

Anaphylaxis: can we tell who is at risk of a fatal reaction?

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Purpose of review

Anaphylaxis is frightening and patients commonly fear their next reaction will be fatal. This review looks at the characteristics of fatal reactions to find if a fatal recurrence is predictable.

Recent findings

Most publications on fatal anaphylaxis are case reports that do not help predict risks. Most epidemiological studies focus on non-fatal reactions. The UK fatal anaphylaxis register demonstrates that over two-thirds of those dying from sting reactions and over four-fifths dying from drug anaphylaxis had no previous indication of their allergy, whereas those dying from food allergy had usually had previous reactions but these were typically not severe. Recent reports of anaphylaxis epidemiology based on diagnostic coding or attendance for treatment may be biased by differences in health service resource utilization according to the cause and course of the reaction.

Summary

Most fatal anaphylactic reactions are unpredictable. The appropriate management after recovery from a severe reaction may be protective against a fatal recurrence. An accurate identification of the cause and effective avoidance is a crucial part of this management, together with effective treatment of asthma for those with food allergy, immunotherapy for sting allergy, the avoidance of drugs that potentiate anaphylaxis, and effective training in self-treatment.

Keywords

anaphylaxis, fatal, iatrogenic, nut, sting

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Introduction

For anyone who has had an anaphylactic reaction, the prospect of a fatal recurrence is daunting, yet there has been little research into the chances of this happening. Since 1992, I have tried to identify and analyse every anaphylactic death in the UK [1,2••]. Taken together with data collected systematically from over 1500 patients with non-fatal anaphylaxis seen in our allergy clinics over the same interval, it becomes possible to analyse the risk factors for fatal reactions. This review relates these findings to the other recent epidemiology of anaphylaxis.

Incidence and causes

Approximately 20 deaths have been identified each year (one each year for each 3 million of population). There will have been additional undetected fatal reactions, such as those to antibiotics taken at home, in which autopsy findings are commonly limited to the infection (often with asthma) for which the antibiotic was taken [3]. Table 1 lists the UK anaphylactic deaths over an approximately 10-year period.

Approximately one in five patients referred to our clinic for anaphylactic reactions attributed to food allergy have negative specific IgE, skin tests and challenge tests for the supposed cause. Up to a quarter of sudden deaths blamed on foods are of a similar pattern and may have been caused by non-allergic anaphylaxis, angioedema or asthma. Epidemiological studies of anaphylaxis have reported 8–20% idiopathic reactions [4••,5], and 'food anaphylaxis' deaths may include some of these. Of the remainder, 70% were attributed to nut allergy with approximately equal numbers of peanuts, tree nuts and mixed or unidentified nuts, and a peak incidence age of 15–24 years of 2.3 deaths in each 100 000 with nut allergy each year [5]. [Calculated from 17 nut-allergy deaths in 10 years in 15–24-year-olds: UK population aged 15–24 years = 7.2 million, assuming 1% have nut allergy. A UK survey gave a lower prevalence [6], and using the unpublished raw data from this, the lifetime risk of dying from their nut allergy was calculated as $R \approx 0.001$ for females and 0.0005 for males (where $R = 1 - \prod_{i=0}^{death} (1 - r_i)$, r_i = risk of dying from nut allergy in each interval i).

Other food allergy fatalities included 14% with cows' milk allergy, with the rest caused by allergy to fish, shellfish, chickpea, hens' egg and banana (Table 1). No other studies have reported complete national statistics for fatal anaphylaxis, but there is much helpful informa-

Table 1. Suspected causes

Sting	47	29 wasp, 4 bee, 14 unidentified
Nuts	32	2 almond, 2 brazil, 1 hazel, 10 peanut, 6 walnut, 11 mixed or unidentified nuts
Food	13	1 banana, 2 chickpea, 2 fish, 5 milk, 2 crustacean, 1 snail
Food?	18	1 ?fish, 5 during meal, 1 ?grape, 3 ?milk, 3 ?nut, 1 ?sherbet, 1 ?strawberry, 1 ?yeast, 1 ?nectarine
Antibiotic	27	1 benzylpenicillin, 10 aminopenicillin, 12 cephalosporin, 1 ciprofloxacin, 1 vancomycin, 2 amphotericin
Anaesthetic	35	19 suxamethonium, 7 vecuronium, 6 atracurium, 7 at induction
Other drug	15	3 ACE inhibitor, 6 NSAID, 5 gelatines, 2 protamine, 2 vitamin K, 1 diamox, 1 etoposide, 1 pethidine, 1 heroin, 1 kabikinase, 1 local anaesthetic
Contrast media	11	9 iodinated, 1 technetium, 1 fluorescein
Other	4	1 latex, 1 hair dye, 1 hydatid, 1 idiopathic

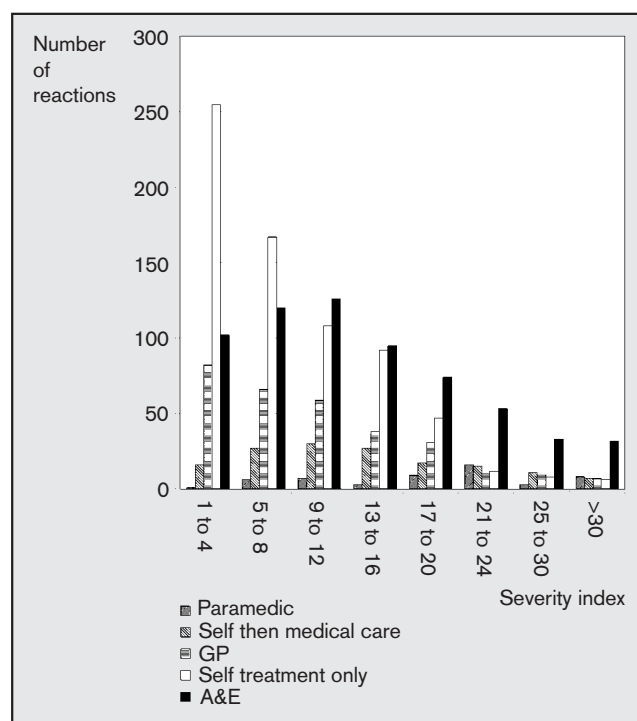
ACE, Angiotensin-converting enzyme; NSAID, non-steroidal anti-inflammatory drug. A third of fatal food reactions followed eating at home, a quarter in restaurants. The remainder were at nursery, school or work (15%), with friends or relatives (12%), out and about or travelling (9%) and camping (3%). A third of fatal sting reactions occurred in the house, a third in the garden and a third elsewhere, including travelling, at work and shopping. Iatrogenic reactions were most commonly fatal when in the hands of anaesthetists, when immediate expert advanced life support was available, maybe because of the severity of the reactions to high intravenous doses of potent allergens. Reproduced from Pumphrey [2••].

tion in case reports and small series. In general, the data in such papers is concordant with the UK study, with the following exceptions: in contrast to the study of Foucard and Malmheden Yman [7], no cases of fatal soy-ingestion-related asthma have been identified in the UK (allergy to soy protein is rarely seen in our clinics), nor has fatal asthma caused by sulphites in wine been identified [8]. Exercise [9] was not an obvious precipitant in any UK fatality (apart from a single recent possible exception), although it may be a common co-factor for recurrent reactions [4••].

Epidemiological studies of non-fatal anaphylaxis in the UK

The incidence of anaphylaxis detected will differ according to the research method used. A recent analysis of diagnostic codes in a UK general practice research database [10] estimated an incidence of 8.4 per 100 000 person-years, with insect stings and oral medicines the predominant causes. A different, more likely diagnosis is found in as many as half the cases referred from general practice to our clinics with suspected anaphylaxis, and compared with that report, we found a higher ratio of food-induced acute allergic reactions to those caused by stings and drugs [11]. Patients seek help from different parts of the health service according to their preference, and the circumstances and nature of their reactions (Fig. 1). This will also be reflected in the statistics collected from general practice.

Figure 1. Each reaction of patients attending clinic was graded for severity by the method described by Pumphrey and Stanworth [11]



This chart analyses the relationship between the severity of reaction and where the patients went for emergency medical help. There were also time trends, such as the marked fall in those seeking treatment from general practitioners over the past few years. All of those treated by paramedics and some of those first treated by general practitioners then went to accident and emergency departments for further treatment of observation.

We regularly see patients with intellectual, cognitive and memory impairment after cerebral anoxia during anaphylactic reactions or bolus intravenous epinephrine (adrenaline) given to conscious patients. The rate of such persistent sequelae must be higher than for fatality, but I can find no reliable statistics.

Trends

Most patients are not admitted to hospital after emergency medicine treatment for anaphylaxis, so an analysis of hospital discharge codes carries a risk of bias to the more slowly evolving forms of 'reaction' for which an alternative diagnostic code might have been more accurate. With this caveat in mind, the studies of Sheikh and Alves [12,13] showed a rapid increase in the rate of anaphylaxis between 1991 and 1995, and a predominance of females from rural, southern and affluent areas. However, I have found no significant change in the number of deaths each year attributed to anaphylaxis in the UK, the past 12 months reflecting the pattern for the previous 11 years. The steady UK death rate from food-

induced asthma differs from the marked decrease in fatal asthma reported by Formgren *et al.* [14]

Mode of death

In contrast to survivable allergic reactions, symptoms in fatal anaphylaxis are commonly limited to one system: deaths were divided equally between shock and respiratory arrest. Shock in some (mostly younger people with healthy hearts) was caused by vasodilation with volume redistribution, leading to pulseless electrical activity when no blood returned to the heart. Death in this group was associated with an upright posture [15•]. In other cases (mostly older people with pre-existing myocardial pathology) shock was caused by dysrhythmia, possibly associated with the local release of anaphylactic mediators in the myocardium [16]. Electrocardiogram changes of myocardial ischaemia are typically found in anaphylactic shock, leading to diagnostic confusion [15•].

Respiratory arrest was either caused by severe bronchospasm (often in those taking daily treatment for asthma) or upper airway angioedema; for some, there was evidence of both these processes. Compared with stings and drug-related anaphylaxis, fatal food allergy was much more commonly caused by asthma and much less often caused by shock; the association of asthma with severe reactions to nuts is well recognized [17]. Asphyxia caused by upper airway swelling was more common in food and sting reactions than in those caused by drugs (Table 2).

Rate of reaction

The interval between eating the food and fatal collapse has usually been 25–35 min (range 10 min–6 h, the longest being a case with vigorous early treatment including epinephrine for mild symptoms who had a sudden rapid deterioration at 6 h). This is longer than for drugs (median 5 min) or stings (median 12 min). Some were resuscitated after this collapse but died later (median 60 h); such resuscitation was most common

after iatrogenic reactions (35%) and least common with sting deaths (16%), presumably a direct consequence of accessibility to medical management of the reaction.

Risk factors

Genetic, environmental and ontogenic factors influence the nature and severity of reactions.

Age

Fatal reactions caused by cows' milk allergy were mostly in children (youngest 5.5 months, median age 8 years), by peanuts in young adults (youngest 13 years, median 21), and by tree nuts in adults (youngest 18 years, median 27). The remaining food allergies affected adults (18–53 years, median 25); there were too few to analyse each allergen individually. Overall, fatal food allergy affected younger people than did fatal sting or drug allergy (median 21 years compared with 56 or 61 years, respectively).

Sex

Seventy-five per cent of UK nut-allergic fatalities were female, but for other foods there was an equal number of males and females. Recent figures from the USA have suggested an equal male:female ratio for fatal nut allergy [18]. Fatal contrast media reactions and sting reactions were more common in males, concordant with previous studies [19,20].

Race

A variety of racial groups was represented in the cases studied. The numbers were too low to assess whether the proportions differed from racial prevalence in the UK. An unexpectedly high proportion of UK milk allergy fatalities were boys of Asian or mixed race.

Geographical distribution

Cases occurred in all regions of the UK, in proportion to the population, apart from a lower incidence in Scotland, probably reflecting the different system of reporting deaths in that country. Diagnostic coding suggested a higher incidence of non-fatal reactions in the south of England and rural areas [13].

Atopy/asthma

A majority of fatal reactions attributed to food allergy were principally asthmatic reactions in those taking daily treatment for asthma. Data for atopy were not so good for sting and iatrogenic deaths as for food allergy. It is probable that there was no strong correlation between atopy and fatal reactions for these other causes. Specific IgE to foods and wasp venom were in some cases low (e.g. 6 KU_A/l to peanut, with a total IgE of 70 KIU/l) and in some high (e.g. >500 KU_A/l to milk, with a total IgE of 4000 KIU/l). There were too few measurements to detect any pattern.

Table 2. Mode of death

	Drug	Sting	Food	Food?	Male	Female
Lower airways	11	3	24	11	21	26
Upper + lower airways	6	4	13	3	5	19
Upper airways	7	8	5	3	16	12
Shock + asphyxia	21	4	2		12	15
Shock	32	18	2		23	29
Disseminated intravascular coagulation	5	1	1		2	4

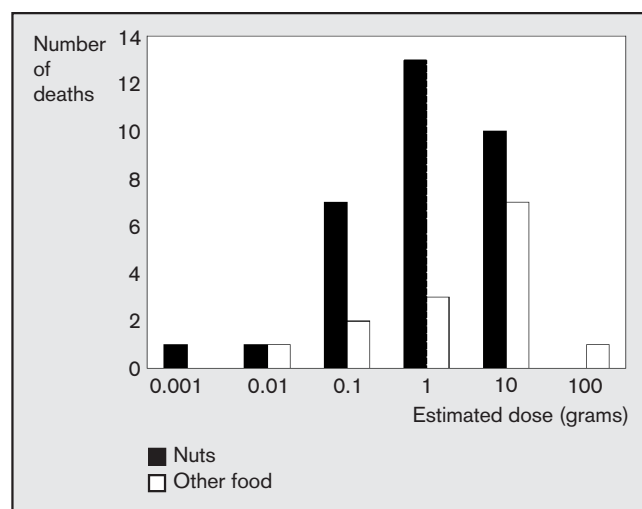
'Food' indicates fatal anaphylactic reactions with a high probability of being caused by the suspected food; 'food?' includes reactions in which there was some doubt about the relationship between the reaction and the suspected food cause: an unknown fraction of these may have been caused by idiopathic anaphylaxis or idiopathic angioedema. Reproduced from Pumphrey [2•].

What made the reactions fatal?

Often a combination of factors may have conspired to make the reaction fatal, including the severity of the allergy, a high dose of potent allergen, underlying genetic tendencies for angioedema, hypotension [21] and bronchospasm (recognized by previous idiopathic or allergen-triggered events), and concurrent disease [22] or medication [23] synergizing with these genetic tendencies. The recorded treatment was optimal in some cases, suboptimal in others, and some were untreated. Although the accuracy of the records was a point of discussion during individual case reviews, it is probable that even with optimal management some cases of anaphylaxis will be fatal.

Many substances have been reported to cause anaphylaxis, but far fewer have been associated with fatal reactions. It seems the latter may be intrinsically more dangerous; for example, nuts seem to be the most dangerous food and amino-beta-lactams such as amoxicillin and cefaclor the most dangerous antibiotics. The probable quantity ingested of the suspected food varied from trace contamination to over 100 g. The distribution was approximately log normal, with modal values of 1 g for nuts and 10 g for other foods (Fig. 2). Most sting deaths followed single stings, and medication was usually the standard therapeutic dose; however, death was so rapid in many of these that it is likely that a much smaller dose might have been fatal. The threshold for IgE-mediated reactions to protein allergens is log normally distributed over 5–7 orders of magnitude [24••]. It seems possible that the threshold dose for anaphylaxis may be similarly distributed, with a similar but higher distribution of thresholds for fatal reactions.

Figure 2. Estimated amount eaten (dry weight) of the food ingredient supposed to have caused the fatal allergic reaction



The distribution of rates for fatal reactions may reflect the amount by which the dose given exceeded the threshold for anaphylaxis.

Asthma has been a major component of fatal reactions in children, and for most fatal reactions to foods. Daily treatment for asthma in some cases has been suboptimal. The evidence suggests that children with mild reactions before developing asthma had fatal reactions not because their allergy had increased, but because their airways were affected by asthma.

Some patients had recurrent angioedema symptoms, thought to be idiopathic until their fatal attack of upper airways angioedema attributed to food allergy.

Antihypertensive drugs such as angiotensin-converting enzyme inhibitors or beta-blockers may be a co-factor for anaphylaxis, particularly noted during insect venom hyposensitization [23]. Other series have reported the use of beta-blocker antihypertensive drugs and underlying coronary artery pathology in those dying from sting reactions [25], but this pattern was not seen in UK sting deaths. Fatal food allergy mostly affects young people, so only two out of 70 patients had been taking such drugs. Angiotensin-converting enzyme inhibitors may by themselves cause life-threatening angioedema affecting the upper airway; in three UK cases this was fatal. Under the new European Academy of Allergy and Clinical Immunology's revised definition of anaphylaxis [26], this would be classified as non-allergic anaphylaxis.

Mastocytosis was present in one sting death and one fatal anaesthetic reaction. The association between mastocytosis, raised basal mast cell tryptase levels and reactions to hymenoptera venom is well documented [22,27]. The severity of reactions to wasp venom but not bee venom was higher in the group with raised basal tryptase in one study, but this was not reported in the other.

Opioid drugs may synergize with muscle relaxants in anaesthetic reactions: antibodies to each cross-react and solid-phase-bound morphine can be used to detect IgE antibodies to suxamethonium [28]. Alcohol or aspirin and exercise or concurrent infection may synergize with food allergy to increase the severity of the reaction. Some reactions are catamenial [29].

Food-allergy-induced shock has only been fatal when patients have been made to stand up [15•].

Early epinephrine treatment is needed to prevent asphyxia from upper airway oedema; tracheostomy has been overlooked as a treatment option when epinephrine was used too late. Some of the deceased had been provided with an epinephrine auto-injector but failed to

use it, often because it had been left elsewhere. Others used their epinephrine without benefit. Epinephrine was given to eight of the UK food allergy fatalities within 30 min of ingestion but they still died, in contrast to the series reported by Sampson *et al.* [30]. Death followed inappropriate treatment given for minor reactions in three cases when the effects of epinephrine overdose were misinterpreted as a worsening of the reaction, leading to further over-treatment.

Conclusion

The information reviewed above demonstrates the difficulty in identifying who may be at risk of a fatal reaction. Different strategies are required for the prevention of fatalities in those who have demonstrated their allergy and those who so far have not.

First-time reactions

The fatal reaction was thought to be the first in the case of 23 out of 34 sting, 17 out of 24 antibiotic, 17 out of 20 muscle relaxant, four out of six non-steroidal anti-inflammatory drug, 13 out of 13 other drug, and 10 out of 10 contrast media-related anaphylactic deaths, although most patients had been stung or exposed to the causative drug previously without reaction. There are no tests with adequate sensitivity and specificity to indicate who might be at risk of a fatal reaction; because of the million-fold range of threshold dose and the sometimes steep escalation in the severity of reaction with even small increases of dose above the threshold, challenge testing with a reduced dose is unlikely to warn of anaphylaxis without causing it.

Many drug-induced fatal reactions received immediate expert management but because of their rapidity, this management was restricted to attempted resuscitation rather than prevention of the progression of the reaction; some first-time fatalities are therefore unavoidable. For other cases, the treatment was not optimal; it is essential that all those carrying out interventions associated with anaphylaxis are aware of the correct immediate management of anaphylactic reactions.

Recurrent reactions

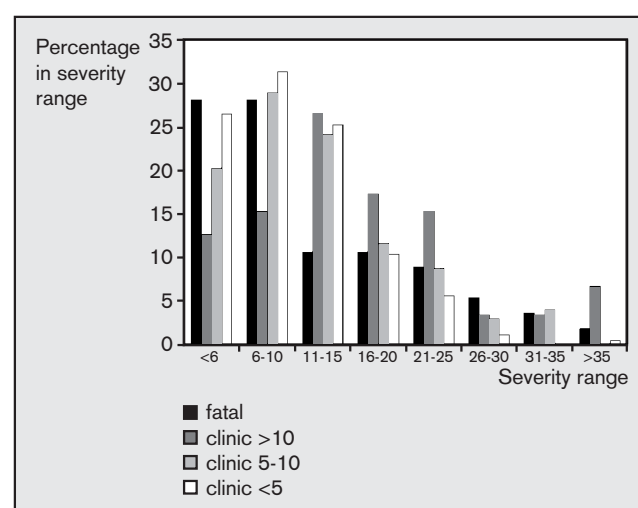
Patients commonly think their reactions will be more severe each time they are exposed; we could find no evidence that this was the case [11]. In a series of reactions, the most severe was as commonly the first, an intermediate one or the most recent. Mullins [4•] reported that only a quarter of those with a recurrence had a reaction more severe than previously. However, severe previous reactions were associated with a severe recurrence, one in six needing epinephrine or emergency medical care. Previous studies of severe venom reactions could find no characteristics that would allow the prediction of severe recurrence [19]. Those dying

from food allergy had usually had previous reactions, but these were typically not severe, indicating that the severity of previous reactions is not a risk factor for a fatal reaction to nuts (Fig. 3).

None of the 11 UK sting fatalities with a known history of previous reactions had been given venom immunotherapy.

Allergen avoidance failed for a variety of reasons: a few were tragic accidents when a patient with a known drug allergy was given the fatal dose. It should be noted, however, that such accidental administration of penicillins to those with 'known penicillin allergy' very rarely leads to a reaction. Recurrent reactions were commonest among those with food allergy. Very few had been given expert advice about avoidance, and although there is a view that recurrence is unavoidable [31], others consider that good advice can greatly reduce patients' risk of recurrence [32]. Commercial catering caused 68% of nut-related reactions. Asking for a meal without nuts proved an unsuccessful avoidance strategy because neither the person serving nor in some instances the caterer realized that the food contained nuts. Peanut flour in Indian commercial catering has caused confusion, as those preparing the food may not recognize this as 'nuts'. For other foods, the source was distributed more evenly between whole foods, domestic cooking, commercial cooking and packaged foods.

Figure 3. The most severe reaction of patients attending clinic and the most severe pre-fatal reaction of those who subsequently died from their food allergy were graded for severity by the method described by Pumphrey and Stanworth [11]



There is a tendency for older patients to have experienced a more severe worst reaction than young patients, but the severity of the deceased's worst pre-fatal reaction gave no clue that they would later die from their allergy.

Non-compliance with steroid therapy and the overuse of inhaled short-acting beta-2 agonists is associated with fatal asthma; this is true also for food-allergy induced asthma. The high daily use of a short-acting beta-2 agonist may lead to epinephrine resistance, making it difficult to treat reactions [33]; optimal asthma control is important for those with asthma and food allergy. Asthmatic female students living away from home seem to be at particular risk from their nut allergy.

Acknowledgements

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