

An update on epidemiology of anaphylaxis in children and adults

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Purpose of review

The purpose of the present review is to describe the epidemiology of food-induced, medication-induced, drug-induced, and insect sting-induced anaphylaxis; to summarize recent changes in the incidence of anaphylaxis internationally; and to discuss recent insights into potential risk factors for anaphylaxis.

Recent findings

Recent studies confirm that the incidence of anaphylaxis, particularly food-induced anaphylaxis, is increasing world-wide. The rise in anaphylaxis incidence appears most pronounced in children under the age of 5 years, which is also the age group most at risk of hospitalization for food-induced anaphylaxis. Identification of factors that may increase the risk of episodes of anaphylaxis remains an important research priority. Recently, two large cohort studies using data from electronic medical records confirmed that individuals with asthma are at higher risk of anaphylaxis and those with severe asthma have the highest risk of all. With respect to modifiable lifestyle factors, several studies have demonstrated a link between latitude and anaphylaxis, with areas with less year-round sunlight reporting a higher prevalence of food-induced anaphylaxis.

Summary

Reports of an increasing incidence of anaphylaxis internationally highlight the need for identification of modifiable risk factors for anaphylaxis. Emerging evidence suggests that low vitamin D levels may be associated with risk of anaphylaxis and food allergy; however, further studies are required to confirm this.

Keywords

adults, anaphylaxis, children, epidemiology, food allergy

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Introduction

The purpose of the present review is to describe the epidemiology of food-induced, medication-induced, drug-induced, and insect sting-induced anaphylaxis; to summarize recent changes in the incidence of anaphylaxis internationally; and to discuss emerging insights into potential risk factors for anaphylaxis. There continues to be an intense interest in the epidemiology of anaphylaxis as it represents the most severe and dangerous manifestation of food-induced allergy and is therefore an important public health priority.

Increasing incidence of anaphylaxis

Recent reports have found that the incidence of anaphylaxis is rising in Australia [1^{••}], the UK [2], and the US [3]. The rise in anaphylaxis incidence appears most pronounced in the youngest age group, with food the most common trigger [1^{••}]. This increase in food-induced anaphylaxis is in line with recent reports of a rise in the general prevalence of food allergy [4]. The relatively

high and increasing incidence in young children suggests that early life factors are important drivers of the change in incidence.

Liew *et al.* [1^{••}] confirm previous reports of an increasing world-wide incidence of hospital admissions for food-induced anaphylaxis, with an incidence in the Australian population (25 million) of around 6 per 100 000 population reported in 2004/2005 – an overall rise of 350% over the previous 11 years. Children under the age of 5 years had the highest rates of hospital admissions for food-induced anaphylaxis (9.4 per 100 000 population) and the rate of increase in hospital admissions over time was also greatest for this age group. Drug-induced anaphylaxis admissions increased by an estimated 150% over the 8-year period studied to 2.6 per 100 000 population in 2004/2005.

Liew *et al.* [1^{••}] also 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 (data on insect sting anaphylaxis admissions were not available). 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.

This study again noted the interesting observation, also reported in previous studies, that although the highest rate of hospital admissions for food-induced anaphylaxis is seen among the 0–4-year-old age group, the highest mortality was seen in teenagers and young adults [1^{••}]. All seven deaths from food-induced anaphylaxis during the period of study occurred in individuals between 5 and 34 years of age. In contrast, both drug-induced hospital admissions and deaths were most common in adults, particularly in those over 55 years of age. Similarly, all insect sting-induced anaphylaxis fatalities occurred in those over the age of 15 years.

A further interesting observation from this study was a pronounced sex switch with men predominant in admissions under the age of 15 years, but women more commonly admitted among adults [1^{••}]. This may reflect the sex switch, which has been observed to occur with the prevalence of underlying food allergy and other allergic conditions including asthma.

The increasing spectrum of foods associated with anaphylaxis

The spectrum of foods commonly responsible for causing allergic reactions including anaphylaxis varies between countries, although peanuts, tree nuts, and seafood were commonly implicated in hospitalizations and deaths from food-induced anaphylaxis in Australia, the US, and the UK [1^{••},5,6].

However, there are now increasing reports of anaphylaxis occurring to a wide range of foods including fruits and other foods not previously commonly associated with anaphylaxis. Asero *et al.* [7] recently reported on a series of 1110 adolescent and adult Italian patients (mean age 31 years, range 12–79 years) diagnosed with food allergy based on history of reaction in the presence of positive skin prick test (SPT) or elevated food-specific serum IgE. Anaphylaxis was reported by 5% of food-allergic individuals, with the most common causes being lipid transfer protein ($n=19$; 13 of these patients reacted to peach), shrimp ($n=10$), and tree nuts ($n=9$). Peanut allergy was uncommon in this population and only one case of anaphylaxis occurred to peanut.

Recently, a number of reports have focused on a newly emerging food allergen, lupin, which was recently intro-

Key points

- The incidence of anaphylaxis, in particular food-induced anaphylaxis, continues to rise in developed countries with the greatest impact on those under 5 years.
- There continues to be an increase in the range of foods reported as causing anaphylaxis.
- Recent studies have identified higher baseline serum tryptase levels as a risk factor for anaphylaxis in patients with venom allergy.

duced into the food chain supply in Europe. Lupin is a member of the legume family, and lupin flour is being increasingly used in bakery products in France and Mediterranean countries. There have been several case reports of anaphylaxis resulting from ingestion of lupin flour [8,9]. The prevalence of lupin allergy in the general population is not known; however, several recent studies have investigated the prevalence of lupin allergy among patients attending allergy clinics. In a recent study from Finland, Hieta *et al.* [10] report on SPT results for lupin among 1522 patients presenting with suspected food allergy from 2005 to 2007. Positive SPT reactions occurred in 25 (1.6%) patients with 18 of these also sensitized to other legumes (soy, peanut, or pea). This is a lower rate than that observed in a previous study [11] in Portugal, where the prevalence of sensitization was reported to be 4.1%. Food challenges were not performed in either study and few of these patients had a history of reactions to lupin.

In a separate study, de Jong *et al.* [12] skin prick tested all consecutive patients ($n=372$) referred to the outpatient allergy clinic of the Erasmus Medical Centre in Rotterdam, the Netherlands, over a 12-month period with additional SPTs to extracts of lupin flour. SPTs with peanut, soy, and lupin flour were positive in 135, 58, and 22 patients, respectively. Nine patients with sensitization to lupine flour underwent double-blind placebo-controlled food challenge, which was negative in eight cases. In contrast, one patient experienced significant symptoms. Four of these nine patients suspected lupin allergy by history. Two other patients with a positive history to lupine declined challenges. In these patients, a 3-day dietary record showed that they could consume lupine without symptoms. The authors suggest their results demonstrate that clinical lupin allergy is very uncommon, even in the presence of sensitization to lupine flour, reporting an estimated prevalence of lupin allergy, among patients with a suspected food allergy referred to their tertiary allergy centre of 0.27–0.81%. In most, although not all cases, sensitization is not clinically relevant and is most likely caused by cross-sensitization to peanut. In selected cases, eliciting doses are low, making significant reactions possible. These contradictory findings suggest

that a more systematic way of assessing the exact impact and prevalence of a newly described food allergy will be important to inform future public health policy such as mandatory food labeling guidelines.

Emergence of oral immunotherapy trials may increase incidence of iatrogenic anaphylaxis as there are now many reports demonstrating a high rate of adverse reactions during updosing in these trials [13]. It is not yet known whether anaphylaxis may differ in presentation spectrum with more biphasic responses although some studies suggest this might be the case [14,15]. Certainly, care may need to ensure that patients undergoing oral immunotherapy do not become complacent to episodes of anaphylaxis and undertreat or mistreat such events [16].

Food-dependent exercise-induced anaphylaxis

There continues to be a number of case reports published describing exercise-induced anaphylaxis (EIA) occurring shortly after the consumption of certain foods [17–24]. An increasingly diverse range of foods have been implicated, including wheat, soy (in tofu), peach, and shellfish. Notably, of eight case reports of EIA published in 2009–2010 either examining allergen identification or successful treatment plans, six were published by clinicians and researchers in Asia [17–24]. Previous reports investigating the epidemiology of EIA on a population scale were conducted in Korea [25] and Japan [26,27], where EIA is estimated to account for up to 14% of hospital admissions for anaphylaxis. It is unclear whether these reports reflect increased awareness and associated reporting in Asian countries or whether these reports reflect a higher prevalence of EIA compared with other countries.

Risk factors for anaphylaxis

Attention has turned recently to identification of factors that may increase the risk of episodes of food-related anaphylaxis including both clinical risk factors and modifiable lifestyle factors. A study by Gonzalez-Perez *et al.* [28•] confirms that individuals with asthma are at higher risk of anaphylaxis and that those with severe asthma may be at highest risk. The authors examined a UK health database for all individuals aged 10–79 years enrolled with a general practitioner for at least 1 year and with at least one health contact in the year before entering the study. The study group included all individuals with a diagnosis of asthma ($n = 177\,000$), of which 45 103 had severe asthma (defined as either hospitalization or any of the following medication use in a 1-year period: ≥ 3 prescriptions for oral corticosteroids, ≥ 12 prescriptions for inhaled β_2 agonists, or ≥ 3 classes of asthma medications). A random sample of 200 000 individuals without

a diagnosis of asthma, matched to the asthma cohort by age and sex, was also included. The anaphylaxis incidence rate was estimated at 34.4 per 100 000 person-years. Compared with those with no asthma, the risk of anaphylaxis was two-fold greater in the nonsevere asthma group and three-fold greater in the severe asthma group. In this study, drug allergy was the most common cause of anaphylaxis (27% of cases), followed by food (24% of cases), and insect stings (12%). Anaphylaxis incidence was higher in women compared with men.

Iribarren *et al.* [29] reported similar findings in a study conducted in northern California, with a 5.2-fold higher incidence of anaphylactic shock among patients with asthma. There was also a clear relationship between asthma severity and food-induced anaphylaxis, with a hazard ratio in the nonsevere asthma group of 5.05 [95% confidence interval (CI) 4.39–5.80] and in the severe asthma group of 8.23 (95% CI 6.59–10.27).

One of the most interesting recent lifestyle factors to be investigated is vitamin D insufficiency and increased risk of food-induced anaphylaxis. There is now an emerging base of evidence demonstrating the relationship between latitude and anaphylaxis to support this contention. Mullins *et al.* [30•] studied the regional variation in prescription of adrenaline auto-injectors (EpiPens, Dey Laboratories, Napa California, USA) as well as emergency department visits for anaphylaxis in Australia as surrogates for food allergy and anaphylaxis. EpiPen prescription rates were higher in southern regions (less year-round sunlight) compared with northern regions, even after controlling for demographic factors, socioeconomic status and access to medical care, including specialist allergy care. Regional differences were greatest in children under the age of 5 years, with a six-fold difference between far southern Australia and far northern Queensland (2318 vs. 383 per 100 000 population per year). Anaphylaxis admissions, of which 42% of cases were attributed to food, were also more common in southern regions, although the association between anaphylaxis admission rates and latitude was not statistically significant. As in previous studies, anaphylaxis admissions were most common in children under the age of 5 years (22.3 per 100 000 population per year), with 81% of admissions in this age group attributed to food. These findings are consistent with an earlier study [31] reporting differences in EpiPen prescriptions by latitude in the US. Rudders *et al.* [32] also recently published a study examining emergency department visits for acute allergic reactions (including anaphylaxis) in the US. Emergency department visits for acute allergic reactions were more common in north-eastern regions (with less sunlight) than in southern regions (an inverse association from the Southern hemisphere), particularly among visits for food-related allergic reaction (OR 1.33; 95% CI, 1.14–1.56; $P < 0.001$).

In a separate US study restricted to the paediatric population, Sheehan *et al.* [33] described patterns of anaphylaxis emergency department visits and hospital visits in 24 paediatric hospitals in 18 states across the US, reporting that cases of anaphylaxis as a proportion of all patient visits were more common in northern cities (less sunlight) than in southern cities (0.88 per 1000 visits compared with 0.63 per 1000 visits; $P < 0.001$). Food-induced anaphylaxis rates showed the greatest difference between the northern and southern states (relative risk for north compared with south: 1.81, 95% CI 1.66–1.98).

Medication-induced anaphylaxis

Studies have identified drug-induced anaphylaxis as the most common cause of fatalities due to anaphylaxis in the UK [34,35], New Zealand [36], and Australia [1^{••}]. In a review of the epidemiology of drug allergy published in 2011, Thong and Tan [37] identified drugs (penicillin and anaesthetic agents given during the perioperative period) as a common cause of IgE-mediated allergic anaphylaxis, with NSAIDs and radiocontrast media identified as common causes of nonallergic anaphylaxis. Several limitations of current data on the epidemiology of drug allergy were highlighted, including failure to differentiate between immunologically and nonimmunologically mediated drug hypersensitivity and limited comparability between studies because of differences in study populations (different ethnicities, inpatients or outpatients, adults or children), different methodologies (spontaneous vs. nonspontaneous reporting), and different methods of confirming the diagnosis of drug allergy, many of which do not include validated in-vivo or in-vitro tests.

Insect venom anaphylaxis

In 2009, Rueff *et al.* [38^{••}] published their findings from a multicenter study examining the association between baseline serum tryptase concentration and risk of anaphylaxis to honeybee or vespid stings. Higher baseline serum tryptase levels were strongly associated with severe anaphylactic reactions among their study group. Notably, in their analysis of other risk factors for anaphylaxis, angiotensin-converting enzyme (ACE) inhibitor medication was found to convey an increased risk, which was independent of age. This study highlights the effect of a common environmental factor affecting aging men (ACE inhibitors) in the modification of anaphylaxis risk in patients with venom allergy. Other factors that were associated with insect-venom anaphylaxis were older age, male sex, and intake of angiotensin-converting enzyme inhibitor medication, along with vespid venom allergy and a previous history of less severe systemic reactions to field stings. Following on from Rueff *et al.* [38^{••}], Guenova *et al.* [39] published their findings confirming an association between basal serum tryptase

levels and severe anaphylaxis to honeybee or vespid stings among older patients. This association is a proposed mechanism for the increase in severe reactions observed in older age groups. This study did not consider the effect of ACE inhibitors; however, it was noted that one third of the patients with elevated serum tryptase levels had a history of hypertension.

Rudders *et al.* [40] reported a previously unrecognized high risk of insect-sting anaphylaxis that requires treatment with more than one dose of epinephrine. The characteristics and treatment requirements of 153 patients presenting to three emergency departments in Boston between January 2001 and December 2006 with stinging insect hypersensitivity were examined. Fifty-four percent of the 153 cases were male, and the median age was 33 years. Of the quarter of all presentations that were diagnosed with anaphylaxis, one in six required more than one dose of epinephrine. Their findings may have implications for epinephrine auto-injector prescribing guidelines for patients at risk of insect-sting anaphylaxis.

Conclusion

In conclusion, the epidemiology of anaphylaxis continues to evolve with an ongoing increase in reporting and prevalence of both diversity of foods inducing anaphylaxis and severity of reaction. Anaphylaxis is likely to represent the tip of the iceberg of food allergic reactions and there is now evolving evidence that food allergy is on the increase in developed countries. Recent data suggest that some modifiable risk factors such as vitamin D insufficiency may play a role in the increasing prevalence of food allergy and anaphylaxis. Good control of co-existent asthma remains a valuable clinical goal.

References and recommended reading

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

- of special interest
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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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