

Chapter 2

An Epidemiological Approach to Reducing the Risk of Fatal Anaphylaxis

Richard S.H. Pumphrey

Abstract Estimates of the population prevalence of anaphylaxis range from 0.03% to 0.95% with immediately-life-threatening reactions affecting <0.1% of the population; wide differences in published statistics are due to differing inclusion criteria and imprecise use of terms such as incidence and prevalence. Expected symptoms in anaphylaxis vary according to the trigger and population studied. The severity of reactions is determined by interaction between genetic and environmental factors and cannot yet be predicted accurately. Whether a reaction is fatal or not depends as much on comorbidity such as asthma or heart disease as it does on severity of allergy or dose and route of exposure to the trigger.

The UK fatal anaphylaxis register is the longest-running and most comprehensive attempt at epidemiology of fatal anaphylaxis; it has recorded around 1 anaphylactic death per 3 million population each year since 1992, about half of these were iatrogenic (predominantly older people) and the rest divided between sting reactions and (mostly in younger people) food allergy. Most deaths were first reactions: fatal recurrent reactions occurred through avoidance failure combined with failure of rescue treatment – lessons from these failures can teach how to reduce future fatalities.

Keyword Epidemiology fatal anaphylaxis

2.1 Introduction

Epidemiology is the “who, what, why, where, and when?” of a disease; it is essential for the development of logical management strategies. In the case of anaphylaxis it asks “Who is affected? What triggers their reactions? Why, where, and when do they become exposed to the trigger for their reactions?” Although it is generally an observational rather than interventional science, it can nevertheless study outcomes of different management strategies, for instance by asking “How many of those dying had been prescribed self-injectible epinephrine and why had this failed to save them?”

But epidemiology depends on clear and simple definition of the population to be studied and here anaphylaxis presents a problem: allergic reactions have a continuous spectrum of severity (Fig. 2.1) [1–3] and manifold combinations of symptoms contributing to this severity. Non-life-threatening reactions may have dramatic presentation with many severe symptoms and fatal reactions may show little before cardiac or respiratory arrest.

R.S.H. Pumphrey (✉)
Honorary Consultant Immunologist, Department of Immunology,
Manchester Royal Infirmary, Manchester, UK M13 9WL
e-mail: richard.pumphrey@nhs.net

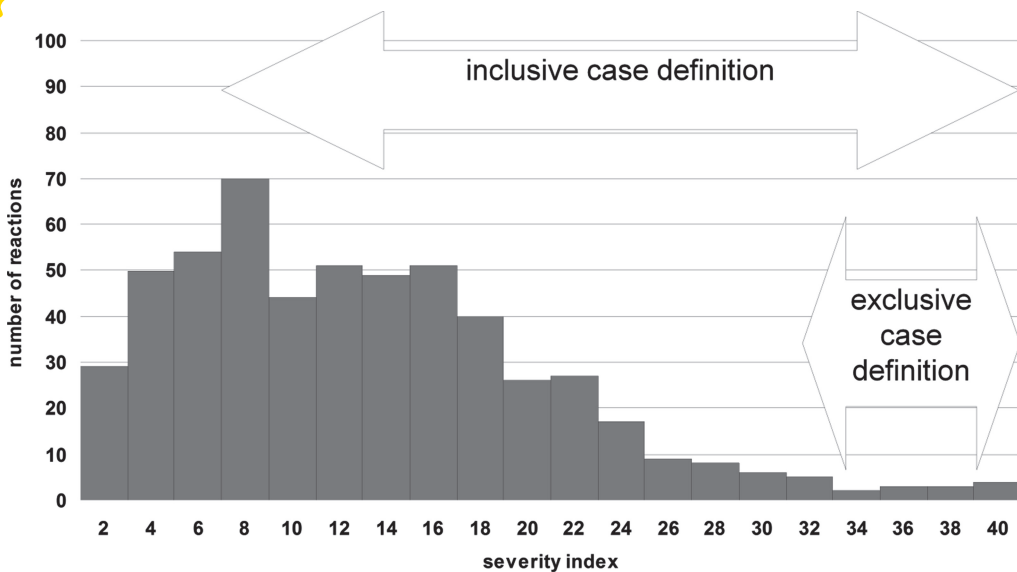


Fig. 2.1 Distribution of severity of 720 reactions in 320 Manchester clinic patients using a weighted symptom score described in reference [1]. Applying different case definitions from published studies such as reference [2] or reference [3], there could be as much as a thirty-fold difference in numbers of the population included in the study

A variety of definitions have been proposed for anaphylaxis, all including descriptions such as “allergic reaction,” “severe, generalized,” “life-threatening.” None of these is perfect because not all anaphylaxis is allergic [4], most authors include cases that did not endanger life, and acute allergic reactions can kill without being generalized.

Whatever the definition, there is general agreement that anaphylactic reactions are best treated by epinephrine [5, 6], and that the first dose should be given early during the course of the reaction. Because the evolution of such reactions is unpredictable, consensus groups have moved away from a bald definition towards detailed descriptions of symptom complexes that are characteristic of allergic reactions that *might* progress to anaphylaxis. A leading example is shown in Table 2.1. The authors [7] estimate it will identify 95% of all cases that will progress to anaphylaxis (i.e., its sensitivity is 0.95) but give no estimate of the definition’s specificity (the fraction of allergic reactions that will not progress to anaphylaxis that are excluded by the Table 2.1 description). Clinical experience and data such as Figure 2.1 suggest that the specificity will be low because so few patients fulfilling the criteria in Table 2.1 would progress to respiratory or cardiac arrest if given no treatment. A low specificity may be unimportant if the objective is to make sure that every case that might need epinephrine is given it early in the reaction, but epidemiology needs a specific definition as much as it needs a sensitive one.

Further discussion of sensitivity and specificity of definitions for anaphylaxis can be found in the publications of the Brighton Collaboration, whose focus is specifically on recording adverse reactions to vaccines [8]. Accepting the inverse relationship between specificity and sensitivity, they resorted to using three levels of certainty: level 1 with highest specificity but lowest sensitivity, and level 3 with highest sensitivity but lowest specificity. Numerical estimates for sensitivity (approximately 0.6–0.7) and specificity (approximately 0.7–0.8) of these definitions have recently been published [9]. Because there is no gold standard for the definition of anaphylaxis, these estimates are based on physician diagnosis and therefore reflect the physician’s opinion about what anaphylaxis is. Such opinion is typically colored by confusion between a *definition* of anaphylaxis and *descriptions of symptom complexes that might progress to anaphylaxis*, resulting in inclusions of non-anaphylactic reactions with symptoms of the type that occur in reactions that might progress to anaphylaxis.

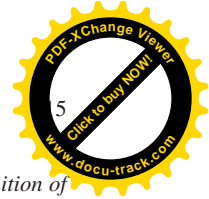
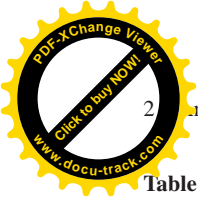


Table 2.1 Anaphylaxis is likely when any one of these three criteria is fulfilled. Note that this is *not a definition of anaphylaxis* but, rather, is a description of symptom complexes that might progress to anaphylaxis

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., dyspnea, wheeze-bronchospasm, stridor, reduced PEF [peak expiratory flow], hypoxemia)
 - (b) Reduced BP (blood pressure) 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., dyspnea, 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 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg 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

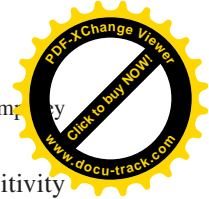
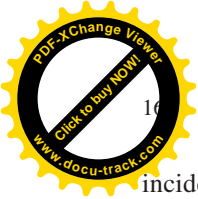
2.2 Prevalence and Incidence of Anaphylaxis

The imprecise use of the terms incidence and prevalence by some reports on the epidemiology of anaphylaxis may cause confusion. The *incidence* of a condition is *the rate of appearance of new cases*. Incidence is a fractional rate with units t^{-1} ; it is usually quoted as cases per 100,000 (or similar fraction) per year (or similar interval). Studies of incidence of anaphylaxis have generally reported the incidence of reactions, not of new cases: those studies that have asked the appropriate question have recorded that most of those presenting with an acute reaction have a history of previous reactions and are therefore not new cases.

In a defined population, at a given time, the *prevalence* of a condition is *the probability that an individual chosen at random will have the condition*. Prevalence is a dimensionless number in the range 0–1. It is usually quoted as a percentage or cases per 100,000. Anaphylactic reactions occur when someone with the underlying hypersensitivity state is exposed to the appropriate trigger in a way that will cause an anaphylactic reaction. Epidemiology of anaphylaxis measures the prevalence of *reactions*, not the underlying hypersensitivity state. Thus the observed prevalence is the product of the prevalence of the hypersensitivity state and the probability of exposure to a sufficient dose of provoking agent by an appropriate route to cause an anaphylactic reaction. The prevalence of anaphylactic hypersensitivity in the general population might be as high as 15% if one worked at finding the optimal dose and route for the allergen – e.g., an intravenous injection of grass pollen extract in people with hay fever, or restinging everyone who had a wasp sting 3–8 weeks after their sting. Fortunately, the probability of exposure is low and kept low by self-preservation. After a mild allergic reaction to nuts, most people carefully avoid nuts. One study [10] found within a median interval of 5.4 years following the initial peanut reaction, 55% had 1–5 (average 2) accidental re-exposures.

2.3 Epidemiological Studies of Nonfatal Anaphylaxis

The Brighton Collaboration definition of anaphylaxis (or more exactly, description of symptom complexes that might occur in anaphylaxis) may be the best achievable for epidemiological recording but is too elaborate for most retrospective studies. An approximation to the prevalence and



incidence of anaphylaxis is known from a variety of approaches that settle for lower sensitivity and specificity such as analysis of prescribing of self-injectible epinephrine [11, 12], coding of hospital admissions [13] or discharges [14], or cases developing in those already admitted to hospital [15], general practitioner records [16], referrals to emergency medicine departments [17, 18] or allergy clinics [1, 19, 20], or self-reported anaphylaxis from a sample population by questionnaire [21].

When the case definition is based on self-injectible epinephrine prescriptions, there is an assumption that anaphylaxis has been adequately diagnosed by the prescribing doctor. An unpublished audit of referrals to anaphylaxis clinics in Manchester, UK, suggested the diagnosis was correct for around half the patients. Because it is impossible to predict which reactions will become dangerous, epinephrine must be given for any reaction with the characteristics in Table 2.1 if it is to have a chance of preventing 95% of evolving allergic reactions becoming life-threatening. Depending on our degree of caution, from 0.1% to 100% of those with a history of acute allergic reaction might benefit by carrying epinephrine in the sense that it would attenuate the severity of a recurrence of their reaction. These considerations indicate that estimates of anaphylaxis prevalence based on self-injectible epinephrine prescriptions may have a tenuous link to the actual prevalence.

When the case definition is based on the diagnostic code, the assumption is both that the diagnosis (usually by a nonspecialist) was correct, and that the condition has been correctly coded. While common conditions are accurately coded, rare conditions such as anaphylaxis are frequently coded incorrectly. It should also be pointed out that most cases of anaphylaxis treated in the emergency department do not get admitted to hospital; unpublished audit of admissions in Central Manchester, UK, suggest that a majority of cases admitted and coded as anaphylaxis were not. Examples include idiopathic angioedema that was dramatic but not life-threatening, gross angioedema of the tongue unresponsive to epinephrine, angiotensin converting enzyme inhibitor (ACEI)-induced angioedema and one patient with acquired C1 esterase inhibitor who was admitted seven times with upper airways angioedema unresponsive to epinephrine before the correct diagnosis was made.

These limitations mean that the statistics presented in the tables here can only give the broadest-brush picture of anaphylaxis around the world. In summary:

1. The continuous spectrum of severity of allergic reactions leads to wide variations in estimates of the prevalence of anaphylaxis (Fig. 2.1). A recent expert review [22] reckoned that the best estimates of population prevalence ranged from 0.03% to 0.95% with one estimate of 1.2–16.8% [2]. This implies that immediately life-threatening reactions (those causing a dangerous degree of shock or severe respiratory difficulty) affect <0.1% of the population, consistent with data in the UK fatal anaphylaxis register indicating 0.005–0.01% of UK deaths were due to anaphylaxis during 1992–2005.
2. Expected symptoms in anaphylaxis vary according to the trigger and population studied (Table 2.2) [1–5].
3. Common triggers for severe reactions comprise iatrogenic, stings, food, and latex; for some reactions no trigger was found – maybe because the patient was underinvestigated or maybe because it was an idiopathic reaction. The relative frequency of each class of trigger and of individual triggers within each class depends on the population studied (Table 2.3). Infants and young children are most likely to have severe reactions to milk and eggs; older children and adolescents to nuts or seafood; and adults to iatrogenic triggers, stings, and foods such as nuts and seafood. When only reactions that caused respiratory or cardiac arrest are considered, iatrogenic causes outweigh stings and foods in most studies that include all three classes in an unbiased way. For food allergy in particular, mild to moderate reactions are so much more common than immediately life-threatening reactions that wide differences in estimates of the dominant causes of anaphylaxis have been reported, depending on the cut-off taken between acute allergic reaction and anaphylaxis.

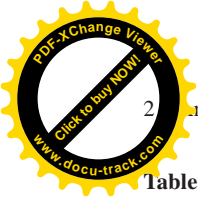


Table 2.2 The probability of various symptoms/signs in anaphylaxis. Frequencies in different publications reflect different concepts of “anaphylaxis” and different catchment populations. Each study omitted frequencies for some symptoms; none mentioned common symptoms such as a sense of impending doom or important symptoms seen occasionally in severe reactions such as fitting or pink froth from the mouth due to pulmonary edema. Each individual symptom/sign has moderate to low sensitivity and most have low specificity, even in the case of a rapidly evolving illness

	Med Rec [23]	Adult ED [24]	Ped ED [25]	Perioperative [26]	Drug induced [27]
Pruritus	0.55	0.56	0.40	—	0.34
Difficulty breathing	0.43	0.43	0.54	—	
Faintness	0.15	0.15	0.04	—	
Sneezing/rhinitis	0.17	0.06	[<0.11]	—	[<0.1]
Chest pain	0.03			—	
Abdominal pain	0.08			—	0.06
Nausea/vomiting	0.09	0.19	0.21	—	0.19
Urgent bowel action	0.01			—	0.05
Erythema	0.36	0.07	0.25–0.35	[<0.72/<0.93]	0.64
Urticaria	0.55	0.49	0.54	[<0.72/<0.93]	0.29
Angioedema (unspecified)	0.56	0.40	0.32	0.12/0.08	0.55
Angioedema tongue	0.15				[<0.1]
Upper airway Angioedema	0.07	0.11	0.18		0.07
Bronchospasm/wheeze	0.26	0.18/0.35	0.19	0.40/0.19	0.51
Stridor		0.01	0.01		
Conjunctivitis	0.23	[<0.06]	[<0.11]		0.10
Tachycardia	0.27				0.24
Bradycardia	0.02			0.01/0.01	0.09
Collapse	0.03	0.02	0	0.51/0.11	0.35
Shock/hypotension	0.05	0.09	0	0.17/0.18	0.55

4. Geographical differences in anaphylaxis are complex and depend on many factors, ranging from prescribing habits [28], stinging insect populations [29], pollen exposure [30], food ingredient prevalence [31], to ethnic [32] and racial genetic characteristics.
5. As well as seasonal variation [33], studies of time trends indicate that anaphylaxis is getting more common [12, 34].

2.4 Factors Determining the Severity of Acute Allergic Reactions

What factors underlie the range of severity of acute allergic reactions seen in Figure 2.1? Broadly we might expect the severity of a reaction to be a product of the degree of allergy and the dose of allergen. Those who regularly perform challenge tests will be familiar with the unpredictable way in which reactions become more severe with increasing challenge dose once the threshold for reacting has been passed. The threshold dose for a reaction may change from day to day and can be affected by the process of challenge: thus cautiously increasing repeated doses during a challenge may be similar in effect to ultra-rush immunotherapy induction and raise the threshold for a reaction. Conversely, a negative sting challenge may be followed by a reaction to a subsequent sting [35], maybe through naturally occurring fluctuations in the reaction threshold or because the challenge sting sensitized the patient.

Allergy tests do not tell us how severe a reaction will be. Although there is good correlation between *negative* specific IgE and/or skin prick tests and *lack of clinical sensitivity*, neither specific IgE level nor skin prick test weal diameter relate closely to the severity of reactions and even the

Table 2.3 Relative frequency of major groups of supposed trigger for anaphylaxis

Source	Cases	Drug (%)	Common drugs	Stings (%)	Food (%)	Common foods	Other (%)	Other=	Idiopathic (%)
ED Hong Kong[18]	282	40	NSAID, antibiotics, Chinese medicines	7	50	Seafood			1
*clinic Switzerland [20]	226	18	NSAID > antibiotics > others	59	10	Celeriac > all others	3	Latex	5
Adult ED Australia [24]	142	28	Antibiotics > NSAID > others	17	17	Seafood > nuts			17
Ped ED Australia [25]	57	5	Antibiotics	5	32	Egg, milk > nuts	1	Latex	32
Clinic Australia[19]	432	8	NSAID > antibiotic > others	20	61	Nuts > egg > others	1		8
†OR France[26]	4904	86	NMBA > antibiotics > others	0	0		14	Latex	0
Ped Hospital code 6457 USA[14]	28 + 25		Immunization/ serum + others	Excluded	32	?	14	Unspecified	
Hospital codes Holland[27]	391	35	Glafenine > antibiotics > others	55	9		1		

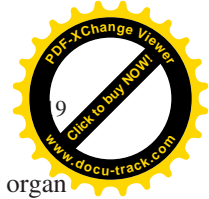
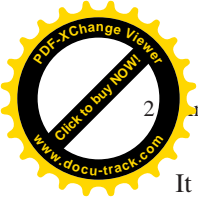
*anaphylaxis defined as including shock.

†compiled from a table of IgE-mediated perioperative reactions 1984–2002: the original table demonstrates strong time trends in the relative frequency of the causative agents.

Double Blind Placebo Controlled Food Challenge (DBPCFC) response only correlated weakly [36]. So what are the other factors that determine severity?

Data from patients in Manchester, UK [37], suggested the severity of coexisting atopic diseases predicted which patients were most likely to develop life-threatening allergic reactions to peanuts and tree nuts. A previous history of atopic eczema correlated with shock during anaphylaxis, rhinitis with upper airway angioedema, and asthma with a principally asthmatic mode of anaphylaxis. Additionally, patients with the lowest serum angiotensin converting enzyme (ACE) concentrations were more likely to develop life-threatening pharyngeal edema, suggesting that this type of reaction may be partly mediated by bradykinin. There was also a relationship between allergen and mode of reaction; for example, pharyngeal edema was more likely with tree nuts (particularly Brazil nuts) than with peanuts. The low ACE levels found in some patients in this study of nut allergy contrasts with the findings in sting anaphylaxis where plasma angiotensinogen levels were lower in those with a history of sting reactions when compared with controls but ACE levels were similar in both groups [38].

Platelet activating factor (PAF) is another mediator with established importance in animal models of anaphylaxis [39, 40]. In human reactions to peanuts, high PAF levels correlated with severity as did low serum levels of PAF-acteylhydrolase (PAF-AH) [41]. In particular, PAF-AH levels were low in serum samples from those dying from fatal peanut reactions; PAF-AH is a major pathway for inactivation of PAF; thus, low levels are associated with enhanced PAF activity. Fatal peanut anaphylaxis typically has a dominant asthmatic component leading to primary respiratory arrest, but PAF-AH levels were not significantly different in life-threatening and non-life-threatening asthma from other causes, indicating specificity for asthmatic anaphylaxis rather than asthma from other causes.



It seems likely that many other allotypic variations will be found that determine which organ system is most affected by anaphylaxis and which mediators cause the most profound effects during anaphylactic reactions, but whether a reaction is fatal or not may be determined as much by comorbidity of coronary artery disease, bronchial hyperreactivity and vascular sensitivity, which in turn have genetic predispositions and may be modulated by cytokines.

2.5 Epidemiology of Fatal Anaphylaxis

There are good reasons to study fatal anaphylaxis. Experimental animal anaphylaxis differs in important respects from that in humans, and experimentation on humans could never be acceptable. We must therefore make the best of whatever observations we can to find who may be affected, what triggers their reactions, the circumstances leading to the reaction, and why whatever treatment was applied had failed. In cases where the fatal reaction was not the first indication of a severe allergy, we can also study why allergen avoidance failed.

While epidemiology of fatal anaphylaxis avoids the problem of deciding whether the reaction was severe enough to be classified as anaphylaxis, it leaves two key uncertainties: whether death was really due to anaphylaxis and whether the suggested trigger agent was really what caused the reaction.

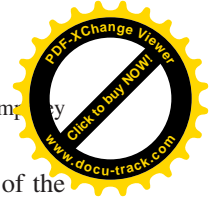
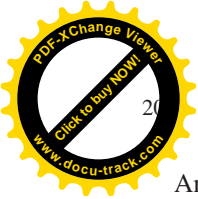
Estimating the likelihood death was due to anaphylaxis is not simple because underlying pathology contributes so much to the lethality of the reaction. For example, when shock and coronary artery spasm lead to myocardial infarction because the coronary arteries were already partly occluded by atheroma, it may be difficult to prove whether sudden death following a dose of antibiotics was due to anaphylaxis or non-anaphylactic myocardial infarction. Similarly, there may be little difference between fatal asthma and fatal anaphylaxis, particularly with food allergy reactions; it may even be meaningless to make such a distinction, particularly if we think of anaphylaxis as an acute allergic reaction that would benefit by treatment with epinephrine.

Nor is it easy to determine what triggered a fatal reaction. With clinic patients, skin prick and challenge tests can be used in an attempt to prove the cause; but in fatal cases, challenge tests and skin prick tests are clearly impossible. Assessment of mast cell tryptase and IgE antibodies to the supposed trigger is possible only when a suitable sample has been retained and even then, insight into the limitations of these investigations is needed for accurate interpretation of the results [42]. Urgent retrieval of samples for these investigations before they are discarded is vital to ascertain the cause of death.

2.6 Fatal Anaphylaxis Around the World

Eighty-nine deaths in Florida 1996–2005 were identified as due to anaphylaxis by diagnostic codes on the death certificate; 41 had autopsies and the autopsy reports were available for 34. But beyond this, the cause of death was not verified by scrutiny of the medical records or details of events surrounding the death [43]. The reaction trigger was identified in 44 deaths: of these, 64% were iatrogenic, 16% triggered by food allergy, and 20% by stings.

A detailed study of 26 deaths attributed to anaphylaxis in a register of all fatalities in Cook County, Chicago 1989–2001 highlighted the role of comorbidity in fatal anaphylaxis [44]. Of these, the authors considered 15 were consistent with anaphylaxis, 8 probably consistent and 2 possibly consistent, recognizing the difficulty in validating the cause of death in a register of this type. Out of 23 with autopsy findings available, 15 had coronary arterial disease and 5 had chronic obstructive airways disease that may have contributed to the lethality of the reaction.



An unpublished Canadian study [45] identified 63 anaphylactic deaths from the records of the chief coroner for Ontario, 32 related to food allergy. Of these 32, 11 were under 18 (two of them 17 years old). Nine of the 11 were known to have been asthmatic, the remaining 2 may have been. The population of Ontario is around 12.5 million, giving a death rate of one child in a 20 million population each year – comparable to the UK rate.

The French anaphylaxis network (Réseau d'Allergo Vigilance) has a register of severe anaphylactic reactions [46] but has not focused on fatal reactions, only four of which (three due to food allergy) were recorded 2002–2003 from a population of 60M [47].

In New South Wales, Australia, 10 fatal reactions to food were recorded 1999–2008 (R Loblay and J Ruhno, personal communications, 2009). Five were attributed to peanuts, three to Chinese food, and two to milk. Eight of these were in children (four male, four female) and at least five of the children had asthma. This gives a death rate of one each year for 6 million population, substantially higher than the UK rate for fatal reactions to food in childhood. One of these cases was widely publicized and details are interesting in that they highlight some of the problems of children with peanut allergy [48]. During a “trivia challenge” at a school camp, this 13-year-old boy had to eat a spoonful of peanut butter as fast as possible. Within seconds of contact, he spat out the food, vomited, developed intense itch, rapid lip and tongue swelling, wheeze, and choking. The first epinephrine was given 13 min after his collapse: resuscitation was unsuccessful. He had had a minor reaction to a sweet containing peanut some months before this and a history of other food allergy, eczema, and asthma. Contributory factors may have included peer pressure to participate in the challenge.

Seven fatal food reactions in Sweden (population 9M) were identified 1993–1996 [49]. Of these deaths two were caused by peanut, three by soy, one by tree nut, and one of unknown food (T Foucard, personal communication, 2008). Subsequently, during 1997–2003 there were two deaths caused by peanuts, one by tree nuts, none by soy and two by unknown food [50]. The authors speculated that the change in incidence might be due to increased awareness of the risk of soy allergy.

2.7 The UK Fatal Anaphylaxis Register

Given the difficulty devising prospective trials of anaphylaxis management, it seemed that studying a large number of fatal reactions might give insight into why prevention and treatment had failed. With this in mind, a register of all fatal anaphylactic reactions in the UK since 1992 was established. The register holds detailed information about the deceased, their medical history, the events leading up to the reaction, the reaction itself, and, where the evidence is sufficient, estimates of the likelihood the cause of death was anaphylaxis and the likelihood for one or more possible trigger factors. This has provided a wealth of data and has taught important lessons for the management of anaphylaxis [51].

There seemed a strong chance that searches for the register might miss cases, particularly deaths attributed to asthma rather than anaphylaxis in asthmatics with food allergy or aspirin sensitivity, deaths due to antibiotics taken by patients at home and sting deaths in older people where the sudden death was most likely to be blamed on myocardial infarction. Retrospective re-investigation of asthma deaths proved futile. Cases in the register suggested that asthma deaths age 0–32 were the ones most likely to have been attacks triggered by food allergy; this led to a year-long prospective study of fatal asthma in this age group. The outcome suggested that most of the food allergy-related acute asthmatic deaths had already been identified through the diligent surveillance of the UK Anaphylaxis Campaign, and that it was unlikely that many cases had been missed. Nevertheless the findings strongly suggest that young people who go into respiratory arrest within an hour of the start of a sudden attack of asthma should be investigated for anaphylaxis. If they have a history of food allergy, this should include examination of their gastric contents for food they were not seen to eat, such as a recent UK case where the stomach contained sesame seeds, pumpkin seeds, linseed, and poppy seeds in a boy with known sesame allergy who had not been seen to eat any such food. Sadly

most cases like this are still diagnosed as due to asthma, the verdict is given as “death from natural causes” and no further investigation is undertaken; retrospective surveys then have no hope of deciding whether the asthma attack had an intrinsic or extrinsic trigger.

More recently the searches of the UK death register have been expanded to include all asphyxia deaths due to upper airways angioedema; this retrieved a few further cases of probable anaphylactic death that the original searches had missed and consolidated data on fatal ACE inhibitor-related angioedema and hereditary angioedema. Some such deaths had already been retrieved because of an improbable diagnosis of anaphylaxis. Amniotic fluid embolus deaths are also under study because the differential diagnosis for some cases included antibiotic or anesthetic anaphylaxis.

There are 536 UK fatalities in the register and following detailed investigation of 345, 272 seem more likely than not due to anaphylaxis while the remaining 73 have more likely other causes of death including at least 2 directly due to epinephrine overdose, 11 with ACEI-related angioedema and no evidence of an allergic trigger, and 4 following insertion of bone cement. Data to assess the remaining 191 is still being collected; from information on the death certificate it is likely that over 100 will prove to have been due to anaphylaxis.

2.7.1 What Has Triggered Fatal Reactions?

Over the last 16 years in the UK, around 20 deaths each year were most probably due to anaphylaxis; about half of these were iatrogenic and the rest divided between sting reactions and food allergy deaths. A small number were triggered by less common agents, including latex, hair dye, and hydatid cyst rupture (Fig. 2.2, Table 2.4). It seems likely that the rate of fatal anaphylaxis in the UK has remained largely unchanged 1992–2005.

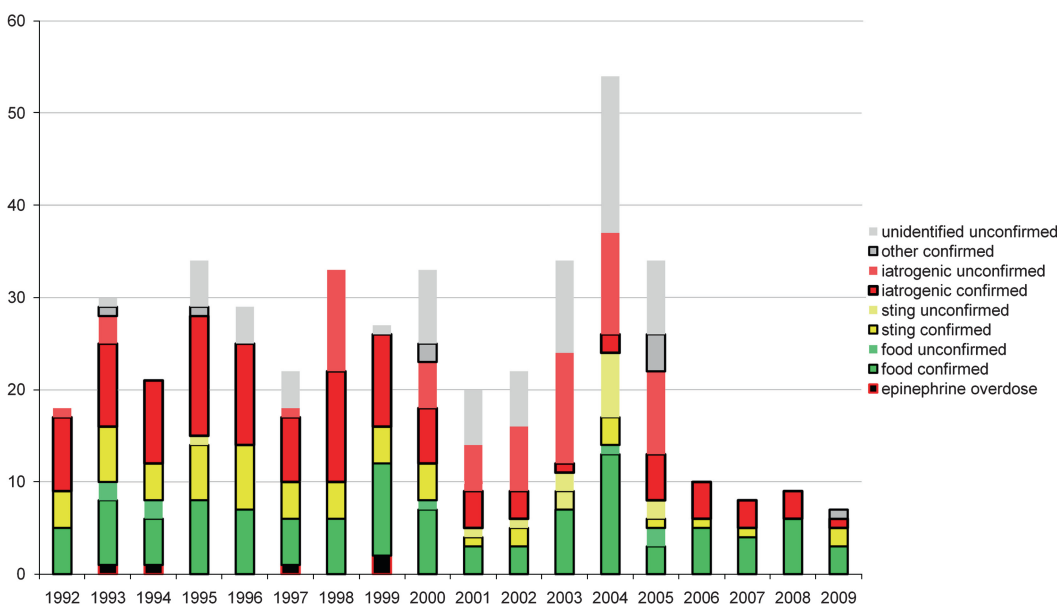


Fig. 2.2 Yearly totals for fatal anaphylaxis in the UK. Confirmed cases have been studied in detail; for some of the unconfirmed cases, anaphylaxis may seem an unlikely cause of death once they have been studied in more detail and so the final numbers will be lower. Extrapolating from the cases reviewed so far, most of the “unidentified, unconfirmed” cases 2003–2005 will have been diagnosed as anaphylaxis on the basis of serum tryptase levels at autopsy and will be found to have low probability of anaphylaxis. The England & Wales Death Register has not yet been searched for 2006–2009; thus, the entries for these years are mainly cases studied in detail immediately following death

Table 2.4 Dominant mode of death in fatal anaphylaxis. The data are taken from the UK Fatal Anaphylaxis Register. The dominant mode of death depends on age and the reaction trigger. At higher resolution, the nature of the food (milk, peanut, tree nut, fish, etc.) or the nature of the iatrogenic intervention (contrast medium, antibiotic, muscle relaxant, NSAID, etc.) also have different modes and age distributions

110 Fatal food reactions

Age	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	>80
Asthma	8	24	8	4	3	2	1		
Breathing difficulty	1	8	8	5	1	1			
Upper airway swelling		1	4	2		2	1		1
Shock and dib	1	4	7	1		1			
Shock		1	2	1					
Other	1	2	2	1					1
	EpiOD	DIC EpiOD	DIC inhV	EpiOD					inhV

48 Fatal sting reactions

Asthma		1				1		1	
Breathing difficulty					1	2	2		
Upper airway swelling					3	1	1	3	1
Shock and dib				1	1			1	2
Shock			1	2	4	6	6	3	1
Other						1	1	1	
						inhV	Epil	MI	

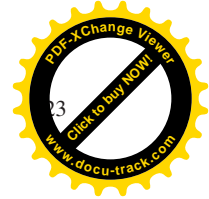
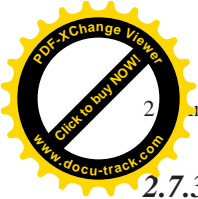
94 Fatal iatrogenic reactions

Asthma		2		2		2	3		
Breathing difficulty			1		2		2		2
Upper airway swelling			1	1	1	2		2	
Shock and dib		1	2	1	2	5	10	6	2
Shock	2			3	4	3	8	8	2
Other			2	1		1	3	4	1
			DIC EpiOD	Bowel infarct		DIC	2xDIC Bowel infarct	3xMI Infected line	EpiOD

EpiOD = overdose of epinephrine. DIC = disseminated intravascular coagulation (but in every case there was also cerebral infarction) MI = myocardial infarction. The cause of the infarcted bowel is unknown but speculation included vasospasm from epinephrine or prolonged shock. Epil = epilepsy following shock/cerebral anoxia. inhV = inhaled vomit during reaction thought to be the cause of respiratory arrest.

2.7.2 Who Died from Anaphylaxis?

There are clear differences in the profiles of those dying from anaphylaxis triggered by different agents, with iatrogenic deaths mostly in older patients, while foods affected a higher proportion of young people (Table 2.4). Most of those dying from food allergy were atopic but iatrogenic and sting deaths did not show this tendency. Overall there were approximately equal numbers of male and female; for food allergy there was a male predominance in childhood and female in early adulthood, similar to patterns of epinephrine pen prescribing [11]. There was a male predominance in sting reactions and fatal contrast medium reactions, contrasting with the female predominance for nonfatal contrast medium reactions. All races were represented but there was a remarkable excess of boys with milk allergy with one or both parents from Africa, the Middle-East, or Far-East: it is not known whether this was for genetic or cultural reasons.



2.7.3 *When Did They Die?*

Fatal reactions showed both circadian and annual variation; both seem most likely to depend simply on the chance of exposure. For example, fatal sting reactions occurred May–November peaking in August when wasp populations are highest, and food reactions were highest in December, probably associated with festive eating.

2.7.4 *How Did They Die?*

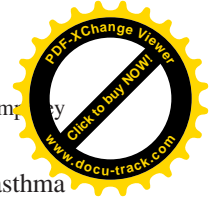
Acute allergic reactions can kill by shock or respiratory arrest (Table 2.4). Those resuscitated from the acute reaction died later (median 60 h post-reaction) from a variety of reasons, related to cerebral infarction, adult respiratory distress syndrome, infections, infarction of the bowel, or bleeding due to disseminated intravascular coagulation. Two additional patients died shortly after anaphylaxis during surgery, but there seemed a more likely cause for their death than the after-effects of the reaction.

Anaphylactic shock is not caused by the same process in every patient. It may be cardiogenic due to the direct effect of the reaction and its mediators on the heart muscle (more typical of older patients with diseased hearts) or peripheral due to vasodilatation and/or fluid leakage from intravascular to extravascular compartments (more typical of younger patients with healthy hearts), or a combination of both. Death outside hospital from peripheral shock has typically followed a change to a more upright posture, highlighting the need to keep shocked patients lying flat [52]; there may be further advantage in raising the legs to help maintain venous return to the heart [53].

Anaphylactic shock causes myocardial ischemia and sometimes infarction. Reduced pulse pressure leads to reduced flow through the coronary arteries: this is made more dangerous if the coronary arteries are narrowed by disease or undergo spasm as part of the reaction. Allergic angina (Kounis syndrome [54]) due to vasospasm in allergic reactions is more likely in hearts with existing arterial disease because of the increased numbers of mast cells. Caution in the use of epinephrine has been urged in such cases (typically middle-aged men developing angina, maybe with a rash and breathing difficulty, within 30 min of starting a drug such as a beta-lactam antibiotic) [55]. Transient left ventricular dysfunction has been described in anaphylaxis, possibly due to multi-vessel epicardial coronary spasm or coronary microvascular impairment or maybe a direct effect on the myocardium of catecholamines released or injected during the reaction; recently a case report emphasized the role of injected epinephrine in myocardial stunning leading to transient left ventricular dysfunction [56].

Primary respiratory arrest in anaphylaxis has a variety of causes: these comprise upper airways angioedema, bronchospasm (often with mucus plugging), inhaled vomit, and pulmonary edema. Upper airway occlusion by angioedema may be part of a generalized reaction, such as following a sting, or a local mucosal reaction from food such as Brazil nuts. Lower airway occlusion by bronchospasm is most commonly due to an acute asthma attack in someone taking daily asthma medication, with or without other indications of an allergic reaction such as urticaria or angioedema. Upper and lower airway occlusion may occur together, such as in a case where tracheostomy was performed because of pharyngeal edema in a Brazil nut reaction, only to find the lungs could not be ventilated because of bronchospasm and mucus plugging. Inhalation of vomit can be fatal in the absence of allergy but is also a possible outcome of an acute allergic gastric reaction in someone with food allergy. Pulmonary edema with shock results from sudden left ventricular failure, and while this may be due to massively severe anaphylaxis, in the UK register it has perhaps more commonly resulted from intravenous bolus injection of epinephrine.

Although anaphylaxis can kill fit and healthy people, most deaths in the UK register resulted from existing pathology made fatal by a relatively mild allergic reaction. Thus an allergic reaction to milk



may cause a fatal attack of asthma in a child with poorly controlled asthma, particularly if the asthma is already exacerbated by a rhinovirus infection. Most fatal allergic reactions to food have been of this type. Optimal daily control of asthma is crucial in reducing the risk of a fatal reaction in those with food allergy [57]. Similarly, a sting reaction that would otherwise be mild may be fatal in someone with systemic mastocytosis. Raised background tryptase levels have been found in many of those presenting with sting anaphylaxis and may be due to clonal mast cell proliferation [58]. Existing coronary artery disease is frequently found at autopsy in those dying from iatrogenic anaphylaxis.

Drugs used to treat asthma, hypertension, arrhythmia, and various other conditions may also enhance the effects of anaphylaxis or make its management more difficult. A recent history of high daily dosage of beta-2 agonists was found in several of those dying from food-allergy-related anaphylaxis/asthma who failed to respond to epinephrine: whether the failure of epinephrine to rescue the patient was because the asthma was very severe or because the excessive beta-2 agonist use reduced the effectiveness of epinephrine by tachyphylaxis is not known. When an anaphylaxis patient with arrhythmia might benefit from treatment with a beta-adrenergic blocking drug, it will be helpful for the cardiologist and allergist to discuss which condition poses the greater risk to the patient and what the optimal management plan might be. Because ACE is the major pathway for bradykinin inactivation, ACE inhibitors may augment the severity of anaphylaxis, in some patients by increasing the likelihood of angioedema, in others by blocking formation of angiotensin II which is one of the homeostatic pathways opposing shock in anaphylaxis [59]. As well as ACE inhibitors, NSAID, aspirin, and beta-blockers were associated with severe reactions to foods [60].

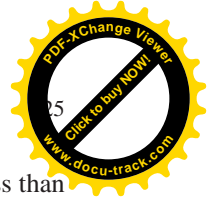
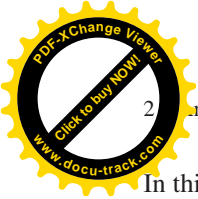
2.8 Fatal First Reactions: Why Was Rescue Treatment Unsuccessful?

For those whose previous history is adequately known, the fatal reaction was thought to be their first for 19 out of 32 antibiotic, 17 out of 20 muscle relaxant, 7 out of 13 nonsteroidal anti-inflammatory drug, 13 out of 13 other drug, 10 out of 10 contrast media-related, and 22 out of 38 insect sting anaphylactic deaths [61]. Most patients had been exposed to the causative drug or been stung previously without reaction. For such patients, management is limited to what can be done at the time of their first reaction and this will depend on where the reaction occurs (Table 2.5).

The commonest place for iatrogenic reactions is the operating room, and this will be fully equipped to provide appropriate emergency care. The main problem here has been recognizing that the sudden change in the patient's condition was due to anaphylaxis in time to prevent progression.

Table 2.5 Circumstances of 278 fatal anaphylactic reactions

Food		Iatrogenic		Sting	
Home	31	Home	30	Home	18
School	7	School	1		2 in bed
Work	5	Work	1	Work	6
					5 outdoors labor, 1 driving truck
Out /about	6			Out /about	11
					2 driving, 1 cycling, 4 walking, 4 sitting, 1 sport
Friend's house	13	OR	60	Orchard/garden	15
Relative's house	8	ER	2	By bee hives	2
Restaurant	23	Ward/department	22		
Takeaway	6				
Wedding	2	Dentist	2		
Abroad	4	GP	1		
Camping	2				



In this situation, the median time to first arrest has been 5 min and for a few the time was less than a minute. The first drug used in treatment has usually not been epinephrine but rather alpha adrenergic agonists such as metaraminol or norepinephrine for hypotension or salbutamol for increased airways resistance. There are case reports that could be taken as supporting either approach [62, 63] but in general the consensus is that epinephrine is the preferred drug for initial treatment of anaphylactic reactions in the OR [64, 65].

2.9 Fatal Recurrent Reactions

2.9.1 *Reducing the Likelihood of a Severe Recurrence*

For the other patients who had a previous reaction, even if this was mild (as was the case for the majority of anaphylactic deaths attributed to food allergy) there is an opportunity to protect the patient against the worst effects of a recurrence. Allergen-specific immunotherapy and other more recently devised methods of attenuating or eliminating the allergic response to allergen exposure are discussed elsewhere in this book. Optimal daily management of asthma, hypertension, and arrhythmia has been discussed above as a way of avoiding factors that will increase the severity of a recurrent reaction.

2.9.2 *Why Did Avoidance Fail?*

For the minority of patients who had a previous reaction and knew what caused it, allergen avoidance failed for a variety of reasons. Iatrogenic fatal recurrent anaphylaxis was largely due to beta-lactam antibiotics and NSAID. Reasons for avoidance failure include:

1. Ignoring a patient's claim of penicillin allergy. Most of the many patients who claim "penicillin allergy" will not react if given penicillin because their allergy was a rash on the second to fourth day of amino-penicillin treatment for a sore throat. If on the other hand their allergy was rapidly developing symptoms following the first dose of a new course, the chance of anaphylaxis on re-exposure is high. Patients commonly do not remember the reaction that led to their label of "penicillin allergy" making it difficult to conclude whether penicillin treatment might be dangerous; fatal reactions have resulted from the decision to treat in the face of such a claim of penicillin allergy. There is evidence in some such cases that the penicillin allergy was side-chain specific and previous treatment with a different beta-lactam antibiotic without a reaction made the doctor discount the earlier history of a severe reaction. Doctors should take a history of penicillin allergy seriously and, if they are uncertain whether it is significant, should err on the side of caution.
2. Bypassing protocols intended to protect patients with drug allergy. Patients have been classified as penicillin allergic and given a red armband warning of their allergy, which was not seen when the antibiotic was injected in the other arm. Penicillin allergy warnings on treatment sheets or GP records have frequently been overlooked or not transferred from old handwritten records to new computer records. Patients have repeatedly detected and rejected inappropriate prescriptions for a drug they thought they were allergic to only to be caught out subsequently when the same drug was prescribed with a different name.
3. Of 16 patients dying from cephalosporin anaphylaxis, five had previously reacted to a penicillin; three died following cefaclor given because of previous amoxicillin reactions on the grounds that only one in ten patients with penicillin allergy react to cephalosporins.



Fatal repeat anaphylaxis to NSAID have followed avoidance failure for reasons such as the patient not recognizing that the new prescription was a potentially cross-reacting drug or the same drug with a different name, or the doctor having been given the records of a patient with similar name and age who was not NSAID allergic and so was not warned of the allergy.

The previous sting history is known for 38 fatal sting reactions on the register: 16 had a previous acute reaction. None of these had had venom-specific immunotherapy. Despite advice that a 3–5 year course of specific immunotherapy is optimal management of proven sting allergy, some patients preferred to rely on sting avoidance and self-injectible epinephrine, especially where there was difficulty attending for specific immunotherapy. Five had self-injectible epinephrine that failed to save them (see below for details). It is not known how many had adopted a diligent sting avoidance strategy. While even obsessive avoidance cannot be totally successful, the risk of being stung can be substantially reduced by a few simple rules. Advice for each region is available on the internet.

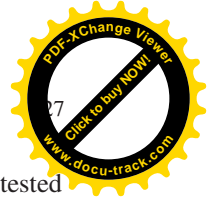
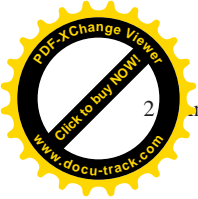
We recently reported 48 additional food-allergy deaths in the UK [66]. The food blamed for fatal reactions was catered (18), domestically prepared (6), packaged/labeled (16), sold loose/unlabelled (2), whole nuts (3), and unknown (3). Fourteen were thought not to have been avoiding the culprit food; avoidance was graded as casual for 16, careful for 7, extremely careful for 6, and unknown for 5. Even with the most diligent avoidance, lapses occurred during festive eating, foreign travel, or when distracted by disruption to routine. Just as much as they need to recognize foods that will cause them to react, patients should be made aware of these potentially dangerous circumstances and be supported in assessing them and developing appropriate coping strategies with increased vigilance in hazardous situations.

2.10 Self-injectible Epinephrine

Since 1905, epinephrine has been known as an effective treatment for an acute attack of asthma [67] and since 1910 as an antidote to anaphylaxis [68]. It seems to have been in routine use to treat anaphylaxis by the 1930s, as demonstrated by a graphic personal account by a beekeeper of his anaphylactic reaction and the severe angina that affected him following the use of 10 minim (0.6 mL) of epinephrine in treatment of his shock and breathing difficulty [69]. Early studies of fatal and near-fatal food allergy emphasized the need for treatment with epinephrine early in the reaction [70, 71] and recommended that those at risk should carry their own epinephrine treatment. For the patient, achieving the correct dose and route was difficult [72] until the auto-injectors for self-treatment with epinephrine that had been available since 1980 [73] were used more generally.

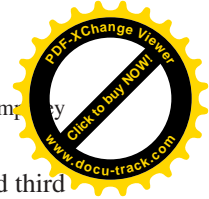
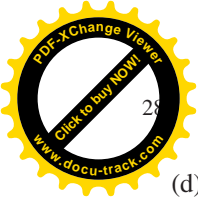
The current widespread availability of auto-injectors has not solved all the problems. There is much we may learn from 31 food allergy and 5 sting-allergic fatalities who had been prescribed epinephrine for self-treatment:

1. In 15/36 treatment failures, an auto-injector was used early in the reaction and apparently correctly. One patient was so confident her epinephrine would save her that she bit into a chocolate knowing it might be risky. She saw the nut, rapidly developed difficulty breathing, and used her pen immediately and apparently correctly. Her symptoms did not remit; she arrested and could not be resuscitated. It must be recognized that although epinephrine is the most effective treatment for anaphylaxis if used early in the reaction, not all patients will be saved. Such failure could be speculatively attributed to a variety of causes:
 - (a) Obesity preventing intramuscular injection. Epinephrine injected into the subcutaneous tissue causes intense vasospasm, and most of the epinephrine will remain there for hours without being absorbed. This, after all, is the rationale for adding epinephrine to local anesthetics to prolong their action. For optimal absorption, the injection must be intramuscular, and even then not all muscles absorb well. The anterolateral aspect of the thigh near the midpoint of its



length is easy to reach and, fortunately, a good site for absorption of epinephrine when tested in active men aged 18–35 [74]. However, with the rising tide of obesity the depth of subcutaneous adiposity is frequently greater than the 16mm of needle in the EpiPen [75–77] and even more often longer than the 10mm of the Anapen. If the vasculature of older humans behaves like that of older rats [78], the absorption of epinephrine may be less effective than in young men. It is worth recording that in none of the autopsies of these cases was the auto-injector needle track dissected to establish which tissue the epinephrine was injected into: this information would have been valuable.

- (b) Overuse of salbutamol for daily asthma treatment. Most of those dying from food anaphylaxis take daily treatment for asthma and it has been possible to establish for some of those whose fatal asthma was triggered by food allergy and whose self-injectible epinephrine failed to save them that the dose of short-acting beta-2 agonist was greatly in excess of the maximum recommended. In such cases epinephrine may no longer be effective at reversing bronchospasm [57].
 - (c) In at least one case, bisoprolol had been prescribed by a cardiologist unaware that the patient was at risk of anaphylaxis and might need epinephrine treatment. This patient had previously used his auto-injector on three occasions following stings and had symptoms of limited severity; but the next sting, after he had started taking bisoprolol, was fatal despite early use of his auto-injector. As patients with sting or food allergy get older there is an increasing risk they will develop hypertension or arrhythmia and may be prescribed a beta-blocker or angiotensin converting enzyme inhibitor (ACEI). Beta-blockers will attenuate the usefulness of epinephrine in anaphylaxis and ACEI may promote hypotension or angioedema in susceptible patients. Patients at risk of anaphylaxis, in particular those carrying their own epinephrine, should be instructed to make sure any doctor prescribing for them is fully aware of this. Ideally patients should attend for regular review and retraining; any new medication should be evaluated in the context of their anaphylaxis rescue package. In practice however, it is my experience that many older patients decline the offer of regular follow-up even if they have used their auto-injector on a number of occasions.
 - (d) Extreme severity of reaction. The need for two or more doses of epinephrine may be an indicator of severity. One patient used two pens and two patients used three pens but still died; retrospective proof whether this was due to their obesity or due to the severity of the reaction is impossible.
2. The dose prescribed was too low for 2/32. One had been given an epinephrine inhaler and told not to take more than 2 puffs at a time when it was thought this treatment might be effective if 20 or more inhalations were used. The other weighed 36kg but had a junior (0.15mg) pen. A second pen had been available but was used incorrectly.
 3. The injection was given late in the reaction in 5/36. One was heard by her husband to shout “anaphylaxis;” he found her collapsed with her pen on the floor; he gave the dose but she showed no improvement. Two had left pens elsewhere and had to retrieve them (of which one was time-expired); one collapsed while waiting in pharmacy queue for pen to be dispensed; for one, the reason was unknown.
 4. Six failed to use their injection correctly, indicating inadequate training.
 - (a) One jabbed the pen on her thigh but withdrew it immediately, spilling most of the epinephrine.
 - (b) One pulled the pen apart, preventing it from activating properly.
 - (c) One man was found dead with the telephone in one hand and his epinephrine injection in the other. He had a history of wasp allergy and there was a dead wasp trapped in his clothing. It seems reasonable to suppose he was uncertain how to use his epinephrine and the progress of the reaction was too swift to allow him to take the treatment.



- (d) In one fatal sting reaction, the first pen is said to have failed to activate, the second and third fired while being removed from their canister, a fourth pen given by a paramedic failed to revive the patient.
- (e) One had been given a pen for nut allergy but was reacting to latex and did not use it [79].
- (f) It is not known why one other failed to use his pen.
5. Eight out of 36 did not have it with them at the crucial time.
- (a) Three had left pen elsewhere, too far away to be retrieved in time for treatment
- (b) Two had not replaced after use (one used the day before, the other several years previously)
- (c) One found her epinephrine to be out of date and so went to hospital; she then died after inappropriate bolus iv injection of epinephrine 1 mg
- (d) Two reason not known

The failure in these latter cases might be attributed to poor training; often the doctor prescribing the pen is unfamiliar with the device [80, 81] and fails to train the patient adequately to ensure they have the device with them when it might be needed, to use it at the correct time in a reaction with a correct injection technique [82–84].

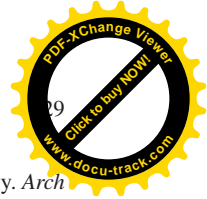
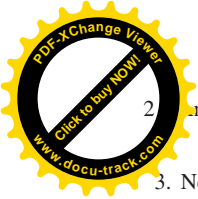
Of 102 fatal reactions to foods, 71 had not been prescribed epinephrine for self-treatment. This is not so surprising when the severity of their worst previous reaction is taken into account – three quarters of those whose death was attributed to food anaphylaxis had never had a severe reaction previously. I have presented one such case to various audiences to see who might have recommended he should carry an epinephrine pen. In UK audiences a small minority would have recommended a pen but in Canada a large majority would have, reflecting national differences of opinion. Of the fatal cases in the UK, at least 2/71 had requested an auto-injector but their doctor refused to prescribe one.

2.11 Conclusion

Detailed study of fatal reactions provides insight that is vital for reducing risk and improving management. Most fatal reactions occur unexpectedly in those with no previous history of reactions; knowing the typical circumstances of fatal reactions allows better planning for training in the correct use of epinephrine and basic life support for the particular mode of anaphylaxis the patient exhibits, including posture appropriate for shock or respiratory distress. In those whose history suggests they may be at significant risk of a life-threatening reaction, the key elements of risk reduction include training in effective allergen avoidance, optimizing their daily management of conditions such as asthma, hypertension, and heart disease to use drugs that will not increase the risk from anaphylaxis or if that is not possible, to achieve a logical balance of risk between the treated condition and anaphylaxis, and lastly, provision of appropriate kit for self-treatment in the event of a reaction. The ways in which self-injectible epinephrine failed teach important lessons, not only about the need for continual review and retraining but also the provision of kit and instructions appropriate for the individual patient, according to their body mass and their attitude to their allergy.

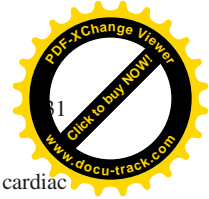
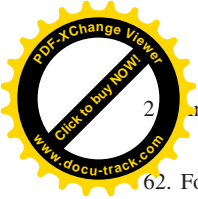
References

1. Pumphrey RS, Stanworth SJ. The clinical spectrum of anaphylaxis in north-west England. *Clin Exp Allergy*. 1996;26(12):1364–1370.
2. Macdougall CF, Cant AJ, Colver AF. How dangerous is food allergy in childhood? The incidence of severe and fatal allergic reactions across the UK and Ireland. *Arch Dis Child*. 2002;86:236–239.



3. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: an investigation into its epidemiology. *Arch Intern Med.* 2001;161(1):15–21.
4. Johansson SGO, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: report of the nomenclature review committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol.* 2004;113:832–836.
5. Kemp SF, Lockey RF, Simons FER. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. *Allergy.* 2008;63:1061–1070.
6. Soar J, Pumphrey R, Cant A, et al. Emergency treatment of anaphylactic reactions guidelines for healthcare providers. *Resuscitation.* 2008;77:157–169.
7. Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol.* 2006;117(2):391–397.
8. Rüggeberg JU, Gold MS, Bayas JM, et al. Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine.* 2007;25(31):5675–5684.
9. Erlewyn-Lajeunesse M, Dymond S, Slade I, et al. Diagnostic utility of two case definitions for anaphylaxis: a comparison using a retrospective case notes analysis in the UK. *Drug Saf.* 2010; 33(1):1–8.
10. Sicherer SH, Burks AW, Sampson-HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. *Pediatrics.* 1998;102:e6
11. 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(4):647–651.
12. 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(3):139–143.
13. Sheikh A, Alves B. Age, sex, geographical and socio-economic variations in admissions for anaphylaxis: analysis of four years of English hospital data. *Clin Exp Allergy.* 2001;31(10):1571–1576.
14. Sheehan WJ, Graham D, Ma L, Baxi S, Phipatanakul W. Higher incidence of pediatric anaphylaxis in northern areas of the United States. *J Allergy Clin Immunol.* 2009;124(4):850–852.e2.
15. The International Collaborative Study of Severe Anaphylaxis. An epidemiologic study of severe anaphylactic and anaphylactoid reactions among hospital patients: methods and overall risks. *Epidemiology.* 1998;9(2):141–146.
16. 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(3):317–319.
17. Stewart AG, Ewan PW. The incidence, aetiology and management of anaphylaxis presenting to an accident and emergency department. *QJM.* 1996;89(11):859–864.
18. Smit DV, Cameron PA, Rainer TH. Anaphylaxis presentations to an emergency department in Hong Kong: incidence and predictors of biphasic reactions. *J Emerg Med.* 2005;28(4):381–388.
19. Mullins RJ. Anaphylaxis: risk factors for recurrence. *Clin Exp Allergy.* 2003;33(8):1033–1040.
20. Helbling A, Humi 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(2):285–290.
21. Boros CA, Kay D, Gold MS. Parent reported allergy and anaphylaxis in 4173 South Australian children. *J Paediatr Child Health.* 2000;36(1):36–40.
22. Lieberman P, Camargo CA Jr, Bohlke K, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. *Ann Allergy Asthma Immunol.* 2006;97(5):596–602.
23. Yocum MW, Butterfield JH, Klein JS, et al. Epidemiology of anaphylaxis in Olmsted County: a population-based study. *J Allergy Clin Immunol.* 1999;104:452–456.
24. Brown AF, McKinnon D, Chu K. Emergency department anaphylaxis: a review of 142 patients in a single year. *J Allergy Clin Immunol.* 2001;108(5):861–866.
25. Braganza SC, Acworth JP, McKinnon DR, Peake JE, Brown AF. Paediatric emergency department anaphylaxis: different patterns from adults. *Arch Dis Child.* 2006;91(2):159–163.
26. Mertes PM, Lambert M, Guéant-Rodriguez RM, et al. Perioperative anaphylaxis. *Immunol Allergy Clin North Am.* 2009;29(3):429–451.
27. Van der Klauw MM, Goudsmit R, Halie MR, et al. A population based case-cohort study of drug-induced anaphylaxis. *Br J Clin Pharmacol.* 1993; 35:400–408.
28. Johansson SG, Florvaag E, Oman H, et al. National pholcodine consumption and prevalence of IgE-sensitization: a multicentre study. *Allergy.* 2009;65(4):498–502.
29. Bilò MB, Bonifazi F. The natural history and epidemiology of insect venom allergy: clinical implications. *Clin Exp Allergy.* 2009;39(10):1467–1476.
30. Gamboa PM, Cáceres O, Antepara I, et al. Two different profiles of peach allergy in the north of Spain. *Allergy.* 2007;62(4):408–414.

31. Dalal I, Binson I, Reifen R, et al. Food allergy is a matter of geography after all: sesame as a major cause of severe IgE-mediated food allergic reactions among infants and young children in Israel. *Allergy*. 2002;57(4):362–365.
32. Yang JJ, Burchard EG, Choudhry S, et al. Differences in allergic sensitization by self-reported race and genetic ancestry. *J Allergy Clin Immunol*. 2008;122(4):820–827.e9.
33. Mulla ZD, Simon MR. Anaphylaxis in Olmsted County: seasonal pattern and suggestions for epidemiologic analysis. *J Allergy Clin Immunol*. 2009;123(5):1194; author reply 1194–1195.
34. Sheikh A, Alves B. Hospital admissions for acute anaphylaxis: time trend study. *BMJ*. 2000;320(7247):1441.
35. Golden DB, Breisch NL, Hamilton RG, et al. Clinical and entomological factors influence the outcome of sting challenge studies. *J Allergy Clin Immunol*. 2006;117(3):670–675.
36. Hourihane JO, Grimshaw KE, Lewis SA, et al. Does severity of low-dose, double-blind, placebo-controlled food challenges reflect severity of allergic reactions to peanut in the community? *Clin Exp Allergy*. 2005;35(9):1227–1233.
37. Summers CW, Pumphrey RS, Woods CN, McDowell G, Pemberton PW, Arkwright PD. Factors predicting anaphylaxis to peanuts and tree nuts in patients referred to a specialist center. *J Allergy Clin Immunol*. 2008;121(3):632–638.
38. Hermann K, von Tschirschnitz M, Ebner von Eschenbach C, Ring J. Histamine, tryptase, norepinephrine, angiotensinogen, angiotensin-converting enzyme, angiotensin I and II in plasma of patients with hymenoptera venom anaphylaxis. *Int Arch Allergy Immunol*. 1994;104(4):379–384.
39. Finkelman FD, Rothenberg ME, Brandt EB, Morris SC, Strait RT. Molecular mechanisms of anaphylaxis: lessons from studies with murine models. *J Allergy Clin Immunol*. 2005;115:449–457.
40. Ishii S, Kuwaki T, Nagase T, et al. Impaired anaphylactic responses with intact sensitivity to endotoxin in mice lacking a platelet-activating factor receptor. *J Exp Med*. 1998;187:1779–1788.
41. Vadas P, Gold M, Perelman B, et al. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. *N Engl J Med*. 2008;358(1):28–35.
42. Williams P, Sewell WAC Bunn, Pumphrey R, Read G, Jolles S. Clinical immunology review series: an approach to the use of the immunology laboratory in the diagnosis of clinical allergy. *Clin Exp Immunol*. 2008;153(1):10–18.
43. Simon MR, Mulla ZD. A population-based epidemiologic analysis of deaths from anaphylaxis in Florida. *Allergy*. 2008;63(8):1077–1083.
44. Greenberger PA, Rotskoff BD, Lifschultz B. Fatal anaphylaxis: postmortem findings and associated comorbid diseases. *Ann Allergy Asthma Immunol*. 2007;98(3):252–257.
45. http://www.anaphylaxis.org/content/programs/programs_research_deaths.asp. Accessed February 17, 2010.
46. Moneret-Vautrin DA, Kanny G, Parisot L. First survey from the “Allergy Vigilance Network”: life-threatening food allergies in France. *Allerg Immunol*. 2002;34(6):194–198.
47. Moneret-Vautrin DA, Morisset M, Flabbee J, Beaudouin E, Kanny G. Epidemiology of life-threatening and lethal anaphylaxis: a review. *Allergy*. 2005;60(4):443–451.
48. http://www.allergy.org.au/mediareleases/peanut_anaph.htm. Accessed 2008.
49. Foucard T, Malmheden Yman I. A study on severe food reactions in Sweden – is soy protein an underestimated cause of food anaphylaxis? *Allergy*. 1999;54:261–265.
50. Foucard T, Yman IM, Nordvall L. Reduced number of fatal and life-threatening reactions to food. Reporting by the medical profession has resulted in effective measures. *Lakartidningen*. 2005;102(46):3465–3468.
51. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy*. 2000;30(8):1144–1150.
52. Pumphrey RS. Fatal posture in anaphylactic shock. *J Allergy Clin Immunol*. 2003;112(2):451–452.
53. Boulain T, Achard JM, Teboul JL, Richard C, Perrotin D, Ginies G. Changes in BP induced by passive leg raising predict response to fluid loading in critically ill patients. *Chest*. 2002;121(4):1245–1252.
54. Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: the concept of allergic angina. *Br J Clin Pract*. 1991;45(2):121–128.
55. Ridella M, Bagdure S, Nugent K, Cevik C. Kounis syndrome following beta-lactam antibiotic use: review of literature. *Inflamm Allergy Drug Targets*. 2009;8(1):11–16.
56. Morel O, Jesel L, Morel N, et al. Transient left ventricular dysfunction syndrome during anaphylactic shock Vasospasm, Kounis syndrome or epinephrine-induced stunned myocardium? *Int J Cardiol*. 2009 Nov 13. [Epub ahead of print]
57. Pumphrey RS, Nicholls JM. Epinephrine-resistant food anaphylaxis. *Lancet*. 2000;355(9209):1099.
58. Bonadonna P, Perbellini O, Passalacqua G, et al. Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum tryptase levels. *J Allergy Clin Immunol*. 2009;123(3):680–686.
59. Hermann K, Ring J. The renin-angiotensin system in patients with repeated anaphylactic reactions during hymenoptera venom hyposensitization and sting challenge. *Int Arch Allergy Immunol*. 1997;112(3):251–256.
60. Moneret-Vautrin DA, Latache C. Drugs as risk factors of food anaphylaxis in adults: a case-control study. *Bull Acad Natl Med*. 2009;193(2):351–362; discussion 362–363. [Article in French].
61. Pumphrey R. Anaphylaxis: can we tell who is at risk of a fatal reaction? *Curr Opin Allergy Clin Immunol*. 2004;4(4):285–290.



62. Ford SA, Kam PC, Baldo BA, Fisher MM. Anaphylactic or anaphylactoid reactions in patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth.* 2001;15(6):684–688.
63. Heytman M, Rainbird A. Use of alpha-agonists for management of anaphylaxis occurring under anaesthesia: case studies and review. *Anaesthesia.* 2004;59(12):1210–1215.
64. Dewachter P, Mouton-Faivre C, Emala CW. Anaphylaxis and anesthesia: controversies and new insights. *Anesthesiology.* 2009;111(5):1141–1150.
65. Harper NJ, Dixon T, Dugué P, et al. Working Party of the Association of Anaesthetists of Great Britain and Ireland. Suspected anaphylactic reactions associated with anaesthesia. *Anaesthesia.* 2009;64(2):199–211.
66. Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999–2006. *J Allergy Clin Immunol.* 2007;119(4):1018–1019.
67. Doig RL. Epinephrin; especially in asthma. *Calif State J Med.* 1905;3(2):54–55.
68. Anderson JF, Schultz WH. The cause of serum anaphylactic shock and some methods of alleviating it. *Proc Soc Exper Biol Med.* 1910;vii:32–36.
69. An Apiarist. Bee-sting anaphylaxis? *BMJ.* 1939;1(4094):1306.
70. Yunginger JW, Sweeney KG, Sturmer WQ, et al. Fatal food-induced anaphylaxis. *JAMA.* 1988;260(10):1450–1452.
71. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med.* 1992;327(6):380–384.
72. Simons FE, Chan ES, Gu X, Simons KJ. Epinephrine for the out-of-hospital (first-aid) treatment of anaphylaxis in infants: is the ampule/syringe/needle method practical? *J Allergy Clin Immunol.* 2001;108(6):1040–1044.
73. Lockey SD. A new method of administering aqueous epinephrine: the EpiPen, an automatic syringe. *J Asthma Res.* 1980;17(4):153–155.
74. Simons FE, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *J Allergy Clin Immunol.* 2001;108(5):871–873.
75. Song TT, Nelson MR, Chang JH, et al. Adequacy of the epinephrine autoinjector needle length in delivering epinephrine to the intramuscular tissues. *Ann Allergy Asthma Immunol.* 2005;94(5):539–542.
76. Pumphrey RSH. When should self-injectible epinephrine be prescribed for food allergy and when should it be used? *Curr Opin Allergy Clin Immunol.* 2008;8(3):254–260.
77. Stecher D, Bulloch B, Sales J, Schaefer C, Keahey L. Epinephrine auto-injectors: is needle length adequate for delivery of epinephrine, intramuscularly? *Pediatrics.* 2009;124(1):65–70.
78. Donato AJ, Lesniewski LA, Delp MD. Ageing and exercise training alter adrenergic vasomotor responses of rat skeletal muscle arterioles. *J Physiol.* 2007;579(Pt 1):115–125.
79. Pumphrey RS, Duddridge M, Norton J. Fatal latex allergy. *J Allergy Clin Immunol.* 2001;107(3):558.
80. Mehr S, Robinson M, Tang M. Doctor – how do I use my EpiPen? *Pediatr Allergy Immunol.* 2007;18(5):448–452. Survey of hospital paediatricians’ familiarity with auto-injectors showed few would have given correct advice to their patients.
81. Sicherer SH, Forman JA, Noone SA. Use assessment of self-administered epinephrine among food-allergic children and pediatricians. *Pediatrics.* 2000;105(2):359–362.
82. Pouessel G, Deschildre A, Castelain C, et al. Parental knowledge and use of epinephrine auto-injector for children with food allergy. *Pediatr Allergy Immunol.* 2006;17(3):221–22.
83. Ferreira MB, Alves RR. Are general practitioners alert to anaphylaxis diagnosis and treatment? *Allerg Immunol.* 2006;38(3):83–86.
84. Grouhi M, Alshehri M, Hummel D, Roifman CM. Anaphylaxis and epinephrine auto-injector training: who will teach the teachers? *J Allergy Clin Immunol.* 1999;104(1):190–193.



<http://www.springer.com/978-1-60327-950-5>

Anaphylaxis and Hypersensitivity Reactions

Castells, M.C. (Ed.)

2011, XIII, 361 p., Hardcover

ISBN: 978-1-60327-950-5

A product of Humana Press