Diagnosis and management of anaphylaxis in precision medicine

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Target Audience: Physicians and researchers within the field of allergic disease.

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Activity Objectives:

1. To recognize anaphylaxis phenotypes based on clinical symptoms and potential triggers and to understand their underlying pathogenesis.
2. To understand the utility of various biomarkers in diagnosing anaphylaxis.
3. To understand appropriate circumstances when rapid desensitization might be considered.
4. To recognize cardiac complications that can occur in patients with anaphylaxis.

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Anaphylaxis is the most severe and frightening of the allergic reactions, placing patients at high risk and demanding prompt recognition and immediate management by health care providers. Yet because its symptoms imitate those of other diseases, such as asthma and urticaria, current data suggest that its diagnosis is often missed, with underuse of tryptase measurement; its treatment is delayed, with little use of epinephrine; and its underlying cause or causes are poorly investigated. Deaths from anaphylaxis are difficult to investigate because of miscoding. Surprisingly, patients treated with new and powerful chemotherapy agents and humanized mAbs present with nonclassical symptoms of anaphylaxis, and patients may present with unrecognized clonal mast cell disorders with *KIT* mutations may present as Hymenoptera-induced or idiopathic anaphylaxis. The goal of this review is to recognize the presentations of anaphylaxis with the description of its current phenotypes, to provide new insight and understanding of its mechanisms and causes through its endotypes, and to address its biomarkers for broad clinical use. Ultimately, the aim is to empower allergists and heath care providers with new tools that can help alleviate patients' symptoms, preventing and protecting them against anaphylaxis. (J Allergy Clin Immunol 2017;140:321-33.)

Key words: *Anaphylaxis, adverse drug reactions, drug hypersensitivity reactions, hypersensitivity reactions, IgE, mAbs*

Anaphylaxis is a word recognized and feared by most, if not all, health care providers because of its association with potential death from cardiovascular collapse or asphyxiation caused by laryngeal edema. Yet its diagnosis is missed in 80% of patients who are seen in the emergency department (ED), undergoing anesthesia and surgery or being treated with chemotherapy, mAbs, or biological agents. Patients are given codes for asthma, urticaria, angioedema, or hypotension, but occurrence of the

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Abbreviations used
ACE: Angiotensin-converting enzyme
ED: Emergency department
FTEIA: Food-triggered exercised-induced anaphylaxis
THIQ: Tetrahydroisoquinoline

alarming signs and symptoms of anaphylaxis together does not trigger an immediate suspicion for a multiorgan system syndrome and does not result in the prompt use of epinephrine or an evaluation of an acute serum tryptase level. The diagnosis of a toxic reaction is often given mistakenly to chemotherapy-induced anaphylactic events.

Because anaphylaxis mimics common syndromes, such as asthma and urticaria, and because it can present without hypotension, its diagnosis is often missed or delayed. There is a new understanding that atypical symptoms, such as pain, can be seen during chemotherapy-induced anaphylaxis and that clonal disorders, such as monoclonal mast cell activation syndrome, are part of the wide spectrum of anaphylaxis. Anaphylaxis occurs more in women. Anaphylaxis can be one of the most traumatic events in a patient's life, with long-lasting and sometimes incapacitating sequelae. Empowering patients by using the correct label, educating them about the potential triggers and causes, providing them with appropriate acute treatment, and giving them an effective treatment plan have been shown to help increase the quality of life and safety of these patients.

The purpose of this review is to redefine the phenotypes and endotypes of anaphylaxis in light of new evidence-based information regarding its presentation and causes. The goal is to help allergists and health care providers recognize newly appreciated anaphylaxis-associated symptoms, look for biomarkers, and apply best practice management and treatment options to improve quality of life for patients with anaphylaxis.

CLINICAL VIGNETTE: "DOC, NOBODY KNOWS WHAT I HAVE"

This was the opening sentence during the first visit of a 39-year-old man and his wife to the allergy clinic after being seen by no less than 10 specialists. They wanted to start a family but would not because he feared he would die any minute of an unknown cause or trigger.

Twenty years ago, as a landscaper at age 19 years, he passed out in the grass after being stung by several wasps. He was revived and given an epinephrine injectable device. A few months later, he had an unexplained L5 fracture and was given a tentative diagnosis of osteoporosis and started on bisphosphonates. He changed jobs because he presented with episodes of flushing, fatigue, fever, abdominal bloating, pain, and diarrhea unexpectedly. He was told he had irritable bowel syndrome, but the symptoms of diarrhea were so unpredictable that he limited his social life. Five years ago, he was cutting bushes, hit a nest, and was stung by many bees. He became flushed with a sense of impending doom, had syncope and seizures, and required an intravenous epinephrine drip before a pulse returned. Last August, he was working at a liquor company moving beer cases, and during a hot and humid day, he felt very flushed, passed out, and was revived in the ED after several epinephrine injections and liters of fluid and told he was dehydrated.

He never had a rash and was told that his osteoporosis, bone fractures, and gastrointestinal problems were unrelated and that he could die at any time because nobody knew why his blood pressure went so low or the specific triggers for these events. A diagnosis of anaphylaxis was not attached to his official chart, which contained more than 200 pages, and an investigation of the potential cause or causes was never undertaken. A tryptase measurement was done during his last ED visit, and the level was found to be increased.

"Could all this be explained by a mast cell disorder?," he asked after going online and reading several hundred documents on mastocytosis. Why would a mast cell disorder be associated with anaphylaxis?

ANAPHYLAXIS: DEFINITION AND NEW CLASSIFICATION

From the initial definition by Charles Richet and Paul Portier in 1901 as an immune reaction that accomplished the opposite of protection (*ana* = absence, *phylaxis* = protection in Greek)[1,2] to a casual definition given recently by an educated lawyer at a trial of an allergic patient who died after intravenous contrast dye injection as "something that can be treated if properly recognized," anaphylaxis has eluded definition because of the lack of a single organ target and a broad spectrum of presentations.[3] This is exemplified by the new International Classification of Diseases, 10th Edition (ICD-10), coding system, which provides one code for anaphylaxis without qualifiers (T78.2XXA) and more than 100 codes (the last one in alphabetical order being T63.94XD) for anaphylaxis qualifiers.

Despite this plethora of possible diagnoses, the symptoms of anaphylaxis continue to be underrecognized for all age groups, sexes, and races; its diagnosis is often missed; its treatment is often delayed, including the lack of epinephrine use; and the underlying causes are underinvestigated across the globe.[4-6] From its initial description as a clinical entity with acute onset of symptoms involving 2 or more organs or associated with hypotension or upper respiratory compromise by expert panels,[7,8] its definition has evolved to a more mechanistic description based on precision medicine into phenotypes with underlying endotypes supported by diagnostic biomarkers.[9] As seen in Fig 1, *A*, anaphylaxis phenotypes are defined by clinical presentation into type I–like reactions, cytokine storm–like reactions, and mixed reactions. The endotypes underlying these phenotypes include IgE- and non–IgE-mediated mechanisms, cytokine release, mixed reactions, and direct activation of immune cells.

Cellular targets for IgE-mediated reactions include mast cells, basophils, and other immune cells and symptoms related to the actions of mediators on the target organs.[10] The common triggers for these reactions include foods, drugs, Hymenoptera venoms, and environmental allergens. Among common allergens are foods, such as peanut, milk, eggs, and nuts; antibiotics, such as β-lactams; chemotherapy agents, such as platins and taxanes; chimeric, humanized, and human mAbs; general anesthetics; and immunotherapy allergens. Flushing, pruritus, hives, angioedema, shortness of breath, wheezing, nausea, vomiting, diarrhea, hypotension, oxygen desaturation, and cardiovascular collapse are classical clinical manifestations caused by the release of inflammatory mediators from mast cells and basophils (Fig 1, *B*). More recently, in addition to these