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ImmunoCAP™ TRYPTASE

Tryptase as a clinical marker – an aid in explaining severe reactions

Insect venom allergy

ThermoFisher SCIENTIFIC

The product is not cleared for this application in the United States

One sting can make a world of difference

Venoms from the *Hymenoptera* order of insects, commonly bees, wasps, and some ants, may cause severe reactions and anaphylaxis. The average prevalence of anaphylaxis after insect stings is around 3%.[1] In addition to cases in the general population, there is also occupational anaphylaxis caused by stings in populations such as beekeepers, gardeners, farmers, truck drivers, and masons.[1]

Increased risk for severe reactions with an underlying mastocytosis

It's common that patients with severe venom reactions have an elevated baseline tryptase level. The importance of identifying these patients has been emphasized as they are predisposed to severe anaphylactic reactions. Increased levels may be, but need not necessarily be, due to an underlying mastocytosis.[1,2]

How can a tryptase test help?

Example: A patient who has had a severe reaction after being stung by an insect and is taken to the emergency ward

How can your patient with a suspected reaction to an insect sting benefit from tryptase measurement? Together with clinical findings, the ImmunoCAP™ Tryptase test results can be a significant help to:[3,4,5-8]

- support the clinical assessment on need for therapy
- guide venom immunotherapy (VIT) treatment
- decide on lifelong treatment

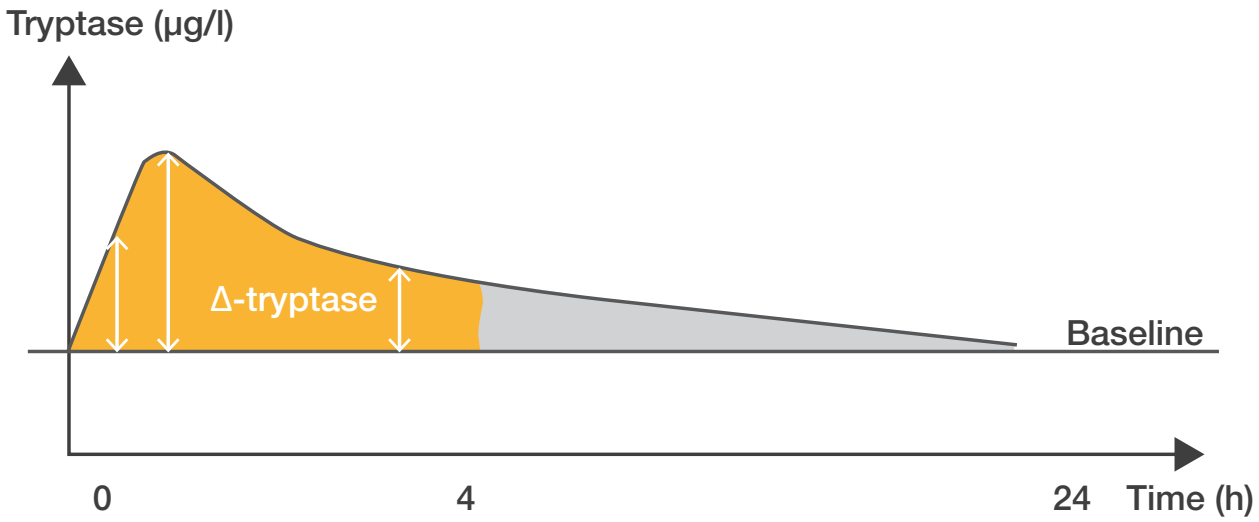
Elevated tryptase helps to confirm mast cell activation

Measurements of transiently elevated tryptase level directly after the reaction can help identify if the reaction was due to mast cell activation. If positive, further allergy investigations, e.g., specific IgE tests should be performed to find the likely trigger of the reaction.[3,4]

- A transient increase in tryptase concentration shortly (within 15 minutes to 3 hours) after a severe reaction, e.g., anaphylaxis, is a marker of mast cell activation.[9,10,11]
- The tryptase level normally returns to baseline at approximately 24–48 hours after complete resolution of all clinical symptoms.[10,11]
- The baseline tryptase level in each individual is normally very stable over time.[12,13]

The difference between the peak level minus the baseline tryptase level is expressed in this document as delta-tryptase (Δ-tryptase).

Below is a schematic image in principle describing the course of events.



Confirmation of mast cell activation if the transient increase in tryptase (Δ-tryptase) is at least 20% above baseline plus 2 µg/l.[10]

Confirmed mast cell activation:[10] Δ-tryptase is ≥ 20 % of the individual's own baseline tryptase + 2 µg/l

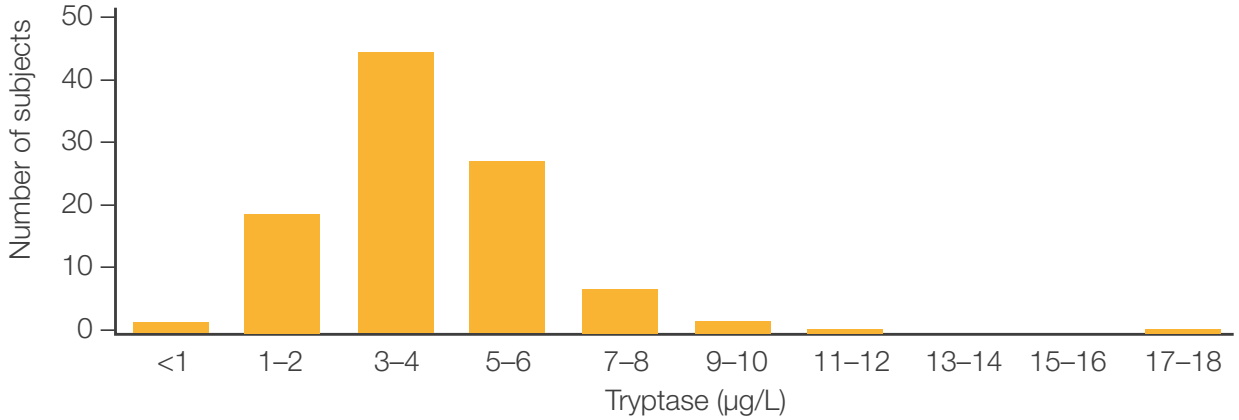
Tryptase – A risk marker for future severe reactions

An elevated tryptase baseline level may indicate an increased risk of anaphylactic reactions. If the patient is found to have a high baseline tryptase, the person may be predisposed to severe anaphylactic reactions and precautionary measures, e.g., an epinephrine autoinjector and specific immunotherapy may be considered.[3,4,14]

The baseline tryptase among healthy individuals varies but in each individual it is normally stable over time.[12,13]

A guide to further mastocytosis evaluation

Baseline tryptase level reflects the number of mast cells and a raised baseline tryptase value may be due to underlying mastocytosis.[9,10,16] Mastocytosis is characterized by increased numbers of mast cells in different organs, which also can be more susceptible for granulation and, thereby, tryptase release. Mastocytosis is classified in different forms, e.g., systemic mastocytosis and cutaneous mastocytosis, and presents many different symptoms like hematological and osteoporosis.[16] Tryptase baseline levels above 20 µg/l, supported by relevant case history, should lead to further investigations of possible mastocytosis.[5,6,16]



Distribution of tryptase concentration in a population of 124 healthy individuals as measured with ImmunoCAP Tryptase test:[15]
- **Geometric mean: 3.4 µg/l**
- **95 upper percentile: 11.0 µg/l**

How can a tryptase test help?

Example: A patient is being considered for venom-specific immunotherapy after previous reactions to bee and/or wasp stings

Tryptase helps to:

Support the clinical assessment regarding need for therapy

Tryptase can help confirm a potential mastocytosis in venom-allergic patients. An underlying mastocytosis is a significant risk factor for repeated severe reactions to venom sting, and an elevated baseline tryptase level in conjunction with other clinical findings which may indicate the need for VIT.[3-8,17,18]

Guide VIT treatment

If the patient is found to have a high baseline, special caution should be observed on each treatment occasion, as the patient may be predisposed to severe reactions.[19]
If severe reactions occur after VIT administration, tryptase can be measured to confirm mast cell activation.[3,4,10]

Decide on lifelong treatment

Venom-allergic patients with underlying mastocytosis should be considered for lifelong immunotherapy, as there is an increased risk of relapse if VIT is discontinued.[3,4]

Interpretations of well-established guidelines

Tryptase should be analyzed in patients with a history of a severe sting reaction. Tryptase should be measured in patients before starting VIT.
– EAACI , AAAAI, WAO, ICON[3-6,8]

A proposed test algorithm – as a guide in tryptase evaluation

Who

- Patients who present with a severe reaction, e.g., anaphylaxis, after being stung by an insect.
- Patients being considered for venom-specific immunotherapy after previous reactions to bee and/or wasp stings.

Why

- Delta-tryptase testing is an aid to confirm mast cell activation as a cause of the severe reaction.
- Baseline tryptase testing is an aid to confirm if there is a risk for repeated severe reactions to bee and wasp stings.
- Tryptase measurement should be considered, together with a thorough case history and relevant specific IgE antibody tests, to help identify the underlying cause of the reaction. Importantly, this can help avoid a potentially life-threatening exposure to the offending substance.
- Baseline tryptase testing is an aid to decide on therapy such as VIT, and to assess the safety and efficacy of VIT. Venom-allergic patients with a history of severe reactions (especially those having an underlying mastocytosis) could be considered for lifelong VIT treatment.

How

- Sample 1 (peak level): as soon as possible after the reaction (15 minutes to 3 hours).
- Sample 2 (baseline level): after complete resolution of all clinical symptoms (approx. 24 to 48 hours, or later).
- Mast cell activation is confirmed if: Δ-tryptase (peak – baseline) is ≥ 20 % of the individual's own baseline tryptase + 2 µg/l.

What is tryptase?

Tryptase is an enzyme and is the most abundant granule protein in mast cells. Within the mast cell, mature tryptase is stored in granules as a heparin-stabilized active tetramer.[20,21]

Proforms of α-tryptase and ß-tryptase are continuously released into the circulation and constitute the individual baseline tryptase level in serum or plasma. Each individual has his/her own unique baseline level of total tryptase, which is normally stable over time.[12,13]

Tryptase as a diagnostic criterion in systemic mastocytosis

The baseline level of tryptase in the circulation reflects the number of mast cells. A persistently elevated baseline level of tryptase above 20 µg/l is an indication of possible mast cell disorders and is recognized by the WHO as one minor diagnostic criterion of systemic mastocytosis.[16]

Tryptase as a marker for mast cell activation

Human mast cells play a central role in inflammatory processes and in severe reactions, such as anaphylaxis. When mast cells are activated, e.g., during IgE-mediated allergic reactions, they release substances, such as histamine and tryptase, into the local surrounding tissues and the blood. Histamine is a well-known mediator causing allergic symptoms.[9]

While the rapid degradation of histamine makes it impractical as a marker for mast cell activation, tryptase remains stable and functional for several hours. This robustness of tryptase makes it a useful tool for confirming mast cell involvement in severe reactions like anaphylaxis. As the serum baseline tryptase level is stable over time, comparisons can easily be made between peak and baseline values.[9,10]

Post mortem

An elevated tryptase level has been described in patients in whom death appeared to be due to anaphylaxis. To determine if this is the case, tryptase should be measured close to the time of death, and possibly at certain intervals thereafter.[22]

ImmunoCAP Tryptase test

The ImmunoCAP Tryptase test measures the total level of tryptase released by mast cells into the circulation. This enables the measurement of transient increases in the level of tryptase after an anaphylactic reaction, as well as establishment of the person's baseline tryptase level. The ImmunoCAP Tryptase test measures all forms of tryptase.

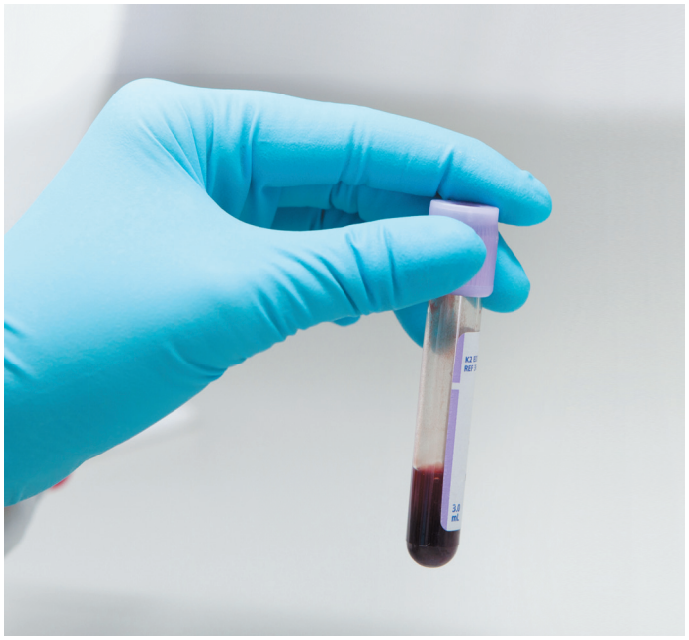
Collecting a sample

The measuring range is 1–200 µg/l and the amount of serum or plasma needed per test is 40 µl. Both serum and plasma samples from venous blood can be used. There is no need for special procedures when collecting blood or preparing the samples.

Timing

To confirm mast cell activation:

Blood samples should be collected as close to the reaction as possible, between 15 minutes and 3 hours after the onset of anaphylactic symptoms. Elevated tryptase levels can usually be detected up to 6 hours following an anaphylactic reaction, and return to baseline levels approximately 24–48 hours after complete resolution of all clinical symptoms.[11,9]



To measure baseline level:

Blood samples can be collected any time (before or after) outside the period of an acute reaction as described above.[10]

Limitations of procedure – please refer to limitations contained in Directions for Use.

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