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REVIEW

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Identifying patients at risk of anaphylaxis

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ABSTRACT

Anaphylaxis is an acute, potentially fatal, systemic hypersensitivity reaction that warrants prompt diagnosis and management. It continues to be challenging to anticipate who may be at risk of a severe, life-threatening allergic reaction. Anaphylaxis can be caused by a range of allergens, such as certain foods, medications, latex, insect stings, etc. Cofactors that augment the severity of clinical symptoms and increase the risk of poor outcomes include exercise, stress, infectious diseases, underlying mast cell disease, active allergic disease such as asthma, advanced age, intake of certain medications, history of previous anaphylaxis, and delayed or missed administration of adrenaline. According to the European Anaphylaxis Registry, food is the major elicitor of anaphylaxis, especially eggs, cow milk, and nuts, in children and adolescents. Reaction to insect venom has also been noted in young adulthood. Early recognition of signs and symptoms and prompt treatment are crucial in anaphylaxis management to avoid serious and even fatal outcomes. It is crucial for both individuals and clinicians to identify the cause of anaphylaxis. Biomarkers of anaphylaxis, such as histamine, tryptase, platelet activation factor (PAF), chymase, carboxypeptidase A3, dipeptidyl peptidase I (DPPI), basogranulin, CCL-2, hsa-miR-451a, may be useful in diagnosis and management. The purpose of this review article is to present a comprehensive overview of current evidence and expert opinions regarding the risk factors that predispose individuals to anaphylaxis. Additionally, it provides insights into potential biomarkers and genetic markers for accurate diagnosis and management. This review underscores the significance of expert guidance in enhancing patient outcomes and enabling self-management of anaphylactic episodes.

Keywords: Anaphylaxis, Biomarkers, Prevention and control, Risk factors, Self-management

INTRODUCTION

Anaphylaxis is a severe and rapid-onset allergic reaction that is marked by breathing difficulties or circulatory issues that can potentially be life-threatening.[1] It is often unpredictable and thus the impact on the health-related quality-of-life (HRQoL) is high, irrespective of the cause.[2,3] The triggers of anaphylaxis can be categorized as either immunologic or non-immunologic, depending on their underlying mechanism. Anaphylaxis caused by an immune response can occur through either an immunoglobulin E (IgE)-mediated pathway or an immune complex-dependent pathway, whereas non-immunologic anaphylaxis involves a direct activation of mast cells and basophils. Regardless of the specific mechanism involved, the symptoms of anaphylaxis are similar and are caused by the release of inflammatory mediators, such as histamine, platelet-activating factor (PAF), tryptase, cysteinyl leukotrienes, and other bioactive mediators.[4,5] The

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effects of these mediators can have significant clinical implications, including peripheral vasodilation, increased vascular permeability, increased mucus production, and contraction of bronchial smooth muscles.[6] Typically, these systemic changes appear within a matter of seconds or minutes following antigen exposure, although biphasic and delayed reactions can occur several hours later. Delayed reactions are more typical to select allergens such as red meat in patients with alpha-gal allergy.

The mechanism of anaphylaxis involves basophil activation, production of vasoactive mediators, stimulation of mast cells, and the activation of other inflammatory cascades.[7] The mediators, which include histamine, leukotrienes, and prostaglandins, incite urticaria, vasodilatation, increase in vascular permeability and vascular leakage, edema, and bronchoconstriction and may lead to a decrease in arterial pressure leading to tachycardia, bronchospasm, and digestive issues.

The prevalence of anaphylaxis varies worldwide and may be increasing in developed countries, which is a cause for serious public health concern.[8,9] Anaphylaxis is estimated to have a lifetime prevalence ranging from 0.3% to 5.1% globally, with an incidence rate of 50–112 episodes per 100,000 persons per year.[6] In Europe, the incidence rate for anaphylaxis caused by any trigger ranges from 1.5 to 7.9 per 100,000 persons per year, and it is estimated that approximately 0.3% of the population will experience an anaphylactic episode at some point in their lifetime.[10] Recent reports indicate a seven-fold increase in hospital admissions related to anaphylaxis caused by any trigger in the United Kingdom over the past few years; however, no significant change in mortality rates were noted (0.047 cases per 100,000 per annum).[11]

In principle, anaphylaxis can be prevented, but it poses challenges to prevent or manage in the community settings where access to healthcare professionals is difficult. Thus, identifying individuals who are at risk of anaphylaxis and providing them with emergency training is of utmost importance. Adrenaline is the first-line treatment for anaphylaxis, and its early administration is associated with better survival outcomes.[12–14] In some cases, patients may need multiple doses of adrenaline or an infusion of adrenaline.[15] As per the Australasian Society of Clinical Immunology and Allergy (ASCIA) guideline, the recommended intramuscular (IM) dose of adrenaline is 0.01 mg/kg up to 0.5 mg per dose.[16] It is recommended to repeat the intramuscular adrenaline dose after 5 min if there is no improvement in the patient's condition. The guidelines of the Resuscitation Council UK state that a repeat IM adrenaline dose should be administered in the contralateral thigh to aid absorption.[17] Previous studies have shown that IM adrenaline administration into the thigh results in faster achievement of the peak plasma adrenaline concentration compared to IM or subcutaneous injection into the upper arm.[18,19]

Anaphylaxis is commonly triggered by certain food items, latex exposure, insect venom, and medications. Individuals with a past history of severe allergic reactions, pre-existing respiratory or cardiovascular disease, uncontrolled severe asthma, delayed administration of adrenaline, previous biphasic anaphylactic reactions, mast cell disease, and those with advanced age are more commonly reported to experience anaphylaxis.[20] The risk of anaphylaxis can also be influenced by the route of allergen exposure. For example, an intravenous injection of a medication that a person is allergic to is more likely to cause a severe allergic drug reaction than when it is administered orally.[21] Fatal anaphylaxis to food allergens has also been reported following skin contact, as well as through kissing and intimate interactions.[22–25]

The risk of anaphylaxis has been shown to have a negative effect on health-related quality of life (HRQoL).[26] Considering the impact on various aspects of an individual's life, such as their educational pursuits, professional endeavors, familial relationships, and social interactions, it becomes imperative to examine the quality of life (QoL) of patients who have encountered anaphylaxis induced by medication, exercise, or hymenoptera venom. This condition significantly hampers their ability to participate in daily activities, including attending school or work, and restricts their mobility and engagement in social interactions with others.[26] As many as 12% of those who have had an anaphylactic shock may experience anxiety, fear, and

depression that can hinder social, family, and professional interactions.[27-31] A recent study has demonstrated a high prevalence of post-traumatic stress disorder (PTSD) and associated psychological distresses in patients with anaphylaxis.[32]

This review article aims to present an overview of the current knowledge and expert opinions concerning the identification of patients at risk of anaphylaxis, potential biomarkers and genetics of anaphylaxis, prevention and management strategies for at-risk patients, and guidance to enhance patient outcomes and enable self-management of an anaphylactic reaction.

RISK FACTORS OF ANAPHYLAXIS

Age

Apart from the known history of anaphylaxis in patients, there are various other risk factors that can increase the chances of a severe and life-threatening anaphylactic reaction (Table 1).[33-50] Age is an important factor influencing the course and severity of anaphylaxis. Diagnosing anaphylaxis in infants (aged 0–2 years) can be challenging as they cannot verbally express their symptoms, which makes it hard to identify the condition.[51] Although elicitors of anaphylaxis are age-dependent, food items are still the most prevalent triggers in children and young adults. Young adults exhibit a higher propensity to consume food products that bear “may contain” warnings, while concurrently failing to disclose their allergies to those in their immediate vicinity. Furthermore, they may exhibit reluctance in filling adrenaline auto-injector (AAI) scripts, not consistently carry their AAI with them, and could be hesitant to use it.[52]

Studies have shown that fatal food-allergic reactions are predominantly observed in adolescents and young adults. It has been observed that a considerable number of teenagers with food allergies engage in risky behavior, which varies depending on social circumstances and perceived risks.[54,55] Another study that primarily focused on young adults reports that the majority of food-related anaphylactic reactions, ie, 76%, occurred in individuals who were at risk of anaphylaxis and consumed food outside their homes.[56] As part of a separate study, a majority of teenagers confessed to not possessing AAIs. The risk-taking behavior of the participants was assessed, and the findings highlight that a few participants chose to remain extremely cautious, whereas others opted to take risks for the sake of a "normal" life.[57] The findings of this research indicate that the increased susceptibility to severe and potentially fatal anaphylaxis among teenagers cannot solely be attributed to their risk-taking behavior. The difficulty of managing their condition while eating outside their home environment and insufficient healthcare assistance were also recognized as important factors.

The likelihood of experiencing anaphylaxis tends to rise with advancing age. This may be attributed to underlying medical conditions like cardiovascular disease (CVD) and chronic obstructive pulmonary disease. According to the results from the European anaphylaxis registry involving 1123 participants, anaphylaxis in older individuals posed a significant risk to life and necessitated more intensive medical intervention.[35]

Drug hypersensitivity

Drug hypersensitivity is another cause of anaphylaxis more frequently noted in adults and hospitalized patients. Drugs such as non-steroidal anti-inflammatory drugs, beta-lactam antibiotics, and quinolones are the common elicitors of drug-induced anaphylaxis.[7] In addition to these drugs, certain anti-diabetes drugs have also been shown to elicit an anaphylactic reaction. Recently published reports have presented cases of anaphylactic reaction to exenatide and dulaglutide that are glucagon like peptide-1 (GLP-1) receptor agonists used for the management of type 2 diabetes.[58,59]

Concomitant medical conditions

Patients having concomitant medical conditions have an elevated risk of experiencing a more severe anaphylactic reaction. For example, severe or uncontrolled asthma may increase the likelihood of anaphylaxis becoming fatal or life-threatening. Asthma is, however, common in individuals with peanut and tree-nut induced allergies, which may account for its high prevalence amongst those

Factor	Background
Age[33]	• Infants: Under-recognition, under-diagnosis; no appropriate adrenaline auto-injector dose • Adolescents/young adult: Increased risk of anaphylaxis triggered by foods due to risk taking behavior, disease denial or treatment non-compliance (not filling scripts for or carrying an AAI) • Elderly: Increased risk of fatality from insect venom anaphylaxis, concomitant cardiovascular diseases and drugs like analgesics and antibiotics
Comorbidities[34,35,39,40,53]	• Asthma if severe or uncontrolled • Patients with cardiovascular disease or taking antihypertensive medication • Allergic rhinitis and eczema: atopic diseases are a risk factor for anaphylaxis triggered by food, exercise, and latex • Intercurrent or recent illness including COVID-19 • Intellectual impairment, communication difficulties, eg, language • Thyroid disease (some patients with idiopathic anaphylaxis) • Hereditary alpha hypertryptasemia, mastocytosis
Impact of concurrent medications[37,38]	• May affect recognition of anaphylaxis: ethanol, sedatives, hypnotics, antidepressants, recreational drugs, sedatives, hypnotics • May increase the severity of anaphylaxis: beta-blockers, ACE inhibitors, angiotensin II receptor blockers, aspirin, NSAIDS
Allergens with increased intrinsic risk of triggering anaphylaxis[38]	• Food: nuts, seafood, food additives, finned fish, shellfish, egg, milk, sesame • Insect stings/bites: Hymenoptera (bees, vespids, ants • Inhalants (cat, hamster, and horse dander; grass pollen) • Natural rubber latex • Medications (such as beta-lactam antibiotics, neuromuscular blockers)
Other relevant factors[35,36,38,41-43,45-50]	• Severity and/or priming effect of previous anaphylaxis episodes • Strenuous exercise • Psychologic stress • Past severe anaphylaxis • Estrogen, progesterone • Sleep deprivation • Alcohol consumption, viral illness, and menstruation • Delayed or failure to use an AAI to treat an anaphylaxis episode • Effective training packages for anaphylaxis patients and their care givers to understand and address AAI behaviors • Uncertainty and fear over how and when to use AAI • Limited access to emergency medical care, for example, remote location, social factors

Table 1. Patient-specific risk factors for anaphylaxis severity and fatality. *AAI, adrenaline auto injector; ACE, angiotensin-converting enzyme; NSAIDS, non-steroidal anti-inflammatory drug.*

experiencing severe reactions.[60] Atopic conditions like eczema and allergic rhinitis also elevate the likelihood of anaphylaxis triggered by exercise, latex, and food, but not anaphylaxis resulting from beta-lactam antibiotics and insect stings.[20]

Mastocytosis

Mastocytosis, an abnormal buildup of mast cells in the skin, bone marrow, and internal organs, has also been reported to increase the risk of severe anaphylactic reactions.[61,62] Mast cells contain

vasoactive and chemotactic mediators that are released in response to allergic reactions and contribute to the symptoms of many diseases such as asthma, urticaria, and rhinitis.[63] On exposure to allergens, mast cells degranulate with immediate (5–30 min) release of preformed mediators from secretory granules (histamine, tryptase, carboxypeptidase A, and proteoglycans), followed by synthesis of arachidonic acid metabolites (prostaglandins, leukotrienes), and platelet-activating factor (PAF), and delayed-phase (2–6 h) generation of cytokines (TNF-a) and chemokines such as CCL2, CC-3, CCL-5, and CXCL-8.[64,65] In case of IgE-dependent mast cell degranulation, IgE binding to the surface of mast cells triggers a complex chain of events, such as calcium ion influx, phospholipid methylation, turnover and cyclic nucleotide metabolism, thus resulting in the release of mediators of immediate hypersensitivity.[65]

Cardiovascular disease

Underlying cardiovascular disease (CVD) may also represent a concomitant disease risk factor.[66] Various studies indicate that during anaphylaxis, the heart, particularly the coronary arteries, is often the primary target. While anaphylactic reactions with cardiovascular symptoms are common and transient, in some cases, they can cause extensive and potentially life-threatening damage to the heart muscle.[67] In such instances, a significant number of mast cells have been reported in the adventitia and tunica media of both large and small intramural coronary arteries. During anaphylaxis, the decrease in blood flow to the coronary arteries due to plasma leakage, systemic vasodilation, reduced venous return, and volume loss due to an increase in vascular permeability can lead to ventricular dysfunction, cardiac output suppression, and further myocardial damage.[68] The cardiovascular symptoms of anaphylaxis include cardiac arrhythmias, ventricular dysfunction, hypotension, shock, and cardiac arrest.[69] Certain therapies such as angiotensin-converting enzyme (ACE) inhibitors and beta-blockers may increase the severity of anaphylaxis.[70] In the murine model, oral treatment with ACE-inhibitors and/or beta blocker augmented systemic anaphylaxis due to enhanced mast cell mediators (histamine, serotonin, leukotriene C4, prostaglandin D_2).[66] Additionally, the use of beta-blockers can complicate the treatment of anaphylaxis as it can interfere with the patient's ability to respond to adrenaline.[71]

Hypersensitivity to cold temperatures

Recent studies have reported occurrence of cold-induced anaphylaxis (ColdA), which is a severe form of hypersensitivity reaction to cold temperatures that can be life threatening and requires urgent response.[72] ColdA can be acquired, hereditary, or idiopathic and is associated with a wide range of triggers including cold air, contact with cold liquids, exposure to cold solid surfaces, and the ingestion of cold food or drinks.[73,74] COLD-CE, a cross-sectional study was carried out in 551 cold urticaria (ColdU) patients. The study identified symptoms of severe disease that included cold-induced generalized wheals, angioedema, acral swelling, oropharyngeal/laryngeal symptoms, and itch of earlobes. In severe cases, ColdA can lead to cardiovascular problems.[75]

Neurologic and psychiatric factors

Individuals of all ages with medical conditions that make it difficult to recognize the triggers or symptoms of anaphylaxis are at a higher risk of experiencing a severe outcome due to a delay or lack of treatment. These medical conditions include, but are not limited to, neurologic disorders, psychiatric disorders (including depression), impaired vision or hearing, and the use of medications such as first-generation H1-antihistamines (eg, diphenhydramine, and chlorpheniramine), sedatives, antidepressants, hypnotics, or central nervous system-active chemicals such as recreational therapy or ethanol.[38,76] In the absence of timely identification of symptoms in these individuals and delayed administration of adrenaline (ie, later than 30 min of onset of allergic symptoms) may further increase the risk of severe anaphylactic reaction.[77]

Cofactors associated with anaphylaxis

Allergic reactions result from allergen exposure alone; however, other triggers may be needed to elicit anaphylaxis.[35,78] Exercise was identified as a cofactor in up to 20.4% of reactions, alcohol consumption in 2.4%–15.2%, acetylsalicylic acid in

6.1%–9%, tiredness in 38%, and symptoms of hay fever (also known as pollinosis) in 16% of anaphylactic cases.[79,80] Other studies have reported several other cofactors that can contribute to anaphylaxis, such as infection, extreme air temperatures, menstruation, cannabis use, ACE inhibitors, beta-blockers, antacids, and sleep deprivation.[81,82] Another study has shown that upright posture during an anaphylactic episode is associated with an increased risk of potentially fatal food-induced and venom-induced anaphylaxis.[83] Considering the impact of these cofactors on the onset of anaphylaxis will aid in management based on precision medicine.

POTENTIAL BIOMARKERS FOR ANAPHYLAXIS

Over the years, research has primarily focused on analyzing the immune component of anaphylaxis, which leads to the release of various mediators that could serve as potential biomarkers. Additionally, it is crucial to gain a comprehensive understanding of the different microenvironments involved in anaphylaxis (such as skin, lungs, heart, nervous system). This will help identify better molecular markers and improve clinical management.[84] Detailed information on some of the potential biomarkers of anaphylaxis, such as tryptase, IgE, angiotensin, chymase, carboxypeptidase, cathepsin, prostaglandin and other inflammatory mediators, are presented in Table 2.[85-110]

GENETICS OF ANAPHYLAXIS

Many genetic studies, including candidate gene studies and genome-wide association studies, have identified a significant number of genetic markers that are linked to an elevated risk of developing allergies.[110,112,113] Several genetic markers have been identified in individuals with specific types of allergies or anaphylaxis.[114] These markers include the *HLA-DPB1*02:01:02* allele for wheat-dependent exercise-induced anaphylaxis.[115] A study conducted on children with food-induced anaphylaxis reported increased levels of *miR-21-3p* and *miR-487b-3p*.[116] In adult patients undergoing anaphylactic treatment in emergency department, hsa-miR-451a is considered the most relevant biomarker in blood samples.[117] Two single-nucleotide polymorphisms in *NLRP3* (*rs4612666* and *rs10754558*) have also been linked to susceptibility to food-induced anaphylaxis.[118] Additionally, mutations in *c-KIT*, particularly the *D816V* point mutation, have been associated with systemic mastocytosis, a hematological disorder.[119] Research has shown that a higher level of alpha tryptase can increase the risk of severe anaphylaxis.[120] Hereditary alpha-tryptasemia (HαT), an autosomal dominant genetic trait reported to occur commonly in the Caucasian population (1 in 20), has been shown to be associated with elevated basal serum tryptase (BST) levels.[121] About 4%–6% of the general population, carry the TPSAB1-α gene which is responsible for elevating BST levels.[122] The prevalence of HαT has been reported to be higher in individuals with mast cell-associated disorders, including anaphylaxis.[123] Identifying genes and understanding the effect of genetic alterations can help prevent anaphylaxis and open up potential avenues for treatment.

DIAGNOSIS AND MANAGEMENT OF ANAPHYLAXIS

Anaphylaxis requires urgent and effective medical intervention, including timely diagnosis, preventive education/training, and empowering individuals to self-manage anaphylactic episodes.

Diagnosis of anaphylaxis

Diagnosing anaphylaxis may pose a challenge due to the similarity of its symptoms to those of other medical conditions. The diagnosis of anaphylaxis typically depends on the patient's medical history, the appearance of clinical signs and symptoms within 2 h of allergen exposure, and a thorough physical examination.[124] Additional tests may include skin prick tests or blood tests to identify the trigger. To confirm anaphylaxis, the measurement of serum levels of mediators that are released during an anaphylactic reaction may be useful, if available. It is important that the test samples are collected, stored, and processed appropriately as these mediators can rapidly degrade.

Anaphylaxis prevention and management training

Individuals at risk of recurrence of anaphylaxis should be educated to avoid the allergen that may

Potential biomarkers	Evidence
Total tryptase (pro, pro', and mature forms of α/β tryptases)[85,87-93,98]	• Tryptase is a serine protease. The alpha form is passively secreted and the beta form is predominantly present in secretory granules of mast cells and basophils • Half-life approximately 2 h • Peaks within 60–90 min after symptom onset but can persist for 6 h • Blood sample should optimally be obtained within 3 h of onset of anaphylaxis symptoms • Elevation of the acute total tryptase level of 20% + 2 ng/L above a baseline is an indicative of a significant mast cell degranulation event • Consider comparing the level measured during the acute event with a baseline level (obtained 24 h after resolution of the acute event) or on stored serum, if available (levels are stable for at least 1 year in stored frozen sera) • If higher in acute serum than in baseline serum, a diagnosis of anaphylaxis is likely • If elevated (≥20 ng/mL) in both acute and baseline sera, the diagnosis of mastocytosis should be considered. • The diagnosis of HαT may be considered in patients with basal tryptase level >8 ng/mL and a history of severe allergic events • If within normal limits in a blood sample taken during anaphylaxis, the diagnosis of anaphylaxis cannot be excluded • Total tryptase level can be measured in postmortem serum (blood samples preferably obtained from femoral vessels rather than the heart; the level needs to be correlated with the clinical history) • High concentration of alpha-tryptase has been observed in patients with systemic mastocytosis, a clonal disorder associated with mutation of the membrane tyrosine kinase KIT, and the concentration of beta-tryptase was increased during anaphylactic reactions • Serum tryptase level may be a noninvasive, promising prognostic long-term biomarker in patients with ACS, STEMI and non-STEMI • In challenges to hymenoptera venom, tryptase concentration has been correlated with severity of anaphylaxis after a sting • Significant increase in baseline tryptase level with increasing age
IgE against Galactose-α−1,3-galactose (alpha-gal)[86,94,96,97]	• May cause red meat anaphylaxis • Responsible for delayed form of anaphylaxis occurring 3–6 h after ingestion of red meat • Independently associated with noncalcified plaque burden and obstructive coronary artery disease. It is also associated with ST-segment–elevated myocardial infarction.
Plasma angiotensin II[86,99]	• Synthesized from angiotensin I by ACE • Normal of serum ACE is 20–70 U/L, but the range varies by age and genotype • Low ACE levels have been found in patients with severe anaphylaxis as assessed by cardiovascular collapse and airway angioedema • May play a role for measurement of the renin-angiotensin system to understand the pre-existing level of risk of severe anaphylaxis

(continued)

Potential biomarkers	Evidence
	• Lower levels of angiotensinogen, angiotensin I and II have been reported in patients with hymenoptera anaphylaxis versus normal controls, and the levels were even lower in patients with severe anaphylaxis
Platelet-activating factor[87,98,100,102–104,111]	• Important mediator in anaphylaxis • Secreted by mast cells, basophils, leukocytes, fibroblasts, endothelial cells neutrophils, eosinophils, platelets, and cardiac muscle cells • Short half-life of 3–13 min when associated with low PAF-AH • Increased concentrations of PAF in plasma during an acute allergic reaction in children and adults • PAF concentration correlates very well with the severity of an anaphylactic reaction • PAF and CRD plays an important role in anaphylaxis caused by peanuts
Chymase[85,87,98]	• Normal level: chymase <3 ng/mL • Predominantly found in mast cells, potentially stable in serum • Unknown half-life • Elevated chymase level reported hours after anaphylactic death
Carboxypeptidase A_3[85,87,98]	• Normal level: carboxypeptidase A_3 <14 ng/mL • Potentially detectable in serum and saliva; limited data suggests a rise in anaphylaxis where MCT is not elevated • Half-life longer than tryptase and this may potentially be an advantage if sampling time >2 h from onset of symptoms
Cathepsin G (dipeptidyl peptidase I)[85,98]	• Unknown half-life • Non-specific biomarker– expressed in many other cells • Elevation of cathepsin G level might correlate with severity scores during food challenge
Prostaglandin F2[106]	• Is a prostaglandin D2 metabolite • Increase in urinary prostaglandin F2 levels suggest mast cell activation in wine-induced asthma
Other inflammatory mediators[95,103,107,108]	• Serum inflammatory mediators such as IL-2, IL-6, IL-10, TNF receptor 1 have been shown to be elevated in blood during severe anaphylaxis • IL-6 has been found to correlate with severity of anaphylaxis • Due to shorter half-life, leukotrienes are difficult to measure in the blood • Increased LTE_4 are associated with anaphylaxis • Histamine can be a useful indicator of mast cell activity/degranulation but requires cold and rapid processing (including centrifugation) as it rapidly degrades

Table 2. Potential biomarkers in anaphylaxis. *ACS, acute coronary syndrome; ACE, angiotensin-converting enzyme; IgE, immunoglobin; IL, interleukin;, hereditary alpha tryptasemia; LTE, leukotriene; MCT, mast cell tryptase; TNF, tumor necrosis factor; PAF, platelet-activating factor; PAF-AH, PAF-acetylhydrolase; STEMI, ST-elevation myocardial infarction.*

trigger an anaphylactic reaction and also learn to recognize the early signs of anaphylaxis. For example, those with food allergy should be advised to carefully read food labels and inquire about ingredients when dining outside.[125,126] Those who are prone to ColdA should be mindful of the possible occurrence of serious systemic symptoms. It is crucial for them to wear suitable cold-weather attire, refrain from engaging in cold-water activities, and avoid overexposure to cold weather. Similarly, individuals who are susceptible to anaphylactoid reactions from radiocontrast media (RCM) should be aware of the risks and be educated to opt for lower osmolality RCM as a preventive measure.[127] While anaphylaxis may present with unusual symptoms, having this information can assist individuals in promptly seeking medical help in the event of a severe allergic reaction.

It is recommended that those at risk of anaphylaxis should be carrying 2 AAIs with them at all times, should be trained on how to use them, and have a personalized emergency management plan in order to manage any future episodes of anaphylaxis.[128,129] Nevertheless, it is worth mentioning that self-administered AAIs are mainly available in high-income countries.[130]

Findings from a prospective study demonstrated the impact of education on anaphylaxis management in patients with a history of anaphylaxis and their caregivers. Participants who underwent specialized training showed notable enhancement in their understanding and skills in emergency response in contrast to those who underwent standard auto-injector training.[131] In another study, an online anaphylaxis program developed for pharmacists by the ASCIA was compared with lectures or no training at all. The effectiveness of the program was assessed using a validated test administered before and after training, as well as at 3- and 7-months following training. The percentage of e-learners who met the minimum standard for anaphylaxis knowledge increased from 45% before training to 87% after 7 months, demonstrating a remarkable long-term improvement compared with other training methods.[132] Another study showed that an in-person training program delivered by a nurse increased the knowledge and confidence of the participants in preventing, recognizing, and treating anaphylaxis.[133]

Allergen immunotherapy

Allergen-specific immunotherapy (ASIT) is a strategy to prevent severe allergic response, through persistent antigenic stimulation which induces T_H2 cell anergy and apoptosis leading to development of tolerance.[134] The mechanism of ASIT involves activation of T-regulatory cells (T_{regs}) resulting in secretion of cytokines IL-10 and TGF-β, thus suppressing of T_H2 immune response and mast cell reactivity. Based on administration routes, the various types of ASIT can be sublingual (SLIT), subcutaneous (SCIT), and oral (OIT); OIT is predominantly used to manage food allergies, while SLIT and SCIT have demonstrated long-term benefit in the treatment of allergic rhinitis.[135] Prior to initiation of ASIT, it is important to assess the levels of specific IgE (sIgE) in individuals with allergy.[136] Component-resolved diagnosis (CRD) is a method used to characterize the molecular components of each allergen involved in a sIgE-mediated response.[111] CRD employs purified native or recombinant allergens to identify the sIgE antibody response directed towards the individual allergens.[137] For example, sIgE specific to *Arachis hypogea* 2 (Ara h 2), a peanut component, has been identified as a marker of severe anaphylaxis in peanut allergy, which makes Ara h 2 a good candidate for peanut ASIT.[138,139]

The guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) provide guidance to healthcare professionals using ASIT.[140] The guidelines specify that patient selection is the key point for decision making regarding ASIT since there are multiple person-dependent factors that decide the success of immunotherapy, e.g., sensitization patterns, microbiome characteristics, other existing comorbidities, and adherence to prescribed treatment. The guidelines also mention that there is sufficient evidence in support of efficacy of ASIT in adults; however, the same is lacking for pediatric patients. The current recommendations for pediatric patients state that ASIT should be considered for children with moderate-to-severe allergic rhinitis and well controlled asthma. Further, anaphylactic reactions are a possible

adverse reaction to ASIT, which highlights that it is necessary to administer immunotherapy in a clinical setting in the presence of trained personnels. The EAACI have also published detailed guidance on the application of venom immunotherapy (VIT), which is used to prevent anaphylactic reaction to insect stings such as honeybee, wasp, and ant stings.[141] VIT is recommended in individuals with systemic sting reactions or generalized skin symptoms if QoL is affected and is not recommended for individuals with only local reactions. Ongoing research in allergen immunotherapy is directed toward enhancing the ability to prevent and manage anaphylaxis and is expected to improve therapeutic interventions and foster a more informed approach to anaphylaxis management in the future.

Having a well-defined plan in place for responding to an allergic reaction is crucial, as is educating family members, friends, and colleagues about the symptoms of anaphylaxis and what steps to take if it occurs.

SUMMARY AND CONCLUSIONS

Gathering information about a patient's medical history is crucial for accurately diagnosing anaphylaxis and eliminating the possibility of other underlying conditions such as acute asthma, vocal cord dysfunction, chronic spontaneous urticaria, multiple insect bites, severe contact dermatitis, histamine intolerance, localized angioedema, syncope, and anxiety/panic attacks. A thorough clinical evaluation should encompass important details about the episode such as the allergen exposure before it occurred, the timing and length of the event, the existence of skin-related symptoms, signs of airway compromise that impacts either the upper or lower respiratory system, the presence of fainting or pre-fainting symptoms, any necessary treatment given, the reappearance of symptoms following a period of improvement, in conjunction with the patient's history of atopic conditions such as eczema or asthma. This would assist in narrowing down on diagnosis and establishing the appropriate preventive measures.[142] Obtaining details of an anaphylactic event is crucial in providing the best care for the patient. This is summarized in Fig. 1. It is important to obtain the background to the event, the route and dose of allergen exposure, timeline of symptoms, treatments administered, and the response to treatment.

Secondary care details and treatment responses are important to obtain. Anaphylaxis events may be psychologically traumatic for patients, but they may also be positive in terms of effectively recognizing symptoms and treatment required. Part of the post anaphylactic event consultation is to identify if there are factors that could be differently managed in the future to better empower the patient and or their family/caregivers. An anaphylaxis management plan should emphasize that adrenaline is the first-line treatment for anaphylaxis, and it is usually most effective when administered by an

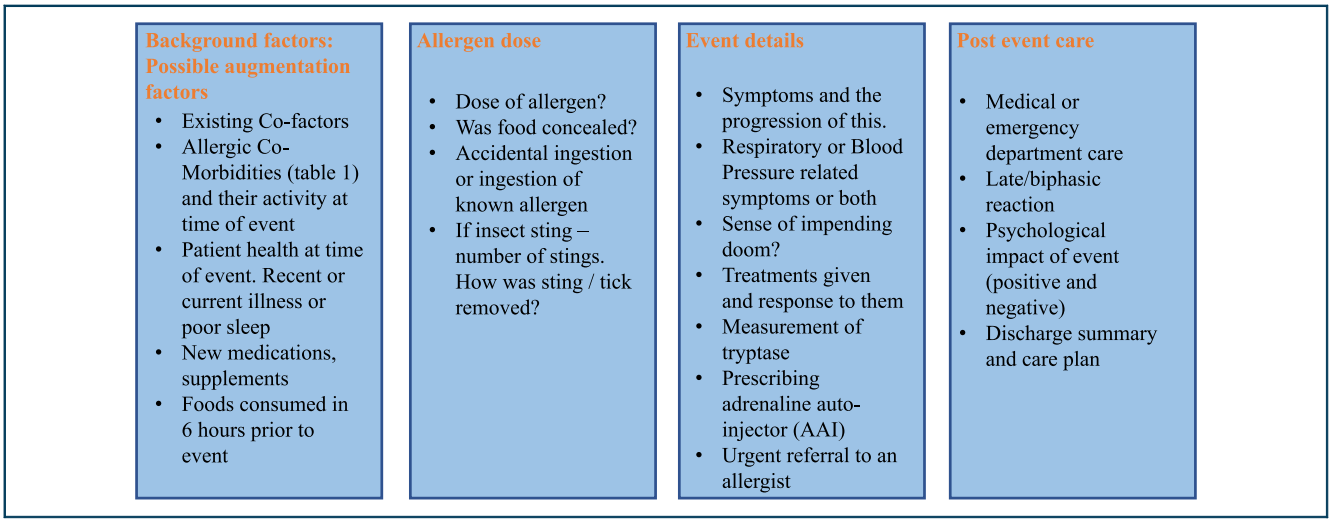

Fig. 1 Guidance for the assessment of an anaphylactic event: check list of crucial questions.

AAI, as suggested by the recently updated guidelines of the EAACI.[14] Other considerations for managing anaphylaxis effectively through appropriate dose of adrenaline includes the patient's body weight and age. Individuals who are perceived to be at risk of anaphylaxis should be provided with an AAI and be trained to use it correctly.

Acute reactions are often directly proportional to the quantum of allergen exposure. In a clinical setting, allergen challenge test might help in determining the potential allergens. A known risk factor in family history and other known potential allergens can help in identifying those at risk using such tests. Allergen sensitization is typically diagnosed through skin tests (for foods, aeroallergens, venom, and drugs), measuring serum allergen-specific IgE in the blood (for foods, aeroallergens, venom, and certain drugs), and performing provocation tests (for drugs and foods). A Working Conference held in 2010 discussed standardizing the method for assessing total serum mast cell tryptase (MCT) and agreed that for a diagnosis of mast cell activation, the acute total serum tryptase level should be at least 120% of the baseline tryptase level + 2 ng/mL (peak MCT $\geq$ [1.2 x baseline tryptase + 2 ng/mL]).[143] Though tryptase is easy to measure and very specific to mast cells, the sensitivity to diagnose anaphylaxis is only around 70%–80%.[143,144] Thus, to measure tryptase, and to find an increase from BST level, 20 + 2 rule is applicable wherein BST level is increased by more than 20% + 2 ng/mL when measured within approximately 4 h of symptom-onset, which is currently considered the diagnostic standard for confirming mast cell activation and anaphylaxis.[145] However, it is important to note that proper timing and handling of samples are crucial to avoid false negative results. Using laboratory tests that are more sensitive can hasten clinical diagnosis of anaphylaxis and may help implement long-term measures for the management of anaphylaxis. It is equally important to understand the variance between clinically measured BST levels. The clonal mast cell disorders and HαT also impact the severity of anaphylaxis, highlighting the importance of differentiating between clinically measured BST levels and using this differentiation to establish a threshold that can accurately distinguish anaphylaxis from BST variability.[146,147] This is particularly crucial for individuals with elevated BST caused by HαT but without clonal mast cell disease. In such cases, the 20 + 2 rule may not yield optimal results, and the diagnosis of anaphylaxis may be complicated by the presence of episodic symptoms like gastrointestinal distress, autonomic instability, or subjective upper respiratory compromise, which may or may not be attributed to mast cell degranulation.

It is also crucial to seek the expertise of an allergy specialist for patients with both asthma and allergies, as their symptoms may overlap and asthma can elevate the risk. Even mild symptoms from certain foods such as nuts, shellfish, fish, and seeds should not be overlooked as future reactions could be severe.[132]

In conclusion, anaphylaxis is a severe and potentially life-threatening condition, and patients who are susceptible remain at a high risk of experiencing a recurrence. Many of the factors that contribute to the severity of reactions are modifiable by timely identification and management. Diagnosing anaphylaxis is challenging due to overlapping symptoms with other medical conditions. Thus, to prevent symptom progression, hospitalization, and fatalities in these patients, it is crucial to promptly recognize anaphylactic episodes and administer first-line treatment with adrenaline. Biomarkers play an important role in identifying the disease condition and facilitate accurate diagnosis. Anaphylaxis involves activation of multiple pathways involving IgE, different cell types, and a wide range of mediators. Using recently identified biomarkers will be useful to reinforce the diagnosis and distinguish anaphylaxis from similar clinical scenarios. Thus, a robust knowledge of the plethora of anaphylactic mechanism would lead to better clinical management of anaphylaxis. Further, it is necessary to improve global awareness on anaphylaxis and provide essential guidance to patients at risk for self-management of anaphylactic symptoms through therapeutic tools like AAIs.

Abbreviations

AAI, adrenaline auto-injector; ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; CVD, cardiovascular disease; IgE, immunoglobulin E; IL, interleukin; HαT, hereditary alpha tryptasemia; HRQoL, health-related

quality-of-life; LTE, leukotriene; MCT, mast cell tryptase; PAF, platelet-activating factor; PAF-AH, PAF-acetylhydrolase; RCM, radiocontrast media; STEMI, ST-elevation myocardial infarction; TNF, tumor necrosis factor; QoL, quality-of-life.

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