typical combination (58.9%). Only 23.22% of patients were attended at a single centre, with a single visit to the Emergency Department being the most common contact with the system (11.31%) (Table 6); 7.74% of cases were attended at the Allergy Outpatient Clinic only and 3.57% at a primary care centre only.

Discussion

The most remarkable findings in our study were an incidence rate of 103.37 episodes of anaphylaxis per

Table 5. Clinical characteristics of anaphylaxis episodes

	N	%
Severity		
Moderate	276	82.14
Severe	60	17.86
Total	336	100
Order of episodes in relation to total number of episodes		
1st	223	67.58
2nd	54	16.36
3rd to 5th	34	10.31
6th to 10th	11	3.33
11th to 20th	2	0.6
20th to 30th	1	0.3
	5	1.52
Total	330	100
Number of episodes during study		
1	235	69.94
2	60	17.86
3	18	5.36
4	12	3.57
5	5	1.49
6	6	1.79
Total	336	100
Systems or organs		
Mucocutaneous	329	97.92
Lower respiratory	191	56.85
Digestive	139	41.37
Cardiovascular	122	36.31
Upper respiratory	104	30.95
Neurological	31	9.23

100 000 person-years (total standardized incidence rate of 112.2), a peak of 313.58 episodes in the 0–4 years age group, and a distribution of incidence rates that varied with age group and gender: in most age groups, incidence tended to be higher in male patients aged less than 10 years and in female patients aged more than 10 years, although the differences did not reach statistical significance.

Published population-based studies using clinical administrative data have shown incidence rates of anaphylaxis ranging from 8.4 to 68.4 episodes per 100 000 person-years [13–23]. In two studies, the prevalence of anaphylaxis was analysed using data for all automatic epinephrine-dispensing devices provided for out-of-hospital use [15, 21]. In these studies, prevalence was 1% of the general population. Extrapolation of data to the general population should consider the possibility of episodes not attended or analysed in health systems, which is a limitation shared by our study.

The standardized incidence rate in our study, which was obtained by recovering clinical data from several large clinical databases, was almost twice the highest incidence rate published to date in the international literature (68.4 episodes per 100 000 person-years) [18]. We do not believe that our increased incidence was the

Table 6. Tracking of anaphylaxis episodes across different clinical settings

Paths followed by patients with anaphylaxis episodes	N	%	Cumulative %
Primary care and allergy outpatient clinic	95	28.27	28.27
Emergency department. primary care and allergy outpatient clinic	90	26.79	55.06
Emergency department only	38	11.31	66.37
Emergency department and allergy outpatient clinic	28	8.33	74.7
Emergency department and primary care	27	8.04	82.74
Allergy outpatient clinic only	26	7.74	90.48
Primary care only	12	3.57	94.05
Hospitalized patients. Primary care and allergy outpatient clinic	9	2.68	96.73
Emergency department. Hospitalized patients. Primary care and allergy outpatient clinic	4	1.19	97.92
Hospitalized patients and primary care	2	0.6	98.52
Only hospitalized patients.	2	0.6	99.12
Hospitalized patients and allergy outpatient clinic	2	0.6	99.72
Emergency department and hospitalized patients	1	0.3	100
Cumulative percentage according to clinical settings visited by patients	N	%	
Emergency department	188	55.95	
Primary care	240	71.43	
Hospitalized patients	20	5.95	
• During hospital stay	8	2.38	
• Day hospital (cancer treatment and other special treatment regimens)	2	0.60	
• Emergency department stay	3	0.89	
• Anaphylaxis episode started before attending the emergency department with final hospital admission	7	2.08	
Allergy outpatient clinic	254	75.60	
Patients who visited only one centre where their anaphylaxis was attended or assessed	78	23.22	

result of counting the same episode twice or more, because only 4 of 70 patients (5.7%) with two or more episodes were recovered at only one care level. Similarly, we do not consider the high percentage of some subtypes of anaphylaxis that are uncommon in other geographical areas, e.g., *Anisakis* (11.1%), as the principal cause of an increased incidence of anaphylaxis in our cohort. Percentages for the causes of anaphylaxis in international series are clearly determined by allergen exposure in the geographical area studied, the

highest difference being recorded with Hymenoptera, which was responsible for 58.8% of episodes in one population-based series [23]. In our series, only 0.3% of cases were caused by Hymenoptera. Consequently, the high incidence of *Anisakis* anaphylaxis observed in our series is offset by the low frequency of *Hymenoptera* anaphylaxis.

Another possible explanation for the higher incidence we observed might be that other series reported only more severe cases, based on the definition of anaphylaxis used (Table S1). The definition used in our study (NIAID-FAAN Symposium) [26] includes non-severe anaphylaxis, whereas other studies include more severe cases than ours. In a series of patients with anaphylactic shock, Helbling *et al.* [23] found an incidence of 8.9 per 100 000 person-years and Peng and Jick [16] found that severe cases with hypotension or shock represented 9% of the total series. In our study, the incidence of patients with shock was 9.23 per 100 000 person-years (8.93% of the total series), figures that are very similar to those published by these authors. On the other hand, our percentage of respiratory and cardiovascular symptoms was 56.85% and 36.6%, respectively, figures that are intermediate in comparison with those published by other population-based studies, in which respiratory symptoms affect 31–88.2% of patients [13–18] (many between 50% and 69% [13, 14, 16]) and circulatory symptoms affect 10–41% [13–18]. In the study by Decker *et al.* [14], using our definition, only three cases of anaphylaxis from 311 would not have been diagnosed. Therefore, the severity of our patients was very similar to that recorded in other published series.

Another way of determining whether or not lesser severity indicates higher incidence in our series is to compare our incidence rate with that of anaphylaxis in series from emergency departments and hospital wards, which at least theoretically contain patients with more severe anaphylaxis (Table S2). Harduar-Morano *et al.* [30] reported 3.3–4.4 anaphylaxis episodes per 100 000 person-years in the emergency department, which is much lower than our incidence of 57.84 episodes per 100 000 person-years in the same clinical setting. In the study by Mulla and Simon [10] from the same area (Florida, USA), but among hospitalized patients with an ICD-9 code related to anaphylaxis, the incidence was 2.8 episodes per 100 000 person-years, which is much nearer to our incidence rate of 6.15 in hospitalized patients. Gaeta *et al.* [3] used a national survey to estimate the incidence of acute allergic reactions (including anaphylaxis) in the emergency departments of general and short-stay hospitals throughout the United States. They reported a high incidence (380 cases per 100 000 person-years) in patients aged 20–70 years. One possible explanation for the differences between our findings and those of Gaeta *et al.* is the fact that, in their case,

patient selection was based on ICD-9-CM codes for acute allergic syndromes, with no further refinement of data, whereas in our case, only patients with anaphylaxis were selected. Therefore, our definition of anaphylaxis and retrieval yields even more patients in some clinical settings than other studies performed in the same settings. In addition, if the hypothesis is that patients with more severe anaphylaxis attend emergency departments or are admitted, then the severity of our patients is at least the same as in other series performed in these clinical settings.

The above findings (definitions of other studies are similar to ours, percentage of respiratory and cardiovascular involvement and shock are also similar to ours, and our incidence of anaphylaxis in our emergency department or among hospitalized patients is intermediate or even higher than those in other studies) suggest that the severity of the anaphylaxis episodes recorded in our study is similar to that of other studies; therefore, the severity of anaphylaxis cannot account for differences in incidence between our study and the rest.

Finally, one possible explanation for the higher incidence of anaphylaxis in our study is a more exhaustive collection of data than in other series. In many studies, episodes are retrieved from a single database; however, we used three different databases. If we had only used clinical records from primary care, which is the first contact with the health system for many patients and the care level that generates the records for many population-based studies of anaphylaxis [16, 17], our series would have lost almost 30% of cases. However, this observation does not explain why our incidence rate was higher than that reported by Decker et al. [14], whose study was based on data from different carers. Another possible explanation for the differences between the two studies is the criteria for retrieving cases or the different degrees of exposure that trigger anaphylaxis episodes. Selection of codes will determine the number of cases collected. In general, the use of specific codes for anaphylaxis and non-specific codes for allergic symptoms or cause will notably increase the number of cases [31, 32]. In the study by Decker et al. [14], the use of non-specific codes was limited to food and venom allergy. Therefore, it is possible that a less effective strategy recovered lower cases than our strategy. For example, in the study by Decker et al., the incidence of drug allergy was lower than that in our series (18.5% vs. 30.95%).

The effectiveness of our method for retrieving cases of anaphylaxis can be compared with that of other methods. Recently, Harduar-Morano et al. [31] published an algorithm that mixes ICD-9-CM codes for symptoms and signs of anaphylaxis (such as those defined by the International Consensus) and for causes

of anaphylaxis. Application of this algorithm revealed an incidence of 4.4 cases per 100 000 person-years in emergency departments in Florida (USA). We were unable to apply this algorithm to all our patients, because only hospitalized patients (2.8%) were coded according to ICD-9-CM. However, the incidence of anaphylaxis in our emergency department was 57.84 episodes per 100 000 person-years, almost 15 times than that reported by Harduar-Morano et al. Likewise, the use of codes proposed by these authors did not reveal any additional patients in a cohort of 114 749 discharges of our hospital, which was the source for retrieval in a series of hospitalized patients with anaphylaxis recently published by our group [33]. Consequently, this comparison confirms the effectiveness of our retrieval method.

The low incidence of hymenoptera anaphylaxis we detected (1 case in 333) may be surprising. The frequency of hymenoptera anaphylaxis varies widely (from 12% to 58.8%), most likely because of differences in the degree of exposure to hymenoptera venom. Helbling et al. [23] found a higher percentage of hymenoptera anaphylaxis (50%): a large percentage of their study sample was from a rural area (43%). In addition, one of the study centres was the main centre for hymenoptera allergy in Switzerland. In the study by Decker et al. [14], 30% of the population was from a rural area and 18.5% was affected by hymenoptera anaphylaxis. In our study, the whole sample lived and worked in an urban setting in which the main economic activity is in the service and industrial sectors. The absence of a high incidence of hymenoptera anaphylaxis in our series explains the absence of peaks in the summer months, as reported elsewhere [13, 34].

However, in September and November of 2004–2005, we recorded fewer cases of anaphylaxis than those in the remaining months of the year. Under-reporting during September and November or over-reporting during the rest of the year may account for these differences. In the pilot study mentioned above, we found that our search strategy was sufficiently powerful to recover nearly all cases of anaphylaxis in the emergency department, and we have no reason to think our case finding does not work well during these months. Therefore, if under-reporting was the cause of the small number of cases during September and November, the percentage of cases recorded in clinical settings other than the emergency department would decrease, whereas the percentage of cases in the emergency department would increase. However, the percentage of anaphylaxis in our emergency department in September and November compared to the total number of cases of anaphylaxis is very similar to the percentage of anaphylaxis during the remaining months of the year (55.88% and 55.44%, respectively).

We found a small number of cases of drug anaphylaxis during September and November. The reasons for this small number are not clear, as upper respiratory infections in Spain are increasingly common and the difference in prescription invoicing between these months and the rest of the year is less than 2.2% [35]. On the other hand, given the small number of months analysed in our study (4 months), it is difficult to draw accurate conclusions. Data from a greater number of years would be necessary to confirm the low incidence of anaphylaxis during September and November.

Distributions of anaphylaxis rates according to age groups were different between male patients and female patients. A peak was observed in the 0–4 year age group for both genders: 325.1 episodes per 100 000 person-years in men and 301.45 episodes per 100 000 person-years in women. Decker *et al.* [14] observed peaks of 75.1 and 65.2 episodes per 100 000 person-years in the 0–9 and 10–19 year age groups, respectively, and lower incidence rates in the remaining age groups. In our series, incidence rates higher than 100 episodes per 100 000 person-years were maintained until the 20–24 year age group except in the 5–9 year age group, whereas almost all groups above this age had rates lower than 100. We do not believe that the high incidence of anaphylaxis in this age group artificially increased the incidence observed in our study, because these patients accounted for only 14% of the total number of cases in our series. Peaks in the first few years of life due to allergic reactions to food have been described in other international series of anaphylaxis in the general population [36].

Although we could not demonstrate statistically significant differences in incidence rates between women and men, we observed that, although male patients had higher rates until 10 years, female patients had higher rates in most of the remaining age groups. Several researchers have reported similar observations: Simons *et al.* [15] also reported a similar distribution of patterns of epinephrine-dispensing devices in both male patients and female patients, although the authors showed that the shift between men and women was observed at age 15. In the case of the study of Sheikh *et al.* [18], the authors found, in the pre-pubertal period, lifetime prevalence was highest in male patients, but then increased very rapidly in female patients, peaking during the fifth decade.

We observed that 75% of patients were assessed in primary care, a percentage that was very similar to that observed for the Allergy Outpatient Clinic (71.4%), whereas only 55.95% of patients were attended at our Emergency Department. Two or more care levels were involved in 78.8% of episodes, and patients frequently received a new evaluation at a primary care centre, the Allergy Outpatient Clinic, or both after their episode. In

other population-based series, a large percentage of patients were attended in emergency departments or other emergency care settings (64–71% [18, 23]). In our series, we only recorded data for our Emergency Department (55.95%) and not from other emergency care settings, thus explaining our lower attendance at this level. Helbling *et al.* [23] examined patients with cases of severe anaphylaxis and found that 95.13% were referred to an allergy outpatient clinic. This figure was higher than the 71.4% recorded in our series. The difference cannot be explained by the different degrees of severity recorded (severe in the series by Helbling *et al.* [23], moderate-severe in our study): a logistic regression analysis (data not shown) revealed that severity of anaphylaxis did not affect where patients requested care or assessment of their episodes. Perhaps the explanation lies in the different clinical settings assessed: Helbling *et al.* [23] also searched for episodes in seven outpatient clinics of board-certified specialists in allergy, whereas we limited our search to public health care in the city of Alcorcon.

The incidence of anaphylaxis in our study is probably lower than the real incidence of anaphylaxis in the city of Alcorcon, as observed elsewhere [37]. We did not record data on possible anaphylaxis from centres such as private hospitals or other public services that attend less severe clinical emergencies. In fact, it is highly likely that some of the patients attended in these settings did not attend a primary care centre or our Allergy Outpatient Clinic. We cannot calculate the real loss of episodes for this reason; we can only estimate the missing episodes to amount to 20%, based on the number of total private consultations made in 2005 in the Autonomous Community of Madrid [24].

A possible bias in our study would be the different methodology used to recover cases in the Allergy Outpatient Clinic and the other clinical settings. However, we consider that this bias was not very important, because only 7.74% of episodes were ascertained in the Allergy Outpatient Clinic exclusively.

Another limitation of our study is that it is based on clinical notes, which may not necessarily be complete, thus leading to some cases being misclassified (under- or over-diagnosis). However, our data were reviewed by two experienced allergists who confirmed the diagnosis of anaphylaxis. The result of their evaluation was consistent with that made in the Allergy Outpatient Clinic for the same patients. In other studies carried out in the general population, the information was compiled by non-allergists and confirmed by general practitioners [16–19, 38]. In addition, our percentage of atopic illnesses among patients in the cohort could be affected by an information bias, particularly if the physicians who held the clinical interviews only asked questions related to the anaphylaxis episode. This limitation is

compensated by the fact that 75.6% of patients were seen and evaluated in the Allergy Outpatient Clinic, where investigation of atopic illnesses is, at least, much more intensive than in other settings. Our study is retrospective, and information and memory bias are inevitable, although these limitations are also shared by all population-based studies of anaphylaxis incidence published to date.

Another limitation of our study compared with other population-based studies was the small number of years studied (2 years vs. 10 years in some studies [14, 16]). However, the absolute number of episodes in our study is only a little smaller than series with a higher number of incident cases (336 against 371 [18] or 382 [17]). Studies covering several years have had to make estimates of episodes from randomized samples, due to logistic problems in retrieving all the cases of anaphylaxis from a database with a large number of registers.

To conclude, the standardized incidence rate of anaphylaxis in the city of Alcorcon was 112.2 episodes per

100 000 person-years (the highest incidence of anaphylaxis published to date), with considerable differences between age groups and a peak in the 0–4 year age group (313.58). Using several databases enabled us to provide a large number of anaphylaxis cases.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Definitions of anaphylaxis used in different clinical studies with their respective incidences.

Table S2. Clinical settings in which several epidemiological studies on anaphylaxis were conducted.

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