Epidemiology of Anaphylaxis: Contributions From the Last 10 Years

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Abstract

Knowledge of the epidemiology of anaphylaxis has improved during the last 10 years thanks to the increased number of publications with improved methodological robustness. Consequently, we better understand the distribution and frequency of anaphylaxis and the characteristics of fatal anaphylaxis.

We now know that anaphylaxis is more frequent than previously thought (up to 50-103 cases per 100 000 person-years), although the distribution differs with the age group (up to 3 times in patients aged 0-4 years), cause (food-induced anaphylaxis is more frequent in young people, drug-induced and Hymenoptera anaphylaxis in older patients), and geographical area (more prevalent in areas with less sunlight). A controversial and unresolved issue is whether this high incidence of anaphylaxis is a real increase or merely the result of better identification of anaphylaxis by the attending physician.

Recurrence of anaphylaxis has been recorded in one-third of cases, although it is the least studied area of the epidemiology of anaphylaxis. Fatal anaphylaxis, on the other hand, has been widely studied. We know that death from anaphylaxis is a rare and extraordinary event (0.12 to 1.06 deaths per million person-years) and more likely in older individuals in the case of drug and Hymenoptera anaphylaxis.

Studies conducted during the last 10 years are highly powered since they include large numbers of patients (national records of hospitalized patients) over long time periods (10-20 years) or have been conducted with representative samples of the general population.

Key words: Anaphylaxis. Epidemiology. Last 10 Years. Frequency. Recurrence. Deaths.

Resumen

En los últimos 10 años se ha incrementado notablemente el conocimiento del que disponemos sobre la epidemiología de la anafilaxia, gracias al aumento de las publicaciones realizadas y a su robustez metodológica, a nuevos progresos en el conocimiento de la frecuencia y a una mejor compresión en la distribución de la enfermedad y de las características de la muerte por anafilaxia.

Con estos estudios, sabemos que la anafilaxia es más frecuente de lo pensado (hasta 50-103 casos por 100.000 personas-año), pero con distinta distribución entre los diferentes grupos de edad (hasta tres veces más en el grupo de 0-4 años), entre los diferentes causas de la anafilaxia (anafilaxia inducida por alimentos más frecuentes en las personas jóvenes, las anafilaxias inducidas por medicamentos, en himenópteros en las edades maduras de la vida) y entre los diferentes territorios geográficos (con más prevalencia en las zonas con menor radiación solar). Un tema controvertido y aún no resuelto es si esta gran frecuencia de la anafilaxia se debe a un aumento real de la misma o a una mejor identificación de la anafilaxia entre los médicos que asisten a estos pacientes.

Las recurrencias de anafilaxia aparecen en muchos estudios en un tercio de los casos, aunque es el tema de la epidemiología de la anafilaxia menos estudiado. Sin embargo, la muerte por anafilaxia se ha estudiado ampliamente. Sabemos que la muerte por anafilaxia es un evento muy raro y extraordinario (0,12 a 1,06 muertes por cada millón de personas-año) y es más probable en las edades más avanzadas de la vida en las anafilaxias por medicamentos e himenópteros.

Los estudios llevados a cabo en los últimos 10 años destacan por su gran potencia, dado que han incluido gran número de pacientes (registros de pacientes hospitalizados que abarcaban todo un país), durante largos períodos de tiempo (10 a 20 años) o han sido realizados con muestras representativas de la población general.

Palabras clave: Anafilaxia. Epidemiologia. Últimos 10 años. Recurrencia. Muertes.

Introduction

Knowledge of the epidemiology of anaphylaxis is not as developed as knowledge of other prevalent allergic diseases, such as asthma or food allergy, probably owing to differences in ideas, concepts, and definitions among experts [1,2] or because many researchers were more interested in knowing the epidemiology of the triggers of anaphylaxis (eg, penicillin or peanut [3]) than in the syndrome common to these triggers. Thus, in the 1990s we knew more about the epidemiology of immediate penicillin allergy than about the epidemiology of one of most serious manifestations of this allergy. During the last 15 years [4-8], and especially in the last 10 years [9-16], the availability of huge clinical databases in different settings (primary care, hospitals) at both regional and national level has meant that the study of the epidemiology of anaphylaxis now centers on the disease as a specific problem in itself, rather than as a mere examination of its causes [9-16]. Consequently, we now have a large amount of reliable data on the features of anaphylaxis in the general population. In 2014, the first study of the prevalence of anaphylaxis in a representative sample of the general adult population of the United States of America was published [15]. Most current knowledge on the epidemiology of anaphylaxis is from the last 10 years,

The authors of the present review consider it interesting to compare our knowledge of the epidemiology of anaphylaxis gained during the last 10 years with our knowledge of this area before this period. Our objective is compatible with the general aims of this section of the Journal of Investigational Allergology and Clinical Immunology. We aim to update and review a major issue in allergy, namely, the epidemiology of anaphylaxis.

Frequency of Anaphylaxis in the General Population

The most widely discussed issues in the epidemiology of anaphylaxis during the last 10 years are whether prevalence or incidence is the best measure of the frequency of anaphylaxis in the general population [17], whether the frequency of anaphylaxis is higher than previously thought [18], and whether the much increased incidence of anaphylaxis published in the last 10 years is real or the result of the different methods used to find cases [13,14,16].

Prevalence of Anaphylaxis

In 2006, Liebermann et al [17] discussed the relevance of using incidence or prevalence to measure the frequency of anaphylaxis. Despite concluding that there were no clear reasons in favor of one or the other, the authors used cumulative prevalence (at least 1 episode of anaphylaxis during the patient's lifetime) to estimate the frequency of anaphylaxis based on the studies published until the date of publication of their paper [8,19-22]. They estimated that 0.05%-2% of the general population had had at least 1 episode of anaphylaxis during their lifetime. The authors deliberately overestimated the prevalence of anaphylaxis, because they believed that the studies reviewed underestimated the true frequency of anaphylaxis.

Cumulative prevalence can be an inadequate measure of the frequency of anaphylaxis, since the reaction is no longer active once the episode has resolved. Given that anaphylaxis is an acute condition with long asymptomatic periods whose risk of relapse decreases over time, knowing the number of new episodes over a specific period could be an adequate measure of frequency. Therefore, incidence is the most frequently used measure of the frequency of anaphylaxis [6,11,13,14,16,23]. However, the results of recent publications are based on prevalence [15,24]. The authors of the present review believe that one measure complements the other.

The prevalence of anaphylaxis varies widely depending on the study (0.02% to 5.1%) [11,15,17,20,24-26], and it is difficult to observe clear differences between older and more recent studies (Table 1). The studies reviewed show different methods for selecting patients: purchase of adrenaline auto-injectors, estimates based on published articles, primary care databases, representative samples of the general population, and systematic reviews [11,27,28]. The most recently published article, and probably the least affected by bias (general population of the USA), is the article by Wood et al [15], who report a cumulative prevalence of 5.1% if the criterion for a diagnosis of anaphylaxis was involvement of 2 or more systems, together with respiratory or cardiovascular involvement, and 1.6% if a hospital visit and threat to the patient's life were added to the above criteria.

Incidence of Anaphylaxis

Most studies on the epidemiology of anaphylaxis are based on incidence rates and are mainly from English-speaking countries. Temporal comparisons are possible because publication has been constant. From 1999 to 2012, we located 8 articles that can be defined as population-based, since the authors used a huge regional and national clinical-administrative database, data from health maintenance organizations (both covering several clinical settings or health care levels) [6-8,13,16], or large primary care databases [11,14,22]. Until 2005, most studies reported incidence rates below or close to 10 episodes per 100 000 person-years [7,8,11,22], except for a 1999 study from Olmsted County in the USA [6], in which the incidence rate was 30 episodes per 100 000 person-years. After 2005, most of the studies report incidence rates of about 50 episodes per 100 000 person-years [13,14]; the incidence rate in our study in the city of Alcorcon, Spain was 111.2 episodes per 100 000 person-years [16]. If the study of Helbling et al [7] is ruled out—the authors selected only patients with severe anaphylaxis and vascular involvement—the differences between the studies are as high as 20-fold (Table 2).

These major differences are explained in the medical literature in several ways. One reason is the lack of an agreed validated definition of anaphylaxis. The most commonly used definition (ie, that proposed by the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network [NIAID-FAAN] symposiums [1,2]) underwent a validation process by Campbell et al [29]. However, the conclusions reached by these authors, while robust in terms of diagnostic accuracy, would not be valid in other geographical areas, because the gold standard used was the clinical practice

Table 1. Studies on the Prevalence of Anaphylaxis

Author	Country	Year	Prevalence	Methodology	Remarks
Neugut et al [20]	USA	2001	1.2-15%	Estimation based on publications on anaphylaxis caused by food, drug, latex, and insect stings	Studies carried out in specific populations and not in wide general populations
Rangaraf et al [25]	Wales	2002	0.02%	Adrenaline auto-injectors sold in Wales	Underestimation: death by anaphylaxis, no prescription in mild anaphylaxis, no purchase of device, and no diagnosis of anaphylaxis Overestimation: Prescription of devices for food allergy related to potential severe anaphylaxis, purchase of 2 devices
Simons [26]	Canada	2002	0.95% over 5 years	Adrenaline auto-injectors sold in a Canadian city	
Lieberman et al [17]	Reviews of publications from UK, Canada, USA	2006	0.05-2%	Review of medical literature on anaphylaxis epidemiology	Voluntary overestimation given to under-estimation of published studies on epidemiology of anaphylaxis
Sheik et al [11]	UK	2008	0.06-0.075	Use of QRESEARCH database, a representative sample of the general population in the UK Diagnostic Read code for anaphylaxis	
Panesar et al [24]	Europe	Publications between 2000-2013	0.3% (95%CI, 0.1-0.5)	Systematic review of European articles on epidemiology of anaphylaxis. Pooled prevalence was obtained from primary care, ambulances, and general population in UK and Italy [10,26,27]	Only 3 studies available to calculate pooled prevalence
Wood et al [15]	USA	2014	Probable anaphylaxis 5.1% (95%CI, 3.4%-6.8%), very likely anaphylaxis, 1.6% (95%CI, 0.8%-2.4%)	Sample of general adult population (>18 years old) in USA	Underestimation due to exclusion of pediatric and adolescent population No validated definition of anaphylaxis

of 2 board allergists, which was not explained. Other reasons include the use of different coding systems or selection criteria (eg, *International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM], ICD-10*, other coding systems used in national record systems, and alphanumeric strings), the different number of codes chosen to find cases (depending on whether codes other than those of anaphylaxis are used or not), or if cases are sought in one [11,14,22] or several clinical settings or care levels (primary care, emergency department, allergy outpatient clinic) [6,8,13,16]. For instance, the incidence of anaphylaxis in the emergency department differed 15-fold between a study carried out in Florida, USA [30,31] using an algorithm with *ICD-9-CM* codes based on the definition of the NIAID-FAAN symposium and a study performed in a Spanish hospital based on alphanumeric strings [16]. Finally, these differences can also be explained by the observation that the frequency of anaphylaxis seems to have increased during the last 10 years. The data presented here prevent us from stating whether the frequency of anaphylaxis has increased during the last 10 years. Below, we examine how the incidence and the prevalence of anaphylaxis are distributed differently between demographic groups and geographic areas.

Available data, especially those collected during the last 10 years, show that the frequency of anaphylaxis is higher than thought 10-15 years ago. If we compare the incidence of anaphylaxis with a very prevalent disease such as asthma based on the upper limit of the 95%CI, the incidence of anaphylaxis is 4-5 times lower than that of asthma [32]. In a recent article, Lieberman [18] stated that even after 15 years of epidemiological research in anaphylaxis, the condition remains an "under-estimated, under-communicated and often under-treated disease". Many studies do not explore settings where cases of anaphylaxis could be found, namely, private practice [16], or they only analyze a clinical setting [11,14,22]. In addition, the illness can be coded with labels other than anaphylaxis (eg, allergic reaction), and these codes are not searched for in studies where *ICD-9-CM* or *ICD-10* codes are used [17,33,34].

Table 2. Studies on the Incidence of Anaphylaxis

Author	Country	Year	Incidence Rate per 100 000 Person-Years	Methodology	Remarks
Yocum et al [6]	USA	1999	30 (95%CI, 25-35)	All health providers in Olmsted County (USA) Search for diagnosis associated with anaphylaxis	All ages
Peng and Jick [22]	UK	2004	8.4	UK General Practice Research Database Coding of Oxford Medical Information Systems	All ages
Helbling et al [7]	Switzerland	2004	Mean 8.9	Hospital system and outpatient allergy clinics of the canton Bern Diagnosis coded by *ICD-10*	Severe anaphylaxis with circulatory involvement All ages
Bohlke et al [8]	USA	2004	10.5 (95%CI, 8.1-13.3)	Records of primary care, allergy specialists, and health maintenance organizations in the west of Washington State, USA Diagnosis coded by *ICD-9-CM*	0-17 years
Sheik et al [11]	UK	2008	6.7- 8.5	Use of QRESEARCH database, a representative sample of the general population in the UK Diagnostic Read code for anaphylaxis.	All ages
Decker et al [13]	USA	2008	49.8 (95%CI, 45.0-54.5)	All health providers in Olmsted County (USA) Diagnosis coded by *ICD-9-CM*	All ages
González-Pérez et al [14]	UK	2010	Cohort without asthma, 21.28 (95%CI, 17.64-25.44) Cohort with asthma, 50.45 (95%CI, 44.67-56.76)	The Health Improvement Network (THIN) database: contains data from more than 2.3 million patients in 300 general practices. Diagnosis coded by *ICD-9-CM*	≥10 years
Tejedor-Alonso et al [16]	Spain	2012	112.2	All public health providers in the city of Alcorcon, Spain Searching of alphanumeric strings which include words associated with anaphylaxis	All ages

Variations in the Frequency of Anaphylaxis

The frequency of anaphylaxis varies according to geographic area and demographic group.

Since 2007, articles from countries with wide variations in latitude in their national territory and therefore different degrees of exposure to sunlight (USA, Australia, and Chile) [35-38] have reported more frequent prescription of adrenaline auto-injectors, a higher incidence of visits to pediatric emergency departments because of anaphylaxis, and admission because of anaphylaxis in areas with less sunlight. Lower production of vitamin D due to reduced exposure to sunlight would explain the higher incidence of anaphylaxis in countries with fewer hours of sunlight.

The effects of sunlight are more commonly observed in the pediatric population and in food anaphylaxis. A study from the USA [39] revealed an increase in the incidence of anaphylaxis, which was noted only among young people in New York state (7% annual increase) and adults (2% annual increase). However, a similar increase was not observed in Florida, which has more hours of sunlight. Another study performed in children in the USA [37] showed that the greatest differences in admissions to the emergency department between nothern and southern states were for food anaphylaxis.

In 2002, Simons et al [26] studied the prevalence of anaphylaxis using the purchase patterns of adrenaline auto-injectors and found that it was almost 3 times higher in the group aged 0-4 years than in the remaining age groups. Although this difference has not been widely reproduced, in a study conducted by our group in different clinical settings in the city of Alcorcon, Spain during 2004-5 [16], we found that the incidence of anaphylaxis in children aged 0-4 years was 3 times higher than in older age groups. This increased presence of anaphylaxis during the first years of life was recently associated with episodes caused by cow's milk and hen's egg during the first 2 years [16,40].

Several authors [16,26] and Sheik et al [11], who examined a representative sample from primary care in the UK, found that the frequency of anaphylaxis differed between males and females. While anaphylaxis was more frequent in males until age 10-15 years, women experienced more episodes after age 15.

In addition, the cause of anaphylaxis differs throughout the patient's lifetime. Foods and drugs are the main causes of anaphylaxis. However, food anaphylaxis is more prevalent during the first and second decades of life, whereas drug anaphylaxis is more common in middle-aged and older patients [16,41-43].

Table 3. Studies on Trends in Anaphylaxis Among Admitted Patients

Author	Study Period	Type of Anaphylaxis	Age Group	Annual Rate Increase	Annual Percentage Increase
Liew et al [12] (Australia) Published in 2009	1994-5 to 2004-5	Food anaphylaxis	0-4 years	1.04 (1.02-1.06) times faster than in older age groups	
		Food anaphylaxis	All ages	1.12 (1.11-1.13)	350% overall
		Nonfood anaphylaxis	All ages	Estimated annual multiplicative rate increase of 1.08 (1.08-1.09)	Increases of 230% over 11 years
	1998-2005	Drug anaphylaxis	All ages	Estimated annual multiplicative rate increase of 1.06 (1.05-1.08)	Increases of 153% between 1998 and 2005
Poulos et al [10] (Australia) Published in 2007	1993-4 to 2004-5	All anaphylaxis	All ages		8.8% per year
		All anaphylaxis	0-4 years	4.1 (1993-4) to 19.7 (2004-5) (per 100 000 person-years)	
		Food anaphylaxis	All ages		13.2% annual increase
		Food anaphylaxis	0-4 years	5.5 increase (throughout the study period)	Males, average annual increase of 18% (15.3-20.7%); Females, average annual increase of 10.7% (6-15.6%)
Lin et al [47] (USA) Published in 2008	1990-2006	All anaphylaxis	0-20 years	4.7 times 1990: 1 per 100 000 person-years 2006: 4.7 per 100 000 person-years	
		Drug anaphylaxis	0-20 years	1993: 0.1 per 100 000 person-years 2006: 0.19 per 100 000 person-years	
Ma et al [48] (USA) Published in 2014	1999-2009	All anaphylaxis	All ages	Annual increases of 2.35 (1.5-2.94)	Hospitalizations due to peanut-related anaphylaxis almost doubled from 4% in 1999 to 7% in 2009.
Gupta et al [46] (UK) Published in 2007	1990-1 to 2003-4	All anaphylaxis	All ages	1990-1: 0.5 per 100 000 person-years 2003-4: 3.6 per 100 000 person-years (7-fold increase)	
Turner et al [43] (England and Wales) Published in 2014	1992-2012 for all anaphylaxis 1998-2012 for triggers of anaphylaxis	All anaphylaxis	All ages	1.073 (95%CI, 1.071-1.075), although a plateau has been observed since 2008	615% over the period studied
		Food anaphylaxis	All ages	1.05 (95%CI, 1.05-1.06)	106% overall
			0-14 years	1.05 (95%CI, 1.05-1.06)	137% overall
		Drug anaphylaxis	All ages	1.04 (95%CI, 1.03-1.05)	82% overall
			60 or more years	1.05 (95%CI, 1.04-1.05)	85% overall
		Insect anaphylaxis	All ages	1.12 (95%CI, 1.10-1.13)	410% overall
			60 or more years	1.17 (95%CI, 1.14-1.19)	
Tejedor et al [49] (Spain) Published in 2015	1998-2011	All types of anaphylaxis	All ages	1.05 (1.04-1.05)	
			0 to 4 years	1.11 (1.09-1.12)	
			5 to 9 years	1.20 (1.17-1.23)	
			10 to 14 years	1.13 (1.10-1.16)	
			15 to 49 years	1.02 (1.01-1.03)	
			50 to 74 years	1.02 (1.01-1.02)	
			75 or more years	1.05 (1.04-1.07)	

Two studies carried out in 2010 using data from clinical-administrative primary care in the UK [14] and a health maintenance organization in California, USA [44] reported that anaphylaxis was more frequent in patients with asthma than in people without asthma and that the risk of anaphylaxis increased in patients with severe asthma. In the study performed in California [44], patients with severe asthma had a higher risk of food-induced anaphylaxis than patients without severe asthma.

Finally, one of the most important and debated questions in recent years is that of whether the frequency of anaphylaxis has really increased to epidemic proportions during the last decade [45]. Data from several studies show an increase in incidence rates for admissions during the period studied (usually 10-15 years) in several national hospital systems (Table 3). These studies have been published since 2007 and cover the period 1995-2012 [10,12,43,46-48]. The only study in which a different approach was followed was that performed in Olmsted County in the USA [13], where the incidence rate from 2 different time periods (1983-1987 and 1990-2000) was used in 2 different studies [6,13]. The methodology used was similar in both studies (codes from electronic records of health care providers). The authors reported an almost 2.5-fold increase between figures from the late 1980s and early 2000s.

In order to describe the increase in anaphylaxis rates using trends in admission because of anaphylaxis in national hospital systems, we tried to use the same measures, although the studies reviewed present different measures (annual and total rate increase, annual and total percentage increase). For all types of anaphylaxis, the studies show annual increases of 1.05 [49], 1.07 [43], and 2.35 times [48] or an annual increase of 8.8% [10], whereas for total increases during the study period, 2 British publications reported increases of 600% [43,46]. The increases are not similar for all causes or for all ages or for different causes of anaphylaxis in different age groups (increases for the various causes of anaphylaxis differ according to age group). In several publications, the annual increase in the frequency of anaphylaxis [12] and the overall increase in the frequency of anaphylaxis [12,47] were higher for food anaphylaxis than for nonfood anaphylaxis. On the other hand, increases in patients aged 0-14 years were higher than in older age groups [10]. Likewise, the distribution of increases varies according to the age group: in patients aged 0-14 years, the increases are higher for food anaphylaxis, whereas in older patients the increases are higher for drug and insect sting anaphylaxis [43]. In the study by Liew et al [12] in Australia, anaphylaxis caused by peanuts and crustaceans was more frequent than that caused by cow's milk, even in the 0-4 year group.

It is important to know whether these increases in the frequency of anaphylaxis are real increases. The assumption that there are real increases in the frequency of anaphylaxis can be rejected for several reasons. First, several other explanations are possible, such as better knowledge of the illness, changes in coding, differences in the care provided, and changes in the threshold for admission [46]. Second, the increase in anaphylaxis admission rates is not accompanied by an increase in the frequency of fatal anaphylaxis, which would support the explanations of the previous paragraph [43]. However, this discordance could also be explained by better management of anaphylaxis, which would ensure that fatal anaphylaxis rates remained stable despite increases in admission rates [43].

The main reason in favor of the increase being real is that increases are observed mainly for food anaphylaxis and children and that increases are consistent with the increase in the frequency of food allergy reported in recent years: the National Center for Health Statistics of the Centers for Disease Control and Prevention reported an 18% increase in the incidence of food allergy among people aged less than 18 years in the USA from 1997 to 2008 [50,51].

Natural History of Anaphylaxis

Although anaphylaxis is potentially fatal, recurrence is a real problem for many patients. However, this aspect of the epidemiology of anaphylaxis has received very little attention during the last 10 years. The main study on the recurrence of anaphylaxis was published in 2003 [52], and only in 4 additional publications was recurrence one of the main objectives [53-56]. Aside from the difficulties involved in collecting data from a cohort, the scarce interest in investigating recurrence of anaphylaxis could be due to methodological difficulties. For instance, it is unknown whether it is better to investigate recurrence of a first episode of anaphylaxis or recurrence of subsequent episodes. It is also important to determine whether the outcome of the study is the first recurrence or all recurrences and whether only new episodes with the same food or drug are considered as recurrences or, conversely, whether other episodes of anaphylaxis caused by triggers with recognized cross-reactivity with the trigger of the first or previous episode of anaphylaxis can be considered as recurrences. The existence of so many variants hampers comparison between studies (Table 4).

Cumulative incidence ranges from 26.5% to 54%, with a follow-up time of 1.5 years to 25 years [13,14,52-57], although most studies report figures below 35%. The reported incidence for the first recurrence is 3.2-19.2 episodes per 100 person-years [14,52,55] and 42.7-57 episodes per 100 person-years when all recurrences are included [52,56].

Nevertheless, the data show that not all patients with anaphylaxis have the same risk of experiencing a new episode. Patients with drug anaphylaxis [55] or *Anisakis* anaphylaxis [56] have a lower risk of new relapses than those with exercise-induced anaphylaxis, idiopathic anaphylaxis, and food anaphylaxis [52,55,56] (Table 4). The recurrence rate of Hymenoptera anaphylaxis can be high in geographic areas where exposure to Hymenoptera anaphylaxis is increased (eg, Australia) [52,56,58,59].

Fatal Anaphylaxis

The last 10 years has seen the publication of 7 studies whose main objective was to study fatal anaphylaxis [10,12,42,43,48,60,61]. Only 3 such studies were published

before this period [6,7,62-64]. Most studies from the past 10 years use national or state records and death certificates coded according to *ICD-10* to determine the incidence of or trends in fatal anaphylaxis among different demographic and clinical groups [7,9,11,45,46,57-59]. In addition, publications from the last 2 years show that the number of registered deaths is high (up to 2000-2500) owing to the large number of years studied [20] or the size of study population (population of the USA) [42,43,48]. In the case of the publications by Pumphrey et al [43,62-64], cases were obtained using voluntary declarations by doctors on deaths from anaphylaxis [62-64], or data were combined from official national death records and information requested from coroners, pathologists, police services, or the media [43].

Incidence of Fatal Anaphylaxis

The incidence of fatal anaphylaxis is very low [65], ranging from 0.12 to 1.06 deaths per million person-years (Table 5), with the prevalence of deaths in patients with severe anaphylaxis standing at 0.3%-2% [66-68]. Therefore, death from anaphylaxis is a very rare and extraordinary event.

The 3 leading causes of fatal anaphylaxis are, in descending order, drugs (50% or more), insect stings, and food. In several series, deaths due to unknown or unspecified causes account for a significant proportion of cases (15-75%) [7,12,42,43,48]. Food anaphylaxis has been reported to be between 2% [12,42,61,69] and 31% in the series by Pumphrey [70,71]. The higher frequency of food-induced anaphylaxis reported

Table 4. Epidemiologic Studies on Recurrence of Anaphylaxis

Author	Study Period and Number of Patients	Population at the Beginning of the Study	CI	Incidence Rate, 100 Person-Years	Risk Factors
Dibbs and Baker [53] (USA), published in 1997	1990-1994 N=50	Pediatric and adolescent patients <19 years	10%		
Gold and Sainsbury [56] (Australia), published in 2000	1990-1994 N=68	<15 years, pediatric patients	54%	42.7 for all anaphylaxis episodes	Children with food anaphylaxis
Mullins [52] (Australia), published in 2003	1995-2000 Maximum duration of follow-up, 5.5 years N=179	Adults and pediatric patients Mean age 27.4 (19.5)	42.8%	57.2 for all anaphylaxis episodes 19.2 for first recurrence of anaphylaxis. 10 for serious recurrences	Idiopathic anaphylaxis and exercise anaphylaxis caused by wheat
Cianferoni et al [54] (Italy), published in 2004	1994-1996 Mean duration of follow-up, 7 years N=76	Pediatric and adolescent patients Mean age 5.8 (4.9)	30%		Patients with oral allergy syndrome, 1 or more positive skin test results for foods and atopic dermatitis
Web (USA), published in 2006	Selection of the cohort 1995-2000 N=601	Adult and pediatric patients Mean age 37 years	34%		
Decker et al [13] (USA), published in 2008	1990-2000 N=248	Adult and pediatric patients Mean age 29.3 years	26.5%		
Gonzalez-Pérez et al [14] (UK), published in 2010	1996-2005 N=609	Adult and pediatric patients Age 10-79 years	21%	10.7 for first recurrence of anaphylaxis in non asthma cohort 8.2 for first recurrence of anaphylaxis in nonsevere asthma cohort 5.5 for first recurrence of anaphylaxis in severe asthma cohort	
Tejedor-Alonso et al [55] (Spain), published in 2013	1998-2005 N=887	Adult and pediatric patients Mean age 45.3 years	28.2%	3.2 for first recurrence of anaphylaxis.	Drug anaphylaxis carries less risk of recurrence than food anaphylaxis

Abbreviation: CI, cumulative incidence

Table 5. Epidemiologic Studies on Fatal Anaphylaxis

Author	Methodology	Period of Study	Mortality Rate per 1 000 000 Person-Years and No.	Risk Factors	Time Trends
Hebling et al [7] (Switzerland), published in 2003	*ICD-10* for Swiss Federal Statistical Office	1996-1998	1.06 (0.7-1.6) 24 cases 13 Hymenoptera 7 drugs 4 not specified		
Pumphrey et al [64] (UK), published in 2000, 2001, and 2004	Initially, data from the Office for National Statistics and from fatal drug reactions of Medicines Control Agency Subsequently, immediate reporting by coroners	From 1992 to the year of publication	0.33 214 cases	Upright posture. Noncontrolled asthma in food anaphylaxis. Tree nuts. Fatal food allergy was more common than sting- or drug-induced anaphylaxis in younger patients.	The authors did not observe changes in the number of deaths.
Poulos et al [10] (Australia), published in 2007	*ICD-10* of National Mortality Database	1997-2004	106 cases		The number of deaths remained relatively constant between 1997 and 2001 at approximately 10 deaths per year.
Simon et al [60] (USA), published in 2008	*ICD-10*, death certificates were obtained from the Florida Department of Health, Office of Vital Statistics	1999-2005	0.50 (95%CI, 0.40-0.62). 89 cases For ages 5-14 years, 0.096 15-34 years, 0.17 35-64 years, 0.61 >65 years, 1.35	Positive correlation with age. Men in Hymenoptera anaphylaxis. Women in drug-induced anaphylaxis.	
Liew et al [12] (Australia), published in 2009	*ICD-10*, National Mortality Database	January 1997 through December 2005	0.64 112 cases Food (6.3%), drugs (57.2%), insect sting (17.9%), undetermined cause (13.4%), medical or surgical procedure (5.4%)	In food anaphylaxis, active asthma. Age-groups 5 to 35 years female predominance. Insect sting–induced anaphylaxis was fatal in adults aged 35 to 84 years. In drug anaphylaxis, adults aged 55 to more than 85 years.	There was no evidence of an increase in the rate of deaths due to anaphylaxis. The rate of deaths from insect sting–induced anaphylaxis decreased by approximately 88% over 9 years. Deaths from drug-induced anaphylaxis were estimated to have increased by 300%. Peaks in deaths from anaphylaxis were observed several years after peaks in admissions for anaphylaxis with the same causes, suggesting that fatal episodes were preceded by nonfatal episodes.
Tanno et al [61] (Brazil), published in 2012	*ICD-10*, Underlying and contributing causes of deaths from the Brazilian Mortality Information System	2008- 2010	0.87 498 cases Drugs (42%), insect bites (35%), foods (2%)		No obvious increase in fatal anaphylaxis rate.

Ma et al [48] (USA), published in 2014	*ICD-10*, Multiple Cause of Death Data (MCDD)	1999-2009	0.63 to 0.76 (mean 0.69) 2229 cases Unspecified anaphylaxis (75%), drug-induced anaphylaxis (7%), insect-induced anaphylaxis (3.3%)	Males Adults aged 75 to 84 years	Mortality rates of fatal anaphylaxis remain stable.
Jerschow et al [42] (USA), published in 2014	*ICD-10*, National Mortality Database in the United States	1999-2010	0.69 2458 cases Medications (58.85%), unspecified anaphylaxis (19.3%), venom-induced anaphylaxis (15.2%), food-induced anaphylaxis (6.7%)	In food-induced anaphylaxis age, African American race, and male sex. In unspecified fatal anaphylaxis, older age and African American race. In drug-induced anaphylaxis, older age.	Increases in the frequency of drug-induced fatal anaphylaxis. Decreases in the frequency of unspecified anaphylaxis.
Turner et al [43] (UK and Wales), published in 2015	*ICD-10*, Office for National Statistics (ONS). Additional information was collected from patient representative organizations, coroners, the police service, pathologists, and media reports.	1992-2012	0.47 (95%CI, 0.42-0.05). Food-induced anaphylaxis in 124 cases. Sting-induced anaphylaxis in 93 cases. Drug-induced anaphylaxis in 263 cases.	In food induced anaphylaxis, age 10-29 years, physician's diagnosis of asthma (78%). Sting-induced anaphylaxis >50 years. Drug-induced anaphylaxis >40 years.	No increase in anaphylaxis for anaphylaxis overall or for anaphylaxis induced by specific causes.

Abbreviation: *ICD-10, International Classification of Diseases, Tenth Revision*

by Pumphrey can be explained by the method used to collect cases, which was based on voluntary declarations by physicians and validation of possible cases by obtaining information from other medical and nonmedical professionals.

Risk Factors for Fatal Anaphylaxis

The frequency of fatal anaphylaxis varies with patient demographic characteristics.

Fatal Anaphylaxis: Distribution by Age

The frequency of the different causes of anaphylaxis varies with age group [12,42,43,70]. Food-induced anaphylaxis was more frequently fatal among patients aged 5-35 years [12,42,43], while insect-induced anaphylaxis and drug-induced anaphylaxis were more frequently fatal in people older than 35-40 years [12,43]. In the study of Liew et al [12], the peaks of fatal anaphylaxis by specific causes were delayed several years with respect to the peaks of hospital admissions for anaphylaxis by the same causes; in other words, death from anaphylaxis is usually preceded by nonfatal anaphylaxis.

Older age implies a greater risk of fatal anaphylaxis [48,60]. In older patients, this risk has traditionally been explained as a reduced capacity to tolerate the effects of hypoxia, hypotension, and arrhythmia. These manifestations indicate underlying cardiovascular or cerebrovascular illnesses [43,48] and, consequently, a reduced capacity to compensate for the cardiovascular problems that are usually associated with fatal anaphylaxis due to drugs or insect venom.

In children, deaths due to anaphylaxis were more frequent in teenagers than in younger children [51,72]. This finding is explained by the increased risk practices of adolescents.

Distribution of Fatal Anaphylaxis According to Sex

In the study of Ma et al [48], males were more likely to die because of anaphylaxis than females. In other studies [42,60], the increased risk is restricted to specific causes of anaphylaxis. However, elsewhere, this relationship was not observed [12]. Simon and Mulla [60] and Jerschow et al [42] found an increased risk for insect-induced anaphylaxis, since men are more frequently exposed to Hymenoptera than women.

Distribution of Fatal Anaphylaxis According to Time of Year

The frequency of fatal Hymenoptera anaphylaxis peaks in spring and summer [60], in line with the annual life cycle of the insects.

Distribution of Fatal Anaphylaxis According to Morbidity, Race, and Posture

Turner et al [43] and Pumphrey [64] found that up to 75% of patients who experienced fatal food-induced anaphylaxis had asthma and that control of asthma was sometimes suboptimal [64]. In a study carried out in an emergency department, underlying lung disease was a predictor of severity of anaphylaxis [58].

African American ethnicity has also been shown to be a risk factor for fatal food-induced anaphylaxis and fatal anaphylaxis of unknown cause [42].

Upright posture during an anaphylactic event [64] is also associated with fatal anaphylaxis owing to empty ventricle syndrome, which is characterized by pulseless electrical activity and lack of venous return to the heart [73].

Distribution of Fatal Anaphylaxis According to Food

In publications from the USA, UK, and Sweden [43,74-78], peanut and other tree nuts were responsible for up to 75% of cases of food-induced anaphylaxis, whereas in the study of Turner et al [43], which spanned 20 years of follow-up until 2013, milk was responsible for 21% of cases of fatal food-induced anaphylaxis in patients aged under 16 years.

Distribution of Fatal Anaphylaxis According to Medications

In their study of drug-induced anaphylaxis, Jerschow et al [42] found that in cases where the culprit drug was identified, the most frequent causes were antibiotics (mainly penicillins and cephalosporins) in 40% of cases, diagnostic agents in 30.4%, and antineoplastic drugs in 12.5%. The findings can be explained by the frequent use of these drugs in current medical practice.

Time Trends in Fatal Anaphylaxis

Deaths from drug-induced anaphylaxis increased by 200%-300% according to findings from 2 studies [12,42], although elsewhere [10,43,48], no increase in the frequency of death was observed for anaphylaxis induced by drugs or other causes.

Summary: Progress Made in the Last 10 Years and Unresolved Issues

The tables show that the number of studies on the epidemiology of anaphylaxis has increased by 100% in the last 10 years compared with the previous 10 years. Not only has the number of studies increased, but the quality of data has also improved owing to the more robust methodologies applied. The vast majority of previous studies [57,58,79-81] were based on experience gained in emergency departments or in allergy outpatient units. In contrast, the most recent studies, despite evident bias, are from the general population and are based on data for whole countries, large populations, or long periods of time. In addition, external validity is good, albeit with limitations, namely, low internal validity owing to the lack of validity of the algorithms used [39], a small positive predictive value for studies that used *ICD-9-CM* codes (63%-72%), and wide variability between health organizations [82,83].

In any case, the incidence and prevalence of anaphylaxis seem higher than previously thought and higher than reported in studies from the late 1990s and early 2000s. We only have indirect evidence of whether the increased frequency of anaphylaxis is due to a real increase in the frequency of anaphylaxis or to increases in the frequency of diagnosis as a result of increased awareness or database search strategies.

The frequency of anaphylaxis varies according to demographic and clinical groups. The highest incidence and prevalence are found in children with food allergy (cow's milk and hen's egg) during the first 2 years of life and can reach 3 times the frequency of other groups. Likewise, the largest increases in the frequency of anaphylaxis have been observed in food-induced anaphylaxis and in children under 15 years.

Recurrence is the least studied area of the epidemiology of anaphylaxis. However, al least 30% of patients who have survived an episode of anaphylaxis experience 1 or more recurrences, mainly anaphylaxis associated with atopy or Hymenoptera venom in high-exposure areas.

Death by anaphylaxis is very rare, and the cause of fatal anaphylaxis varies with the age group. Fatal food-induced anaphylaxis usually occurs before 35 years, while drug and Hymenoptera anaphylaxis occur after 40-50 years. Fatal anaphylaxis seems to be more frequent in older people than in younger people.

New studies in non–English-speaking areas could examine the same epidemiologic problems using a methodology similar to that used in English-speaking areas. These studies must validate their algorithms against widely accepted gold standards and be carried out in different geographic areas simultaneously. In addition, they must use the same methodology as in the large epidemiologic studies on asthma from the 1990s [84,85]. Such studies would reveal differences between countries/regions with different cultures, costumes, food habits, and environments and would show the differences to be real. The coming years could see studies based on samples from the general population similar to that performed by Wood et al [15].

The higher frequency of anaphylaxis observed in recent years means that this condition will be an increasingly common presenting complaint at allergy outpatient clinics. This is particularly true of pediatric patients with food allergy, in whom recurrence is a major problem whose prevention and management is far from adequate [86-88]. Deaths from anaphylaxis, while very rare, continue to be recorded.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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