ORIGINAL ARTICLE

Anaphylaxis pathogenesis and treatment

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Abstract

Anaphylaxis is a serious allergic reaction that is rapid in onset and sometimes leads to death. Understanding mechanisms, triggers, and patient-specific risk factors for severe or fatal anaphylaxis is critically important. Diagnosis of anaphylaxis is currently based on established clinical criteria. Epinephrine (adrenaline) is the first-line medication for anaphylaxis treatment and delay in injecting it contributes to biphasic reactions, hypoxic-ischemic encephalopathy, and fatality. Here, we focus on four important areas of translational research in anaphylaxis: studies of potential new biomarkers to support the clinical diagnosis of anaphylaxis, laboratory tests to distinguish allergen sensitization from clinical risk of anaphylaxis, the primary role of epinephrine (adrenaline) in anaphylaxis treatment, and strengthening the overall evidence base for anaphylaxis treatment.

Anaphylaxis pathogenesis typically involves IgE and the high-affinity IgE receptor, however, other immunologic, IgE-independent mechanisms and direct mast cell activation by non-immunologic triggers such as exercise and cold air or water are also important (Fig. 1) (1). In young people, food is the most common trigger; in middle-aged and older adults, medications and insect stings are relatively common triggers. Regardless of the mechanism or trigger, mast cells and basophils initiate and amplify anaphylaxis, leading to a cascade of mediators, including tryptase and histamine. Target organs in anaphylaxis include the skin, respiratory tract, gastrointestinal tract, cardiovascular system and central nervous system. Anaphylaxis is characterized by sudden onset and rapid progression. Patient risk factors for severe or fatal anaphylaxis potentially include very young or old age, pregnancy, comorbidities such as asthma, cardiovascular disease, and mastocytosis, and concurrent medications such as β-blockers and angiotensin-converting enzyme inhibitors (2, 3).

Biomarkers of anaphylaxis

Currently, only two biomarkers are measured in clinical laboratories: total tryptase levels and histamine levels (3, 4). These tests are not typically available on an emergency basis; hence, the critical importance of making a prompt clinical diagnosis. They are not specific for anaphylaxis; for example, tryptase can be elevated in myocardial infarction, mastocytosis, and other diseases. Serial tryptase levels measured during the course of anaphylaxis, including a baseline (post-event) level, appear to be more helpful than a single measurement at one time point. Tryptase is seldom elevated in food-triggered anaphylaxis or in patients who are normotensive during anaphylaxis. Absence of an elevated tryptase level does not rule out the clinical diagnosis of anaphylaxis (3).

Other potentially useful biomarkers are being investigated, including mature β tryptase (G5 antibody), platelet-activating factor (PAF), bradykinin, chymase, mast cell carboxypeptidase A3, dipeptidyl peptidase I, IL-33 and other cytokines, and some leukotrienes and prostaglandins (3–9). In human anaphylaxis, serum PAF levels increase transiently and correlate with severity and fatality (5). Low levels of PAF acetylhydrolase are found in fatal anaphylaxis and failure of PAF inactivation by this enzyme might help to identify patients at risk of severe or fatal anaphylaxis.

Allergen sensitization *vs* clinical risk of anaphylaxis

Sensitization to food (as an example) is common in the general population, especially in young people; however, the level of sensitization as determined from skin prick test results and allergen-specific IgE levels in serum does not necessarily predict occurrence or severity of future anaphylactic episodes (10).

In vitro tests currently used in research, including allergen-specific cytokine production and component-resolved diagnosis (CRD), might or might not distinguish allergen sensitization from clinical risk of anaphylaxis and reduce the need for potentially risky, time-consuming food challenge/provocation tests. We have discovered that food-dependent cytokine responses are ubiquitous in the general population and that

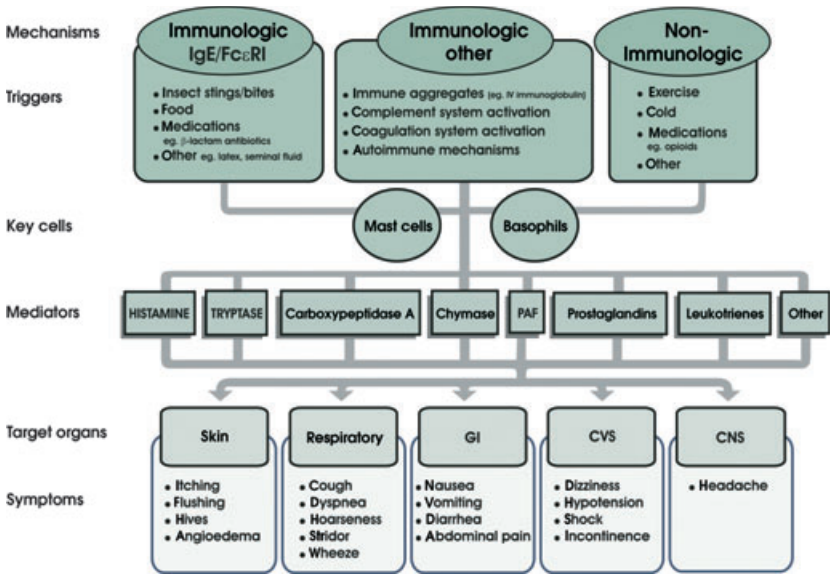

Figure 1 Anaphylaxis pathogenesis. Reprinted from The Journal of Allergy and Clinical Immunology, 121/2, Simons FER, Anaphylaxis. 2008 Mini-primer on allergic and immunologic diseases, S402-S407, Copyright (2008), with permission from Elsevier.

although such measurements are important research techniques, they are of limited value in predicting the clinical risk status of an individual (11). By CRD, only about 20% of children who are sensitized to a food as determined by positive skin prick tests and food-specific IgE levels in serum are actually clinically reactive to that food (12). CRD might potentially have some ability to predict food challenge test results; however, additional validation is needed (13).

Epinephrine in anaphylaxis treatment

Epinephrine is uniquely life-saving in the initial treatment of anaphylaxis because its alpha-1 adrenergic agonist vasoconstrictor effects prevent and relieve laryngeal edema, hypotension, and shock (14). Failure to inject epinephrine in a timely manner increases the risk of biphasic anaphylaxis, hypoxic-ischemic encephalopathy, and fatality (2, 3). In one study, only 14% of 164 patients with anaphylaxis received epinephrine before respiratory or cardiac arrest, which occurred within a median time of 5 min of exposure to the trigger in iatrogenic anaphylaxis, 15 min in stinging insect venom anaphylaxis, and 30 min in food anaphylaxis (15).

A Cochrane systematic review, although not identifying any adequate randomized controlled trials of epinephrine in anaphylaxis, found compelling data for epinephrine use from fatality studies and studies of peri-operative anaphylaxis documenting prompt responses to epinephrine injection in continuously monitored patients (16).

In a randomized controlled clinical pharmacology study conducted at baseline in children at risk of anaphylaxis, the mean time to peak epinephrine levels was 8 min after intramuscular injection from an epinephrine auto-injector *vs* 34 min after subcutaneous epinephrine injection (17).

In contrast to epinephrine ampules, which are universally available (18), epinephrine auto-injectors for treatment of anaphylaxis in community settings are available in only 60% of countries worldwide, and their high median cost ($98 US) is a barrier to use in many countries (19). The alternatives are unsatisfactory; for example, in unsealed syringes prefilled with epinephrine, degradation of the medication occurs within 3–4 months (20).

Reasons for failure to self-inject epinephrine during an anaphylactic episode include: use of an antihistamine or an asthma inhaler, never receiving a prescription for an epinephrine auto-injector, or not having an epinephrine auto-injector available when anaphylaxis occurred (21).

In the past, limitations of epinephrine auto-injectors included availability of only two fixed doses (0.15 mg and 0.3 mg), relatively short shelf-life (12–18 months), and lack of safety features to prevent unintentional injections of epinephrine, with resulting injury and/or loss of effective dose (14, 22). More user-friendly epinephrine auto-injectors are being introduced; for example, an auto-injector with a fixed dose of 0.5 mg is now available, the shelf-life of some products has been lengthened to 24 months, and several types of auto-injectors now have safety features to reduce the possibility of unintentional injections (23, 24). Development of novel auto-injectors (23, 24) and alternative epinephrine formulations (25) is ongoing.

Strengthening the overall evidence base for anaphylaxis treatment

No randomized controlled trials that are free from methodologic problems and meet current standards have been performed with epinephrine, antihistamines, or glucocorticoids

in the initial treatment of anaphylaxis (2, 3, 26–28). The evidence base for epinephrine injection in anaphylaxis is stronger than the evidence base for the use of other medications in this medical emergency (2, 3, 14, 16). It includes observational studies, randomized controlled trials at baseline in patients at risk, studies in animal models, *in vitro* studies, and epidemiology studies (14–23, 25). Anaphylaxis guidelines unanimously recommend prompt injection of epinephrine as the life-saving first-line medication in anaphylaxis. Epinephrine is designated by the World Health Organization as an essential medication for anaphylaxis, and as noted previously, epinephrine ampules are universally available worldwide, in contrast to epinephrine auto-injectors (18, 19). For ethical reasons, placebo-controlled trials of epinephrine should not be conducted in anaphylaxis (2, 3, 26).

Guidelines differ in their recommendations for administration of antihistamines and glucocorticoids in anaphylaxis (26); use of these medications in anaphylaxis is based mainly on use in urticaria and asthma, respectively (27, 28).The possibility of conducting randomized placebo-controlled trials with antihistamines, particularly with glucocorticoids, in anaphylaxis should be considered. Glucocorticoids are ideal candidates for study because their relatively slow onset of action provides a window of time in which informed consent can be obtained, and baseline vital signs and other measurements can be made. Indeed, during the past 3–4 decades, many randomized placebo-controlled trials of different systemic glucocorticoids have been conducted in acute asthma (29, 30). If such trials are conducted in anaphylaxis, important precautions will be mandatory. The studies will need to be conducted in selected well-equipped centers with skilled, experienced healthcare professionals and critical care back-up. All patients enrolled should receive state-of-the-art care with prompt epinephrine injection(s), placement in the supine position, supplemental oxygen, intravenous fluid resuscitation, and other interventions as indicated (2, 3, 26).

Conflict of interest

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