

REVIEW

Anaphylaxis: mechanisms and management

J. K. Lee and P. Vadas

Division of Allergy and Clinical Immunology, St Michael's Hospital, University of Toronto, Toronto, ON, Canada

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Summary

Anaphylaxis is a serious allergic reaction that can be rapid in onset and occasionally fatal. This is a review of the literature on the epidemiology of anaphylaxis, diagnostic criteria, mechanisms, and management. This current review of the literature is intended for clinicians, trainees, and researchers as a comprehensive review of anaphylaxis with a focus on incorporating the latest advances in the field.

Correspondence:

P. Vadas, Division of Allergy and Clinical Immunology, St Michael's Hospital, University of Toronto, Toronto, ON, Canada M5B 1W8.

E-mail: vadasp@smh.ca

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Introduction

The prevalence of allergic disease is increasing, as is the frequency of allergic reactions, ranging from mild to fatal anaphylaxis. Anaphylaxis is an ever-evolving area of active research with substantial insights made particularly in recent years. This article is intended to provide an overview of the pathogenesis of anaphylaxis based upon the current state of knowledge so that patients can receive the highest quality of evidence-based care. The review of the literature focuses on the latest evidence as it pertains to anaphylaxis in the areas of:

- Definitions
- Epidemiology
- Fatal anaphylaxis and risk factors
- Pathophysiology and mechanisms
- Clinical diagnosis and differential diagnosis
- Investigations
- Fatal anaphylaxis and risk factors
- Treatment
- Prevention and education

Methods

In compiling this review the authors used the search terms of 'anaphylaxis' and 'anaphylactoid' to search for all

relevant papers as they pertain to the specific areas of focus outlined above. The search was conducted on Ovid Medline database from 1948 to March week 3, 2011 limited to the English language. A parallel search using the PubMed was performed to find any potentially missed publications. All relevant references from articles were also examined and information included if it was felt to be pertinent. Please refer to Appendix S1 for details of the search.

Definition

Anaphylaxis as a clinical entity is difficult to define as there is heterogeneity in terminology, criteria, and definitions as was highlighted at the National Institutes of Allergy and Infectious Disease, the Food Allergy and Anaphylaxis Network joint Symposia, the World Allergy Organization (WAO) [1–3]. Moreover previous studies have included diverse patient populations as well as varying methodologies of data collection [4–6]. Generally, the consensus is that anaphylaxis is a severe form of allergic reaction that is rapid in onset and if left untreated may cause mortality [1].

Since 1959, several classification systems have been used for anaphylaxis such those by Mueller [7] and Brown [8]. The older criteria classify a patient experiencing urticaria and localized angioedema of the face as

experiencing anaphylaxis. In contrast, with the more recent consensus definition, a diagnosis of anaphylaxis is made if there is respiratory or cardiovascular involvement during an allergic reaction. A consensus definition of anaphylaxis adopted and widely agreed upon [3, 9] was proposed by Sampson et al. [1] and presented below.

Anaphylaxis is present when any one of three conditions exist:

1. Acute onset of an illness (defined as from minutes to several hours) with involvement of skin and/or mucosal tissue (e.g. generalized urticaria, pruritus, flushing, swollen upper airway) with at least one of the following:
 - a. Respiratory compromise [e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia]
 - b. Reduced blood pressure or associated symptoms of end-organ dysfunction [e.g. hypotonia (collapse), syncope, incontinence].
2. Two or more of the following rapidly occurring symptoms (minutes to several hours) following exposure to a likely allergen for the patient in question:
 - a. Involvement of the skin-mucosal tissue (e.g. generalized urticaria, pruritus, flushing, swollen upper airway)
 - 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 the patient in question (minutes to several hours):
 - a. Infants and children: low systolic BP (age specific) or > 30% decrease in systolic BP (low systolic blood pressure for children is defined as: < 70 mm Hg from 1 month to 1 year; < [70 mm Hg + (age × 2)] from age 1 to 10 years, and < 90 mm Hg from 11 to 17 years)
 - b. Adults: systolic BP of < 90 mm Hg.

Criterion 1 encompasses the majority of anaphylaxis as most reactions include cutaneous manifestations [8, 10–12]. Examining the aforementioned criteria does bring to light the fact that cutaneous manifestations are not always found in anaphylaxis. In fact, cutaneous manifestations may be absent in 20% of anaphylaxis, particularly when it involves intra-operative anaphylaxis in adults [13, 14] and food or insect stings in children [15–17]. Furthermore in rapidly occurring anaphylaxis such as those that occur in the operating room, cutaneous signs may only appear after the normalization of BP. In fact cutaneous manifestations are often absent in patients with fatal or near-fatal anaphylaxis [16].

As per the new WAO guidelines, anaphylaxis in this paper will be defined as meeting the clinical criteria above [3]. As such anaphylaxis will encompass reactions under the term anaphylactoid. The use of the term 'anaphylactoid' to describe non-IgE-mediated reactions is discouraged by the European Academy of Allergology and Clinical Immunology [13, 18]. It is worth noting that the Joint Task Force on Practice Parameters representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma, and Immunology; and the Joint Council of Allergy, Asthma, and Immunology continues to make a distinction between anaphylaxis and anaphylactoid in their latest anaphylaxis practice parameter published in 2010 [9]. Anaphylaxis and anaphylactoid reactions are often clinically indistinguishable.

Epidemiology

Population-based studies estimate the incidence of anaphylaxis in western countries in the range of approximately 4–50 per 100 000 person-years [4, 6, 19–23]. True lifetime prevalence is difficult to study but it appears to be increasing and in the range of 0.05–2% [24, 25]. Admission figures provide another clue. Admissions data from national databases of Australia and the United Kingdom reveal a population prevalence of 8.0 per 100 000 and 3.6 per 100 000, respectively, in these countries [19, 20]. These numbers are thought to underestimate the true population prevalence of anaphylaxis as admission for anaphylaxis is uncommon and as many as 57% of anaphylaxis are either unrecognized or not labelled in the emergency department as anaphylaxis [26, 27]. Generally, it has been well documented that the incidence of anaphylaxis over the past few decades has been doubling or more [20, 28–30]. The highest number of incident cases is in children and adolescents [25, 29].

The prevalence of anaphylaxis is increasing rapidly throughout the world for reasons that are not completely understood. A UK study found a sevenfold increase (from 5/million to 36/million) in hospital admissions for anaphylaxis over a 15-year period between 1990 and 2005 [19]. In comparison, a US study for anaphylaxis admissions showed an increase from 17 to 42/million New Yorkers aged 0–20 years from 1994 to 2005 [29]. In this US study, males were more likely to be hospitalized (risk ratio 1.45; 95% confidence interval, 1.26–1.66) and blacks were not disproportionately hospitalized [29, 30].

Children appear to be having a disproportionate increase in food-induced anaphylaxis. In Australia, children aged 0–4 years had a fivefold increase (from 39 to 193/million) in hospital admissions for food-induced anaphylaxis over a 10-year period [20].

As noted above, demographic characteristics of persons suffering fatal vs. non-fatal anaphylaxis is an area of

active research interest. In general, there are an estimated 500–1000 fatalities in the United States per year [31]. In the United Kingdom, the anaphylaxis mortality prevalence estimate is 0.33 deaths per year per million population for all causes [32, 33]. In Australia, a country known to have a higher prevalence of atopy including asthma [34–36] the mortality rate is nearly double with an estimated 0.64 deaths per year per million population [20, 28].

Liew et al. [28] reported that death from food-induced anaphylaxis in Australia occurred predominantly in females aged 10–35 years. Conversely, 95% of deaths from insect anaphylaxis occurred in males and primarily occurred in ages 30–84 years [28]. Drug-induced anaphylactic fatalities were more gender neutral and peaked in middle age or older individuals [28, 37]. Of concern is the apparent increase in the incidence of drug-induced anaphylaxis [28] particularly as biologic therapies become more widely used [38–42]. Moreover, with increased use of diagnostic radiocontrast media there are an increasing number of reactions occurring [43]. On the other hand, these data show that deaths from food-induced anaphylaxis at least appears to be stable. Although one study on insect sting anaphylaxis showed that mortality has actually dropped 88 percent [28], there are issues with under recognition and under reporting of anaphylaxis deaths [33, 44–47]. In fact, across Britain [33], New Zealand [48], United States [49], and Australia [28] they may be stable with 20% of insect stings being fatal.

Cause of anaphylaxis

Causes of anaphylaxis differ in children from adults. Foods represent the most common cause of anaphylaxis in childhood. A recent retrospective study in the setting of a pediatric emergency department showed that 86% of presentations were due to allergic reactions to foods followed by reactions to medications and insect stings [50]. A prior history of anaphylaxis was seen in 14% of cases in this group with a diagnosis of other allergic disorders such as asthma, eczema, or allergic rhinitis seen in 60% [50]. In adults, medications are the most frequent culprit followed by reactions to stings and diagnostic agents [37]. Indeed, a retrospective study comparing fatal and non-fatal anaphylaxis in Australia over a 10-year period showed that age-specific hospitalization rates for food anaphylaxis were highest in the 0–4 age group (9.4/100 000 population) in contrast to drug-induced anaphylaxis which was highest for the 55–84 year age group (3.8/100 000 population) [28]. Of note in this study was the predominance of males in the < 15 year age group for both food and drug-induced anaphylaxis [28]. Another recent study on all anaphylaxis cases in the United States revealed that inciting agents were food (29.6%), insects (11.1%), medications (22.2%), others (7.4%), and

unknown (29.6%) [51]. It is worth mentioning that theoretically any food containing any protein may be implicated.

Among the foods, peanut appears to be the most common cause of food-induced anaphylaxis in the United States [29, 52]. Furthermore, it appears that peanut allergies were responsible for the highest rate (328%) of increase in anaphylaxis admissions in Australian children followed by shellfish (300%) [20]. Particularly troublesome is that these reactions tend to be severe and can occur with the first apparent ingestion in 74% of peanut reactions [53]. Likewise, tree nut reactions are also known to occur with the first recognized exposure in up to 68% of cases [53]. Accidental ingestion tends to cause more severe unexpected reactions and these typically occur outside the home [53]. This observation reinforces the need for parents and care givers to be adequately trained to recognize and treat these reactions wherever they may occur [54].

Fatal anaphylaxis in the United Kingdom was due to: medication (44%), food (31%), insect sting (23%), and other (4%) [32, 33]. This rank order is similar to an Australian study where death from anaphylaxis was due to: medication (57%), insect sting (18%), and food (6%) [20, 28]. Similarly coroner-derived data from a New Zealand city hospital mirrors this finding showing fatal anaphylaxis caused by medications, insect stings, and foods in 56%, 22%, and 11%, respectively [48].

Diagnostic agents and medications appear to be a growing cause of anaphylaxis [37, 55–57].

Recently it has been discovered that the world-wide supply of unfractionated heparin has been contaminated with over-sulphated chondroitin sulphate (OSCS) causing non-IgE-mediated anaphylactic reactions when given parenterally. OSCS directly activates the kallikrein pathway which in turn generates complement derived C5a and C3a anaphylatoxins leading to anaphylaxis (see 'Pathophysiology and mechanisms') [58].

It is worth noting that anaphylaxis to biologic agents such as monoclonal antibodies (mAbs), cytokines, and fusion molecules is increasing, which likely reflects their more widespread use. Both anti-murine and anti-idiotypic antibodies directed against mAbs have been identified [59–61]. The rates for anaphylaxis and IgE-mediated reactions to mAbs ranges from 0.6% of infusions for trastuzumab [62] to 2–3% for infliximab [63].

Other causes of anaphylaxis may be physical triggers. Cold-induced anaphylaxis is a well known phenomena wherein exposure to cold with or without core body temperature drops can trigger systemic anaphylaxis [64]. Variants may include anaphylaxis or dermographism occurring only with cold exposure [65]. In other patients, exercise alone is known to trigger anaphylaxis [66, 67] and in some, a combination of exercise in conjunction with food ingestion are required [68, 69].

Intrinsic risk factors

Risk factors can be approached via intrinsic patient factors and external factors not related to the patient.

Risk factors for anaphylaxis include the presence of other allergic conditions [14, 27]. The question of atopy as a risk factor is intriguing as it appears to be a risk factor in cases of orally administered agents, exercise, latex, radio-contrast, and idiopathic anaphylaxis. Atopy is not a risk factor for parenterally administered medications, suxamethonium, penicillin, insulin, and hymenoptera stings [70, 71].

Overall, female gender is a risk factor for anaphylaxis to latex, diagnostic agents, muscle relaxants, aspirin, and idiopathic causes [71–75]. It should be noted, however, that in another large study of the surgical patient population it appears that male patients were more susceptible to latex anaphylaxis [76].

Increased socio-economic status is associated with anaphylaxis [77].

Recently it has been suggested that a patient's geographic location may indeed be a risk factor for anaphylaxis due to variations in vitamin D levels [78, 79]. This was first alluded to by auto-injector prescription data showing a higher number of prescriptions per 1000 people in the United States in areas where there could potentially be lower sunlight exposure [78].

The types of symptoms that a patient is having may help identify high risk patients who may need to receive multiple doses of epinephrine injection [51]. This study again highlighted the fact that those with more severe anaphylaxis (those who required additional epinephrine dosing) were significantly less likely to have urticaria [51]. Features significantly associated with the requirement for repeated doses of epinephrine were wheezing and cough, hypotension and shock, stridor, cyanosis and laryngeal oedema, nausea and vomiting, and cardiac arrhythmias [51].

Determination of specific binding epitopes on an allergen such as peanut or milk in the future may potentially provide information for risk stratification as patients who have antibodies binding to stable linear epitopes may have more severe reactions as compared with those with IgE binding to conformational epitopes.

Extrinsic risk factors

The constancy of administration is a risk factor with regular dosing being less likely to trigger anaphylaxis [80–82].

The weather and seasons are known risk factors and largely relate to insect sting exposures [78, 83]. In addition the particular stinging insect species, and recent stings leading to mast cell or basophil priming are also extrinsic risk factors [24].

Extrinsic risk factors also include medications [β -blockers, ACE-I, ARBs, angiotensin inhibitors, ASA, and non-steroidal anti-inflammatory drug (NSAIDs)], as well as alcohol and exercise. Medications can predispose to anaphylaxis or interfere in the treatment of anaphylaxis. β -blockers interfere with the compensatory action of endogenous epinephrine release as well as with treatment with exogenous epinephrine [84]. β -blockers even in the form of topical ophthalmic drops may decrease the effects of endogenous or exogenous epinephrine at beta receptors [85, 86]. Similarly α -blockers may decrease the physiological effects at alpha receptors [87, 88].

ACE inhibitors appear to intensify allergic reactions to stinging insects [89, 90]. Angiotensin receptor blockers theoretically can also interfere in a manner similar to ACE inhibitors. However, ACE inhibitors may not be contraindicated in patients receiving venom immunotherapy. A single centre study of 157 patients receiving venom immunotherapy while on ACE inhibitors had no increase in their reactions [91].

Tricyclic anti-depressants can worsen anaphylaxis by preventing re-uptake of epinephrine in cells. Monoamine oxidase inhibitors (MAOI) may cause dangerous interactions with certain foods and drugs. These include hypertensive crises with sympathomimetic drugs and central excitatory syndromes with tyramine containing foods [92, 93]. As MAOIs act by increasing the concentration of noradrenaline in sympathetic nerve endings there is a concern that a hypertensive crisis can be triggered by the use of epinephrine in patients taking MAOI and in particular indirectly acting amines [92, 94]. Angiotensin converting enzyme inhibitors, and to a lesser extent, angiotensin II receptor blockers also may blunt the endogenous compensatory mechanisms and have been associated with more severe or prolonged symptoms [95]. These are all modifiable risk factors.

Fatal anaphylaxis and risk factors

The major causes of mortality in anaphylaxis were explored in a number of reviews [32, 33, 37, 96–98]. In descending order of frequency they were:

1. Asphyxia 45% (from lower and or upper airway)
2. Shock 41%
3. Unknown 9%
4. DIC 3%
5. Epinephrine overdose 2%

The severity of a previous reaction was not necessarily predictive of death [98], although it is predictive of severe reactions in the future.

The presence of recognized risk factors should enable clinicians to implement appropriate risk reduction and modification strategies [99, 100].

A prior anaphylactic event is often the forerunner of repeat anaphylaxis. However, it is well known that a previous mild allergic reaction does not preclude the possibility of anaphylaxis and even death in some cases. This concept was seen in a study of 83 children with peanut hypersensitivity in the United States that were followed for 5 years [101]. In this patient cohort, 12/17 (71%) patients who had experienced a life-threatening reaction had subsequent repeat life-threatening reactions [101]. In addition, 19/43 (44%) of patients who experienced a non-life-threatening reaction had a subsequent life-threatening anaphylactic event [101]. Another Australian pediatric study showed that only 14% of anaphylaxis admissions had a prior history of anaphylaxis [50]. In short, using past history of anaphylaxis as a screen for possible life-threatening anaphylaxis is insufficient.

Co-existent atopic disease may be a clinical predictor of anaphylaxis risk [50], particularly when it comes to peanut and tree nut allergies [102]. Asthma, especially poorly controlled asthma, is a well known risk factor for fatal anaphylaxis particularly if it is in adolescents and young adults [16, 28, 96, 103, 104]. It is recognized as a co-morbid condition in more than 90% of fatal anaphylaxis [16, 32, 96, 104]. In adults the presence of any respiratory co-morbid condition was seen in up to 17% of fatal anaphylaxis [28, 37].

Fatal anaphylaxis can be extremely rapid in that death can occur within minutes of ingestion of the allergen [16]. Early administration of epinephrine within 30 min of allergen ingestion is key to preventing fatal anaphylaxis [16]. Biphasic reactions can also be fatal and patients should always be discharged from hospital with epinephrine auto-injectors [16]. Biphasic reactions generally occur within 24 h but may recur days later [14, 105].

Underlying cardiovascular disease was documented in up to 33% of anaphylaxis fatalities [28, 37].

Curiously older age at first reaction is another clinical predictor of anaphylaxis risk in both children [106] who react to foods and adults who react to medications [28]. In the pediatric population, age more than 10 years at the time of the fatal anaphylaxis is noted in 54–65% of fatalities [96, 104]. In the adult population, 75% of fatalities from drug-induced anaphylaxis occurred in those 55–85 years of age [28].

For unknown reasons, 95% of insect sting anaphylaxis deaths occur in males [28].

A delay in access to epinephrine is also a prominent and consistent risk factor in fatal anaphylaxis as it seen in 80–87% of fatalities [16, 32, 37, 96, 97, 104].

Aside from patient-related factors mentioned, there are factors extrinsic to the patient. Chief among these is the allergen itself. Peanuts and tree nuts in particular are known to cause a disproportionate amount of anaphylaxis; these foods are identified as the causative agent in 38–81% of fatal anaphylaxis [96, 104]. The reasons for

this are unclear. Recently it has also been found that some patients experience severe delayed reactions to a newly identified carbohydrate allergen, galactose- α -galactose, in beef, pork, and lamb [107]. These patients had negative prick tests to commercial antigens but had positive prick and intra-dermal tests to fresh meat [107].

Also largely beyond a patient's control are hidden ingredients that can be consumed in unknown quantities and thereby lead to or contribute to severe anaphylaxis. These unrecognized routes of exposure were documented in a study of children and adolescents who had fatal or near-fatal anaphylactic reactions following accidental ingestion of either peanut, nuts, milk, or egg in candy, cookies, and pastry [16].

A study in the southern United States recently found that fatal anaphylaxis is more likely to occur in the months of March, April, July, and August [49].

A recent report identified platelet activating factor (PAF) acetylhydrolase deficiency as an independent risk factor for severe and fatal anaphylaxis [108].

Pathophysiology and mechanisms

Central to anaphylaxis is the production of IgE and its interaction with receptors (mainly Fc ϵ RI) predominantly on MCs and to a lesser extent on basophils. Subsequent exposure to allergen allows IgE to cross-link to activate Fc ϵ RI on the surface membranes of MCs and basophils, leading to cell activation and ultimately mediator release. This has been called the 'classical pathway' of anaphylaxis.

In addition, once allergen-specific IgE has been produced by sensitization, it contributes to the intensity of anaphylaxis by enhancing expression of Fc ϵ RI on mast cells and basophils [109–111]. MCs do appear to be involved both in terms of initiating and amplifying anaphylaxis [109–115]. IgE-antigen-induced mast cell degranulation and cytokine production involves stem cell factor (SCF) and c-kit (CD117), the SCF receptor [112, 113, 116].

Once activated, MCs can trigger release of mediators including histamine, proteases (mainly tryptase), mast cell carboxypeptidase A3 (CPA3) and chymase, PAF, prostaglandins (PGD₂), and leukotrienes (LTC₄), as well as chemokines, and cytokines [24]. It is now thought that sphingosine kinase is a factor determining MC responsiveness [114]. Upon mast cell activation and degranulation, CPA3, the chymases, and tryptases are released in complexes with heparin proteoglycan [117].

Mast cells also launch the complement cascade via trypsin and trigger the contact system via kallikrein [24]. The contact system then goes on to activate Factor XII. Factor XII in turn can initiate clotting leading to disseminated intravascular coagulation and activate plasmin which will go on to activate the complement cascade

thereby releasing potent anaphylatoxins [58]. It appears that some agents such as OSCS and peanut allergens can directly activate the kinin-kallikrein pathway in human plasma, which can lead to the generation of bradykinin, a potent vasoactive mediator [58].

In isolation, the histamine 1 (H1) receptor has been implicated in coronary artery vasoconstriction and bronchial constriction [1, 24]. Histamine 2 (H2) receptors appear to regulate coronary vasodilation and cardiac inotropy and chronotropy. In combination, H1 and H2 ultimately play a role clinically in determining pulse pressure and causing headaches due to net vasodilation of the vasculature in the head and neck.

Additionally H3 receptor activity appears to be a down-regulator of anaphylactic events.

Various cytokines are released during anaphylaxis and typically peak before the patient's arrival in the emergency department, whereas histamine levels often peak at emergency department arrival [118]. Levels of IL-6, soluble TNF receptor I, MC tryptase, and histamine correlated to hypotension during anaphylaxis [118].

Circulating PAF concentrations are significantly higher in patients with acute allergic reactions and are directly related to the severity of anaphylaxis [108]. The mechanism for the systemic spread of MC activation in anaphylaxis may not be due to haematogenous spread of the allergen as it does not explain the rapidity of anaphylaxis [119]. PAF induces histamine release from human lung and peripheral blood-derived MCs but not skin MCs [119]. Activation of PAF receptor-coupled $G\alpha$ leads to degranulation through PLC γ 1 and PLC β 2 in human mast cells with a maximal response at 5 s [119]. As such it is more likely that PAF mediates an amplification loop for MC activation in anaphylaxis [119]. There is also animal experience showing that with large amount of allergen, IgG-antigen complexes can activate macrophages by cross-linking of Fc γ RIII and leading to release of large amounts of PAF [120]. The involvement of IgG antibodies partially block the 'classical pathway' of anaphylaxis but mediate the PAF pathway [121].

Accordingly, PAF acetylhydrolase which breaks down PAF may be deficient in patients prone to severe anaphylaxis [108].

Other potential immunologic mechanisms in anaphylaxis include involvement of immune aggregates, IgG, IgM, platelets, and T cells; shift in eicosanoid metabolism towards leukotriene formation [24]. Common to all pathways in anaphylaxis are the enhancing effects of IL-4 and or IL-13 through a STAT6-dependent γ -c independent mechanism [121]. Enhancement is rapid and thought to involve increased sensitivity to mediators such as PAF, histamine, serotonin, and cysteinyl leukotrienes [121].

Other mechanisms can directly degranulate mast cells and thereby cause anaphylaxis independent of IgE. These causes include exercise, cold exposure, radiation, ethanol,

insect venom constituents, radiocontrast media, opioids, and vancomycin [24].

Clinical diagnosis and differential diagnosis

Target organs and systems affected by anaphylaxis include skin (90%), respiratory (70%), gastrointestinal (30–45%), cardiovascular system (10–45%), and central nervous system (10–15%) [23, 24]. In pregnant patients, anaphylaxis can cause uterine spasms that can mimic labour and may lead to miscarriage [122–126].

Another interesting phenomena that occasionally occurs is the Bezold Jarisch reflex causing paradoxical bradycardia during extreme hypovolemia in 10% of patients with anaphylaxis [14]. In addition, anaphylaxis may present with coronary artery spasm causing symptoms of angina and myocardial infarction [127]. In severe anaphylaxis arrhythmias may develop [127].

Cardiovascular symptoms rapidly progress to severe arrhythmias and circulatory collapse and, in cases of intraoperative anaphylaxis, circulatory collapse may be the sole feature of anaphylaxis [128].

Patients may present with a wide constellation of signs and symptoms of anaphylaxis; as a result, anaphylaxis is under-diagnosed and under-reported [8, 21, 22, 24]. Some healthcare professionals are reluctant to diagnose anaphylaxis in the absence of overt shock even though haemodynamic changes are not required for the diagnosis [1].

Other clinical pitfalls are obtaining blood pressure measurements after epinephrine administration, and a failure to recognize that non-specific clinical signs such as confusion, presyncope, syncope, incontinence, sweating, dyspnea, stridor, and wheezing may be due to cardiovascular or respiratory compromise [12]. When respiratory symptoms are the predominant feature in a known asthmatic, anaphylaxis may be mistaken for a 'rapid' asthma exacerbation [129]. Use of antihistamine may mask cutaneous manifestations [130] notwithstanding that 10–20% of patients do not have cutaneous manifestations to begin with [2]. During haemodialysis, surgery, or childbirth there are considerable physiologic shifts in volume status with changes in vital signs that may make anaphylaxis difficult to recognize [131–134].

Aberrant MCs carrying the D816V c-kit mutation have been found in a significant number of cases of unexplained 'idiopathic' anaphylaxis [135] or anaphylaxis due to hymenoptera venom [136, 137]. In fact, the association of clonal MC disorders with hymenoptera allergy was more specific than that with food- or drug-induced systemic reactions [136]. Clonal MC disorders should be suspected in patients presenting with profound cardiovascular manifestations such as hypotension and syncope in the absence of urticaria [138].

Anaphylaxis can resolve spontaneously within minutes to hours if there is sufficient endogenous production of

compensatory mediators such as epinephrine, angiotensin II, endothelin. On the other hand, reactions can progress within minutes to respiratory and or cardiovascular arrest [23].

Biphasic anaphylaxis occurs when symptoms return following the apparent resolution of the initial anaphylactic event. Biphasic reactions have been reported to develop in 1–20% of anaphylaxis and typically occur in the first 8 h after the initial reaction with cases of recurrences reported up to 72 h later [1, 139].

Anaphylaxis can be protracted in that it lasts for days in some extreme cases [16].

Acute anaphylactic reactions that may or may not involve immunologic mechanisms include direct mast cell and/or basophil degranulation, exercise induced, food-exercise induced, and catamenial anaphylaxis.

An exhaustive list of age-dependent [24, 129] differential diagnoses can be broken down into common disorders vs. rare disorders.

Common disorders include:

- Urticaria
- Angioedema
- Asthma
- Vasovagal presyncope and syncope
- Vocal cord dysfunction
- Anxiety disorders
- All causes of distributive shock
- Myocardial infarction or cerebral vascular accident
- Other causes of acute respiratory distress

Rare disorders:

- Anisakiasis
- Scrombroidosis
- Sulphites
- Catamenial anaphylaxis
- Mastocytosis and other clonal mast cell disorders
- Mast cell leukaemias
- Hydatid cyst rupture
- Systemic capillary leak syndrome
- Flushing disorders [140]

Flushing may be caused by:

- Vancomycin and other antibiotics
- Griseofulvin
- Niacin
- Levodopa
- Amyl nitrate
- Bromocriptine
- Alcohol
- Menopause
- Malignancies:
 - Carcinoid
 - Intestinal tumours secreting VIP or substance P

- Pheochromocytoma
- Medullary carcinoma of the thyroid

Patients previously thought to have idiopathic anaphylaxis may have mast cell abnormalities on bone marrow biopsy [135]. A bone marrow biopsy in patients with idiopathic anaphylaxis or profound hypotension following insect stings may show evidence of clonal mast cell disease [135, 136] even when baseline tryptase values are normal [141].

Investigations

Skin prick testing (SPT) is useful to help identify the cause of anaphylaxis but does not predict severity of reactions [1, 8, 24, 32]. Like SPT, the level of serum-specific IgE does not correlate with reaction severity and cannot be used to identify individuals at risk for anaphylaxis [1, 8, 24, 32, 37].

Characterization of B-cell epitope responses shows some potential to predict reaction severity based on specific allergen epitopes [142]. For example, children with peanut allergy who have an increased diversity of IgE-binding epitopes appear to have increased severity of reactions [143].

Numerous mediators and pathways may be activated during systemic reactions [24, 109, 118]. A decreased C4 and C3 will indicate the activation of the complement system. A decrease in high molecular weight kininogen demonstrates the formation of the activation complexes of the contact system. The coagulation pathway may be activated with decreased factor levels such as V and VII as well as a decrease in fibrinogen levels [24, 109, 111, 118, 120].

There have been efforts to use serum tryptase and histamine to aid in the diagnosis of anaphylaxis. The utility of this was evaluated in serial serum samples taken 15 and 60 min after a venom sting [144]. Excluding mild reactions and using a clinical diagnosis as the gold standard for anaphylaxis, it was determined that using a tryptase value of 12.0 mcg/L as a cut-off resulted in a sensitivity of 0.36 and specificity of 0.93 [144]. Using a tryptase cut-off of 9.0 mcg/L improved the sensitivity to 0.55 while retaining the same specificity [144]. When serial measurements are used in conjunction, an increase of 2.0 mcg/L or greater has a more robust yet still low sensitivity of 0.73 but high specificity of 0.98 [144]. Serial tryptase and histamine determinations increase the sensitivity to 0.90 [144]. In food-induced anaphylaxis, basophil involvement may predominate over mast cell involvement leading to normal histamine and tryptase levels [24]. Optimally, histamine should be measured in blood samples obtained within 15–60 min of onset and tryptase in samples obtained within 15–180 min [24]. Plasma histamine levels decline rapidly due to rapid

inactivation by N-methyltransferase and diamine oxidase [145, 146]. Although not widely available, a test for mature β -tryptase has been developed and may be more sensitive and specific for anaphylaxis [147].

Because histamine is not secreted in the urine [148], urinary histamine measurement do not assist in the diagnosis.

Diagnostic changes in basophil surface activation markers such as CD63 and CD203c after venom anaphylaxis have been reported [149]. In the future, markers such as mature β -tryptase, mast cell CPA3, chymase, and PAF may be available and offer further insight [108, 147, 150].

Identification of food-specific IgE levels with $>95\%$ predictive values for clinical reactivity have been published (using ImmunoCap; Phadia AB, Uppsala, Sweden). These levels are for bovine milk (≥ 15 kU/L), egg (≥ 7 kU/L), peanut (≥ 14 kU/L), tree nuts (≥ 15 kU/L), and fish (≥ 20 kU/L) [151–155]. In infants lower values are used for milk (≥ 5 kU/L) and egg (≥ 2 kU/L) [151, 153–155].

Treatment

Non-pharmacologic measures such as airway management, fluid resuscitation, and removal of the offending allergen play a key role in managing anaphylaxis regardless of setting. The patient should be kept supine with legs raised to prevent death due to 'empty ventricle syndrome' with pulseless electrical activity [156]. All patients should proceed to a hospital in the event of anaphylaxis in the event of recurrent symptoms.

The median time from onset of symptoms to fatal cardiopulmonary arrest was <30 min in a series of over 200 anaphylaxis deaths [98]. Irrespective of the trigger or mechanism of anaphylaxis, the initial management is the same [1].

Fluid management is critical as massive fluid shifts can occur due to increased vascular permeability within minutes [157]. Treatment with both H1 and H2 receptor blockers may be more effective than an H1 antihistamine alone. Kaliner et al. [158] showed that healthy volunteers treated with the combination of cimetidine and hydroxyzine had fewer symptoms following histamine infusion than treatment with either H1 or H2 blockers alone. The use of H1 blockers in the treatment of anaphylaxis has not been studied in randomized control trials [159] because antihistamines cannot be substituted for epinephrine as first line treatment [159–161]. A Cochrane systematic review of the literature has found no randomized controlled trials supporting the use of H1 antihistamines in anaphylaxis [159].

While antihistamines may prevent hives and pruritus, they do not reverse upper or lower airway obstruction or cardiovascular compromise [129, 162].

The mainstay of management is epinephrine (adrenaline). Pharmacokinetic studies have shown that the in-

tramuscular (IM) route of administration is preferable with a faster onset of action and more sustained levels as compared with the subcutaneous route [163–166]. Other dosage forms such as inhaled and sublingual epinephrine have also been tried but are neither widely available nor have proven consistent efficacy [167–169]. Epinephrine autoinjectors and standard needles may not provide IM access in some overweight or obese individuals [170, 171].

Delayed administration of epinephrine is a risk factor for severe and biphasic reactions and a fatal outcome [10, 98, 157, 163, 172]. A clinician should not wait for overt signs of distributive shock or cardiovascular compromise to administer epinephrine [173–179]. Due to the fact that patients who have fatal anaphylaxis tend to have a delay in epinephrine administration from the time of allergen exposure, it is recommended that epinephrine be given as soon as possible [16]. In children, epinephrine is given at a dose of 0.01 mg/kg body weight to a maximum dose of 0.3 mg in a 30 kg child. For adults, the standard dose is 0.2–0.5 mg. Retrospective studies show that 16–35% of patients require a second dose of epinephrine to treat their initial reaction [24]. Because up to 20% of patients will experience biphasic or protracted symptoms [139] patients should be monitored for a minimum of 4–6 h after treatment and discharged with prescriptions for two epinephrine autoinjectors [139]. Although there is no consensus on the monitoring period required, for moderate to severe anaphylaxis or if symptoms did not respond promptly to epinephrine treatment, consideration should be given to monitoring the patient for an extended period of time.

In patients who remain hypotensive and unresponsive to IM epinephrine and fluid resuscitation, intravenous epinephrine may be required. The intravenous route should be used by experienced personnel because of the potential for adverse reactions. In these cases there may already be inadequate perfusion in muscle tissues and this can be clinically recognized by a patient in distributive shock. In dogs, it has been found that a constant administration of epinephrine IV is superior to bolus doses [180]. As such, it is recommended that patients receive epinephrine by a slow continuous epinephrine infusion and the rate of administration be titrated to the response with continuous haemodynamic monitoring [178, 181].

The key therapeutic actions of epinephrine include both α -1, β -1, and β -2 adrenergic agonist effects [163, 172, 178, 182]. The adverse effects of epinephrine include anxiety, fear, restlessness, headache, presyncope, palpitations, tremor, and pallor [163, 172, 178, 182]. Ventricular arrhythmias, angina, myocardial infarction, pulmonary oedema, hypertensive emergency, and intracranial haemorrhage are rare side-effects of epinephrine administration and are more commonly associated with intravenous administration [163, 172, 178, 182, 183].

There are no absolute contraindications to epinephrine use in anaphylaxis [163, 173–179], a concept emphasized in a systematic Cochrane review [175]. Epinephrine may be used judiciously in patients with coronary artery disease, because anaphylaxis may cause coronary artery spasm, which can be reversed by epinephrine [184–189].

Some relative contraindications for epinephrine use may include patients on mono-amine oxidase inhibitors, tricyclic anti-depressants, or stimulant medications or illicit substances, all of which may be predispose to an increased risk of adverse effects of epinephrine. In addition, caution is needed in patients with recent intracranial surgery, aortic or cerebral aneurism(s), uncontrolled hyperthyroidism, or hypertensive emergencies.

It should also be noted that even in 69 patients who self-administered epinephrine accidentally without anaphylaxis, there were no long-term adverse sequelae [190].

Currently, efforts are underway to develop an effective sublingual epinephrine delivery system [167, 191, 192].

β -blockers may blunt the response to epinephrine. Patients using β -blockers may require treatment with glucagon and aggressive fluid resuscitation. Such patients may have a relative bradycardia and refractory hypotension [193]. Glucagon has both inotropic and chronotropic effects independent of β -receptors [193–196]. A dose of 1–2 mg in adults and 20–30 mg/kg (maximum of 1 mg) administered intravenously over 5 min as a bolus is recommended. This can be repeated or followed by an infusion of 2–20 micrograms per minute. It should be noted that a common side-effect of glucagon is emesis, particularly with rapid administration.

Interestingly although it is common clinical practice to administer moderate to high dose glucocorticoids during anaphylaxis, a recent Cochrane systematic review concluded that there is insufficient high-quality evidence to either support or not support the use of glucocorticoids in the management of anaphylaxis [197]. The theoretical benefit is that it may reduce the number of biphasic reactions although the evidence for this is lacking [139, 198]. Nevertheless, the WAO continues to recommend glucocorticoid use in anaphylaxis management [199]. A typical regimen may include methylprednisolone 1–2 mg/kg/day or equivalent for 3–4 days since most biphasic reactions occur within 72 h [139].

Bronchodilators can be used if the bronchospasm is not responsive to initial epinephrine given. Salbutamol at 2.5–5 mg via nebulizer in 1–3 cm³ of normal saline or water or equivalent may be given. Neither laryngeal oedema nor shock can be treated with bronchodilators and antihistamines alone or in combination [119, 182].

Vasopressors such as dopamine can be used if hypotension persists despite intravenous fluids and maximal infusion of epinephrine. There is some reported benefit to using vasopressin in adults with refractory anaphylaxis [200].

A novel approach involves the use of omalizumab. Omalizumab may potentially play a therapeutic role by depleting free IgE and down-regulating Fc ϵ RI receptors on mast cells and basophils. This would potentially arrest the intracellular activation signal by blocking IgE/Fc ϵ RI aggregation [201].

A number of case reports describe use of methylene blue for the treatment of refractory anaphylaxis [202–206]. Methylene blue may prevent PAF-mediated anaphylaxis by blocking nitric oxide (NO)-mediated vascular smooth muscle relaxation [207]. Endothelial nitric oxide synthase-derived NO appears to be the principal vasodilator in anaphylactic shock [207]. However, methylene blue itself may cause anaphylaxis in sensitized patients [208–211].

Prevention and education

Pretreatment strategies have been used successfully. There are well-established protocols to prevent anaphylaxis to radiocontrast agents, cold-induced anaphylaxis, and fluorescein. When prevention strategies fail, avoidance strategies can prove to be highly effective as was the case for latex [212–215].

In insect sting anaphylaxis, venom immunotherapy is highly effective in reducing risk of reaction [24, 216–218]. Immunotherapy is not indicated in children with mild cutaneous systemic reactions or in either children or adults with large local reactions [216, 218]. Other areas where desensitization is effective include anaphylaxis from seminal fluid or from medications such as antibiotics, aspirin, NSAIDs, insulin, chemotherapeutic and biologic agents [219–225].

On the horizon for desensitization is the sublingual route of administration; 'engineered' recombinant proteins; CpG-oligonucleotide conjugated allergens, peptides, or polymers of major allergens; and a mixture of major recombinant allergens [24, 226]. Immunomodulators like omalizumab or anti-CD63 antibodies may be used for these desensitization protocols, particularly if the patient is at risk from multiple allergens [24].

Upon discharge from the emergency department patients should be prescribed an epinephrine auto-injector and follow-up should be arranged with an allergist [227]. In addition, at the follow-up visit at-risk individuals should be advised to carry two self-injectable epinephrine doses, carry medical identification, and have a personalized anaphylaxis emergency action plan [24]. In spite of education and efforts at prevention, many patients will experience recurrent episodes of anaphylaxis [228, 229].

Management of co-morbid conditions that can contribute to anaphylaxis such as asthma, COPD, ischaemic cardiac disease, and systemic mastocytosis can assist in the optimal therapy. Effective management should also include a full review of all medications, weighing the risks and benefits of each medication such as β -blockers,

angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, MAOI, NSAIDS, aspirin, and other medications that can potentially interfere with treatment [90, 92, 129, 226, 230, 231].

Conclusion

Anaphylaxis is a common potentially life-threatening reaction that appears to be increasing in both prevalence and incidence. With the increase in the prevalence of

atopy in general and the introduction of new biologic therapies, medications, and imaging media this trend is likely to continue. Given the lack of rapid diagnostic tests, the diagnosis requires a high index of suspicion and prompt initiation of definitive therapy, with epinephrine and adjunctive agents. The follow-up management requires a formal allergy assessment to identify potential triggers, to educate the patient on appropriate avoidance and other risk reduction strategies and development of an anaphylaxis action plan.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search strategies and resources

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

Appendix 1

Search strategy:

OVID Medline Database

Selected dates: 1948 to March week 3, 2011 limited to the English language

Search Terms: Anaphylaxis, Anaphylactoid, Passive Cutaneous Anaphylaxis, Anaphylaxis (as key word), anaphylactoid (as key word) all terms were exploded

Combined Selections with the OR command

Number of Results 20570

Other sources if not in above:

Cochrane Systematic Reviews.

Inclusion Criteria for studies examined:

English Language, Peer Reviewed Journals

Additional Sources

A parallel search of Pub Med data base was commenced following above for any missed articles.

In addition, information from conferences, symposia and sessions on anaphylaxis were incorporated. Sources of information from anaphylaxis conference sessions include: the Canadian Society of Allergy and Clinical Immunology in Halifax 2009, the American College of Asthma Allergy and Immunology in Miami 2009, World Allergy Organization Congress in Buenos Aires 2009, the American Academy of Asthma Allergy and Immunology in New Orleans 2010 and the EAACI London 2010. One or both authors were present at relevant sessions of the conferences noted above to incorporate any new research or insights.