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Opinion

The Critical Role of Tryptase Testing in the Rapid Diagnosis of Anaphylaxis: A Call for Point-of-care Assays

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Anaphylaxis is a life-threatening consequence of allergic reactions characterized by the rapid onset and progression of systemic symptoms.[1] Swift identification and management of anaphylaxis are crucial to patient outcomes, yet diagnosing this condition remains a significant challenge due to its variable presentation and overlap with other medical emergencies. Tryptase, a protease released from mast cells, serves as a sensitive biomarker that can aid in the confirmation of anaphylaxis.[2] Despite its clinical utility, the current standard of care for tryptase testing in the United States, a single Food and Drug Administration-cleared assay typically only available as a send-out laboratory test, often results in delayed results, which can be detrimental in acute settings. This article advocates for the implementation of point-of-care (POC) tryptase assays to enhance real-world diagnosis of anaphylaxis, potentially enabling timely therapeutic intervention in difficult cases and diagnostic certainty in specific clinical settings.

The diagnostic challenge of anaphylaxis lies in its diverse clinical manifestations, ranging from mild cutaneous reactions to cardiovascular and respiratory compromise, a spectrum that can obscure diagnosis, particularly in patients with conditions that mimic anaphylactic symptoms.[3] While anaphylaxis is generally diagnosed in acute care settings based on symptoms involving at least two organ systems (e.g., dyspnea, wheezing, rash, hypotension, tachycardia, nausea, vomiting) with a history of allergic disease or exposure to a probable allergen,[4] perioperative diagnosis is more nuanced, as clinical symptoms may be masked by or overlap with procedural and anesthesia-related conditions. This complexity has prompted contemporary guidelines to recommend rapid epinephrine treatment in all suspected cases, with allergy evaluation following recovery.[5] Clinical diagnostic criteria alone often fall short in emergent cases where time-sensitive decisions are paramount, or in perioperative and intensive care settings where confounding symptoms may exist. While schemas such as the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network consensus criteria demonstrate reasonable sensitivity of 95% and specificity of 70% when implemented perfectly by experts,[6] their real-world application is limited or impossible in emergency patient care and perioperative settings.

In this context, serum tryptase levels offer a valuable diagnostic adjunct, with elevated levels correlating strongly with anaphylaxis and testing endorsed in consensus guidelines for all suspected cases.[7] Tryptase demonstrates sensitivity exceeding 40% and specificity greater than 82% as a standalone biomarker, with even better combinatorial performance when integrated with clinical signs such as hypotension or respiratory changes.[8,9] Sensitivity improves when compared with established baseline levels, with post-reaction values considered significant when the formula (basal tryptase × 1.2) + 2 ng/mL equals or exceeds the pre-reaction value.[10,11]

Current protocols for tryptase testing in serum or plasma utilize the ImmunoCAP™ Tryptase assay (Thermo Fisher, Waltham, MA, USA), performed on the Phadia™ immunoassay platform. As these instruments are typically available only at large academic or centralized laboratories, test results often take more than 24 to 48 h. This delay is problematic in acute care settings, where rapid diagnostic confirmation can guide immediate therapeutic interventions. For instance, in a patient presenting with hypotension and respiratory distress, prompt differentiation between anaphylaxis and other causes such as septic shock or cardiovascular disorders can significantly alter the management approach. Though lab testing should not delay the administration of epinephrine and other life-saving measures, following closely with rapidly-resulting tryptase testing may help with treatment monitoring and elucidation of cases specific to anaphylaxis.[12]

Despite these advantages, reliance on centralized testing facilities limits timely tryptase availability. Over five years across a large primary and tertiary care network in eastern Massachusetts, 25,326 tryptase tests were ordered, with 3,537 (14.0%) returning positive. These included 1,895 cases associated with suspected, probable, or confirmed anaphylaxis, with other diagnoses including mast cell neoplasms, non-anaphylactic allergic disorders, and myeloid neoplasms. Critically, hospital safety reports identified two fatal anaphylaxis cases in which rapid tryptase testing might have enabled earlier intervention, as well as multiple instances of testing delays causing missed diagnoses, including perioperative anaphylaxis.

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POC testing solutions, which provide rapid results at the patient's bedside or care unit, could vastly improve the diagnosis and management of anaphylaxis.[13] POC assays for tryptase would allow immediate measurement and interpretation, facilitating quicker clinical decision-making and potentially improving patient outcomes.[14] The development and implementation of such assays are feasible, given advancements in immunoassay technologies and the proven efficacy of POC testing in other areas of medicine.[15]

In deploying a POC assay for tryptase, several analytical considerations must be addressed. Ideally, whole blood (WB) would be accepted as the sample type, consistent with POC testing methodologies for analytes such as troponins or B-type natriuretic peptide. WB tryptase levels have been measured successfully in the research setting and have been shown to correlate with serum tryptase values.[16] Furthermore, tryptase appears to demonstrate significant stability within WB, suggesting that this approach may be readily adapted to the scale of a POC device.

While tryptase is the most established biomarker for mast cell activation, its interpretation requires nuance; roughly one-third of anaphylaxis patients may exhibit post-reaction levels within the reference range,[17] particularly in drug hypersensitivity reactions. Although measuring additional analytes such as histamine, chymase, carboxypeptidase A3, prostaglandin D2 metabolites, and platelet-activating factor could improve diagnostic specificity,[18] the limitations of these adjunct biomarkers (e.g., biochemical instability, lack of standardized assays) render tryptase the most immediately feasible and clinically translatable marker for POC use. Single tryptase assays have limited utility in patients with persistently elevated baseline levels, such as those with hereditary alpha-tryptasemia, mast cell activation syndrome, renal failure, or systemic mastocytosis.[19,20] This necessitates the establishment of individual baseline values and application of validated metrics like the 20% + 2 formula to determine clinical significance. Importantly, diagnostic testing must never interfere with rapid epinephrine administration when clinical suspicion is high. Conversely, mild-to-moderate anaphylactic reactions, pediatric cases, and food-induced anaphylaxis frequently demonstrate modest tryptase elevations that fall within or only marginally exceed reference ranges.[7] In both scenarios, readily available tryptase testing serves to enhance diagnostic certainty and treatment confidence in difficult cases without obstructing treatment in clinically obvious ones.

In conclusion, while serum tryptase testing is a valuable tool in the diagnosis of anaphylaxis, the current delays associated with widespread send-out testing undermine its clinical utility in urgent and emergent care scenarios. The adoption of POC tryptase assays could bridge this gap, offering real-time diagnostic information that may enhance diagnostic certainty and streamline the immediate management of anaphylaxis. As professionals in laboratory medicine, we strongly advocate for investment in POC tryptase testing technologies to enhance diagnostic accuracy and improve patient care in acute allergic emergencies.

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Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

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