# Risk assessment in anaphylaxis: Current and future approaches

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**Risk assessment of individuals with anaphylaxis is currently hampered by lack of (1) an optimal and readily available laboratory test to confirm the clinical diagnosis of an anaphylaxis episode and (2) an optimal method of distinguishing allergen-sensitized individuals who are clinically tolerant from those at risk for anaphylaxis episodes after exposure to the relevant allergen.**

**Our objectives were to review the effector mechanisms involved in the pathophysiology of anaphylaxis; to explore the possibility of developing an optimal laboratory test to confirm the diagnosis of an anaphylaxis episode, and the possibility of improving methods to distinguish allergen sensitization from clinical reactivity; and to develop a research agenda for risk assessment in anaphylaxis.**

**Researchers from the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergology and Clinical Immunology held a PRACTALL (Practical Allergy) meeting to discuss these objectives.**

**New approaches being investigated to support the clinical diagnosis of anaphylaxis include serial measurements of total tryptase in serum during an anaphylaxis episode, and measurement of baseline total tryptase levels after the episode. Greater availability of the test for mature β-tryptase, a more specific mast cell activation marker for anaphylaxis than total tryptase, is needed. Measurement of chymase, mast cell carboxypeptidase A3, platelet-activating factor, and other mast cell products may prove to be useful. Consideration should be given to measuring a panel of mediators from mast cells and basophils. New approaches being investigated to help distinguish sensitized individuals at minimum or no risk from those at increased risk of developing anaphylaxis include measurement of the ratio of allergen-specific IgE to total IgE, determination of IgE directed at specific allergenic epitopes, measurement of basophil activation markers by using flow cytometry, and assessment of allergen-specific cytokine responses.**

**Algorithms have been developed for risk assessment of individuals with anaphylaxis, along with a research agenda for studies that could lead to an improved ability to confirm the clinical diagnosis of anaphylaxis and to identify allergen-sensitized individuals who are at increased risk of anaphylaxis. (J Allergy Clin Immunol 2007;120:S2-24.)**

***Key words:*** *Anaphylaxis, mast cell, basophil, IgE, FcεRI, histamine, tryptase, mast cell carboxypeptidase, allergens, insect venom allergy, food allergy*

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*Abbreviations used*

ACE: Angiotensin converting enzyme
C3a, C5a: Fragments of complement C3 and C5 proteins referred to as anaphylatoxins
CCDs: Cross-reacting carbohydrate determinant
HHMC: Human heart mast cell
Kit: Transmembrane tyrosine kinase receptor for stem cell factor
$LTC_4$: Leukotriene $C_4$
PAF: Platelet-activating factor
$PGD_2$: Prostaglandin $D_2$
SCF: Stem cell factor
SPT: Skin prick test

Anaphylaxis is a serious systemic allergic reaction that is rapid in onset and may cause death.[1-4] Critically important unmet needs in anaphylaxis risk assessment currently include (1) lack of an optimal, readily available laboratory test to confirm the clinical diagnosis of an anaphylaxis episode and (2) lack of an optimal method of distinguishing between individuals who are sensitized to allergens known to trigger anaphylaxis but are not at increased risk of anaphylaxis on exposure to these allergens, and those who are not only sensitized but also at increased risk of developing symptoms and signs of anaphylaxis on exposure, and of possible fatality.[5]

Inability to confirm the clinical diagnosis of anaphylaxis likely contributes to underrecognition and undertreatment of the disease.[5,6] Many more individuals are sensitized to allergens than are actually at risk for anaphylaxis,[7,8] leading to quandaries in risk assessment that may contribute to quandaries in making recommendations for long-term risk reduction.[9] Researchers from the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergology and Clinical Immunology held a PRACTALL (Practical Allergy) meeting to review effector mechanisms in anaphylaxis (Fig 1, *A* and *B*) and to deliberate issues with regard to confirming the diagnosis of anaphylaxis (Fig 2) and confirming the anaphylaxis trigger (Fig 3).

The diagnosis of anaphylaxis is based primarily on the clinical history[1,5,10,11] (Table I; Fig 2). Clinical criteria for accurate, early identification of anaphylaxis have recently been promulgated.[1] Although the clinical diagnosis can sometimes be supported by laboratory tests—for example, measurement of histamine concentrations in plasma, or of total tryptase concentrations in serum or plasma—these currently available tests have intrinsic limitations.[12] The blood sample must be obtained within minutes (histamine) to a few hours (tryptase) after onset of symptoms (Table II). This is impossible in the many patients who experience anaphylaxis in community settings and arrive in the emergency department some time later with resolving symptoms. Also, even when blood samples are optimally timed, tryptase levels are often within normal limits,[12] particularly in individuals with food-induced anaphylaxis.[13,14] Laboratory tests with increased sensitivity and practicality are therefore urgently needed to confirm the clinical diagnosis of anaphylaxis, improve recognition of the disease, and implement long-term risk reduction measures. Ideally, a rapid diagnostic test will eventually be developed for use in healthcare settings during and after immediate treatment of anaphylaxis. Currently, this goal may not be realistic in a disease that potentially causes death within minutes and mandates prompt intervention.[13,15]

Accurate risk assessment in anaphylaxis also involves verification of the trigger factor, where possible, because avoidance of the specific trigger and/or trigger-specific immunomodulation are critical steps in long-term risk reduction[5] (Table III; Fig 3). Sensitization is readily confirmed by using allergen skin tests or measuring allergen-specific IgE concentrations; however, substantial numbers of sensitized individuals do not develop any symptoms after exposure to the relevant allergen.[7,8] This discordance is not well understood, nor is it fully understood why, rarely, individuals with negative allergen skin tests and undetectable allergen-specific IgE levels develop severe or even fatal anaphylaxis to the antigen.[16,17]

In this workshop, effector mechanisms in anaphylaxis were reviewed, with emphasis on IgE-dependent mechanisms. Algorithms for risk assessment in anaphylaxis were developed, and a research agenda was created listing studies that will lead to improved risk assessment in anaphylaxis. Two important issues were discussed in depth: (1) development of an optimal test for laboratory confirmation of the clinical diagnosis and (2) development of improved methods for identification of individuals at risk of anaphylaxis from specific allergens, focusing particularly on 2 common triggers, insect venoms and foods, as examples.