Tryptase (serum, plasma)

1 Name and description of analyte

1.1 Name of analyte
Tryptase (serum or plasma).

1.2 Alternative names
Mast cell tryptase (EC 3.4.21.59), mast cell protease II, mast cell neural proteinase, mast cell serine protease II, mast cell proteinase II, and tryptase M.

1.3 NLMC code not available

1.4. Function(s) of analyte
Tryptase is a serine esterase of molecular mass 134 kDa. It is a tetramer existing in an α and β form (encoded by separate genes) with β-tryptase being the predominant form stored in mast cell granules. It is involved in the allergenic response and is suspected to act as a mitogen for fibroblast cells, having vasoactive, pro-inflammatory and chemotactic properties. It can activate the complement and coagulation pathways, as well as the kallikrein–kinin contact system.

It is released into the bloodstream during mast cell activation by either IgE- or non-IgE mediated mechanisms. This occurs as part of a normal immune response as well as in allergic (hypersensitivity) reactions. Plasma [tryptase] is considered a marker of systemic mast cell activation since it is highly concentrated in mast cells, being present in basophils at an approximately 500-fold lower concentration.

2 Sample requirements and precautions

2.1 Medium in which measured
1. Tryptase can be measured in serum or plasma (EDTA, citrate or heparin). *Note that it is tryptase protein concentration rather than enzyme activity that is measured.*
2. Tryptase measurements in bronchoalveolar and nasal lavage samples have been described in allergic rhinitis; however, there are no clinical indications for such measurements.
3. Tryptase can be measured in serum obtained from blood post-mortem.

2.2 Precautions re sampling, handling etc.
Blood should be separated within 3 h of venesection. Tryptase is stable in serum/plasma for 24 h at room temperature, up to 7 days at +4–8°C and for up to 1 year frozen at -25°C or below.

3 Summary of clinical uses and limitations of measurements

3.1 Uses

Measurement of serum/plasma tryptase is a marker of mast cell degranulation. It is of value in the confirmation of anaphylaxis and in the assessment of allergic disorders and mast cell syndromes such as mastocytosis.
Tryptase can be measured in serum obtained post-mortem to determine if anaphylaxis is a probable cause of death.

3.2 Limitations
[Tryptase] may be within the reference interval in some patients with acute mast cell activation if specimens are obtained >12 h following the onset of symptoms.

4 Analytical considerations

4.1 Analytical methods
There is only one commercially available method for measuring total [tryptase]. The ImmunoCap Tryptase assay from Phadia Laboratory Systems, Uppsala, Sweden, is a fluorescence enzyme immunoassay (FEIA). The assay does not distinguish between α- or β-tryptase (both inactive monomeric and active tetrameric forms). This methodology is available on various platforms.

The ImmunoCAP solid phase consists of a cellulose derivative enclosed in a capsule. Anti-tryptase, covalently coupled to the solid phase, reacts with tryptase in the patient sample. After washing, enzyme-labelled anti-tryptase antibodies are added to form a complex. After incubation, unbound enzyme-anti-tryptase is washed away, and the bound complex is incubated with a developing agent. After the reaction has been stopped, the fluorescence of the eluate is measured. The fluorescence is directly proportional to the [tryptase] in the sample.

4.2 Reference method
None.

4.3 Reference materials
None available commercially. The assay manufacturer uses an in-house material purified from human lung.

4.4 Interfering substances
Rheumatoid factor and human anti-mouse antibodies (HAMA) can interfere with the immunoassay causing false positives. A reagent is used in the assay to suppress the activity of heterophilic antibodies.

4.5 Sources of error

5 Reference intervals and variance

5.1.1 Reference interval (adults)
1.0–11.4 (the upper limit of normal is up to 15 in some centres) ng/mL (μg/L).
Peaks of >40 ng/mL are associated with anaphylaxis.
Individuals with systemic mastocytosis usually have values of >20 ng/mL.

5.1.2 Reference intervals (others)

Infants <6 months have a higher median concentration (6.1 ng/mL cf. ~3.5 ng/mL for adults).
The reference interval does not differ between males and females.

5.1.3 Extent of variation

5.1.3.1 Interindividual CV: 76%

5.1.3.2 Intraindividual CV: 7%

5.1.3.3 Index of individuality: 0.09

5.1.3.4 CV of method: typically <7%.

5.1.3.5 Critical difference: 23%

5.1.4 Sources of variation
None.

6 Clinical uses of measurement and interpretation of results

6.1 Indications and interpretation
Increased serum/plasma [tryptase] can be helpful in the following instances.

1. In anaphylaxis (type I immediate hypersensitivity) reactions, to confirm mast cell activation. There is no laboratory test that can diagnose anaphylaxis in real-time; the diagnosis is primarily clinical.
   In anaphylaxis, the minimal elevation of total [tryptase] considered to be clinically significant is suggested to be {≥2 + (1.2 x baseline tryptase)}. Individuals with an elevated baseline [tryptase] may be predisposed to severe anaphylactic reactions.

   Mast cell granules release tryptase during anaphylaxis, with measurable amounts appearing in blood within 30–60 min. Levels decline under first-order kinetics, with a half-life of approximately 2 h.
   After a suspected reaction, timed blood samples should be taken for mast cell tryptase as follows: (1) as soon as possible after emergency treatment has started, (2) within 1–2 h (maximum 4 h) from the onset of symptoms, (3) at follow-up, at least 24 h post-event to determine the baseline value. Serial measurements are essential for interpretation.

   Parenterally-administered triggers (medication, insect venoms) are associated with higher serum [tryptase].

2. In post-mortem diagnosis of anaphylaxis as a possible cause of death.
3. As a World Health Organisation (WHO) diagnostic criterion for mastocytosis. This is a group of haematological disorders characterised by an abnormal increase in the number of mast cells in different tissues e.g. skin (cutaneous mastocytosis), or in organs throughout the body, such as bone marrow, gastrointestinal tract, liver, spleen and lymph nodes (systemic mastocytosis). The WHO established a set of diagnostic criteria that includes a serum baseline
   tryptase of >20 ng/mL as a minor criterion.

   Note that, serum tryptase should be assayed when the patient is in a baseline state (i.e. not immediately following an episode of symptoms) for the purposes of diagnosing mastocytosis, because elevations in mediators

obtained immediately after a symptomatic episode indicate mast cell activation, but do not distinguish between anaphylaxis and mastocytosis.

Tryptase may be measured in individuals with a raised bone mineral density on dual energy X-ray absorptiometry scanning to rule out mastocytosis.

Basal serum tryptase should be measured at regular intervals (at least annually) in all patients with systemic mastocytosis, as an increase may indicate disease evolution or progression, or the development of a bone marrow neoplasm, such as myeloid leukaemia.
In those with systemic mastocytosis that transitions into more aggressive conditions such as mast cell leukaemia, concentrations are often markedly elevated (>500 ng/mL).

Measurement of tryptase to evaluate the likelihood of mastocytosis is appropriate in an adult with any of the following:

- urticaria pigmentosa (maculopapular cutaneous mastocytosis) or mastocytoma
- episodic signs of mast cell activation affecting at least two organ systems e.g. flushing, tachycardia, diarrhoea, sweating, fatigue, musculoskeletal pain, hypotensive syncope, osteoporosis in a young adult, unexplained hepatosplenomegaly
- patients with signs or symptoms suggestive of systemic disease (e.g. recurrent episodic flushing attacks with tachycardia, syncope, and abdominal complaints).

4. In myeloproliferative variants of hypereosinophilic syndrome (HES) an elevated serum [tryptase] may be found.
5. To help diagnose a mast cell activation disorder.
6. As a prognostic marker in haematological neoplasms.
7. In the assessment of recurrent debilitating urticaria.
8. In the assessment of recurrent angioedema.

6.2 Confounding factors

<u>Anaphylaxis</u>

A [tryptase] within reference limits cannot be used to refute a clinical diagnosis of anaphylaxis because:

- clinically relevant increases may be seen within the normal reference interval
- even in optimally timed samples, tryptase is seldom elevated in children with food-triggered anaphylaxis, or when the main severe feature is respiratory
- [tryptase] is less likely to be elevated in non-hypotensive anaphylactic episodes
- localised rather than systemic release of tryptase may occur in some cases of anaphylaxis where degranulation occurs at mucosal sites
- there may be IgE-dependent anaphylactic pathways that by-pass mast cells and involve basophils and/or other cell types.

Mastocytosis

In patients with cutaneous mastocytosis, basal [tryptase] may be relatively low.

7 Causes of abnormal results

7.1 High values

7.1.1 Causes

- anaphylaxis
- allergen challenge
- systemic mastocytosis
- mast cell activation syndrome
- acute myelocytic leukaemia
- myelodysplastic syndromes
- hypereosinophilic syndrome (myelocytic variant)
- IgE-mediated allergy conditions e.g. asthma
- onchocerciasis (during active treatment)
- chronic renal failure
- chronic liver failure
- chronic eosinophilic leukaemia
- bone marrow suppression states
- after administration of recombinant stem cell factor

7.1.2 Investigation

See 6.1

7.2 Low values

Not of clinical significance

7.2.1 Causes

None

7.2.2 Investigation

Not applicable

7.3 Notes

None

8 Performance

8.1 Sensitivity, specificity etc. for individual conditions

- specificity for anaphylaxis: 87–100%, dependent on the threshold used
- sensitivity for anaphylaxis: 35–93%, dependent on the threshold used
- specificity for mastocytosis: >98%
- sensitivity for mastocytosis: ~83%.

9 Systematic reviews and guidelines

9.1 Systematic reviews

1. Bonadonna P, Pagani M, Aberer W *et al*. Drug hypersensitivity in clonal mast cell disorders: ENDA/EAACI position paper. Allergy 2015;70:755–63. *The authors conclude that during a suspected allergic reaction, elevations of serum*

tryptase are closely correlated to severity of reaction and particularly to hypotension.
2. Valent P, Escribano L, Broesby-Olsen S *et al*. Proposed diagnostic algorithm for patients with suspected mastocytosis: a proposal of the European Competence Network on Mastocytosis. Allergy 2014;69:1267–74. *The authors determined that tryptase is an important parameter for diagnosis of mastocytosis in those with atypical symptoms and borderline findings.*

9.2 Guidelines

1. Anaphylaxis: assessment and referral after emergency treatment. NICE Clinical Guideline 134, December 2011.
2. Drug allergy: diagnosis and management. NICE Clinical Guideline 183, September 2014.
3. Krishna MT, Ewan PW, Diwarkar L *et al*. Diagnosis and management of hymenoptera venom allergy: British Society for Allergy and Clinical Immunology (BSACI) guidelines. Clin Exp Allergy 2011;41:1201–20.
4. Ewan PW, Dugué P, Mirakian R *et al*. BSACI guidelines for the investigation of suspected anaphylaxis during general anaesthesia. Clin Exp Allergy 2010;40:15–31.

9.3 Recommendations

1. Lieberman P, Nicklas RA, Randolph C *et al*. Practice Parameter: Anaphylaxis – a practice parameter update 2015. Ann Allergy Asthma Immunol 2015;115:341–84. *Recommendations on the evaluation and management of patients with suspected anaphylaxis.*

10 Links

10.1 Related analytes

Other potential markers of mast cell and/or basophil degranulation include:

- mature β-tryptase
- plasma histamine (returns to baseline in 15–30 min)
- urinary histamine metabolites (N-methylhistamine and N-methylimidazole acetic acid)
- mast cell carboxypeptidase A3
- chymase
- platelet-activating factor (PAF)
- urinary prostaglandin D_2 metabolite (11-beta prostaglandin $F_{2\text{-}\alpha}$)
- urinary leukotriene C_4 metabolite (leukotriene E_4)
- basogranulin

10.2 Related tests

- total IgE
- specific IgE
- skin-prick allergen testing

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