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Anaphylaxis (M Sánchez Borges, Section Editor)

Definition, Epidemiology, and Pathogenesis

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Opinion statement

Anaphylaxis is a severe reaction that is rapid in onset and may lead to death. The prevalence of anaphylaxis seems to be increasing. However, knowledge about the epidemiology of anaphylaxis is based on data from various sources: clinical practice, large secondary clinical and administrative databases of primary care or hospitalized patients, and recent surveys with representative samples of the general population. The different inclusion criteria, settings, geographic area, and time at which these studies are performed may explain the huge difference in prevalence, incidence, and triggers. Nevertheless, it is clear that the incidence and prevalence of anaphylaxis are higher than previously thought. Publications from the last 5 years reveal an incidence of between 12.8 and 112 episodes per 100,000 person-years. Furthermore, depending on the trigger of anaphylaxis, the symptoms of the reaction could differ enormously, the mechanism initiating the anaphylactic reaction, and the effector cells involved; therefore, the biomarkers may differ according to these factors. However, many of these data are missing in epidemiologic studies. Thus, in order to increase the knowledge of anaphylaxis, there is a need to improve epidemiologic research standardizing information provided, as summarized in this review.

Introduction

Anaphylaxis is a severe, life-threatening multisystem syndrome that is rapid in onset and potentially fatal [1, 2]. It most often represents an immunologic response, resulting from sudden systemic degranulation of mast cells (MC) and basophils [3].

The main problem in anaphylaxis is that nowadays the diagnosis is based on suggestive clinical symptoms after an exposure to a potential triggering agent or event [1], given that no biomarker allows an unequivocal diagnostic confirmation of anaphylaxis. For this reason, anaphylaxis is still underdiagnosed by physicians and remains underrecognized by patients, and all these factors lead to undertreatment of these severe reactions, enhancing the risk of morbidity and mortality.

This review highlights and summarizes the most important epidemiologic studies of anaphylaxis from the last years and discusses the reasons why anaphylaxis is still underdiagnosed. It also suggests a proposal on the information that would be useful to unify outcomes of epidemiologic studies. Finally, it gives an overview on the different mechanisms of anaphylaxis depending on the trigger and the effector cells involved.

Definition and epidemiology: which are the main gaps we need to overcome?

To be able to obtain a real prevalence and incidence of anaphylaxis, the first crucial step is the use of a common definition and diagnostic criteria. Currently, no definition of anaphylaxis is universally accepted; several have been proposed in the last years [4••]. However, the most used of these are the definitions proposed by the World Allergy Organization (WAO) [5] which defines anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death and by the European Academy of Allergy and Clinical Immunology (EAACI) which defines anaphylaxis as a severe life-threatening generalized or systemic hypersensitivity reaction [6]. On the other hand, the most accepted diagnostic criteria are those defined by Sampson et al. in 2006 [1].

Also, it is important to use the appropriate nomenclature regarding epidemiology terms such as incidence and prevalence. As described in the EAACI protocol for a systematic review in epidemiology of anaphylaxis [7], the incidence is the number of new cases of anaphylaxis that occur during a given period in a defined population. Incidence may also be studied as incidence rate and cumulative incidence. Prevalence is the proportion of a defined population known to have experienced anaphylaxis. Epidemiological measures may be further divided into point prevalence, period prevalence, and lifetime prevalence and also explore the fatalities ratio [7].

Most epidemiologic studies are based on analysis in settings where patients with anaphylaxis have been attended. The most widely published series include those from emergency departments [8–11]. Data of some epidemiologic studies also come from regional databases [12–15] and from health organizations [16].

However, inclusion criteria differ, and the information collected in these studies is also different, making it difficult to compare the prevalence or the incidence in diverse areas and settings. No comprehensive worldwide epidemiologic study on anaphylaxis exists nowadays. Thus, the ideal research design to analyze the true global epidemiology of anaphylaxis would be to develop a large-scale, prospective, simultaneous study in different countries using a common methodology. Figure 1 depicts a proposal on the main data that would be important to report.

Which are the main studies providing the current knowledge on the epidemiology of anaphylaxis?

The prevalence of anaphylaxis varies widely in published studies, although data suggest that the prevalence is increasing, particularly in developed countries

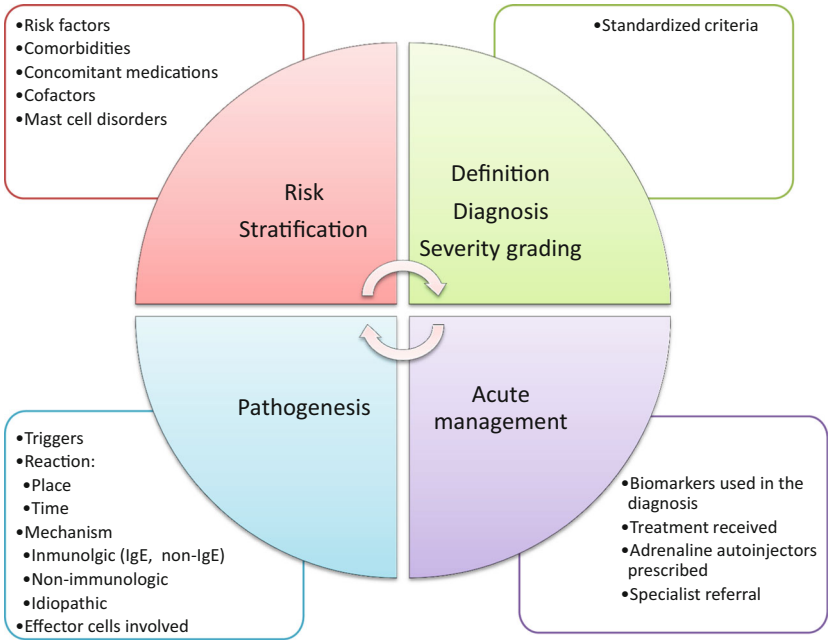

Fig. 1. Standardization of epidemiologic studies in anaphylaxis

[13–22]. The different estimates may be due to the diverse study designs, populations, time frames, and the fact that most of them are retrospective studies.

The main results of the most relevant epidemiologic studies are summarized in Table 1, which highlights the variability in outcomes, emphasizing the need for standardization.

The lifetime prevalence of anaphylaxis (the percentage of people who have experienced anaphylaxis at some time during their lifetime) reported in most studies is between 0.05 and 2 % of the general population [17], despite the assumption that it is possibly an underestimation [23]. In fact, recently, Wood et al. [24••] have reported the first study to define the prevalence of anaphylaxis among a representative sample of adults (≥18 years) from the general population of the USA, and it suggests that the true prevalence is probably higher (5.1 %). The main limitation is the lack of validation of the questionnaire used to identify anaphylaxis and the exclusion of children in the sample, a population with higher rates of anaphylaxis.

Few epidemiologic studies to date have examined the incidence of anaphylaxis in the general population. Most incidence studies are retrospective, reporting the incidence of anaphylaxis in emergency departments (ED), allergy clinics, and critical care units (Table 1). The reported incidence ranges from 6.7 to 112.2 episodes per 100,000 person-years.

This huge disparity could be due to the use of diverse definitions and case selection criteria (diagnostic coding, databases) or a true temporal trend, as discussed before. In example, the group of Tejedor-Alonso et al. [12] used electronic medical records from primary care clinics, allergy clinics, ED visits, and hospitalizations, and tracked patients with anaphylaxis across different clinical settings. The incidence rate was 112 episodes per 100,000 person-years

Table 1. Summary of the main epidemiological studies on anaphylaxis

Study	Country setting	Type of study	Year	Incidence (per 100,000 person-years)	Prevalence (%)	Pediatric population	Adult population	Main trigger (percentage)	Diagnosis based also on tryptase	Register of epinephrine use (% of use)
Yocum et al. [14]	USA Population cohort	Retrospective	1983–1987	21	NA	Yes	Yes	1st Food (NA) 2nd Drugs (NA) 3rd Insect sting (NA)	No	No
Helbing et al. [15]	Switzerland Allergy clinics	Retrospective	1996–1998	8.7	NA	Yes	Yes	NA	No	No
Sheikh et al. [30]	UK National health dataset	Retrospective	2001	6.7	NA	Yes	Yes	NA	No	Yes (10.7 %)
Silva et al. [27]	Portugal	Retrospective	2001–2009	NA	NA	Yes	No	1st Food (78 %) 2nd Drugs (10 %) 3rd Hymenoptera (2.7 %)	No	Yes (25 %)
Peng et al. [32]	UK Population dataset	Retrospective	2004	8.4	NA	Yes	Yes	1st Insect sting (32 %) 2nd Drugs (30 %) 3rd Food (22 %)	No	No
Bohlke et al. [16]	USA	Retrospective	2004	10.5	NA	Yes	No	1st Food (42.4 %) 2nd Insect sting (22.4) 3rd Drugs (11.8 %)	No	Yes (78.8 %)
Sheikh et al. [31]	UK National health dataset	Retrospective	2005	7.9	NA	Yes	Yes	NA	No	Yes (21 %)
Worm et al. [26]	Germany, Austria, Switzerland Allergy department	Retrospective	2006–2010	NA	NA	Yes	Yes	1st Insect sting (50.4 %) 2nd Food (24.3 %) 3rd Drugs (16.7 %)	No	No
Poulos et al. [20]	Australia National Hospital Database	Retrospective	2007	NA	8.8 %	Yes	Yes	1st Non-food (65 %) 2nd Food (35 %)	No	No
Decker et al. [13]	USA Population-based study	Retrospective	2008	49.8	NA	Yes	Yes	1st Food (33.2 %) 2nd Insect sting (18.5 %) 3rd Drugs (13.7 %)	No	No
Yang et al. [50]	Korea Seoul National University Hospital	Retrospective	2008	NA	NA	Yes	Yes	1st Drugs (35.3 %) 2nd Food (21.3 %) 3rd Idiopathic (13.2 %)	No	No
Gelincik [25•]	Turkey Allergy department	Retrospective	2008–2011	NA	2.11 %	No	Yes	1st Drugs (90 %) 2nd Insect sting (5.4 %) 3rd Foods (1.6 %)	No	Yes (16.9 %)
González-Pérez et al. [33]	UK Health database	Retrospective	2010	43.1	NA	Yes	Yes	1st Drugs 2nd Foods	No	No
Chen Hsin et al. [51]	Taiwan Emergency department of a memorial hospital	Retrospective	2011	12.8	NA	Yes	Yes	1st Drugs (77 %) 2nd Idiopathic (8 %) 3rd Food (5 %)	No	Yes (57 %)
Sánchez-Borges [52]	Venezuela Allergy outclinic	Retrospective	2011	NA	7.39 %	Yes	Yes	1st Drugs (54 %) 2nd Food (24 %) 3rd Oral mite (8 %)	No	No

Table 1. (Continued)

Study	Country setting	Type of study	Year	Incidence (per 100,000 person-years)	Prevalence (%)	Pediatric population	Adult population	Main trigger (percentage)	Diagnosis based also on tryptase	Register of epinephrine use (% of use)
Huang et al. [22]	USA Emergency department in New York	Retrospective	2012	NA	NA	Yes	No	1st Food (71 %) 2nd Unknown (15 %) 3rd Drugs (9 %)	No	Yes (79 %)
Tejedor-Alonso et al. [12]	Spain Health area of Alcorcon	Retrospective	2012	112	NA	Yes	Yes	1st Food (34.23 %) 2nd Drugs (30.95 %) 3rd Idiopathic (21.7 %)	No	No
Solé et al. [53•]	Latin American Online Survey	Retrospective	2012	NA	NA	Yes	No	1st Food (36.1 %) 2nd Drugs (27.7 %) 3rd Insect sting (26.2 %)	No	Yes (34.6 %)
Sala-Cunill et al. [54•]	Spain Emergency department of Vall d'Hebron Hospital	Prospective	2013	NA	NA	No	Yes	1st Drugs (50 %) 2nd Food (34.5 %) 3rd *Anisakis* (4.9 %)	Yes	Yes (55 %)
Wood et al. [55]	USA National survey	Retrospective	2014	NA	5.1 %	Yes	No	1st Drug (61 %) 2nd Insect sting (41 %) 3rd Food (38 %)	No	Yes (11 %)

and this was higher than previously reported, with a peak of 314 episodes per 100,000 person-years in the age group 0–4 years [12].

Limited data have been published to date on the epidemiology of anaphylaxis in low- and middle-income countries. A Turkish study led by Gelincik et al. [25•] used a novel two-stage approach involving International Classification of Disease (ICD)-10 codes with additional analysis of clinical codes to extract data on patients admitted with a recorded primary diagnosis of anaphylaxis to all 45 hospitals in Istanbul. Overall, 2.11 % of patients were diagnosed of anaphylaxis [25•]. In this study, surprisingly the main triggers involved were drugs (90 %), and food was involved in only 1.65 % of cases.

Some studies, as the ones by Worm et al. [26] and Silva et al. [27], collect anaphylaxis cases during a time period; however, they do not provide incidence or prevalence rates. Nevertheless, they are very useful to improve the general knowledge of anaphylaxis and to compare elicitor triggers in different countries. In fact, in the study by Worm [26, 28] in a central European population, the main elicitors were insect stings, followed by food and drugs; on the other hand, the study by Silva [27], on a pediatric population from Portugal, the main trigger was food, followed by drugs and hymenoptera stings (Table 1).

The group of Yocum [14] was one of the first to analyze the incidence of anaphylaxis in the USA, reporting an incidence rate of 21 per 100,000 person-years and concluding that anaphylaxis is infrequent. Nevertheless, subsequent studies have demonstrated that this rate is underestimated [29]. Also, the ongoing rise in cases has been reported. Sheikh et al. published a UK epidemiologic study of anaphylaxis in 2001 [30] and another one in 2005 [31] showing an increased incidence of anaphylaxis from 6.7 to 7.9 per 100,000 person-years. Poulos et al. [20] reported an epidemiologic study between 1993–1994 and 2004–2005, and they observed increases in hospital admissions for anaphylaxis in Australia that were consistent with trends observed in the UK [30]. They particularly observed a large increase in admissions for food-related anaphylaxis in children [20].

Peng et al. [32] reported a national UK study based on a population dataset in 2004, and they found an incidence rate of anaphylaxis of 8.4 per 100,000 person-years, the same incidence reported by the group of Helbing [15] in Switzerland in 2004 (8.7 per 100,000 person-years). Bohlke [16] and afterwards Decker [13] also performed an epidemiologic study of anaphylaxis in the USA with an incidence rate of 10.4 and 49.8 respectively, also suggesting an increase of the incidence of anaphylaxis. Gonzalez Perez [33] reported similar incidence rates of anaphylaxis in the UK in 2008 (43.1 per 100,000 person-years).

Regarding the management of anaphylaxis and the use of biomarkers in the diagnosis, few studies have collected these data, as shown in Table 1. However, it is clear that there is an important undertreatment of anaphylaxis. Epinephrine use ranges from 10 % in a UK study published in 2001 by Sheikh [30] to 79 % in a US study published by Huang et al. [22]. Arroabarren et al. [34] demonstrated that after the application of a protocol, the management of anaphylaxis improved, with an increase in the use of epinephrine from 27 to 57.6 %, reinforcing the argument of a need in education. Gibbison et al. [19]

reported the increasing trend of anaphylaxis cases requiring admission to critical care units, constituting 0.1 % of admissions to pediatric units and 0.3 % of admissions to adult units [19].

Pathogenesis

The pathogenesis of anaphylaxis may vary depending on the triggers and the effector cells involved, despite that some of the activated pathways may be common to different types of anaphylactic reactions. The following sections review the potential mechanisms and triggers.

IgE-mediated anaphylaxis

Anaphylaxis is predominantly due to an immediate hypersensitivity reaction that is initiated by an allergen interacting with allergen-specific IgE bound to its high-affinity receptor (FcεRI) expressed on effector cells, predominantly MC and basophils [35]. Sensitization to an allergen occurs when naive CD4+ Th0 cells differentiate into Th2 cells and secrete cytokines such as interleukin (IL)-4, IL-5, and IL-13 that stimulate B cells to produce allergen-specific IgE (sIgE) [35].

The allergen/IgE complex initiates intracellular signaling; this results both in release of preformed MC mediators and in de novo synthesis [36]. Mast cells are found in the gastrointestinal tract, skin, lungs, and heart. Expression of particular mast cell mediators differs among MC in different tissue locations [37]. Therefore, the severity and symptoms of anaphylaxis may be partially dependent on the route of allergen exposure (i.e., ingested or injected) and the tissue mast cell population activated [38] and also on the mechanism that produces MC degranulation. In addition, FcεRI complexes are also expressed on monocytes/macrophages, Langerhans cells, myeloid and plasmacytoid dendritic cells (DCs), eosinophils, neutrophils, platelets, and bronchial smooth muscle cells, although the exact involvement of each of these cell types in anaphylaxis is not fully understood [36].

The main triggers involved in this type of anaphylaxis are foods, medications, stinging insect venoms, as well as *Anisakis*, latex, and other less common triggers [39].

Non-IgE-mediated anaphylaxis

Although IgE-mediated anaphylaxis is the most frequent type of anaphylaxis, several other immunologic and non-immunologic mechanisms of anaphylaxis have also been described [38, 40].

Immunologic mechanisms

The most relevant non-IgE-mediated immunologic mechanisms are

- *Complement generation* (anaphylatoxins C3a and C5a). Some substances, such as peanuts, have been described to have the ability to rapidly activate complement, with production of large amounts of the anaphylatoxin C3a. The rapid production of C3a through an antibody-independent pathway stimulates macrophages, basophils, and, to a lesser extent, mast cells to secrete platelet-activating factor (PAF) and

histamine, which contribute to the induction of anaphylaxis by increasing vascular permeability [41].

- *Contact and coagulation system activation* [42]. At the end of 2007, oversulfated chondroitin sulfate-contaminated heparin was reported to have increased potency for activating FXII and triggering prekallicrein (PK)-mediated bradykinin formation in human plasma [43, 44]. Activation of FXII-driven contact system cascades leads to increased vascular permeability with edema and hypotension. In fact, recently, it has been published by Sala-Cunill et al. that the activation of contact system correlates with the severity of anaphylaxis [45].
- *IgG*. It has been difficult to confirm the contribution of allergen-specific IgG to human anaphylaxis, but it has been proposed that IgG-mediated anaphylaxis in humans requires considerably more antigen than IgE-mediated anaphylaxis, such as in reactions to infused drugs such as contrast media, biological agents, and antivenoms. This most likely reflects the much higher affinity of IgE binding by FcεRI than IgG binding by FcγRIII [46]. In fact, Khodoun et al. compared various blood markers between IgE- and IgG-mediated anaphylaxis in mice to potentially determine whether IgG-mediated anaphylaxis occurs in humans. Their observations suggested that decreased blood neutrophil FcγRIII expression without increased IL-4Rα expression may help to determine if IgG immune responses are involved [46]. Macrophages and basophils have been shown to play a major role in IgG-mediated systemic anaphylaxis through the release of PAF (instead of histamine) [47, 48].

Non-immunologic mechanisms

Some drugs, such as codeine and morphine, ethanol, and physical factors, such as exercise, can induce mast cell degranulation directly [49].

Idiopathic mechanisms

In some patients, anaphylaxis with no apparent trigger has been described. These patients could present a mastocytosis, a clonal mast cell disorder, or a reaction to previously unrecognized allergens, as is the case of alpha-gal allergy.

Some agents are able to induce more than one mechanism of anaphylaxis, such as radiocontrast media, NSAIDs, and biologic agents [49].

Conclusion

The incidence and the prevalence of anaphylaxis are increasing worldwide. This increase could be explained by an improvement of awareness of the syndrome or a true increase of the frequency. However, anaphylaxis is still underrecognized and not optimally managed. Designing epidemiologic studies with common methodology and developed in a wide range of geographical areas will improve the current knowledge of

this serious event. Also, it is clear that there is an urgent need to further determine mechanisms involved in its occurrence and define risk factors which will aid in the development of prevention and future treatment strategies.

Compliance with ethics guidelines

Conflict of interest

Anna Sala-Cunill declare no conflicts of interest.
Victoria Cardona declare no conflicts of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by the authors.

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- •• Of major importance

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