

Epidemiology of anaphylaxis

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Purpose of review

The prevalence of allergic disorders has more than doubled in the last two decades leading to increased community concern and anxiety, and unprecedented demand for allergy-specialist services. However, although allergic reactions are common, anaphylaxis is uncommon and fatal anaphylaxis is rare. This review examines recent developments in the epidemiology of anaphylaxis, focusing on new information that may assist in identifying those at increased risk of severe reactions and adverse outcomes.

Recent findings

Recent studies suggest an increase in prevalence of anaphylaxis in industrialized countries. Examination of the demographic characteristics of anaphylaxis has revealed potential approaches to better recognize those at greatest risk. Novel laboratory approaches to identify patients at increased risk of severe reactions have been suggested.

Summary

Increased knowledge of the epidemiology of anaphylaxis has provided insights into the characteristics of those patient groups most at risk of adverse outcomes. However, these characteristics have poor specificity and limited applicability for detection of at-risk individuals in the clinical setting. Further research is required to facilitate more accurate assessment of an individual's risk for anaphylaxis or fatal outcome. This would represent a major advance in clinical management and enable better allocation of existing healthcare resources.

Keywords

anaphylaxis, epidemiology, food allergy, peanut, risk factors

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Introduction

Anaphylaxis is the most severe form of an allergic reaction and, if untreated, can result in death. Knowledge of the epidemiology of anaphylaxis will assist in development of improved prevention and management strategies for patients. With the apparent rapid rise in the prevalence of allergic disease in westernized countries, recent research has focused on whether there is also a parallel rise in the prevalence of anaphylaxis. Information on the prevalence of anaphylaxis would enable a more accurate assessment of the actual population risk of anaphylaxis and mortality from anaphylaxis in allergic individuals, determine if they are linearly related, and provide the potential to augment clinical services appropriately to improve management and minimize adverse outcomes. A second priority area of research has been to identify clinical and laboratory markers that can be used to distinguish those most at risk of anaphylaxis and possible death from amongst the broader group of patients with allergies who may only express mild to moderate allergic manifestations. Understanding the demographic characteristics of nonfatal and fatal ana-

phylaxis may facilitate the development of a more individualized approach to management of patients with specific allergies. The extremely rare but devastating consequence of sudden death in a healthy individual may foster the practice of defensive medicine as well as promoting considerable anxiety in the patient and their family. More precise identification of patients significantly at risk of anaphylaxis will enable targeting of those who will most benefit from evolving novel therapeutics and allow focused support services for those who are exquisitely allergic.

Estimates of the prevalence of anaphylaxis

The population prevalence or incidence of anaphylaxis has been difficult to quantify because of a lack of consensus on the definition of anaphylaxis, analysis of different sample populations (e.g. Emergency Department presentations, hospital admissions, general practitioner presentations, specialist allergist presentations), and the use of varying methodologies for data collection. Population studies have estimated the incidence or prevalence of anaphylaxis in western countries to be in the range of 8–50 per

100 000 person-years [1^{••},2], with a lifetime prevalence of 0.05–2.0% [3]. The reported population incidence rates of anaphylaxis vary internationally, with studies from the US reporting 49.8 per 100 000 person-years, UK 8.4 per 100 000 person-years [4], and Australia 13 per 100 000 person-years [5]. The UK incidence estimate was derived from a GP database [4], the US incidence rate was determined from a population cohort in Minnesota, and the Australian minimum incidence of anaphylaxis in the population was estimated on the basis of the number of anaphylaxis cases presenting to an allergy specialist in a captured population [5]. In contrast to the very high incidence rate reported by Decker *et al.* [1^{••}], Bohlke *et al.* [6] reported a lower US incidence rate of anaphylaxis of 10.5 per 100 000 person-years for children and adolescents enrolled at a health maintenance organization. The marked differences in incidence and prevalence rates between studies are more likely to reflect differences in sample populations, data collection methods, and varying definitions of anaphylaxis than true differences in incidence of anaphylaxis between countries.

Anaphylaxis admissions data from National database systems in the UK and Australia revealed a population prevalence of 3.6 per 100 000 (2003/2004) [7] and 8.0 per 100 000 (2004/2005) [8] in these countries, respectively. Using a state-wide administrative database the rate of anaphylaxis admissions for New Yorkers aged 0–20 years was 4.2 per 100 000 (2005) [9]. These admission figures are likely to underestimate the true population prevalence of anaphylaxis as not all anaphylaxis presentations will result in hospital admission and misclassification of the presenting disorder in hospital settings has been reported to occur frequently. A review of National Electronic Injury Surveillance System data from 34 participating Emergency Departments over a 2-month period in 2003 found that 57% of likely anaphylactic events were not assigned an ED diagnosis of anaphylaxis [10].

Definition of anaphylaxis

The use of varying definitions of anaphylaxis has been particularly problematic when attempting to determine the population prevalence of this condition. Several classification systems have been used (e.g. Mueller [11] or Brown [12]) that would classify a patient experiencing urticaria and localized angioedema of the face as having anaphylaxis; however, such a presentation would not meet current criteria for the diagnosis of anaphylaxis. A recent consensus document has defined anaphylaxis as a 'serious allergic reaction that is rapid in onset and may cause death', and proposed diagnostic criteria for use in clinical care [13]. By these criteria, a diagnosis of anaphylaxis can be made if there is involvement of the respiratory or cardiovascular systems during an allergic

reaction; or if a less severe reaction occurs in the setting of previously diagnosed allergy and likely exposure to the relevant allergen (see below).

Clinical criteria for diagnosing anaphylaxis (adapted from [13]):

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled:

- (1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
 - (a) Respiratory compromise [e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia]
 - (b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction [e.g. hypotonia (collapse), syncope, incontinence]
- (2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - (a) Involvement of the skin-mucosal tissue (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula)
 - (b) Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - (c) Reduced BP or associated symptoms [e.g. hypotonia (collapse), syncope, incontinence]
 - (d) Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
- (3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):
 - (a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP (low systolic blood pressure for children is defined as: less than 70 mmHg from 1 month to 1 year; less than $[70 \text{ mmHg} + (\text{age} \times 2)]$ from 1 to 10 years, and less than 90 mmHg from 11 to 17 years)
 - (b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

These consensus definitions for anaphylaxis are helpful in that they assist clinical care; however, use of the broader definitions outlined in criteria 2 and 3 results in heterogeneity of anaphylaxis diagnoses that may hinder research as they may overestimate the number of individuals at serious risk of a fatal outcome from anaphylaxis (criteria 2) or include those who may not have experienced an allergic reaction (criteria 3). The application of a more stringent definition such as that outlined in criteria 1 of the consensus definitions may be more

appropriate and useful for research, particularly in the search for clinical and laboratory predictors of an adverse outcome.

Causes of anaphylaxis and demographic characteristics

The most common causes of anaphylaxis in children differ from those in adults. Foods are the most common cause of anaphylaxis in childhood, whereas medication and insect sting anaphylaxis are more common in adults. Other less common causes in both children and adults include latex, immunotherapy-related reactions, exercise, cold, or idiopathic. A recent retrospective study [14[•]] of anaphylaxis presentations to a paediatric emergency department reported that foods were the causative trigger in 86% of presentations, with medication and insect stings accounting for 5 and 4% of presentations, respectively, and no cause identified in 5%. In this study, a prior history of anaphylaxis was noted in only 14% of cases, whereas concurrent diagnosis of other allergic disorders (asthma, eczema, or allergic rhinitis) was common (60%) [14[•]]. This highlights the difficulties associated with identification of those at risk of anaphylaxis and suggests that presence of other allergic conditions may provide some assistance in this regard. In contrast to anaphylaxis in childhood, medication and insect venom are more common triggers of anaphylaxis in adults. Consistent with this, hospital admissions for food-induced anaphylaxis occurred predominantly in children aged 0–4 years, whereas admissions for nonfood causes of anaphylaxis occurred predominantly in adults at least 35 years and elderly, and to a lesser extent in 15–34-year-olds [8].

The demographic characteristics of anaphylaxis differ depending on the causative allergen. In a retrospective study of fatal anaphylaxis and nonfatal anaphylaxis admissions in Australia over a decade, Liew *et al.* [15^{••}] reported that the age-specific hospitalization rates for drug-induced anaphylaxis were highest for the 55–84-year age group (3.8/100 000 population), whereas the age-specific hospitalization rates for food anaphylaxis were highest in the 0–4-year age group (9.4/100 000 population). Interestingly, for both food and drug-induced anaphylaxis admissions, there was a predominance of males in the less than 15-year age groups, whereas females outnumbered males for the greater than 15-year age groups.

Epidemiology of fatal anaphylaxis

Data from national mortality reporting systems in the UK and Australia estimate the prevalence of anaphylaxis fatalities from all causes to be 0.33 deaths per year per million population in the UK [16] with a higher rate of 0.64 deaths per year per million population in Australia [8,15^{••}]. Fatalities in the UK were reported to be due to

medication (44%), insect sting (23%), food/possible food (31%), and other (4%), whereas in the Australian study, deaths were predominantly due to medication/probable medication (57%) and insect sting (18%), with food being an uncommon cause (6%). A study of 18 anaphylaxis fatalities identified from a New Zealand city hospital coronial database [17] found a similar distribution of causative agents to that described for Australia (medication 56%, insect sting 22%, food 11%) raising the possibility that the reported differences between the UK and Australia may reflect ecological and/or dietary exposure differences between the regions.

Interestingly, a comparison of the demographic characteristics of fatal anaphylaxis and anaphylaxis admissions revealed marked differences in the case of food and insect sting events, which were not observed for drug-induced events [15^{••}]. For food anaphylaxis, admissions peaked in males under 5 years of age, whereas deaths occurred predominantly in females aged between 10 and 35 years. A similar divergence of demographic characteristics for fatal and nonfatal anaphylaxis was noted for insect sting events, with admissions mostly involving males aged 5–9 years, whereas insect anaphylaxis deaths occurred mostly in those aged 30–84 years almost exclusively (95%) in males. In contrast, drug-induced anaphylaxis admissions and fatalities both peaked in the 55–85-year age group. These divergent demographic findings for fatal and nonfatal anaphylaxis can assist in tailoring management approaches for patients with specific allergy, and serve to identify those groups with highest risk of fatality from amongst those diagnosed with specific allergy.

Time trends in anaphylaxis prevalence

Recent studies suggest that the prevalence of anaphylaxis is rising rapidly, particularly amongst young children. A study from the UK [7] found a seven-fold increase (from 5 to 36/million) in hospital admissions for anaphylaxis over a 15-year period between 1990 and 2005. Similar increases in UK general practice presentations of anaphylaxis [7] make it unlikely that admission rate data reflect lower thresholds for admission or mild allergic reactions mislabelled as anaphylaxis. In a US study, admissions for anaphylaxis increased from 17 to 42/million in New Yorkers aged 0–20 years between 1994 and 2005 [9]. Similarly, Decker *et al.* [1^{••}] reported that the incidence of anaphylaxis during the period from 1990 to 2000 was almost double that reported in a similar study between 1983 and 1987 [18].

In Australia, hospital admissions for anaphylaxis were reported to have increased by 8.8% per year between 1994 and 2005, equating to a 250% increase over this period, with increases affecting both food-induced (230%

increase) and non-food-induced (350% increase) anaphylaxis [8,15^{••}]. Interestingly, the increase in food-induced anaphylaxis occurred predominantly in children aged 0–4 years, with this group showing a five-fold increase (from 39 to 193/million population) in hospital admissions for food-induced anaphylaxis over the 10-year period of study [8]. Furthermore, when time trends were examined for the specific food allergens, the highest rate increases in anaphylaxis admissions were shown for peanut (328% increase) and shellfish (300%), whereas admissions for cow's milk anaphylaxis had increased to a lesser extent (154%) [15^{••}]. These findings emphasize the increasing burden on paediatric allergy services that has occurred in the past decade and suggest that allergen-specific factors that may have manifested in recent years (e.g. dietary avoidance practices or food preparation methods) may play a role in rising prevalence.

Liew *et al.* [15^{••}] examined time trends in fatal anaphylaxis and found that despite rising rates of anaphylaxis from all causes, deaths from food-induced anaphylaxis have remained stable and insect sting anaphylaxis fatalities have fallen by 88% in the past decade. In contrast, and of significant concern, rates of death from drug-induced anaphylaxis have risen by 300% over the last decade, which is greater than the rise in admissions for the same condition, highlighting the need for further research to better improve both drug allergy diagnosis and management.

Predictors of anaphylaxis and fatal anaphylaxis

To be able to identify patients who may be at increased risk of developing anaphylaxis from amongst the wider population of patients who are confirmed to have a specific allergy is important since only a minority of reactions are likely to be life-threatening. A prior anaphylaxis event can predict subsequent repeat anaphylaxis; however, anaphylaxis can also commonly occur following a previous mild allergic reaction. In a study of 83 children with peanut hypersensitivity, 12/17 (71%) of patients who had experienced a life-threatening reaction had a subsequent repeat life-threatening reaction; however, 19/43 (44%) patients who experienced a non-life-threatening reaction had a subsequent life-threatening reaction [19]. Furthermore, only 14% of anaphylaxis admissions had a prior history of anaphylaxis [14[•]]. Therefore, a history of anaphylaxis on its own has a poor ability to identify those patients who might subsequently develop anaphylaxis. Other clinical predictors of anaphylaxis risk have been proposed and include coexisting atopic disease [14[•],20^{••}], particularly asthma [21], and older age at first reaction of food allergy [22]. However, these risk factors have limited applicability due to low specificity- for example, a large proportion of food-

allergic patients have associated asthma and other atopic conditions, yet only 1% of allergic reactions are severe (anaphylaxis). Peanut and tree nut allergy are often cited as risk factors for anaphylaxis, although it is not clear whether these allergens are more commonly associated with persistent food allergy and therefore also anaphylaxis or whether these allergens are more likely to provoke a severe reaction. Unfortunately data about the likelihood of an allergen-provoking anaphylaxis must be collected retrospectively with inherent design weaknesses of selection and recall bias or from studies undertaken in animals with limited potential to extrapolate findings to the clinical setting.

More is known about clinical risk factors for fatality amongst those who have an episode of anaphylaxis. Studies of fatal anaphylaxis due to foods in the UK, US, and Australia [15^{••},23,24] have identified consistent risk factors for fatal food-induced anaphylaxis – co-existent asthma (90–100% of fatalities), age more than 10 years at the time of the fatal anaphylaxis episode (54–65% of fatalities), absence of or delayed access to an adrenaline auto-injector (80–87% of fatalities), and peanut or tree nut allergy (38–81% of fatalities). Liew *et al.* [15^{••}] reported risk factors for drug-induced anaphylaxis deaths as elderly age group (75% of fatalities were aged 55–85 years), the presence of cardiovascular (33% of fatalities) or respiratory (17% of fatalities) comorbidity. No specific risk factors for fatality due to insect sting anaphylaxis were identified other than male predominance (95% males) [15^{••}]. Recently Simon and Mulla [25^{••}] reported risk factors associated with 89 fatal episodes of anaphylaxis identified over a 10-year period in Florida between 1995 and 2006 from a state-based database of death certificates. The authors found fatal episodes of anaphylaxis were more likely to occur in older individuals, in an emergency department, and in the months March, April, July, and August [25^{••}].

There are currently no readily available or reliable investigative tests that can be used to predict the likelihood of a person developing anaphylaxis. Neither the size of the skin prick test wheal nor the level of the serum-specific IgE correlates with reaction severity and cannot be used to identify those at increased risk for a severe allergic reaction/anaphylaxis.

One promising approach to the laboratory identification of individuals at increased risk of a severe reaction is the characterization of B-cell epitope responses. Specific allergenic epitopes may correlate with reaction severity [26]. Furthermore, each allergic patient has a unique fingerprint of IgE-specific allergenic epitopes and characterization of an individual's allergenic epitope profile may provide additional information in determining the risk of severe reactions or anaphylaxis. Flinterman *et al.* [27[•]]

reported that amongst children with peanut allergy, an increased diversity of allergenic epitopes correlated with increased severity of reaction. Each patient's specific profile of B-cell responses to allergenic epitopes remained stable over 20 months [27], suggesting that an individual's specific profile of reactivity remains stable in the short to medium term. This approach may offer a novel strategy to identify those at increased risk of anaphylaxis in the setting of other food allergies and possibly also other causes of anaphylaxis.

The potential importance of allergenic epitopes as predictors of reaction severity is further highlighted by the findings of Commins *et al.* [28] who reported that the presence of specific IgE antibodies to a novel carbohydrate allergen galactose- α -1,3-galactose was associated with severe allergic reactions to beef, pork, and lamb. Further research into allergenic epitopes and characterization of each patient's epitope profile may lead to new approaches for identifying patients at increased risk of anaphylaxis.

Future directions to improve knowledge of epidemiology of anaphylaxis and fatal anaphylaxis

Understanding risk factors for the development of both anaphylaxis and death from anaphylaxis remains a research priority especially in the current setting of an evolving epidemic of food allergy. It appears that the rising prevalence of food allergy has translated to a similar increase in hospital admissions for anaphylaxis, and in the case of drug-induced anaphylaxis an increase in fatalities. International collaborations aimed at addressing preventable risk factors will benefit enormously from the improved standardization of allergy definitions including the definition of anaphylaxis with adoption of consensus definitions. Although anaphylaxis registries have been mounted in both the US [29,30] and the UK [24] these are expensive resources that are potentially biased by enrichment of patients with significant allergy.

The identification of risk predictors of anaphylaxis will be especially helpful in clinical management. It remains unclear whether every individual with food allergy is at risk of anaphylaxis, and the ability to define those at risk would allow more focused allocation of resources. Although we can provide some indicators for groups of individuals at increased risk of anaphylaxis, such as adolescents with peanut allergy and those with poorly controlled asthma, individuals outside these groups also develop anaphylaxis and improved predictors are needed. Finally accurate and detailed information about circumstances surrounding deaths from anaphylaxis remains limited by the necessity of retrospective data collection. However, retrospective exam-

ination of information regarding anaphylaxis and anaphylaxis deaths remains an important avenue of investigation that is vital to the quest to prevent unnecessary deaths.

Conclusion

Anaphylaxis remains the most feared consequence for patients with allergy. There is now substantial evidence that the prevalence of anaphylaxis is rising in parallel with the rise in other allergic disorders particularly in the under 5-year age group. Importantly, deaths from drug-induced anaphylaxis have also risen at an alarming rate amongst the elderly. Continuing research into improved diagnostic predictors of anaphylaxis remains an important priority.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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