

Review article

Practical allergy (PRACTALL) report: risk assessment in anaphylaxis

Effector mechanisms in anaphylaxis were reviewed. Current approaches to confirmation of the clinical diagnosis were discussed. Improved methods for distinguishing between allergen sensitization (which is common in the general population) and clinical risk of anaphylaxis (which is uncommon) were deliberated. Innovative techniques that will improve risk assessment in anaphylaxis in the future were described.

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There are two important unmet needs in anaphylaxis risk assessment. The first of these is lack of an optimal, readily available laboratory test to confirm the clinical diagnosis of an anaphylaxis episode. The second, is a lack of an optimal method of distinguishing between allergen-sensitized individuals who are clinically tolerant and those who are at risk for anaphylaxis after exposure to the relevant allergen.

Researchers from the American Academy of Allergy, Asthma and Immunology and the European Academy of Allergology and Clinical Immunology held a Practical Allergy (PRACTALL) meeting in New York City, April 21–23, 2006, on the topic of risk assessment in anaphylaxis. They began by reviewing effector mechanisms in anaphylaxis. Then, they discussed the possibility of developing improved, practical laboratory tests to confirm the diagnosis of an anaphylaxis episode, and the possibility of developing improved methods to distinguish allergen sensitization from clinical risk.

Mechanisms in anaphylaxis

Effector mechanisms in anaphylaxis do not need to be differentiated with regard to clinical diagnosis and acute treatment; do not need to be differentiated with regard to clinical diagnosis and acute treatment; nevertheless, it remains critically important to understand them with regard to long-term risk reduction measures, which are trigger- and mechanism-specific. PRACTALL meeting participants focused mainly on anaphylaxis mechanisms involving IgE, the high affinity IgE receptor on mast cells and basophils, and products of mast cell and basophil activation; however, other mechanisms were also examined.

The potential relevance of murine anaphylaxis mechanisms to human anaphylaxis was reviewed. In addition, the human heart as both an effector organ and a target organ in anaphylaxis was discussed.

Confirming the clinical diagnosis of anaphylaxis: current and future approaches

PRACTALL meeting participants affirmed that the diagnosis of anaphylaxis is based primarily on the clinical history, and noted that useful clinical criteria for accurate early identification of anaphylaxis have recently been promulgated. Laboratory tests that are currently available to support the clinical diagnosis of anaphylaxis have intrinsic limitations. Plasma histamine levels typically peak within 5–10 min of symptom onset and decline to baseline by 60 min; moreover, the blood sample requires special handling. Serum total tryptase levels need to be obtained within a few hours of symptom onset, and even when optimally timed, tryptase levels are generally not elevated in individuals with food-induced anaphylaxis.

Inability to confirm the clinical diagnosis of anaphylaxis by use of rapid and readily available laboratory tests likely contributes to under-recognition and under-treatment of the disease.

New approaches to support the clinical diagnosis of anaphylaxis are therefore needed. Those being investigated include: serial measurements of total tryptase in serum during an anaphylaxis episode, and measurement of baseline total tryptase levels after complete resolution of the anaphylaxis episode, to assist retrospectively with interpretation of total tryptase levels obtained during the episode. In the future, greater availability of the test for mature (beta) tryptase, which is 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 in serum or plasma might prove to be useful, and consideration should be given to measuring a panel of mediators from mast cells and basophils.

Distinguishing between allergen sensitization and clinical risk: current and future approaches

Many individuals in the general population are sensitized to allergens, but few are actually at risk for anaphylaxis. For example, up to 25% of individuals have detectable insect venom-specific IgE levels, and approximately 60% of individuals have detectable food-specific IgE levels, yet most of these people do not experience symptoms and signs of anaphylaxis when exposed to the allergens to which they are sensitized. This discordance between sensitization and clinical risk may lead to quandaries in risk assessment and quandaries in making recommendations for long-term risk reduction.

PRACTALL meeting participants concluded that risk assessment in anaphylaxis should go well beyond detection of sensitization to allergens using skin tests and/or quantitative *in vitro* tests to detect allergen-specific IgE. Greater attention should be paid to relevant clinical factors including age; co-morbidities such as asthma, mastocytosis, or ischemic heart disease; concurrent chemical or medication use; or strenuous exercise; any of which might significantly increase the risk of an anaphylaxis episode and/or fatality during anaphylaxis. The role of allergen challenge tests, which are time-consuming, costly, and not without risk, should be defined more clearly.

Current and future approaches to risk assessment were discussed extensively, using Hymenoptera venom allergy and food allergy as two specific examples. In addition, unique aspects of risk assessment in individuals with medication-induced anaphylaxis, peri-operative anaphylaxis, transfusion-related anaphylaxis, Anisakis-induced anaphylaxis, and anaphylaxis from novel triggers were discussed.

The role of cellular tests was examined, particularly the evolving role of the basophil activation test in which

upregulation of basophil surface markers such as CD63 or CD203c are measured after stimulation with different concentrations of allergen. It was noted that although this test is now being used in some European medical centers to sort out clinical situations in which the history, the allergen skin tests, and the allergen-specific IgE levels are discordant, it remains a research tool in most non-European countries.

Additional new approaches being investigated to help distinguish sensitized individuals at minimum or no risk from those at risk from anaphylaxis include: measurement of the ratio of allergen-specific IgE to total IgE, determination of IgE directed at specific allergenic epitopes, and assessment of allergen-specific cytokine response patterns.

Outcomes from the PRACTALL anaphylaxis meeting

To facilitate risk assessment of individuals with anaphylaxis, algorithms for confirming the diagnosis of anaphylaxis and confirming the anaphylaxis trigger were developed. A research agenda was prepared, listing

studies that might lead to improved understanding of the mechanisms and pathogenesis of anaphylaxis in the future, as well as to improved ability to confirm the clinical diagnosis of an anaphylaxis episode, and improved ability to identify allergen-sensitized individuals who are at increased risk of anaphylaxis. Eventually, evidence-based risk assessment in anaphylaxis will be possible.

The complete report of the PRACTALL Anaphylaxis Meeting on risk assessment in anaphylaxis, including the algorithms and the research agenda, can be found in Simons et al. (1).

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Reference

1. Simons FER, Frew AJ, Ansotegui IJ, Bochner BS, Golden DBK, Finkelman FD et al. Risk assessment in anaphylaxis: current and future approaches. *J Allergy Clin Immunol* 2007;**120**:S2–S24.