

Current Trends in Prevalence and Mortality of Anaphylaxis

Ignacio J Ansotegui, MD PhD^{1,*}

Mario Sánchez-Borges, MD PhD²

Victoria Cardona, MD PhD^{3,4}

Address

¹Department of Allergy and Immunology, Hospital Quironsalud Bizkaia, Carretera Leioa Unbe 33 bis, 48950, Erandio, Bilbao, Bizkaia, Spain
Email: iansotegui.bil@quironsalud.es

²Department of Allergy and Clinical Immunology, Centro Medico Docente La Trinidad y Clinica El Avila, Caracas, Venezuela

³Allergy Section, Department of Internal medicine, Hospital Universitari Vall d'Hebron, Barcelona, Spain

⁴Allergy Research Group, Institut de Recerca Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain

Published online: 5 July 2016

© Springer International Publishing AG 2016

This article is part of the Topical Collection on *Anaphylaxis*

Keywords Anaphylaxis · Epidemiology · Fatality rates · Admission rates

Opinion Statement

It has not been until the last decade that we have gained insight to the global epidemiology of anaphylaxis, due to the methodological difficulties of such studies. Heterogeneity in definitions, severity grading and study designs have hampered compiling robust data which can be consistently analysed and compared. Also, previous International Classification of Diseases coding for anaphylaxis has been suboptimal further hindering epidemiological studies. Under-diagnosis is still a major pitfall in anaphylaxis, despite the efforts of national and international scientific societies to improve education of all health care professionals and implement clinical practice guidelines. Further collaborative projects are needed to overcome this gap. Currently, it seems that worldwide incidence of anaphylaxis and admission rates are increasing both in children and adults, according to recent studies. This may be partly due to an improvement in recognition, but most likely, due to a rise in allergic diseases in general and of food and drug allergy in particular. On the other hand, fatality rates seem to remain stable or to decrease slightly. We optimistically could hypothesize that this is a result of improved management, both acutely and in the long-term, but published data are still scarce. Prevention strategies are needed in order to halt this scaling trend; ongoing education on recognition and treatment will aid to improve anaphylaxis outcomes.

Introduction

It has not been until last decade that we have gained insight about the global epidemiology of anaphylaxis. Previously, most studies showed information regarding prevalence and incidence of allergic reactions to specific triggers like venom stings, drugs or foods, but nothing or very little about epidemiological data of anaphylaxis.

Several reasons could explain the difficulties in studying the epidemiology of anaphylaxis during the

twentieth century: it was considered to be a rare disease, there were many differences in the definition of anaphylaxis, poor identification of clinical cases in primary care and emergency settings (underdiagnosis), and lack of appropriate clinical databases.

The objective of this review is to evaluate the recently published literature regarding prevalence and mortality, in children and adults, of anaphylaxis.

Definition of anaphylaxis

Within the framework of the International Collaboration in Asthma, Allergy, and Immunology (iCAALL), the World Allergy Organization (WAO) and three member organizations of the WAO: the American Academy of Allergy, Asthma and Immunology [AAAAI], the American College of Allergy, Asthma and Immunology [ACAAI], and the European Academy of Allergy and Clinical Immunology [EAACI], recently published an international consensus (ICON) document on anaphylaxis [1••]. This document reviews the major anaphylaxis guidelines developed and published independently by these collaborating organizations [2–4]. All of these anaphylaxis guidelines include clinical criteria for diagnosis aiming for a rapid identification of patients with a likely diagnosis of anaphylaxis, taking into account the concepts of a sudden onset of a serious and generalized allergic reaction that can be life-threatening or fatal. But there are slight differences in these guidelines regarding the importance of underlying mechanisms, triggers and risk factors relevant to anaphylaxis diagnosis. The variability in definitions increases the difficulties in good epidemiological data.

One of the major problems in anaphylaxis is under-diagnosis. Calderon et al. [5] reported that only 4.4 % of patients attending an emergency department in Puerto Rico were diagnosed with anaphylaxis. Meanwhile, almost 20 % of patients that met the diagnostic criteria for anaphylaxis were just identified as “allergic reactions.” Most healthcare professionals can easily recognize anaphylaxis in the 80–90 % of patients with cutaneous involvement but under-diagnosis is common when skin symptoms and signs are absent [6].

Anaphylaxis has been misclassified in both the International Classification of Diseases (ICD)-9 and ICD-10 versions (WAO update). The new updated revision, ICD-11, is an opportunity to improve the classification of allergic diseases, including anaphylaxis, and facilitate future epidemiological studies [7, 8•].

Epidemiological tools to determine the frequency of anaphylaxis

It is still controversial to elucidate which is the best tool to measure the frequency of anaphylaxis. Incidence rate (number of new cases of anaphylaxis that occur during a defined period per unit person-time), cumulative incidence (the number of new cases of anaphylaxis that occur during a given period per the population at risk), point prevalence (proportion of the population that has experienced

anaphylaxis at a specific time, such as a particular date), period prevalence (proportion of the population that has experienced anaphylaxis during a given period), or life time prevalence (proportion of the population that at some point in their life will have experienced anaphylaxis) are used to determine the frequency of anaphylaxis [9]. Probably a pooled analysis of data of prevalence and incidence is the best way to estimate anaphylaxis frequency. An important factor to take into account in the prevalence of anaphylaxis is that the condition disappears once the episode has been resolved. Therefore, it is important to consider if episodes were unique or anaphylaxis has been recurrent.

Many of the epidemiological studies published use different methodology with diverse inclusion criteria and results of prevalence and incidence are often not comparable [10]. That is the reason why the prevalence of anaphylaxis ranges from 0.3 to 5.1 % depending on the study [11••]. Regarding the incidence, it ranges from rates of 10 episodes per 100,000 person-years, in studies before 2005 [12–15], to more than 50 episodes per 100,000 person-years in more recent studies [16–19].

Large-scale, prospective, simultaneous studies in different countries using a common methodology would be desirable [20] (Fig. 1). Nowadays, there is a lack of comprehensive worldwide epidemiologic studies on anaphylaxis. Most information about the epidemiology of anaphylaxis comes from general population surveys and secondary analyses of clinical and administrative databases [7] [8•] [11••] [19, 21–27] [28•]. With this information, we can estimate the increase of the frequency of anaphylaxis, the time trends in admissions and/or

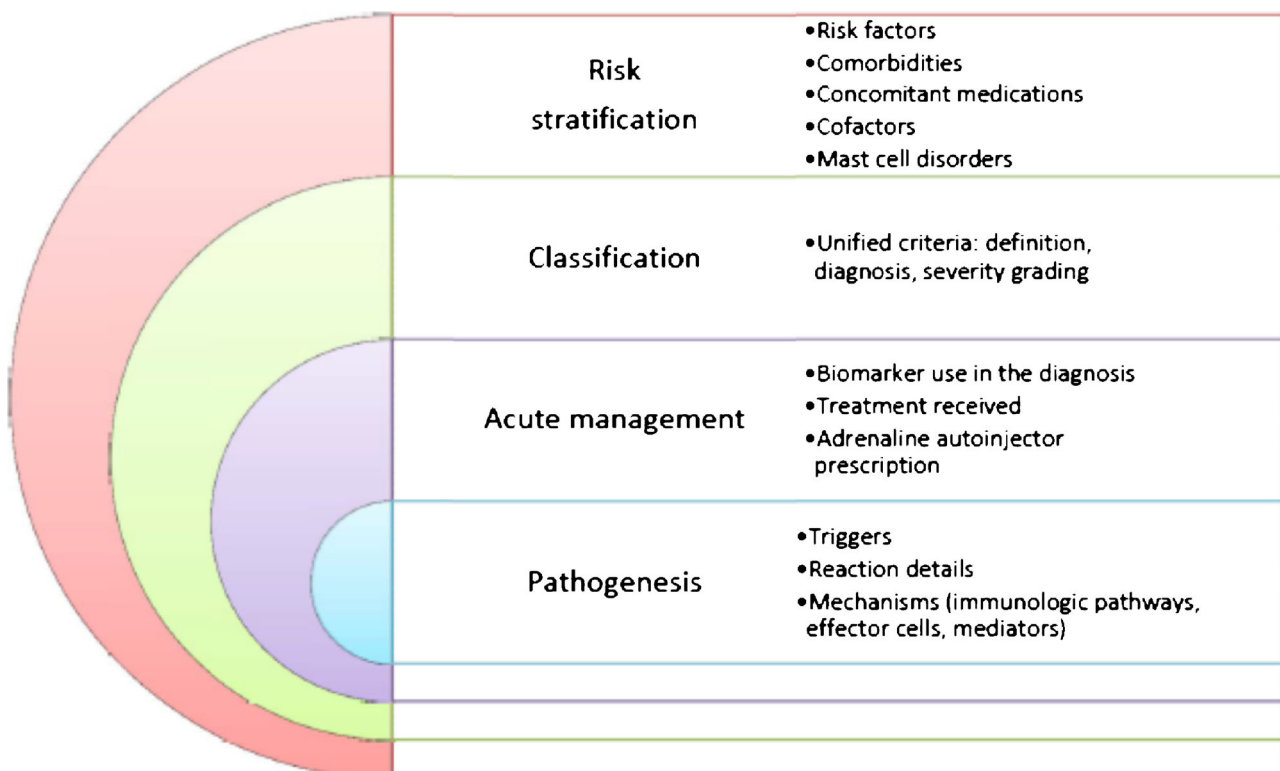


Fig. 1. Proposal for the design of future epidemiological studies on the epidemiology of anaphylaxis.

hospitalizations as well as the case fatality rate (proportion of cases of anaphylaxis that proves fatal, within a time period). In a survey of 1000 unselected United States (US) adults who received hospital care for anaphylaxis, the lifetime risk of symptoms was over 1.6 % [21].

Time trends in hospital admissions

Time trends in hospitalizations obtained from the US Healthcare Cost and Utilization Project Kids' In-Patient Database showed that admissions for food induced anaphylaxis in US children aged <18 years increased more than double from 2000 to 2009 [22•]. Nocerino et al. published similar increase in hospitalizations, from 2006 to 2011, for food induced anaphylaxis in children, mainly in those aged 5–14 years [23•]. Australian publications report that hospitalization rates for food-induced anaphylaxis continue to increase across all age groups. The higher increase was observed in the age groups 5–14 years and 15–29 years, but still the highest admission rates occurred in children age 0–4 years [24•].

Different studies in the USA and Spain indicated that the incidence of anaphylaxis in children aged 0–4 years was three times higher than in the remaining age groups [18, 19, 29] and this might be attributed to anaphylaxis by cow's milk and hen's egg during the first 2 years [18, 30].

In a UK study, hospital admissions due to anaphylaxis of any cause from 1992 to 2012, there was an increase of 615 %, although a plateau was observed in the last 4 years of the study. The major increase in this study was due to insect sting anaphylaxis [25••]. The admission rates from drug- and insect sting-induced anaphylaxis were highest in the elderly while food-induced anaphylaxis admission rates were highest in young people. The incidence of fatal food reactions showed a marked peak during the second and third decades of life [25••].

A recent study also observed an increase in emergency department (ED) consultations for anaphylaxis of paediatric patients in Canada [31]. The percentage of anaphylaxis cases among all ED visits more than doubled over the 4-year period from 0.20 % (95 % CI, 0.18–0.24) to 0.41 % (95 % CI, 0.36–0.45), with the largest annual increase between 2013–2014 and 2014–2015 (0.11 %).

Fatal anaphylaxis

Very few studies about fatal anaphylaxis have been published in the last years [25••] [26] [27••]. These articles collected data from several years in large populations and showed a considerable number of registered deaths from anaphylaxis (near 2500). In any case, death from anaphylaxis is a very rare and extraordinary event [19]. In the USA, overall mortality rates ranged from 0.63 to 0.76/million population (186–225 deaths per year) and appeared to be stable from 1999 to 2009 [26]. Another study analysing 2458 fatalities [27••], reported that drugs (58.8 %) were the most common trigger followed by unspecified or unknown inducers (19.3 %), insect stings (15.2 %) and foods (6.7 %). As drug anaphylaxis is more frequent in older patients, the fatalities were also associated with older age [27••]. But there are other factors and demographic characteristics to take into account in the estimation of risk to suffer fatal anaphylaxis.

In the UK, although hospital admissions for anaphylaxis from 1992 to 2012 increased by 615 % the number of fatalities remained stable at 0.047 cases/million population [25••]. Fatality rates for anaphylaxis from drugs and insect stings were highest in the elderly and the incidence of food anaphylaxis fatalities peaked in the second and third decades of life [25••].

Older age was associated with increased rates of fatal anaphylaxis regardless of the anaphylaxis cause [27••]. The risk of fatal anaphylaxis in the elderly might be higher due to underlying cardiovascular or cerebrovascular illnesses and the increased use of drugs such as ACE inhibitors, angiotensin receptor antagonists, and beta blockers in this population [19] [25••]. Not well controlled asthma has been found in 75 % of fatal food-induced anaphylaxis [25••]. Regarding ethnicity, African American race has also been shown to be a significant risk factor for all anaphylaxis causes, with the exception of venom-induced anaphylaxis [27••].

Also the triggers are important to elicit a fatality. Jerschow et al. [27••] reported that most (74 %) of the fatal drug-induced anaphylaxis had not identified the culprit drug. Among those with an identified culprit drug half were antibiotics followed by radiocontrast agents and chemotherapy. Regarding foods, peanut, tree nuts, cow's milk, shellfish, soy, hen's egg and fish were the major causes [10–19] [21] [22•] [23•] [24•] [25••].

Long-term management of anaphylaxis

Despite that it is well-known that the use of adrenaline, both in medical settings and in the day to day life of patients is suboptimal, it seems to have improved in the last years [32]. Therefore, it would be reasonable to hypothesize that stabilization in fatalities may be secondary to improved management [31]. Nonetheless, allergy specialists and professional allergy organizations should endeavour to disseminate and increase the implementation of current anaphylaxis practice guidelines.

Also, it is of paramount importance to identify patients at risk of anaphylaxis recurrences in order to implement adequate avoidance measures and to establish self-care management plans. Correctly diagnosing the culprit cause of the reaction is not always an easy task. Nevertheless, major advances in diagnostic procedures have enabled the identification of previously unsuspected allergens. Noteworthy is the role of molecular diagnosis which may identify sensitization to molecules such as omega-5-gliadine or alpha-gal, which are not easily recognized by conventional diagnostic techniques. Also, it may aid by proving or ruling out other major causes of anaphylaxis, through the assessment of sensitization to allergen protein families known to frequently cause systemic allergic reactions (seed storage proteins, lipid transfer proteins, etc.) [33].

Summary

Although anaphylaxis was considered to be a rare disease, hospitalization rates continue to increase year after year. Large-scale, prospective, simultaneous studies in different countries using a common methodology would be necessary to increase the epidemiological knowledge of anaphylaxis. A worldwide accepted definition of anaphylaxis would be one of the first requirements to

facilitate epidemiological studies. The new International Classification of Diseases ICD-11 will be a good opportunity to classify most allergic diseases and will be helpful in the correct identification of clinical cases of anaphylaxis in all settings. The latest studies have reported an increased trend of admissions for anaphylaxis; meanwhile, fatality rates have remained stable or decreased slightly.

Compliance with Ethical Standards

Conflict of Interest

Dr. Ignacio J Ansotegui and Dr. Mario Sanchez Borges declare that they have no conflict of interest. Dr. Cardona reports personal fees from ALK, personal fees from CIRCASSIA, personal fees from LETI, non-financial support from SHIRE, non-financial support from THERMOFISHER, outside the submitted work.

Human and Animal Rights and Informed Consent

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

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

- 1•• Simons FER, Arduso LR, Bilò MB, Cardona V, Ebisawa M, El-Gamal YM, et al. International consensus on (ICON) anaphylaxis. *World Allergy Organ J*. 2014;7:9. This document reviews and compares the major anaphylaxis guidelines developed and published independently by AAAAI/ACAAI, EAACI & WAO
2. Simons FER, Arduso LRF, Bilò MB, Dimov V, Ebisawa M, El-Gamal YM, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J*. 2011;4:13–37.
3. Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol*. 2010;126:477–80. e1–e42
4. Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernández Rivas M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy*. 2014;69:1026–45.
5. Calderón E, Méndez J, Nazario S. Anaphylaxis diagnosis and treatment at an emergency department in Puerto Rico. *P R Health Sci J*. 2013;32:170–4.
6. Wang J, Young MC, Nowak-Węgrzyn A. International survey of knowledge of food-induced anaphylaxis. *Pediatr Allergy Immunol*. 2014;25:644–50.
7. Tanno LK, Calderon MA, Goldberg BJ, Akdis CA, Papadopoulos NG, Demoly P. Categorization of allergic disorders in the new World Health Organization International Classification of Diseases. *Clin Transl Allergy*. 2014;4:42.
- 8•. Tanno LK, Calderon MA, Goldberg BJ, Gayraud J, Bircher AJ, Casale T, et al. Constructing a classification of hypersensitivity/allergic diseases for ICD-11 by crowdsourcing the allergist community. *Allergy Eur J Allergy Clin Immunol*. 2015;70:609–15. This article sows a proposal for new classification of allergic diseases to be included in the new International Classification of Diseases (ICD-11)
9. Last JM. A dictionary of epidemiology. 4th edition. New York: Oxford University Press; 2000.
10. Panesar SS, Javad S, de Silva D, Nwaru BI, Hickstein L, Muraro A, et al. The epidemiology of anaphylaxis in Europe: a systematic review. *Allergy*. 2013;68:1353–61.
- 11••. Tejedor Alonso MA, Moro Moro M, Múgica García MV. Epidemiology of anaphylaxis. *Clin Exp Allergy*. 2015;45:1027–39. Excellent review on Epidemiology of Anaphylaxis
12. Helbling A, Hurni T, Mueller UR, Pichler WJ. Incidence of anaphylaxis with circulatory symptoms: a study over a 3-year period comprising 940 000 inhabitants of the Swiss Canton Bern. *Clin Exp Allergy*. 2004;34:285–90.
13. Bohlke K, Davis RL, DeStefano F, Marcy SM, Braun MM, Thompson RS. Epidemiology of anaphylaxis among children and adolescents enrolled in a health

- maintenance organization. *J Allergy Clin Immunol*. 2004;113:536–42.
14. Sheikh A, Hippisley-Cox J, Newton J, Fenty J. Trends in national incidence, lifetime prevalence and adrenaline prescribing for anaphylaxis in England. *J R Soc Med*. 2008;101:139–43.
 15. Peng MM, Jick H. A population-based study of the incidence, cause, and severity of anaphylaxis in the United Kingdom. *Arch Intern Med*. 2004;164:317–9.
 16. Decker WW, Campbell RL, Manivannan V, Luke A. St. Sauver JL, Weaver A et al. The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. *J Allergy Clin Immunol*. 2008;122:1161–5.
 17. González-Pérez A, Aponte Z, Vidaurre CF, Rodríguez LAG. Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. *J Allergy Clin Immunol*. 2010;125:1098–1104.e1.
 18. Tejedor Alonso M A, Moro Moro M, Múgica García M V, Esteban Hernández J, Rosado Ingelmo A, al. VAC e. Incidence of anaphylaxis in the city of Alcorcon (Spain): a population-based study. *Clin Exp Allergy*. 2012;42:578–89.
 19. Tejedor-Alonso MA, Moro-Moro M, Múgica-García M V. Epidemiology of anaphylaxis: contributions from the last 10 years. *J Investig Allergol Clin Immunol*. 2015;25:163–75.
 20. Sala-Cunill A, Cardona V. Definition, epidemiology, and pathogenesis. *Curr Treat Options Allergy*. 2015;2:207–17.
 21. Wood R A, Camargo C A, Lieberman P, Sampson H A, LB S, al. ZM e. Anaphylaxis in America: the prevalence and characteristics of anaphylaxis in the United States. *J Allergy Clin Immunol*. 2014;133:461–7.
 - 22•. Rudders SA, Arias SA, Camargo CA. Trends in hospitalizations for food-induced anaphylaxis in US children, 2000–2009. *J Allergy Clin Immunol*. 2014;134:960–2.
- This article reports the increase of hospitalizations for food-induced anaphylaxis in US children over a decade
- 23•. Nocerino R, Leone L, Cosenza L, Berni CR. Increasing rate of hospitalizations for food-induced anaphylaxis in Italian children: an analysis of the Italian Ministry of Health database. *J Allergy Clin Immunol*. 2015;135:833–835.e3.
- This study shows the increase of hospitalizations for food-induced anaphylaxis in Italian children
- 24•. Mullins RJ, Dear KBG, Tang MLK. Time trends in Australian hospital anaphylaxis admissions in 1998–1999 to 2011–2012. *J Allergy Clin Immunol*. 2015;136:367–75.
- This article reports the increase burden of anaphylaxis among adolescents and adults in Australia. It also includes data of fatal anaphylaxis
- 25••. Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992–2012. *J Allergy Clin Immunol*. 2015;135:956–963.e1.
- This study analyses the trends in anaphylaxis admissions and fatalities by age, sex, and cause in England and Wales over a 20-year period in a large population
26. Ma L, Danoff TM, Borish L. Case fatality and population mortality associated with anaphylaxis in the United States. *J Allergy Clin Immunol*. 2014;133:1075–83.
 - 27••. Jerschow E, Lin RY, Scaperotti MM, McGinn AP. Fatal anaphylaxis in the United States, 1999–2010: temporal patterns and demographic associations. *J Allergy Clin Immunol*. 2014;134:1318–1328.e7.
- This article analyses the epidemiologic features and time trends of fatal anaphylaxis in the United States from 1999 to 2010
- 28•. Simons FER, Ebisawa M, Sanchez-Borges M, Thong BY, Worm M, Tanno LK, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. *World Allergy Organ J*. 2015;8:32.
- Update of the WAO Guidelines regarding epidemiology, clinical diagnosis, risk factors and management in healthcare and community settings
29. Simons FE, Peterson S, Black CD. Epinephrine dispensing patterns for an out-of-hospital population: a novel approach to studying the epidemiology of anaphylaxis. *J Allergy Clin Immunol*. 2002;110:647–51.
 30. Vetander M, Helander D, Flodström C, Ostblom E, Alfvén T, Ly DH, et al. Anaphylaxis and reactions to foods in children—a population-based case study of emergency department visits. *Clin Exp Allergy*. 2012;42:568–77.
 31. Hochstadter E, Clarke A, De Schryver S, LaVieille S, Alizadehfar R, Joseph L, et al. Increasing visits for anaphylaxis and the benefits of early epinephrine administration: a 4-year study at a pediatric emergency department in Montreal, Canada. *J Allergy Clin Immunol*. **Published Online First: 19 April 2016.** doi:10.1016/j.jaci.2016.02.016.
 32. Grabenhenrich LB, Dölle S, Moneret-Vautrin A, Köhli A, Lange L, Spindler T, et al. Anaphylaxis in children and adolescents: the European Anaphylaxis Registry. *J Allergy Clin Immunol*. 2016:1–11.
 33. Cardona V, Ansotegui JJ. Component-resolved diagnosis in anaphylaxis. *Curr Opin Allergy Clin Immunol*. **Published Online First 2016.** doi:10.1097/ACI.0000000000000261.