REVIEW ARTICLE

Anaphylaxis: past, present and future

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Abstract

Anaphylaxis is a clinical emergency, and recent reports suggest increased prevalence. A diverse set of primary genetic and environmental influences may confer susceptibility to anaphylactic reactions. Anaphylaxis presents diagnostic and therapeutic challenges. It often manifests with a broad array of symptoms and signs that might be similar to other diseases. The management of anaphylaxis consists of emergency treatment of acute episodes as well as preventive strategies to avoid recurrences. Treatment is complicated by its rapid onset and progression, presence of concurrent diseases or medications, and need for long-term allergen avoidance. Health care professionals must be able to recognize the signs of anaphylaxis, treat an episode promptly and appropriately, and provide preventive recommendations. Recognizing the gaps in our understanding and management of anaphylaxis may help identify promising targets for future treatment and prevention and areas that require further study.

The term anaphylaxis stems from the Greek words ανα *ana* (against) and φυλαξις *phylaxis* (protection) and was first coined by Professor Charles Robert Richet in 1902, Nobel Prize Winner for Medicine and Physiology, and by Dr Portier to describe a set of symptoms that was the opposite of immunity(1). Arthus was the first to experimentally describe anaphylaxis in rabbits, and Auer in 1911 expanded these initial observations and concluded that lethal anaphylaxis in experimental models of rabbits is caused by heart failure associated with impaired coagulation. He also suggested that anaphylaxis can be diagnosed only when an exposure to a previously tolerated substance causes severe symptoms and signs on subsequent exposure and implicates that a certain factor is responsible for these deleterious effects of the second exposure (2). It took almost six decades until the crucial role of IgE and mast cells in anaphylaxis in both animal models (3) and man (4) was elucidated.

The majority of anaphylaxis cases in humans were initially reported to occur in those exquisitely hypersensitive to horse serum, penicillin (5) or insect stings (6), while food-related cases were rarely reported before the last three decades. Further, although it was well recognized that epinephrine favorably combats the allergic reaction (7), it was only at the beginning of this century that it was finally established that IM epinephrine should be used as first-line treatment for anaphylaxis (8, 9).

In this review, we seek to highlight current knowledge and concepts regarding the definition, pathophysiology, diagnosis, and management of anaphylaxis as well as some of the current gaps regarding its understanding and treatment. Finally, we indicate potential future research directions that might bridge these gaps.

Current definitions

Based on the World Health Organization (WHO) definition, anaphylaxis is a severe, life-threatening generalized or systemic hypersensitivity reaction (10). However, this definition can be problematic given that the term 'life-threatening' may be interpreted differently by health care providers. A recent meeting in the US sponsored by the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) has established a consensus definition to satisfy epidemiological, research, and

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clinical needs. According to this definition, anaphylaxis is considered likely if any one of the following three criteria is satisfied within minutes to hours (Table 1) (9).

Anaphylaxis mediated by IgE, IgG, complement, or immune complexes is defined as immune-mediated anaphylaxis *vs* nonallergic anaphylaxis (previously known as an anaphylactoid reaction) (10).

Prevalence and incidence (Table 2)

The American College of Allergy, Asthma and Immunology Working Group has concluded that data on anaphylaxis incidence and prevalence are sparse, often imprecise, and may underestimate the true incidence of anaphylaxis. This is a direct result of the absence of a universal consensus on the definition of anaphylaxis, inadequate International Classification of Diseases (ICD) codes, and incorrect use of the terms prevalence and incidence in reports of anaphylaxis (11–14).

Prevalence and incidence estimates may be based on data collected from Emergency Medical Services (EMS) systems (15), emergency department (ED) or hospital admissions (11, 13, 16), visits to allergists (17), all medical records obtained from residents of a specific area (18, 19), and analysis of epinephrine auto-injectors (EAI) prescriptions (20). Each of these has potential limitations.

In a study on EMS-reported anaphylaxis rates in 10 US states and one Canadian city (Toronto), it was found that in nine EMS system databases, totaling over 2.8 million runs, between 0.34% and 0.82% of the runs were for allergy/anaphylaxis, and roughly 0.5% were for allergy/anaphylaxis complaints, with epinephrine administered in roughly one-tenth of these. A significant limitation of the manuscript was the lack of standardization of case definitions among sites (15).

Table 1 Definition of anaphylaxis

1. Acute onset of illness with cutaneous and/or mucosal involvement AND at least one of the following:
a. Respiratory compromise (e.g. dyspnoea, bronchospasm, stridor, hypoxia)
b. Cardiovascular compromise (e.g. hypotension, collapse)
2. Two or more of the following occur rapidly after exposure to a likely allergen (minutes to several hours):
a. Involvement of skin or mucosa (e.g. generalized hives, itch, flushing, swelling)
b. Respiratory compromise
c. Cardiovascular compromise
d. Or persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
3. Hypotension after exposure to known allergen for that patient (minutes to several hours): age-specific low blood pressure† or greater than 30% decline from baseline (or less than 90 mm Hg for adults).

†Hypotension for children is defined as systolic blood pressure <70 mm Hg from 1 month to 1 year, <(70 mm Hg+[2Xage]) from 1 to 10 year, and <90 mm Hg from 11 to 17 year.

Reports from Australia suggest that the incidence of anaphylaxis based on ICD codes is as high as 1 per 1000 ED presentations (14). Studies determining rates according to hospital admissions suggest a much lower estimate of 10.8 per 100 000 hospital admissions in Australia (21) or 36 per million of population in the UK (22). Limitations include diagnostic coding inaccuracies, inclusion of only admitted cases (11, 21, 22) and reliance on a single hospital's database, which might not be representative of the national data (14). A retrospective study in Korea between 2000 and 2006 on anaphylaxis, including inpatients, outpatients, and ED visitors in the Seoul National University Hospital, reports a rate of 0.014% during the study period (23). Evaluating anaphylaxis cases in allergy clinics provides mainly information regarding triggers, associated factors, and use of epinephrine, but is less useful in providing prevalence or incidence estimates, because of the selection bias associated with such studies (17).

Reports on the incidence of all provider-diagnosed anaphylaxis are extremely rare. A study on children and adolescents enrolled at a health maintenance organization in Seattle between 1991 and 1997 aimed at determining anaphylaxis incidence based on confirmation of data collected from automated databases and chart review using the ICD-9 codes of anaphylaxis and related diagnosis. This study estimates an incidence of 10.5 episodes per 100 000 person-years. The authors noted that the majority of episodes were treated in the ED and concluded that anaphylaxis in this population was frequently diagnosed as another related condition such as allergic urticaria or angioneurotic edema (13).

In the US, two reports on the prevalence of anaphylaxis in Olmsted County, Rochester, Minnesota were published. The first, conducted by Yocum et al. in 1999, was a retrospective population-based cohort study in which the medical records of 1255 Olmsted County residents identified by computer-linked, medical diagnostic indices were reviewed retrospectively to identify residents whose clinical episodes met the criteria for anaphylaxis (18). The definition of anaphylaxis in this study differed from the current proposed definition (Table 1) as it required one symptom of generalized mediator release, such as flushing; pruritus or paresthesias of lips, axilla, hands, or feet; generalized pruritus; urticaria or angioedema; and conjunctivitis or chemosis. In addition, the authors required involvement of at least one of the following systems: oral and gastrointestinal, respiratory, or cardiovascular. The reported average annual incidence rate of anaphylaxis was 21 per 100 000 person-years (18). A more recent retrospective 10-year report on all providers of medical care to residents of Olmsted County suggests that the incidence of anaphylaxis is as high as 49.8 per 100 000 person-years (19). Consistent with other reports (22, 24), this group reports an increase in the annual anaphylaxis incidence rate from 46.9 per 100 000 persons in 1990 to 58.9 per 100 000 persons in 2000 (19). The definition of anaphylaxis in this study was comparable to that of Yocum et al. and differed from the recently suggested definition (Table 1), but the authors state that re-analyzing the data using the NIAID/FAAN criteria did not significantly affect the findings. Although this study

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Table 2 Anaphylaxis rates

Study	Country	Publication year	Anaphylaxis rate (%)	Data collection method	Comments	References
Kane et al.	US, Canada	2004	0.5	EMS	Per all runs during the study follow-up period	(15)
Braganza et al.	Australia	2006	0.1	ED	Per ED presentations of patients under 16 years attending one pediatric hospital in Australia over 3 years	(14)
Gupta et al.	UK	2007	0.0036	ED	Per population	(22)
Poulos et al.	Australia	2007	0.01	ED	Per hospital admissions	(21)
Yang et al.	Korea	2008	0.014	ED, inpatients and outpatients visitors	Per all patients who visited the Seoul National University Hospital in 2006	(23)
Boros et al.	Australia	2000	0.59	Parent report of anaphylaxis in children registered in the South Australian DETE system and participating in the study (2% of the total population of children enrolled at DETE sites)	Per participating children	(26)
Simons et al.	Canada	2002	0.95	EAI dispensing rates	Per the entire Manitoba population during a 5-year period	(20)
Kemp AS	Australia	2003	0.18	EAI Jr dispensing rates in children less than 10 years.	Per the entire Australian children population (younger than 10 years)	(25)
Bohlke et al.	US	2004	0.01	All care-providers data	Per participants of a Group Health Cooperative in Seattle between 1991 and 1997	(13)
Yocum et al.	US	1999	0.021	All care-providers data	Per residents of Olmsted County	(18)
Decker et al.	US	2008	0.049	All care-providers data	Per residents of Olmsted County	(19)

US, United states; EMS, Emergency Medical Services; ED, Emergency Department; UK, United Kingdom; DETE, Department of Education, Training and Employment; EAI, epinephrine auto-injector; EAI Jr, EAI Junior.

attempts to obtain a true population-based estimate of anaphylaxis incidence, it is retrospective and is limited to the predominantly white, middle class population of Olmsted County (19).

Studies estimating the incidence of anaphylaxis in Canada based on real-time prescription information for EAI have been published (20). Estimates based on EAI prescription in Manitoba, Canada suggest that during a 5-year period, 0.95% of the population had an EAI dispensed for out-of-hospital treatment. There were substantial variations in EAI dispensing rates across subsets of the population, ranging from 1.44% for individuals younger than 17 years of age, to 0.90% for individuals 17–64 years of age (inclusive), to 0.32% for those aged 65 or older (20). However, EAI may be an unreliable marker of anaphylaxis as exemplified by reported disparities between EAI prescriptions and estimated anaphylaxis rates. Studies in Australia, for example, report a current crude rate of EpiPen provision of one per 544 children (25), which is way below the estimated prevalence of anaphylaxis (one in 166 children), possibly because of under-distribution of EAI (26). In addition, EAI may be prescribed for food-related allergic reactions that do not necessarily meet the definition of anaphylaxis.

A common conclusion in the majority of studies, regardless of study design or geographic area, is that the rate of anaphylaxis has increased during the last decades. This is reflected by higher report rates for anaphylaxis in all age groups in recent years (11, 21, 22). This increase may be as high as 350% for food-induced anaphylaxis and 230% for nonfood-induced anaphylaxis over the last decade (11).

Given the disparities in different studies using different methodologies and the lack, until recently, of worldwide accepted definition of anaphylaxis, future prospective studies based on the recent consensus definition are required to better estimate anaphylaxis incidence and prevalence.

Triggers

The three principal immunologic triggers of anaphylaxis are foods, insect stings, and drugs, although the relative contribution of each of these to anaphylaxis may differ according to the study design, study population, or geographic area. Foods are reported to be primary inciting allergens for anaphylaxis and account for 33.2–56% of all anaphylaxis cases (27). Further, food-induced anaphylaxis hospital admissions are reported to have increased, mainly in the first two

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decades of life (28). Peanut and tree nut account for the majority of severe reactions (18), but fish and shellfish are also reported to cause severe reactions, especially in Asia (29) and parts of Europe (30).

In studies conducted in the US, insect stings are the second leading culprit for anaphylaxis and account for 18.5% of anaphylactic cases, followed by medications (13.7%) (19), mainly β-lactams (8), but more recently, biologic modifiers such as infliximab, omalizumab, and cetuximab (31) have been implicated in anaphylaxis. However, insect stings (32) or drugs (23) are reported to be the leading cause of anaphylaxis in other studies. Other less common triggers include latex, immunotherapy, cleaning agents, and environmental allergens (19).

Nonimmunologic triggers include exercise, cold exposure, radiocontrast materials, and opioids. It should be noted that the 20% of anaphylaxis cases in which no trigger is identified are considered idiopathic anaphylaxis (8).

Clinical presentation

Anaphylaxis symptoms involve several organ systems including the skin, causing mainly urticaria (80–90% of episodes), respiratory tract (70% of episodes), gastrointestinal tract (30–45% of episodes), cardiovascular (10–45% of episodes) and central nervous system (10–15% of episodes) (8, 32).

In 10% of anaphylaxis cases, there are no cutaneous symptoms, and in 4% of cases, there is bradycardia, especially in association with insect sting anaphylaxis (33). Cardiovascular symptoms are more common in events occurring in the operating room and are associated mainly with muscle relaxants and latex (8). Unusual manifestations include syncope alone (reported in patients with mastocytosis) and seizures (8, 31). Prolonged episodes with hypotension can trigger disseminated intravascular coagulation characterized by massive activation of coagulation and fibrinolytic enzymes that may result in depletion of platelets and coagulation factors (consumption coagulopathy). Platelet-activating factor (PAF) released from mast cells may play an important role in this process (34).

Biphasic allergic reactions, defined as a second reaction occurring 1–72 h after initial recovery (9), were reported in 11% of children presenting with anaphylaxis to a pediatric ED (35). Biphasic reactions account for 25% of cases of fatal and near-fatal food reactions and 23% of drug/biologic reactions, but they occurred in only 6% of anaphylaxis of mixed causes and are uncommon with insect stings. Biphasic reactions rarely occur without initial hypotension or airway obstruction (36).

Up to 20% of those presenting with anaphylaxis have a second episode, and 5% have a third event. The median time of presentation with a second episode is 395 days (19). Peanut/tree nut accidental ingestion is the most common trigger associated with recurrences (37). Recurrences occur mainly in women and are not necessarily associated with a history of atopy (37).

Anaphylactoid reactions are usually less severe and can thus be prevented with premedication (38). High osmolar (ionic) contrast material triggers anaphylactoid reactions in about 10% of patients receiving it and low osmolar in 1% of patients. Fatality is rare and comparable between high and low osmolar contrast agents (8).

There are several proposed grading systems for anaphylaxis severity. Brown developed a system based on the premise that unequivocal compromise of either the cardiovascular or respiratory system defines a severe reaction (39). According to this grading system, it was found that in older age groups, insect venom and iatrogenic causes were independent predictors of severity and that preexisting lung disease was associated with an increased risk of hypoxia (39).

Factors influencing the incidence of anaphylaxis

Numerous factors may affect the incidence of anaphylaxis:

Previous history of anaphylaxis

This is suggested to be the only known reliable predictor of future anaphylaxis (40). However, at least 25% of adults (41) and 65% of children (42) presenting with anaphylaxis do not report a previous episode.

Atopy

Atopy is common in subjects who experience anaphylaxis, regardless of its origin. The extracellular cytokine milieu associated with atopic diseases may contribute to the increased risk of an anaphylactic reaction (12). However, some studies suggest that atopy does not confer an additional risk of anaphylaxis (40).

Socioeconomic factors

Studies suggest an increased number of episodes in higher socioeconomic populations (12).

Gender

In adults, anaphylaxis is more common in women potentially because of estrogens enhancing mast cell activation and allergic sensitization as was shown in an animal model (17, 43). However, in studies estimating anaphylaxis incidence in children, males predominate (12).

Geography

Recent studies suggest higher rates of anaphylaxis in northern *vs* southern areas. These are mainly based on EAI distribution data (44). It has been suggested that this north–south gradient might be because of differences in vitamin D status (44).

Season

In the US, anaphylaxis peaks between July and September (when the leading culprit is insect stings) (19). The Practical

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Allergy (PRACTALL) meeting held by researchers from the American Academy of Allergy, Asthma and Immunology and the European Academy of Allergology and Clinical Immunology underscored the importance of relevant clinical factors including age, comorbid conditions (e.g. asthma, mastocytosis, and ischemic heart disease), medication use, or strenuous exercise as these may increase the risk of anaphylaxis and/or fatality (45).

Genes potentially involved in anaphylaxis (Table 3)

In addition to the environmental influences discussed earlier, studies suggest that a complex of genes affects the anaphylactic response. Anaphylaxis is reported to be associated with several gene groups including genes affecting the anatomic barrier, genes associated with the innate immune system in general and mast cells in particular, and genes associated with the adaptive immune system. The function of some of the genes implicated in the pathogenesis of anaphylaxis is described in the following paragraphs:

Genes affecting the anatomic barrier and allowing sensitization

Filaggrin

Filaggrin gene defects increase the risk of developing allergic sensitization, atopic eczema, and allergic rhinitis. Restoring skin barrier function in filaggrin-deficient people in early life may help prevent the development of sensitization and halt the development and progression of allergic disease (46).

Innate system genes

NLRP3

Nucleotide-binding domain and Leucine-rich Repeat-containing (NLR) family pyrin domain containing 3 (NLRP3) controls the activity of inflammasomes, which leads to cleavage of the procytokines IL-1β and IL-18. Recent studies have shown associations of human NLRP3 polymorphisms with susceptibility to various inflammatory diseases including food-associated anaphylaxis. Two NLRP3 single-nucleotide

Table 3 Genes implicated in the pathogenesis of anaphylaxis

Group	Name of gene	Comments	References
Barrier genes	Filaggrin	Increased risk of developing allergic sensitization and not necessarily anaphylaxis	(46)
Innate immunity genes	NLRP3: SNPs (rs4612666 and rs10754558)	Significantly associated with susceptibility to food-induced anaphylaxis	(47)
Innate immunity and mast cells genes	C-KIT	Mutations associated with anaphylaxis after hymenoptera stings and may also underlie cases of idiopathic anaphylaxis	(48, 49)
	SWAP-70	Anaphylactic responses are strongly reduced in mice with mutations in this gene	(50)
	PAF V279F is found in more than 30% of Japanese subjects	Mutations increase the risk for various inflammatory diseases in Japanese subjects. PAF and PAF-AH activity affect severity of anaphylaxis	(51, 52)
	Sphk1	Sphingosine 1-phosphate receptors play a critical role in regulating human mast cell functions, including degranulation and cytokine and chemokine release	(53)
	Rcan	Rcan1 is a novel negative regulator in FcεRI-induced mast cell activation	(54)
	CCRL2	Enhance tissue swelling and leukocyte infiltrates	(55)
Adaptive immunity	STAT-6 (13/15-GT repeat heterozygosity and the 15GT repeat homozygosity)	Polymorphisms higher in children in the Japanese population with allergic disease	(56)
	IL-4 (Ile75Val variant of IL-4Rα gene)	Polymorphisms of IL-4 have been implicated in drug allergy especially in women	(58, 59)
	IL-10 (−819 C > T and −592 C > A variants)	Polymorphisms of the IL-10 promoter have been associated with β-lactam anaphylactic reactions	(58, 59)
	IL-13, 18 (promoter polymorphisms in IL13 -1055, IL18 -607 and IL18 -656)	Latex allergy phenotype was significantly associated with polymorphism in the promoter site of these cytokines	(60–62)
Unknown function	DOCK8	Absence of DOCK8 protein associated with severe atopy and anaphylaxis	(63)

NLRP3, NLR (Nucleotide-binding domain and Leucine-rich Repeat-containing) family pyrin domain containing 3; SNP, single-nucleotide polymorphism; PAF, platelet-activating factor; PAF-AH, PAF-acetylhydrolases; Sphk1, sphingosine kinase; Rcan, regulators of calcineurin; FcεRI, Fc epsilon receptor I; CCRL2, chemokine (CC motif) receptor-like 2; STAT-6, signal transducers and activators of transcription 6; IL, interleukin; IL-4Rα, IL4 receptor alpha; DOCK8, dedicator of cytokinesis 8.

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polymorphisms (rs4612666 and rs10754558) were significantly associated with susceptibility to food-induced anaphylaxis (47).

Mast cells genes

C-KIT. The concomitant presence of systemic reactions (especially anaphylaxis) after hymenoptera stings and increased tryptase levels are reported to be associated with a clonal mast cell disease characterized by a C-KIT mutation, usually involving exon 17, with the imatinib-resistant type D816V being most frequent (48). C-KIT mutations may also underlie cases of idiopathic anaphylaxis (49).

SWAP-70. Mast cells express the unusual phosphatidylinositol 3-kinase (PI3K)-dependent, Rac-binding protein SWAP-70. It was shown that IgE-mediated passive cutaneous and systemic anaphylactic responses are strongly reduced in mice with mutations in the SWAP-70 gene although no similar studies are reported in humans (50).

PAF. Platelet-activating factor is a phospholipid that acts as a mediator of inflammation, and rapid degradation of PAF by intracellular and extracellular PAF-acetylhydrolases (PAF-AH) is one of the mechanisms regulating the level of PAF. The most common loss-of-function mutation in PAF-AH, V279F, is found in more than 30% of Japanese subjects and is thought to be a risk factor in various inflammatory diseases (51). Further, studies reveal that serum PAF levels were directly correlated, and serum PAF-AH activity was inversely correlated with the severity of anaphylaxis (52).

Sphingosine kinase (*Sphk1*). It was also reported that susceptibility to *in vivo* anaphylaxis is determined both by sphingosine-1-phosphate (S1P) within the mast cell compartment and by circulating S1P generated by mammalian Sphk1 predominantly from a nonmast cell source(s) (53).

RCan. A new family of regulators of calcineurin (Rcans) has been shown to modulate calcineurin activity. Rcan1 was identified as an endogenous negative regulator in FcεRI-mediated signaling and mast cell degranulation. Accordingly, Rcan1 deficiency was shown to result in increased passive cutaneous anaphylaxis *in vivo* in mice (54).

CCRL2. Chemokine (CC motif) receptor-like 2 (CCRL2) is an orphan receptor with homology to other CC chemokine receptors. It was shown that the mast cell-expressed orphan serpentine receptor mCCRL2 can enhance tissue swelling and leukocyte infiltration in mice (55).

Genes affecting the adaptive system and IgE production

STAT-6

The signal transducers and activators of transcription 6 (STAT-6) protein is a key transcription factor involved in both IL-4- and IL-13-mediated biologic responses. It was found that the dinucleotide repeat polymorphism of the STAT6 exon 1 (13/15-GT repeat heterozygosity and the 15GT repeat homozygosity) was higher in children in the Japanese population with allergic diseases (bronchial asthma, atopic dermatitis, and/or food-related anaphylaxis) compared to controls (56).

Interleukin-4 (*IL-4*)

IL-4 is an essential cytokine for isotype switch of B cells to IgE. In mice and human beings, IL-4 has been associated with drug allergy in a small number of genetic studies of penicillin allergy (57). Polymorphisms of IL-4 have been implicated in drug allergy especially in women with the Ile75Val variant of IL-4Rα gene (58, 59).

IL-10

IL-10, produced by T_H2 cells and macrophages, is thought to inhibit T_H1 cytokine production and to promote B-cell survival, proliferation, and differentiation. Polymorphisms of the IL-10 promoter have been associated with β-lactam anaphylactic reactions especially the −819 C > T and −592 C > A variants in some studies, but not consistently (58, 59).

IL-13 and IL-18

A significant positive association was also reported between atopic disease and the IL-13 promoter -1055 TT genotype, a polymorphism that results in an increase in IL-13 protein production through putative dysregulation of IL-13 transcription (60). IL-18 is a proinflammatory cytokine, which strongly induces IFN-gamma production. IL-18 has been implicated in atopic dermatitis, and IL-18 -137 and -607 promoter polymorphisms have been associated with altered cytokine expression (61). In line with this, the latex allergy phenotype was significantly associated with promoter polymorphisms in IL-13 -1055, IL-18 -607, and IL-18 -656 (62).

Genes with unknown function

Novel homozygous or compound heterozygous deletions and point mutations in the gene encoding the dedicator of cytokinesis eight protein (DOCK8) led to the absence of DOCK8 protein in lymphocytes. Most patients had severe atopy with anaphylaxis (63).

Pathophysiology (Fig. 1)

Mast cell activation through either IgE-mediated mechanisms or through non-IgE-mediated mechanisms results in the release of preformed mediators such as histamine, heparin, tryptase, chymase, carboxypeptidase A3, tumor necrosis factor α (TNFα), and cathepsin G, and newly formed mediators such as PAF, PGD_2, leukotriene C_4, cytokines such as IL-5, IL-6, IL-8, IL-13, TNFα, and GM-CSF and chemokines such as MIP-1α, MIP-1β, and MCP-1 (64) and possibility also activated kallikrein (65).

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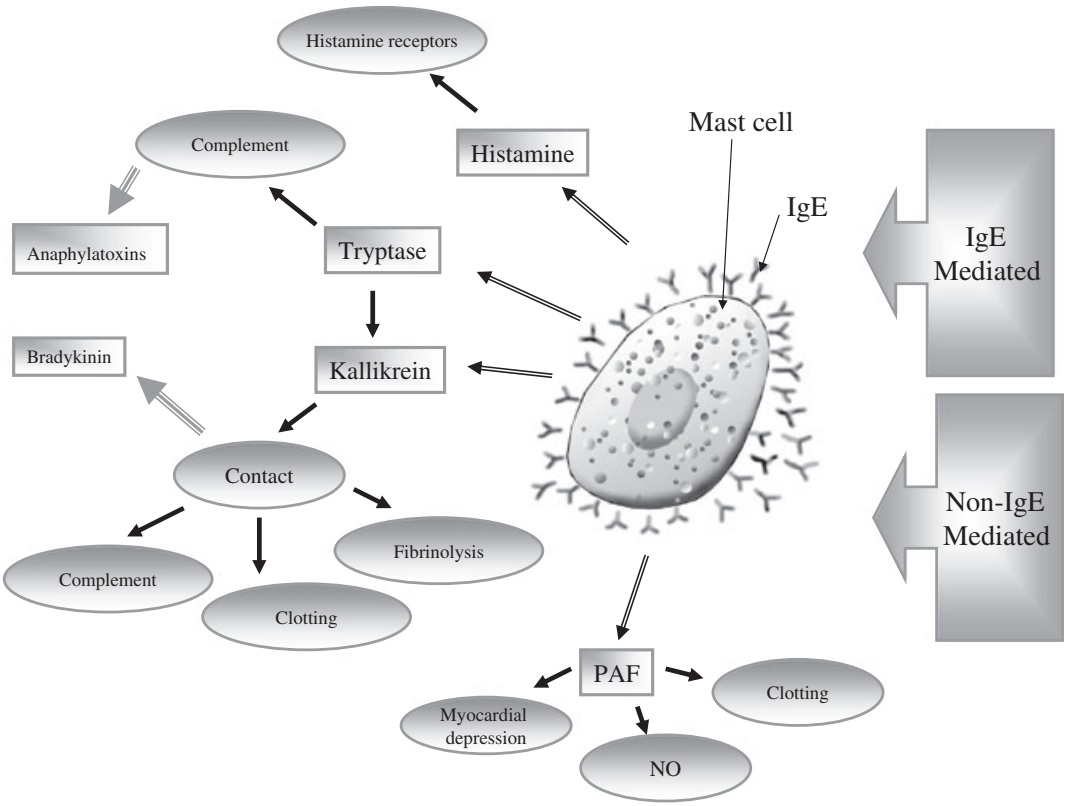

Figure 1 Anaphylaxis pathogenesis. Because of space limitation not all mast cell mediators and their effects are depicted in the figure.

Histamine actions are mediated through the H1–H4 receptors leading to coronary vasoconstriction and cardiac depression (H1-receptor), systemic vasodilatation and tachycardia (H2-receptor), inhibition of norepinephrine release (H3-receptors) and possibly chemotaxis and mediator release by inflammatory cells (H4-receptors) (66). Heparin (67) and possibly tryptase activate prekallikrein (68) and the contact system (69) with subsequent release of bradykinin and activation of the clotting and complement systems. Tryptase also activates the complement system directly (64). Of the newly formed mediators, PAF has been suggested to play a major role in anaphylaxis. Platelet-activating factor decreases coronary blood flow and myocardial contractility, increases activation and recruitment of neutrophils and eosinophils, and induces local and systemic platelet aggregation as well as peripheral vasodilatation and severe hypotension possibility through the induction of NO (70).

Because of the physiologic changes induced by an anaphylactic reaction, compensatory mechanisms are activated including increased secretion of neuroepinephrine as well as activation of the renin–angiotensin–aldosterone system. These compensatory mediators may also have negative effects. Activated cardiac mast cells contain and release renin that results in local activation of the renin–angiotensin system. Mast cell chymase as well as plasma kallikrein also contribute to the production of renin (71). The angiotensin II that is produced induces norepinphrine secretion from local sympathetic nerve endings potentially leading to cardiac arrhythmias (71, 72).

Diagnosis

Anaphylaxis remains a clinical diagnosis; identification of specific triggers relies on a careful history supplemented by confirmatory testing including prick skin tests, allergen-specific IgE, and if necessary, allergen challenges. However, this review will focus on laboratory tests that might help establish the diagnosis of anaphylaxis itself, including the following:

Tryptase and histamine levels

Currently, total tryptase and histamine are the only anaphylaxis markers measured in clinical laboratories. The commercially available fluorescence immunoassay measures both α- and β-tryptase. The baseline serum level in the absence of an allergic or anaphylactic reaction is considered an indicator of the whole body mast cell load and, if elevated, may indicate the presence of systemic mastocytosis (normal threshold levels are up to 10 ng/ml). An increase in serum tryptase level within 1–5 h after the first symptoms of a suspected systemic hypersensitivity reaction characterizes IgE-mediated anaphylaxis (8).

In contrast, histamine levels are less useful for anaphylaxis assessment as elevated levels last only 1 h after the onset of

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symptoms, and special handling of the blood sample is required. However, histamine metabolites in the urine can last up to 24 h and may serve as a useful anaphylactic marker (31).

In regard to food-induced anaphylaxis, tryptase measurement may be less useful as mucosal tissue mast cells contain less tryptase compared to connective tissue mast cells and consequently when an antigen is ingested and binds to mucosal mast cells, usually less tryptase is released (31).

Basophil activation tests

Newer tests for anaphylaxis evaluation include determining CD63 and CD203 expression in active basophils (73) (through flow cytometry) and PGD2 levels (74).

Assessing PGF2 and carboxypeptidase levels could help establish the diagnosis in cases of mastocytosis given that these mediators are selectively localized in mast cell granules (31).

Differential diagnosis of anaphylaxis

Several clinical conditions may present with clinical features suggesting anaphylaxis including vasovagal reactions, flushing syndromes, respiratory or cardiovascular diseases, poisoning, mast cell clonal disorders, and psychogenic conditions.

Vasovagal reactions are probably the most common condition masquerading as anaphylaxis. These reactions usually are not associated with urticaria and dyspnea, the skin is typically cool and pale, and the heart rate is low. However, as noted previously, bradycardia following an initial tachycardia may occur in anaphylaxis as well, mainly in association with venom allergy (75). Patients with comorbid conduction defects or using sympatholytic medications may present with bradycardia rather than tachycardia during an anaphylactic reaction.

Flushing syndromes should be considered in the differential diagnosis of anaphylaxis. These may be either wet, i.e. associated with sweating (e.g. postmenopausal state or spicy foods) or dry flushing syndromes (e.g. metastatic carcinoid). The 'alcohol flushing response,' (76) sometimes as an indicator of underlying malignancy, may present with flushing, nausea, and tachycardia after drinking alcohol. Up to 36% of East Asians may experience this response, predominantly because of an inherited deficiency in the enzyme aldehyde dehydrogenase 2 (76).

Pulmonary embolism, asthma and paradoxical vocal cord motion, foreign body aspiration, acute poisoning, hypoglycemia, and seizure disorders may also present with features similar to an anaphylactic reaction. Mastocytosis, hereditary angioedema, and psychiatric disorders such as acute anxiety can also contribute to diagnostic confusion (8). In addition, anaphylaxis has been described in association with the acute coronary syndrome, 'Kounis Syndrome' (77).

Management of anaphylaxis

The keys to the management of anaphylaxis are rapid diagnosis, implementation of primary and secondary prevention measures (Table 4) to a known allergen and prompt administration of intramuscular epinephrine (8).

Primary anaphylaxis prevention is based on allergen desensitization through immunotherapy. In the case of food allergies, desensitization remains experimental and is not yet used in routine clinical practice. There are currently no known guidelines describing the optimal candidate for desensitization or the safest and most effective dosing schedule. Food allergen immunotherapy through the oral or sublingual routes might be less risky than subcutaneous (78). Significantly increased thresholds to food-induced allergic reactions after oral immunotherapy was described in 100% of those with milk (79–81) and egg allergy (82) and more than 90% of those with peanut allergy (83). A recently described desensitization protocol to milk consisted of administration of increasing amounts of milk at weekly intervals at the clinic under medical supervision. The starting dose was one drop of milk, doubled every week to achieve a total intake of 200 ml in approximately 4 months (79). Encouraging results have also been described with hazel-nut (84), milk (80), and peach (85) sublingual immunotherapy. It is likely that the nature of this increased threshold is transient and reflects desensitization rather than true tolerance given that avoidance of these foods was shown to increase sensitization as well as to lower the threshold of subsequent reactivity (81, 83). The efficacy of the immunotherapy, extent of desensitization *vs* tolerance, and the quantity/frequency of allergen consumption required to maintain this effect are currently unknown.

Secondary prevention measures for food-associated anaphylactic reactions include patient/caregiver education on strict allergen avoidance and the need for Medic-Alert bracelets and EAI. It was recently shown that among food-allergic individuals who experienced an accidental exposure, almost 47.0% attributed at least one such event to inappropriate food labeling for allergens, 28.6% to failure to read a food label, and 8.3% to ignoring a precautionary statement (86). These results are consistent with other studies suggesting that a significant proportion of accidental exposures are because of both manufacturer and consumer error (87). Improved product labeling must be combined with enhanced consumer education on the constant necessity to scrutinize food labels for allergens.

The development of rapid desensitization for the treatment of drug hypersensitivities is aimed at providing essential medications while protecting patients from IgE and non-IgE hypersensitivity reactions. Desensitization for type I hypersensitivity reactions in penicillin-allergic patients was first developed more than 50 years ago (88). Other empiric protocols were developed to treat hypersensitivity reactions to essential drugs that could not be substituted, such as antibiotics (89–102), allopurinol (103), aspirin (104) and clopidogrel (105), insulin (106), chemotherapy agents (107, 108), and biologics (109, 110). Secondary prevention relies mainly on identification of allergic patients, avoidance of the culprit drug and drugs that cross-react and use of a Medic-Alert bracelet (8).

Regarding insect sting–induced anaphylaxis, immunotherapy is a common practice for hymenoptera sting–allergic

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Table 4 Primary and secondary prevention measures for main anaphylaxis triggers†

Trigger	Primary prevention	Route of desensitization	References	Secondary prevention	References
Foods	Milk	PO, SL	(79–81)	Avoidance of allergenic food; education of allergic individuals and their care givers on importance of avoidance, improved labeling of pre-packaged foods for allergens, wearing of Medic-Alert bracelet stating specific food allergy	(86, 87)
	Egg	PO	(81, 82)		
	Peanut	PO	(83)		
	Tree nut	SL	(84)		
	Peach	SL	(85)		
Drugs	β-lactams (penicillin, cephalosporin)	PO, IV,	(88–92)	Avoidance of the culprit drug and drugs that cross-react, Medic-Alert bracelet	(8)
	Carbapenem	IV	(93, 94)		
	Macrolides	PO	(95)		
	Vancomycin	IV	(96)		
	Anti-tuberculosis drugs (isoniazid, rifampin, and ethambutol)	PO	(97)		
	Fluoroquinolones.	IV, PO	(98, 99)		
	Clindamycin	PO	(100)		
	Sulfamethoxazole	PO	(101, 102)		
	Allopurinol	PO	(103)		
	Aspirin	PO	(104)		
	Clopidogrel	PO	(105)		
	Insulin	SC	(106)		
	Chemotherapy	IV, IP	(107, 108)		
	Biologic modifiers (e.g. rituximab, infliximab, trastuzumab, and interferon)	IV, SC	(109, 110)		
Insects	Bee/wasps/mixed vespid	SC, SL	(111–113)	Avoidance of bright clothing and perfume and sites where wasps are likely to congregate. Removal of stinger in the case of honeybees. Use of bait insecticides or growth regulators or conventional insecticides for fire ant control and wearing socks	(116–119)
	Fire ant	SC	(115)		
	Bee venom + omalizumab	SC	(114)		

PO, per os; SL, sublingual; SC, subcutaneous; IV, intravenous; IP, intraperitoneal.
†Only the most common foods, drugs, and insect desensitization approaches are mentioned.

patients and may be used according to a conventional, cluster (111), rush (112), or ultrarush (113) schedule. Protocols have been developed, which incorporate omalizumab to attenuate adverse effects (114). Recently, a successful 1-day immunotherapy protocol for fire ant was reported in three cases less than 3 years of age (115). Secondary prevention measures include avoiding bright clothing and perfume and sites where wasps are likely to congregate such as picnic grounds. It is also suggested that the allergic individual be extremely careful to avoid bees and wasps in the immediate vicinity (e.g. not walking with exposed feet, not drinking directly out of cans, covering food) (116, 117). Fire ants can be controlled by bait or conventional insecticides (118). In addition, wearing socks was reported to provide protection from fire ant stings (119).

Although epinephrine is the only effective first-aid treatment of anaphylaxis, studies of fatal food-induced anaphylaxis have documented that epinephrine is not usually given soon after the onset of symptoms or after exposure to an offending trigger (14). Further, studies suggest that most physicians are not clear about current anaphylaxis treatment guidelines, particularly the recommended dose and route of administration of epinephrine (120).

Because delay in administration of epinephrine is associated with poor outcome in anaphylaxis and because the benefits of epinephrine administration far outweigh the risks in otherwise healthy individuals (14), EAIs such as EpipenTM, Epipen Jr.TM, and Twinject® should always be prescribed for those diagnosed with a known anaphylactic trigger and must be self-carried at all times (8, 9, 117). However, studies indicate that the rate of EAI prescription is low across different settings: pediatric and military hospitals (121, 122), general community practices (hospital or office-based) (123), and EDs (124). Among those identified with anaphylaxis in the ED, 33–97% are discharged home (124–126). On dismissal, only 16–33.6% (124, 126) are prescribed an EAI, and rates of referral to an allergist vary between 0% and almost 80% (18, 126). Epinephrine administration in the ED and insect sting as the inciting allergen were significantly associated with EAI prescription, while being less than 18 years was associated with referral to an allergist (126). Another study found that

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medical residents were significantly less likely to prescribe an EAI compared to more senior staff (122). Among those prescribed an EAI, mainly those older than 55 years and those seen at an outpatient clinic compared to those seen in the ED fill the prescription (127). It is also worth noting that even in those prescribed EAI and filling the prescription, it is not always self-carried. Our group has recently reported that among children with peanut allergy living in Quebec, less than 50% self-carry the EAI while at school (128). Lack of anaphylaxis management plans in schools is another factor contributing to poor management (129).

There are no contraindications to epinephrine administration for an anaphylactic reaction, and it is prudent to administer epinephrine in uncertain situations when someone may not yet meet the diagnostic criteria for anaphylaxis but was exposed to a known trigger. Adverse effects because of unintentional injections are considered rare, but nonetheless occur. In a recent study based on databases of the American Association of Poison Control Centers and the Food and Drug Administration's Safety Information and Adverse Event Report System, it was shown that between 1994 and 2007, 60% of 15 190 unintentional EAI injections occurred between 2003 and 2007. The median age was 14 years, and 85% were injected in a home or other private residences. Injuries resulting in permanent sequelae were rarely reported, and currently there is no consensus regarding treatment of these cases (130). Improving EAI design and developing better training programs and guidelines for monitoring the capability of those prescribed an EAI to correctly use it are clearly required.

Following administration of epinephrine, all patients should be transported to a medical facility, given the potential for a biphasic reaction and the attendant requirement for additional treatment (8). Airway, breathing, and circulation should be continuously monitored with continuous pulse rate oximetry and potentially arterial blood gas measurements. Any patient with respiratory distress or hypoxia should be placed on supplemental oxygen. An inhaled $[\beta]_2$-agonist may benefit the patient in respiratory distress. In severe or refractory reactions, intubation and mechanical ventilation may be required. Patients with poor circulatory status, hypotension, or anaphylactic shock should receive aggressive fluid resuscitation. H_1 and H_2 antagonists are considered second-line treatment of anaphylaxis (9). Potent vasopressors, such as norepinephrine, vasopressin, or metaraminol, could be used in cases of hypotension refractory to epinephrine and fluid resuscitation (9). Corticosteroids have never been shown in placebo-controlled trials to affect the course of anaphylaxis or prevent biphasic reactions (131), but may treat related diseases such as asthma and allergic rhinitis, and have been incorporated into algorithms of anaphylaxis management (8, 9).

Methylene blue was suggested to be beneficial in cases of severe refractory anaphylactic shock potentially because it reduced NO production and subsequent vasodilatation (132). Methylene blue treatment may be particularly useful in cases of anaphylactic shock characterized by high PAF levels in which NO is thought to play a major role (70).

The use of β-blockers might complicate the treatment of anaphylaxis (133). In cases of anaphylaxis occurring in patients using β-blockers and when epinephrine is ineffective in the management of hypotension, IV glucagon should be given (9). Other drugs reported to be associated with increased severity of anaphylactic reactions include angiotensin-converting enzyme inhibitors (134), angiotensin II receptor blockers (135), and drugs with α-adrenergic receptor-blocking activity (thioridazine and amitriptyline), which antagonize the action of epinephrine in anaphylactic collapse (136). An equally effective substitute less associated with severe anaphylaxis should be used when possible (133). There are also concerns regarding epinephrine use in patients treated with monoamine oxidase inhibitors because of potentially increased stimulation of the sympathetic system (137).

Idiopathic anaphylaxis is a corticosteroid-responsive condition, and patients are advised to use an H_1 antagonist daily and have an EAI and prednisone available at all times. Frequent idiopathic episodes (≥6 per year/≥2 in the last 2 months) are treated prophylactically with prednisone and H_1 antagonists (138).

Fatal outcome

In the UK, severe anaphylaxis is fatal in 0.65–2% of cases (139), resulting in 1–3 deaths per million people annually. Death usually occurred within the first hour after development of anaphylaxis (139). Fatality rate estimates in Australia are 0.64 deaths per million population per year (11). The annual death rate for anaphylaxis in Florida based on ICD codes on death certificates was 5.02/10 000 000. Death from anaphylaxis in Florida was more likely to occur in older individuals (above 65 years), in an ED, and during March and April and July and August (140). The main causes of fatal anaphylaxis in Australia, Turkey, Korea, and Shanghai are drugs (23, 141, 142), while in the UK and the US, the main factor is reported to be food allergy (mainly nuts) (142). The differences may be because of varying ecologic and/or dietary exposures and differences in data retrieval methodologies.

Temporal trends in anaphylaxis deaths in Australia reveal low or decreased mortality rates from food- and insect sting–induced anaphylaxis, respectively, and increased mortality rates from drug-induced anaphylaxis (11).

Risk factors for food-induced anaphylaxis fatalities include age 10–35 years, active asthma, peanut allergy, ingestion of food prepared outside of the subject's residence, and delayed administration of epinephrine. Risk factors for drug-induced anaphylaxis fatalities include age 55–85 years, presence of respiratory or cardiovascular comorbidities, and use of antibiotics or anesthetic agents. Risk factors for insect sting–induced anaphylaxis deaths include age 35–84 years and male sex (11). Upright posture has been found to be associated with anaphylaxis death in general (33).

Gaps and future directions in anaphylaxis research

Anaphylaxis is a life-threatening condition, and although there have been important advances, significant gaps regard-

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ing its epidemiology, pathogenesis, diagnosis, and treatment still remain. Data regarding the epidemiology of anaphylaxis including prevalence rates are sparse, mainly retrospective, and do not use a consensus definition.

Studies on the pathogenesis of anaphylaxis elucidated important mechanisms, regarding in particular the emerging role of mediators such as PAF, DOCK8, and S1P. Although it is still unclear from these advances how genetic and environmental factors interact, they may contribute to new diagnostic and therapeutic strategies. Genetic analysis of NLRP3, PAF, S1P, SWAP70, and Rcan1 polymorphisms may emerge as laboratory markers of those at risk for severe anaphylaxis and provide new venues for anaphylaxis management.

Preventive measures that have recently shown promise include allergen nonspecific and allergen-specific immunotherapy. Allergen nonspecific measures include a traditional Chinese medicine, Guo Min Kang, that was shown in mice models to suppress type I hypersensitivity reactions (143), and the use of nonspecific functional foods aimed at normalizing the Th1/Th2 imbalance and decreasing IgE antibody production. The latter include substances such as Curcuma aromatica (144). Future directions should include initiation of randomized, placebo-controlled studies comparing new methods of desensitization to existing strategies. These include modification of allergen dose or extract (145), addition of biologic modifiers to reduce side-effects (146), and exploring new routes of delivery (147). Finally, given the disparities in anaphylaxis management at the level of physicians, patients and the community, new laws, guidelines and educational programs addressing these gaps, and ensuring appropriate treatment of anaphylaxis should be developed and disseminated among all potential care givers. Studies exploring and monitoring the efficacy of such approaches are needed.

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