

Anaphylaxis: Bench to Bedside



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Anaphylaxis has long been a condition associated with extreme anxiety for patients and clinicians alike. We have begun to acquire a deeper understanding of the immunologic pathways, and the tools necessary to identify the risk factors that promote reactions and can serve as targets for preventative treatment. The articles in this theme issue of the *Journal of Allergy and Clinical Immunology: In Practice* reflect the accelerating pace of advances in this unique area within allergy-immunology.

In the past, evaluation and management of the patient with anaphylaxis was limited to performing allergy tests to determine the cause (which is often elusive and difficult to prove without intentional challenge) and prescribing an epinephrine auto-injector (EAI). In recent years, astute clinical observation and bench-to-bedside research have partnered to reveal more of the spectrum of disease, the clinical patterns of anaphylactic reactions, and the risk factors for severe and life-threatening anaphylaxis. These now provide the clinician with more targeted approaches to evaluation and more options for preventative treatment. Akin et al¹ introduce us to the spectrum of anaphylaxis and mast-cell–related conditions. They provide a framework for the clinician to obtain a targeted history of the event and its circumstances, and use appropriate investigations to clarify the contributing factors and risk of severe reactions. Dispenza et al² provide an instructive overview of the advances in our understanding of mast cells in anaphylaxis. They describe the role of IgE receptors and intracellular signaling pathways, inhibitory receptors and pathways, and the development of new treatment approaches targeting these pathways. Carter et al³ describe a wide range of extrinsic and intrinsic factors that can modulate the clinical expression of anaphylaxis. They review advances in our understanding of receptors on mast cells, various white blood cells, and platelets, and a growing recognition of risk factors that can lower the threshold for reaction or increase the severity of anaphylaxis. Stone et al⁴ review the lessons learned from the rollout of the COVID-19 vaccines, including potential

mechanisms and patterns of reactions, recognition of non-immunologic responses, and approaches to evaluation and management of patients with potential risk factors or a history of previous vaccine reaction. Bonadonna et al⁵ take us through the diagnostic process using the most current investigative tools for venom-IgE and the rationale for a stepwise evaluation for potential underlying mast cell disorders. They provide the clinician with clear explanation of how to interpret serum tryptase measurements, when to explore other markers of mast cell disorders, and the role of bone marrow biopsy.

These review articles were meant to focus on areas in which there have been the greatest advances in clinical research as well as the greatest impact on what we can do in practice. One recurrent theme in these reviews is that whether we study anaphylaxis to foods, drugs, insect stings, exercise, or unknown causes, in recent years we recognize a central role for mast cells. We now have ever-improving tools with which to probe the regulation, activation, function, and modulation of mast cells. These invariably enter the discussion of anaphylaxis, be it the mechanisms, manifestations, cofactors, severity, causative agents, or treatment. This leads to some overlap and potential repetition among the reviews regarding mast cells in anaphylaxis, but the focus in each article is within a specific context that has some unique features from other discussions of anaphylaxis. The latest and still-evolving observation connecting mast cell disorders and anaphylaxis is the finding that approximately 6% of the population has excess copies of the *TPSAB1* gene and therefore higher than average levels of baseline serum tryptase.⁶ Although most individuals with hereditary alpha-tryptasemia (H α T) are asymptomatic, there may be an increased risk for severe anaphylaxis.^{7,8} In individuals with mastocytosis, insect venom anaphylaxis, or idiopathic anaphylaxis who have baseline serum tryptase level of more than 8 ng/mL, testing for H α T should be considered because H α T is present in 10% to 20% of such patients who have severe anaphylaxis.^{8,9}

We must not let our focus on mast cells blind us to the potentially important role of other players in this drama, including platelets, neutrophils, lymphocytes, and even neural pathways and mediators. We often forget that the mast cell has a partner in crime: the circulating basophil. Although basophils have a lower concentration of histamine when compared with mast cells, they are an important source of histamine in response to an IgE-mediated event. It is also postulated that basophils may have a more prominent role in late-phase reactions due to their ability to release IL-4 and IL-13,¹⁰⁻¹² which may also support the local production of allergen-specific IgE in tissues.¹³⁻¹⁵ The assays for assessing the contribution of basophil activation such as the basophil activation test and other measures, for example, CD203c, are currently limited to research protocols and therefore not available commercially in the United States.

In this theme issue, we present developments of importance to the clinician that have resulted from insightful exploration of the

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Conflicts of interest: D. B. K. Golden reports that he is on advisory boards for Genentech, Novartis, ThermoFisher, Aquestive, and Allergy Therapeutics and receives clinical trials support from Genentech, Novartis, ThermoFisher, Pfizer, GlaxoSmithKline, Merck, and Regeneron. M. C. Carter has no conflicts of interest to declare.

Received for publication May 19, 2023; accepted for publication May 21, 2023.

Available online May 25, 2023.

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J Allergy Clin Immunol Pract 2023;11:2049-50.

2213-2198

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<https://doi.org/10.1016/j.jaip.2023.05.020>

immunologic players and pathways that lead to anaphylaxis. We are also reminded that there are always new and unexpected observations as well as knowledge gaps that are revealed as we explore anaphylaxis. These reviews suggest a future in which we will be better able to prevent anaphylaxis and target those at greatest risk.

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