Epidemiology of severe anaphylaxis: can we use population-based data to understand anaphylaxis?

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Purpose of review
The observed increase in incidence of allergic disease in many regions over the past 3 decades has intensified interest in understanding the epidemiology of severe allergic reactions. We discuss the issues in collecting and interpreting these data and highlight current deficiencies in the current methods of data gathering.

Recent findings
Anaphylaxis, as measured by hospital admission rates, is not uncommon and has increased in the United Kingdom, the United States, Canada, and Australia over the last 10–20 years. All large datasets are hampered by a large proportion of uncoded, 'unspecified' causes of anaphylaxis. Fatal anaphylaxis remains a rare event, but appears to be increasing for medication in Australia, Canada, and the United States. The rate of fatal food anaphylaxis is stable in the United Kingdom and the United States, but has increased in Australia. The age distribution for fatal food anaphylaxis is different to other causes, with data suggesting an age-related predisposition to fatal outcomes in teenagers and adults to the fourth decade of life.

Summary
The increasing rates of food and medication allergy (the latter exacerbated by an ageing population) has significant implications for future fatality trends. An improved ability to accurately gather and analyse population-level anaphylaxis data in a harmonized fashion is required, so as to ultimately minimize risk and improve management.

Keywords
allergy, anaphylaxis, epidemiology

INTRODUCTION

Anaphylaxis is a term used widely to describe a severe allergic reaction; however, there is no single definition agreed worldwide [1]. There has been significant interest in the epidemiology of anaphylaxis, perhaps driven by trends of increasing allergic disease observed in much of the developed world over the past 3 decades. Measurement of population-based patterns and causes of severe allergic reactions might serve several purposes, including estimating the regional burden of disease, identifying trends in causal/triggering agents, tracking trends over time, and in finding associations which may help to predict or prevent severe disease or death. In this review, we aim to outline how studying the epidemiology of anaphylaxis might assist in the prevention of anaphylaxis and anaphylaxis-related fatalities at an individual and population-based level.

UNDERSTANDING ANAPHYLAXIS

Understanding the pathophysiology of anaphylaxis is crucial to predicting risk and interpreting epidemiological associations. However, human data are limited, and performing allergen challenges under medical supervision to investigate mechanisms raises significant ethical and safety concerns. Where such challenges have been performed, individuals with prior severe reactions may be excluded

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KEY POINTS

- Anaphylaxis is increasing but fatal anaphylaxis remains rare.

- Medications appear to be the most common cause of anaphylaxis admissions and fatalities in the United Kingdom, the United States, and Australia.

- Triggers such as medications, foods, and insect venoms are associated with specific demographic patterns and clinical presentations.

- Large data sets are hindered by lack of robust utilized coding systems, with underreporting, miscoding, and many cases of 'unspecified' triggers in admissions and fatality registers.

and the challenges themselves are designed (through dose limitation) to avoid severe reactions, and are therefore less likely to provide a valid picture of the whole population of individuals at risk from severe reactions. Some investigators have sought to capture blood/bio samples for mechanistic studies from individuals presenting to the emergency departments during or immediately following anaphylaxis, but these are prone to difficulties in defining the circumstances prior to arrival in the hospital and lack 'baseline' samples to allow detailed assessment of inflammatory mediators. Unfortunately, animal models of mediators and mechanisms of anaphylaxis, particularly food-induced anaphylaxis, cannot be extrapolated to humans (Table 1) [2–4,5▪,6–14].

DEFINING ANAPHYLAXIS AND SEVERE ANAPHYLAXIS: WHY IS IT IMPORTANT?

Anaphylaxis is most commonly accepted to be a potentially life-threatening systemic IgE-mediated allergic reaction, with a spectrum of severity. To accurately compare anaphylaxis data from different regions and across centres within regions, it is useful to have harmonized definitions of anaphylaxis. However, ongoing regional variations in definition persist (Table 2) [15–19], which are further confounded by confusion between what constitutes a 'definition' of anaphylaxis as opposed to a 'description of symptoms', that is, the clinical presentation of anaphylaxis [20]. Indeed, the NIAID criteria for anaphylaxis (which have gained widespread acceptance) are not a definition *per se*, but were developed to capture at least 95% of cases [19].

In terms of accurately defining anaphylaxis, we are faced with a number of important challenges. Anaphylaxis is typically defined as a generalized reaction; however, at least in the United Kingdom

and Australia, we have found that coroner's reports of fatal anaphylaxis (particularly to food) often describe only symptoms localized to the throat and lower airways before collapse and death (Pumphrey R, personal communication). Severe anaphylaxis may, therefore, initially present without significant systemic symptoms. Not all episodes of anaphylaxis necessarily result in a life-threatening situation. Many individuals experiencing anaphylaxis will exhibit symptom resolution without receiving appropriate treatment. For example, in a prospective survey of teenagers attending the UK allergy clinics, 245 of 969 had at least one episode of anaphylaxis (according to NIAID criteria) in the previous year; only 41 (17%) had used or been administered epinephrine (adrenaline), despite all being prescribed an autoinjector device. Thus, over 80% of teenagers in this cohort recovered spontaneously from symptoms (including loss of consciousness and difficulty in breathing) despite not receiving epinephrine [21].

Arguably, our greatest challenge is the inability to predict which patients, including those not previously known to be allergic, are most at risk of fatal reactions [22▪▪]: can the literature assist us in addressing this question? In this regard, it may be helpful to focus on data related to 'severe' or life-threatening anaphylaxis. However, what are the determinants of severity? Is it the reaction itself or the outcome of the reaction (which includes treatment and any homeostatic compensation by the allergic individual)? If an individual has anaphylaxis (with both respiratory and cardiovascular symptoms) but promptly receives a single dose of intramuscular epinephrine with good effect, is this still to be considered a severe reaction?

One approach to narrowing anaphylaxis literature to more severe reactions is to only include cases or reports which have case definitions requiring hospitalization, on the assumption that only severe cases need hospitalization. However, the decision to admit an individual peri and postanaphylaxis may depend not only on severity but also on local practice, individual healthcare professional, and patient preference, which may, in turn, be influenced by national guidelines. Arguably, near-fatal (requiring intensive care) or fatal anaphylaxis may be a more objective criterion of severity, but even here, many factors will influence an admission to ICU.

METHODOLOGICAL CHALLENGES IN GATHERING AND USING POPULATION-BASED ANAPHYLAXIS DATA

The use of different definitions of anaphylaxis and severe anaphylaxis is just one challenge in terms of

Table 1. Significant differences in the literature with regard to the pathophysiology of anaphylaxis in murine models and the mechanisms which may occur in humans

Murine models		Humans	References
1:4 to 1:10	Neutrophil:lymphocyte ratio in peripheral blood	2:1 to 1:1	[2]
Polymeric IgA (low serum levels) IgD, IgE, IgM IgG1, IgG2a, IgG2b, IgG3	Immunoglobulins	Monomeric IgA, two serotypes (IgA$_1$ and IgA$_2$), IgA$_1$ abundant in serum IgD, IgE, IgM IgG1, IgG2, IgG3, IgG4	[3]
Yes	High-affinity IgE receptor (FcεRI) on mast cells and basophils	Yes	[4]
No	FcεRI receptor on antigen-presenting cells	Yes	[4]
Yes	IgE-dependent anaphylaxis	Yes	[4]
Yes	IgG-dependent anaphylaxis	No evidence for IgG-mediated activation of human mast cells If present, likely to require very high levels of antigen exposure	[4,5■]
Very high: in murine models of peanut allergy, dose/weight equivalent to a human eating ≅1000 peanuts!	Allergen dose required through oral exposure to cause anaphylaxis	Very low doses (mg), for example, for peanut allergy, 10% of individuals react to 1/70 of a peanut	[6,7]
+	Sensitivity to histamine	++++	[8,9]
Yes	Anaphylaxis inhibited by H1-antihistamines	Little clinical evidence for this. Significant interspecies differences exist in histamine receptor pharmacology	[10,11,12]
Yes	Basophils secrete platelet-activating factor	Unclear	[13,14]

deriving accurate anaphylaxis-related data. Different methodologies are used in the literature; many studies use self-report, which may overestimate the true incidence by at least a factor of 10 [23]. Further confusion may arise from variations in the use of epidemiological terms. 'Incidence' is the number of 'new' cases occurring during a given time period in a defined population, but many studies do not distinguish between those having their first 'ever' episode, and others with previous anaphylaxis who have a further anaphylaxis within the study period (and are therefore, strictly speaking, not 'new' cases). Identification of cases by medical coding systems, such as the ICD-10 system, is a common methodological approach, but is prone to misclassification [23,24]. Retrospective data collection is

Table 2. Current descriptions of anaphylaxis in the literature

EAACI [15]	WAO [16]	AAAAI/ACAAI [17]	ASCIA [18]	NIAID [19]
A severe life-threatening generalized or systemic hypersensitivity reaction An acute, potentially fatal, multiorgan system, allergic reaction	A serious life-threatening generalized or systemic hypersensitivity reaction A serious allergic reaction that is rapid in onset and might cause death	An acute life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity that results from the sudden release of mediators from mast cells and basophils	Anaphylaxis is a serious, rapid-onset, allergic reaction that may cause death Severe anaphylaxis is characterized by life-threatening upper airway obstruction, bronchospasm, and/or hypotension	Anaphylaxis is a serious allergic reaction that involves more than one organ system (e.g. skin, respiratory tract, and/or gastrointestinal tract). It can begin very rapidly, and symptoms may be severe or life-threatening

subject to incomplete reporting and recall bias. Determining causality of anaphylaxis can be challenging, particularly for reactions because of medication/iatrogenic causes where medicolegal concerns may affect reporting. Population-based datasets are hampered by a large proportion of uncoded, 'unspecified' causes of anaphylaxis [25■,26,27■,28■]. Using stricter criteria to define anaphylaxis (e.g. admission to intensive care) reduces the number of cases, resulting in the same challenges as those encountered in defining the epidemiology of rare diseases, where very large sample sizes are needed. It also has the likelihood of skewing trigger data toward those where exposure more commonly occurs in the hospital setting (such as parenteral medications and contrasts agents) and avoids severe cases where resolution occurs prior to admission or results in a fatal outcome. Prospective collection of data, for example, through case registries, is susceptible to similar issues regarding the case definition, and in any event is unlikely to include all cases [22■■].

Both anaphylaxis and fatal anaphylaxis commonly occur in the community and not in a medical setting, so the circumstances of reaction and description of symptoms are usually acquired from nonmedical witnesses, further complicating categorization. Using data from national death registries and coroner's reports to attribute cause and risk factors is particularly problematic. In these instances, reports of symptoms are second-hand and usually entered into coroner's reports by the attending police official. Despite these shortcomings, data registries and admission statistics remain a valuable source of information which can provide insights into at risk populations.

WHAT DO WE KNOW ABOUT THE EPIDEMIOLOGY OF SEVERE AND FATAL ANAPHYLAXIS?

Fatal anaphylaxis is a rare occurrence. Estimates of all-cause fatal anaphylaxis rates across the United Kingdom [25■], the United States [26,27■], and Australia [28■] over the past 2 decades range from 0.064 to 0.099 deaths per 100 000 population per annum. These rates are likely underestimates; however, the true extent of misdiagnosis (such as acute severe asthma and coronary infarct) and miscoding is unknown. In a European anaphylaxis registry, only 5.5% of 1155 cases of severe anaphylaxis (laryngeal oedema, bronchospasm, cyanosis, shock) involved cardiorespiratory arrest [29]. In a subsequent paediatric series from the same registry, 1.3% (26/1970) cases involved life-threatening or fatal reactions (five cases) [30■].

Rates of hospital admissions for anaphylaxis are reported to have increased in the United Kingdom [25■], the United States [26], Canada [31], and Australia [28■,32] over the past 2 decades; however, an increase in all-cause fatality rates has only been observed to date in Australia not the United Kingdom [25■], Canada (Ontario) [33], or the United States [27■]. There was a seven-fold increase in the UK hospitalizations for (all-cause) anaphylaxis from 1992 to 2012 (using government hospital datasets), but no significant increase in fatalities over the same time period (0.047 cases per 100 000 per annum) [25■]; a similar pattern has been reported in the United States, with a modest annual increase in all-cause hospitalizations between 1999 and 2009 of 2.2% but not fatalities [27■] (Table 3). In contrast, an analysis of government hospital and death registry datasets in Australia found an increase in both hospitalizations and all-cause fatalities: admissions increased almost four-fold (from 5.0 to 19.2 per 100 000 population) between 1997 and 2013, with a near doubling of fatalities (0.05 to 0.09 cases per 100 000) over the same time period [28■]. In both the United States and Australia, an increase in fatalities because of medication-related anaphylaxis has been reported [27■,28■]. This may, in part, reflect the significant changes in prescription and intraoperative/intervention practice such that at-risk individuals are being exposed to more medications and contrast agents.

Despite a worldwide focus on increasing food allergy prevalence, the most frequent cause of reported anaphylaxis-related deaths across Europe, the United Kingdom, North America, and Australia is medication [25■,26,27■,28■,29,30■,31]. Although anaphylaxis to food is relatively common, fatal food-triggered anaphylaxis is rare, with a reported incidence of 1.35–2.71 per million person-years [34]. The community focus on food allergy deaths may, perhaps, be explained by the fact that in children and young adults, food is the commonest cause of severe anaphylaxis and these deaths appear, at least superficially, to be the most preventable.

FOOD ANAPHYLAXIS: POPULATIONS AND INDIVIDUALS AT RISK

Children and young adults are proportionately overrepresented in food-related anaphylaxis admission and fatalities. In the recent UK, US, and Australian reports, young people under 19 years accounted for 4.8 to 15.8% of total fatalities, but only 0–3.4% of those because of medication deaths and 0–1.6% because of insect stings [25■,27■,28■]. The trend is similar for admissions [25■,26,28■]. Australia has a

Table 3. Rates of hospitalization and fatalities (per 100 000 population per annum) in the United Kingdom, the United States, and Australia

	The United Kingdom [25▪]			The United States [26,27▪]		Australia [28▪,32]	
	1992	1998	2012	1999–2001	2008/2010	1997	2013
All-cause anaphylaxis							
Hospitalizations	1.0	3.7	7.0	2.1 [26]	2.5 [26]	5.0	19.2
Fatalities	0.036	0.043	0.054	0.076 [26]	0.071 [26]	0.054	0.099
Anaphylaxis: food							
Hospitalizations	ND	1.2	2.4	0.61 [26]	0.83 [26]	1.6	8.9
Fatalities	0.010	0.012	0.012	0.003 [26]	0.004 [26]	0	0.009
				0.005 [27▪]	0.005 [27▪]		
Anaphylaxis: venom							
Hospitalizations	ND	0.09	0.46	ND	ND	ND	ND
Fatalities	0.008	0.008	0.005	0.009 [26]	0.009 [26]	0.027	0.013
				0.013 [27▪]	0.010 [27▪]		
Anaphylaxis: medication							
Hospitalizations	ND	0.78	1.4	ND	ND	1.4ᵃ	4.4
Fatalities	0.018	0.026	0.028	0.013 [26]	0.013 [26]	0.005	0.013
				0.027 [27▪]	0.051 [27▪]		

ᵃData for 1999.
ND, no data available.

higher rate of reported hospitalization because of food anaphylaxis than elsewhere. However, the rate of fatal food anaphylaxis is similar to the United Kingdom (Table 3), and the rates for both regions are almost double that reported for the United States. It is interesting to speculate on the possible reasons for this. Accurate reporting of admissions data may be responsible for some differences. The prevalence of food allergy appears higher *per se* in Australian children [35] and could account for the differences in admission rates, whereas perhaps lack of health insurance is a disincentive for hospitalization (rather than observation in emergency only) in the United States. The differences in fatality rates – if not because of incorrect attribution of causality or miscoding – could be related to the differences in the management of anaphylaxis between regions, or possibly some underlying environmental protective factor. This reinforces the need to establish accurate national fatality registries for anaphylaxis-related deaths.

An emerging trend is the differences in risk for fatal anaphylaxis by racial/ethnic origin: African-American heritage was a significant risk factor for fatal anaphylaxis because of food more than other causes in the United States [27▪], and has also been associated with increased asthma mortality [36]. Whether this is because of inequalities to healthcare or some predisposing factor is unclear. Within the UK Fatal Anaphylaxis Registry, there is an excess

of deaths in male children because of cow's milk allergy in families of African, Middle East, or Far East descent [20]. In a retrospective analysis, Buka *et al.* [37] found a higher rate of severe anaphylaxis in British children from families of South Asian descent, an observation that was not because of confounding by socioeconomic deprivation. Differences in the prevalence of peanut allergy have been observed amongst infants where parents are born in Asia versus Australia [38], although whether this is associated with a more severe phenotype is unclear.

Another emerging trend in fatal anaphylaxis to food has been a change in the triggering allergen. Traditionally, peanut has been thought to cause most deaths; however, other allergens are now seen to be as likely to cause severe reactions. In the United Kingdom, cow's milk is now the commonest cause of fatal anaphylaxis in children [25▪]; in Australia, seafood is now the most common food allergen implicated in fatal food-induced anaphylaxis, although peanut remains the most common cause of death in children [28▪].

A history of asthma is common in cases of fatal food anaphylaxis [25▪], more so than for other causes of anaphylaxis [27▪,28▪]. However, in the UK registry, many cases of fatal food anaphylaxis did not have a history of increased symptoms or reliever use (implying a change in asthma control) prior to the fatal event. Around 50% of children

[39,40] and up to 25% of adults [29,41] with food allergy have asthma, yet the vast majority will never have a fatal allergic reaction; thus, the utility of asthma as a predictor for fatal reactions is poor, although this does not negate the value of improving asthma control as an important strategy in risk management.

VENOM

It is noteworthy that in North America and the United Kingdom, the rates of severe anaphylaxis because of venom appear to be falling [25■,26,27■,33]. Rates of venom fatalities in Australia have been relatively stable since 1997, with no significant decrease, but importantly have not increased in line with food and medication-related fatalities [28■]. The reason(s) for this are unknown, but may be related to a falling population ('colony collapse') for bees that has occurred over the last decade, something also now affecting the wasp population in the United Kingdom [42]. Species-specific data relating to the proportion of venom anaphylaxis are lacking, and in any event, it can be very difficult to identify the responsible insect for most cases of insect-related anaphylaxis. The Central European Registry reports wasp to be the most common trigger for venom-induced anaphylaxis, presumably on the basis of investigations performed as a workup toward desensitization [43]; however, in Australia Honey Bee, not wasp, accounts for the majority of both venom immunotherapy prescriptions [44] and fatalities because of insect anaphylaxis [28■]. Curiously, venom is the most common cause of anaphylaxis in adults in the European Registry [29], despite the fact that the national datasets report anaphylaxis to medications are more common. This may be explained by the fact that many allergic reactions because of medications are not referred to allergy clinics, where healthcare professionals would then submit these data to the registry. In contrast, venom anaphylaxis is a common referral condition because of the widespread availability of desensitization protocols which can significantly reduce the adverse impact of the diagnosis on health-related quality of life [45,46].

In the United States [27■] and Australia [28■], fatal anaphylaxis to insect venom is significantly more common in middle-aged adult men. In the United States, it is further associated with being white, and in Australia, a rural setting, and upright posture during anaphylaxis (e.g. being driven seated in a car to a healthcare facility) were identified as apparent significant risk factors for death from insect allergy [28■]. Upright posture is likely to be a risk factor for other anaphylaxis-related fatalities

[20] excluding contrast and anaesthetic agent deaths (hence many anaphylaxis management plans specify keeping patients supine during treatment and observation). Its prominence in Australian insect fatalities are likely related to stings in remote (often rural/farm settings), where transportation to medical assistance is often not by ambulance in the first instance.

DRUG/IATROGENIC CAUSES

Defining the epidemiology of severe anaphylaxis for this group of triggers is particularly challenging because of underrecognition, limited reporting, and possible concerns as to medicolegal consequences. The majority of anaphylactic reactions because of iatrogenic causes occur in older age groups [24,26,28■,47], often in patients with comorbidities such as coronary artery disease, obesity, and chronic obstructive airways disease [28■]. Whether this is because of reverse causality is unknown; in a large series of anaphylaxis presenting to emergency departments, cardiovascular disease (and use of anti-hypertensives) was significantly associated with age but conferred no additional predictive value for severe reactions on logistic regression analysis [48■]. A similar age distribution is reported for Korea [49] and the United Kingdom. Hospital admissions for drug-induced anaphylaxis increased from 0.78 to 1.4 per 100 000 population per annum over the period 1992–2012, predominantly in the 60+ age group. The mean age of fatal cases because of drugs/iatrogenic causes was 58 years (95% confidence interval, 56–61 years), with fatalities rare in those under 40 [25■]. In the United States, fatal drug-induced anaphylaxis was significantly more common in African-Americans [27■].

The literature indicates that antibiotics (particularly β-lactams) and muscle relaxants are the primary identified causes of medication-related fatal anaphylaxis (Fig. 1) [50]. NSAIDs appear to be common triggers for all-cause and severe anaphylaxis, but less so for fatal anaphylaxis. This may be because of a different route of exposure, with NSAIDs commonly taken via the oral route. In a cohort from Korea, drug-induced anaphylaxis was independently associated with more severe anaphylaxis than other causes [49], a finding seen elsewhere [51]. This is often assumed to be because of a parenteral route of exposure; however, in a prospective Australian cohort of 315 cases of anaphylaxis presenting to the emergency department, both injected and oral drugs (predominantly antibiotics) were strongly predictive for hypotensive reactions [48■].

It is possible that many medication-related anaphylaxis hospitalizations and fatalities are coded as
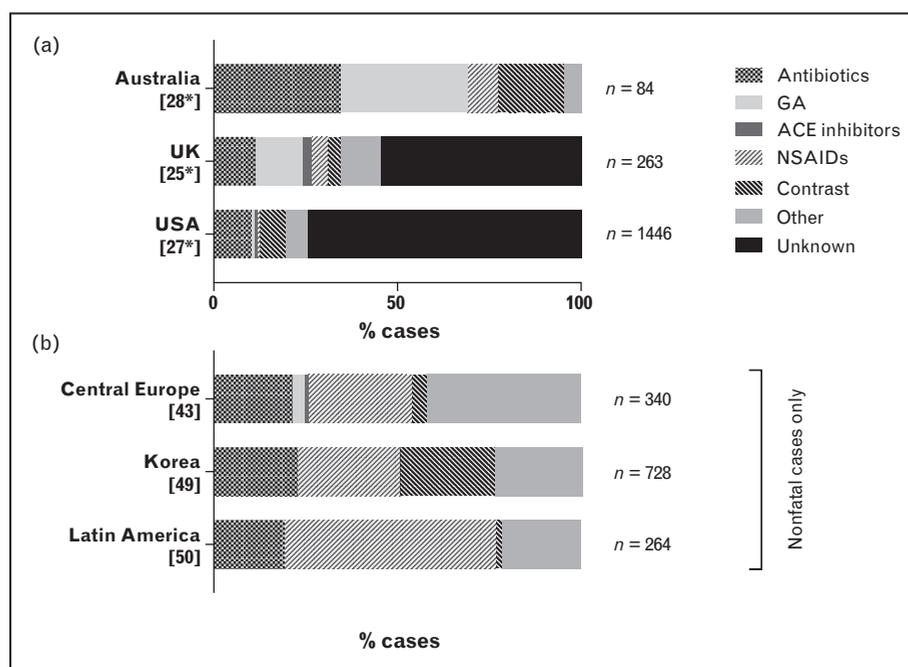
FIGURE 1. Triggering agents for medication-induced anaphylaxis from series of fatal reactions (a) and anaphylaxis registries (nonfatal reactions) (b). Reproduced with permission from [50].

'unspecified cause' in registries (from all regions), resulting in significant underreporting. This again highlights the need for a coordinated approach to the collection of high-quality accurate data to inform prescribing practice and identify risk factors so as to mitigate against serious allergic reactions and deaths.

Contrast agents are an important cause of anaphylaxis. Palmiere and Reggiani Bonetti [52] reviewed 34 fatalities because of contrast reported in the literature and a further eight cases in their own hospital network. Postmortem findings were nonspecific but consistent with an IgE-mediated mechanism. Of note, the vast majority of cases had their fatal event following a first exposure to the contrast agent; thus, the mechanism of primary sensitization remains unknown.

MAST CELL TRYPTASE AS A BIOMARKER FOR ANAPHYLAXIS

There is currently no reliable sensitive and specific biomarker for anaphylaxis or for risk of anaphylaxis. Anaphylaxis has been assumed to be largely mast cell or basophil mediated, usually involving an IgE-mediated mechanism, and although an elevated mast cell tryptase (MCT) is the most well known and used biomarker of recent anaphylaxis, it has poor sensitivity. Moreover, the value of MCT in attributing anaphylaxis, as the cause of death, is hindered by a lack of specificity in elevation of

MCT postmortem [53]. Individuals with a raised baseline MCT are known to be at increased risk for severe reactions to venom [54,55]; in a retrospective analysis in patients attending an allergy clinic in Spain, Fellinger et al. [56] reported a similar finding for other causes of anaphylaxis, although fewer than two-thirds of cases were because of insect stings. Whether a raised baseline MCT is an independent risk factor for anaphylaxis because of drugs is therefore unclear. Although Sahiner et al. [57] proposed that baseline MCT is of value in predicting severity of reactions in a small cohort of food-allergic children, the significant overlap between baseline MCT levels limits the conclusions which can be made.

LEARNING FROM EPIDEMIOLOGY?

It is noteworthy that in series of fatal anaphylaxis from the United Kingdom [25▪], the United States [27▪], and Australia [28▪], the age distribution varies significantly according to the eliciting agent. This raises important questions about differences in the pathogenesis of anaphylaxis between different triggers. The symptoms of anaphylaxis also vary according to trigger in fatal [20], severe (with hypoxemia and/or hypotension) [48▪], and nonfatal reactions [58]. Although cardiovascular compromise is common in severe reactions to drugs and insect venom [48▪,58], this is uncommon in food-triggered reactions, where life-threatening manifestations are

Table 4. Differences in the epidemiology and pathophysiology of anaphylaxis because of food versus nonfood causes

	Food	Medication/iatrogenic causes	Venom sting
Age distribution: anaphylaxis (all severity)	Most common in preschool children, less common in older adults	Predominantly older ages	All ages
Age distribution: fatal anaphylaxis	Young adults into fourth decade of life. Rare in younger children	Unusual until fifth decade of life	Fourth to sixth decade
Symptoms	Respiratory	Cardiovascular (respiratory less common)	Cardiovascular (respiratory less common)
Asthma/atopy	Common	Uncommon	Uncommon
Onset	Less rapid	Rapid	Rapid
Site of antigen presentation	Usually orogastric route	Usually parenteral route	Parenteral
Triggering threshold dose	++ Interperson variability (up to 4 log)	Poor data for medications	Less variability for insect stings
Mechanism	No or relatively modest increases in MCT generally observed	Increased MCT often seen	Increased MCT often seen
Sex	M=F	M=F	M>>F
Ethnic distribution	Possible higher risk in persons of Asian decent. My be more common in male children of African American decent	More common in persons of African-American decent	More common in Caucasians

MCT, mast cell tryptase.

generally because of laryngopharyngeal and/or respiratory compromise; where cardiovascular arrest occurs, this is generally secondary to respiratory arrest [20]. Children with food-related anaphylaxis tend to present with respiratory and not cardiovascular symptoms [59]; this may give rise to delays in the use of epinephrine in those presenting with anaphylaxis [60].

On one level, the differences in symptoms with differing triggers might be predicted given the routes of exposure; parenteral allergens (e.g. venom, nonoral medication) result in rapidly systemic exposure, and therefore might be expected to cause cardiovascular involvement more than food allergens which need to be absorbed across the orogastrointestinal mucosa. However, this explanation may be too simplistic. Food allergens such as peanut can be rapidly absorbed through the buccal mucosa resulting in plasma levels sufficient to trigger a systemic effector cell response [61]. Furthermore, there is some evidence to suggest that severe allergic reactions to oral medication (such as antibiotics) frequently cause cardiovascular manifestations – in common with parentally administered medication in terms of symptoms elicited – rather than

respiratory involvement seen with food-triggered anaphylaxis, despite the fact that gastrointestinal absorption is still required [48■]. The epidemiological data therefore raise the possibility that food-induced anaphylaxis might not have the same pathophysiologic basis as anaphylaxis caused by other triggers (Table 4). In this context, it is interesting to note that MCT is often 'not' increased in severe/fatal food-induced anaphylaxis [62,63], and when observed, the increase is generally more modest than that seen in severe anaphylaxis because of other, nonfood triggers [48■,63]. Evaluating this prospectively through mechanistic assessments might lead to important advances in our understanding of determinants of severity in food-allergic individuals.

CONCLUSION

Anaphylaxis is not uncommon and appears to be increasing in North American, the United Kingdom, and Australia. Fatal anaphylaxis remains a rare occurrence, but the fear of such a reaction, particularly to food triggers, is widespread. Lack of universal definitions, underreporting, miscoding,

misdiagnosis, and lack of robust national data collecting systems hinder the interpretation of current data. Our current lack of knowledge about the mechanisms of anaphylaxis further impairs our capacity to understand why different allergic triggers are associated with different presentations, risk factors, and age/sex susceptibilities.

Given the worldwide trends for increasing rates of anaphylaxis to food and medication, there are significant implications for future fatality trends with an ageing population accumulating comorbidities such as cardiovascular disease and diabetes. An improved ability to accurately gather and analyse population-level anaphylaxis and fatal anaphylaxis data in a harmonized fashion is required so as to ultimately improve risk assessment and management.

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Conflicts of interest

There are no conflicts of interest.

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

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■■ of outstanding interest

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