

How to interpret mast cell tests

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ABSTRACT

Mast cell tryptase (tryptase) is an enzyme produced almost exclusively by mast cells that is easy to measure using a widely available test. In this article we discuss the physiology of the mast cell and how that relates to IgE-mediated anaphylaxis and mastocytosis. We also describe the technical aspects of testing tryptase and the reported normal ranges in health. Finally we explore the diagnostic performance of serum mast cell tryptase measurements, when used to confirm anaphylaxis, estimate future anaphylaxis risk and in diagnosing/monitoring leukaemia.

INTRODUCTION

Anaphylaxis is a systemic life-threatening allergic reaction, which is typically caused by an IgE-mediated response to allergen with resultant degranulation of mast cells. This degranulation results in a range of symptoms including respiratory distress secondary to bronchospasm and/or haemodynamic collapse secondary to vasodilatation, capillary leak and direct cardiac effects of mast cell mediators. The diagnosis of anaphylaxis is made clinically.

There is some debate over the precise definition of anaphylaxis. [Box 1](#) and [table 1](#) outline differences in definitions between the UK and the USA. [Box 1](#) shows the UK definition widely used by the National Institute for Health and Care Excellence (NICE) in the UK and [table 1](#) shows the definition widely used in the USA.^{1 2} The definitions are quite different and it is important to consider the definition used when reviewing the available research because the definition used influences the severity of the cases included in the study and the relevance of that study to clinical practice.

Even with clear definitions it may be difficult to diagnose anaphylaxis in some cases, for example, post mortem, following an unwitnessed out-of-hospital collapse or under anaesthetic. In these challenging cases it would be helpful to

have a reliable test that can confirm or refute the diagnosis of anaphylaxis.

In addition to having a specific and sensitive test for anaphylaxis it would also be very useful, in an ideal world, to have a test that could predict risk of future anaphylaxis in allergic children. Such a test would help to inform clinicians and parents as to the risk and benefits of carrying an adrenaline autoinjector and the stringency required for allergen avoidance measures.

Mast cell tryptase (tryptase) is an enzyme produced almost exclusively by mast cells that is easy to measure by a widely available laboratory test. The evidence underpinning the role of this enzyme as a diagnostic marker of anaphylaxis, and as a predictor of future anaphylaxis risk is discussed below. The role of tryptase in diagnosing anaphylaxis has been explored extensively in adults but to a much lesser degree in children and in this paper we explore the practical applications of this research. In addition to anaphylaxis mast cells are implicated in a number of haematological disorders including mastocytosis and the role of tryptase in the diagnosis of these conditions is also discussed below.

Physiological background—the mast cell

Mast cells are a part of the innate immune system involved with pathogen sensing and mediation of an inflammatory response. They develop from the CD34+ multipotential bone marrow cells. The developing mast cells are initially found circulating in peripheral blood but later settle in organs that have direct interaction with the external environment such as gut, respiratory tract and skin. Mast cells degranulate in response to a range of stimuli including trauma, high temperatures and the binding of antibody. It is this latter mechanism that is responsible for the classical type 1 hypersensitivity reaction. In type 1 hypersensitivity reactions the body produces

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Interpretations

Box 1 Diagnosing anaphylaxis¹

'Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction which is likely when both of the following criteria are met:

1. Sudden onset and rapid progression of symptoms
2. Life-threatening airway and/or breathing and/or circulation problems

Skin and/or mucosal changes (flushing, urticaria, angio-oedema) can also occur, but are absent in a significant proportion of cases'.

Table 1 Diagnosing anaphylaxis²

Mucosal symptoms	Respiratory symptoms	Cardiovascular symptoms
Hives/itchy rash Swelling of lips/tongue Swelling of back of throat	Difficulty breathing (eg, wheeze, cough, stridor)	Hypotension Collapse
Vomiting/stomach cramps		

To diagnose anaphylaxis symptoms from two columns need to be present with minutes to hours of allergen exposure.

Definition from National Institute for Health in the USA.²

IgE antibodies on first exposure to a harmless environmental antigen (usually a protein), for example, peanut. On subsequent exposure the IgE binds the antigen and then activates mast cells. The mast cells then release the contents of their secretory granules (cytokines, histamine, tryptase, chymase) resulting in a type 1-hypersensitivity reaction (figure 1). These responses are notable for their speed of onset, which is explained by the fact that IgE antibodies are already bound to mast cells under steady state conditions, and some of the mediators released by mast cells are preformed.

Physiological background—mast cell tryptase (tryptase)

The tryptase enzyme (also known as mast cell tryptase or β -tryptase) is highly specific to the mast cell. The

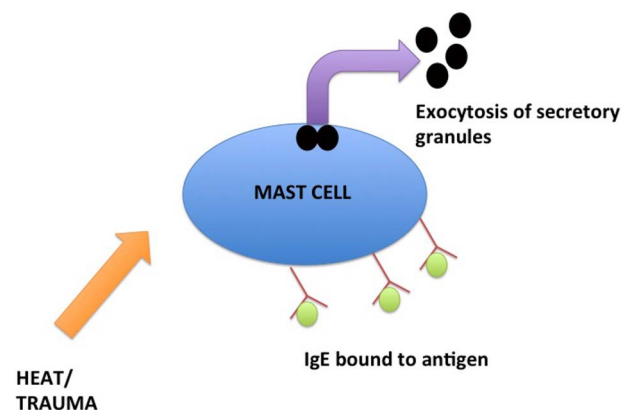


Figure 1 Diagram depicting mast cell degranulation.

role of tryptase in the immune response and anaphylaxis is unclear. Tryptase can degrade mediators of bronchodilation and has effects on nitric oxide mediated vasodilatation possibly contributing to bronchospasm and hypotension, respectively.³ Following an anaphylactic reaction tryptase levels may rise, with peak secretion from the mast cell at 15 min to 2 hours.³ The peak level in the blood is usually measurable at 1–6 hours after the onset of anaphylaxis. Tryptase has a half-life of around 2 hours and the levels return to normal at around 24 hours.⁴ Based on these timings it is recommended that when used to aid the diagnosis of anaphylaxis at least three samples are taken.³ The first is taken at the onset of the reaction, another at 1–2 hours and the third at 24 hours. An additional sample may need to be taken at 1 week after the reaction to establish a true baseline tryptase level.⁵ This approach would be similar to that suggested by NICE.¹ While in the majority of cases a raised tryptase level will represent anaphylaxis it is worth noting that there are other causes of an elevated blood tryptase level (outlined in table 2).³

TECHNOLOGICAL BACKGROUND

The only commercially available method for measuring tryptase levels is the sandwich ELISA known as (ImmunoCAP Tryptase) produced by (ThermoFisher Scientific Diagnostics, Phadia, Sweden). The Sandwich ELISA is more sensitive than the standard ELISA technique and samples do not require purification prior to testing. The ImmunoCAP Tryptase involves the following steps.⁶

1. The antitryptase is added to the patients' serum and binds to the tryptase.
2. The sample is washed and enzyme-labelled antibodies against tryptase are added creating a complex.
3. The complex is incubated with a developing agent.
4. At the end of the reaction the fluorescence is measured and is directly proportional to the amount of tryptase in the sample.

Blood samples for tryptase analysis can be collected as a clotted sample and sent to the laboratory at room temperature. The serum should be separated from blood and analysed. The tryptase enzyme is very stable and can be stored for 2 days at room temperature, for 5 days at 2–8°C and for longer periods if stored at –2°C to –7°C. This contrasts with histamine which is unstable and degrades rapidly making testing of histamine levels challenging.

Table 2 Potential non-anaphylaxis causes of an elevated tryptase³

Trauma	Apoptosis/cell death	Drugs	Haematological
Scar formation	Hypoxia	Opiates	Mastocytosis
Polytrauma	Myocardial Infarction		Myeloid leukaemia
Wound healing			

Normal ranges

Tryptase levels should be viewed as a continuum with no clear normal range. The baseline and normal ranges vary between populations and fluctuate within individuals (discussed in more detail later). Despite this however there are data on median tryptase levels in well, non-atopic individuals and these levels are often used as reference points in research papers. In children aged 6 months to 18 years the median baseline tryptase level is 3.5 µg/L (assessed on a total of 410 healthy and non-atopic children).^{7–9} This level is similar to that seen in healthy adults. A study of 126 atopic adults aged 12–61 years (61 male and 65 female) found the mean tryptase level to be 3.8 µg/L with 95% of healthy adults having a tryptase level <11.4 µg/L.¹⁰ Children under 6 months show higher levels of tryptase with a median level of 6.1 µg/L.⁸ This level then gradually reduces.⁸

INDICATIONS AND LIMITATIONS

In a child presenting shocked in whom anaphylaxis is a possibility can tryptase measurements be used to confirm or refute anaphylaxis as a cause?

Anaphylaxis is primarily a clinical diagnosis and the role of tryptase is as a tool to help confirm or refute the diagnosis when there is an element of clinical uncertainty. There have been a number of suggested approaches for how one might interpret tryptase levels to diagnose anaphylaxis. The first is to use 11.4 µg/L as an upper limit and to confirm anaphylaxis in anyone with a level above that.¹¹ This value has been chosen as it presents the 95th centile seen in a population of healthy adults. The other is to use a measure of 1.2 times the baseline level +2 µg/L as a cut-off.¹¹

Until recently there were very little data on how effective either of these approaches is in diagnosing anaphylaxis in children. Most of the available data are based on adult populations with anaphylaxis. A recently published Canadian study looking at 203 children with anaphylaxis measured the tryptase levels at 30 min and 2 hours.¹¹ Overall only 19.2% of the children in that study had a maximum tryptase level >11.4 µg/L.¹¹ Furthermore even in the group with the severest reactions only 71% of children had a tryptase level above 11.4 µg/L.¹¹ Of the 203 children; 68 had a baseline tryptase level measured. Of those with anaphylaxis 60.3% had a maximal tryptase level of >1.2 times their baseline +2 µg/L.¹¹ This study is the largest paediatric anaphylaxis study exploring the role of tryptase as a diagnostic test for anaphylaxis and it demonstrates that a tryptase level is not a sensitive test for anaphylaxis.¹¹

These results are consistent with data from adult studies with a similarly designed adult study of 102 patients with clinically confirmed anaphylaxis finding that tryptase levels were not elevated beyond baseline (baseline measure at 1 week after the event) in 36.3%

of patients.⁵ The authors also went on to highlight that in their study food allergy induced anaphylaxis was less likely to result in an elevated blood tryptase level when compared with venom or drug induced anaphylaxis. This finding is not consistent within the literature with other groups reporting similar blood tryptase levels in food, venom and drug-induced anaphylaxis.¹² More research is required to understand how food/venom and drug-induced anaphylaxis affect tryptase levels.¹² The possibility that tryptase levels are less reliable for determining food-induced anaphylaxis is significant for the paediatric population because the majority of paediatric anaphylaxis is secondary to food. Recent data suggest that tryptase levels in food anaphylaxis do not differ significantly from those seen in other forms of anaphylaxis, with higher levels associated with more severe reactions whatever the cause.¹²

For the general paediatrician, measuring tryptase levels in cases of suspected anaphylaxis may be of limited value. Tryptase levels are not sensitive for anaphylaxis and there remains uncertainty as to how to interpret levels and at what level, if any, can it be used as a diagnostic cut-off.¹¹ Tryptase level measuring is unlikely to be helpful in cases of clear-cut anaphylaxis, but where the cause for systemic symptoms is not clear, for example, unexplained hypotension during anaesthesia—finding a raised mast cell tryptase can be useful for supporting the diagnosis of anaphylaxis.

In a child who has died of suspected anaphylaxis can tryptase levels be measured postmortem to confirm anaphylaxis as a cause of death?

Diagnosing a case of fatal anaphylaxis postmortem can be difficult. Thus, having blood markers to help confirm this diagnosis is in theory very helpful. Tryptase levels have been shown to be raised in cases of anaphylactic deaths and it had been suggested that tryptase levels postmortem can be used to confirm anaphylaxis.¹³ It has also been shown however, that a modest rise in tryptase levels is common postmortem due to other factors such as hypoxia and asphyxia with 34.5% of non-anaphylactic postmortem cases demonstrating a tryptase level of >11.4 µg/L.¹⁴

There are currently several controversies related to the use of measuring tryptase levels post mortem and these include:

1. There is no consensus on a cut-off level at which anaphylaxis can be confirmed as occurring with authors suggesting a range of >45 µg/L to >110 µg/L.^{14 15}
2. The mode of death can significantly affect the tryptase level and in particular death by asphyxia can cause a significant tryptase rise.¹⁵
3. There is no consensus on the best site for sampling with differences in tryptase levels observed between samples taken from femoral vessels and from the heart.^{15 16}
4. There is no consensus as to the best timing of sampling.¹⁴

Interpretations

5. The existing data focus on adults and must be interpreted cautiously with regard to anaphylaxis in children.

From the evidence available tryptase levels can be useful post mortem but care needs to be taken to ensure that the time of sampling, site of sampling and nature of death are recorded. A very high tryptase level $>110 \mu\text{g/L}$ is very suggestive of anaphylaxis having occurred but lower levels cannot rule out or rule in anaphylaxis. More data are required before tryptase levels can be interpreted reliably in children post mortem.

In a child with known allergy can a baseline tryptase level be used to predict the likelihood of future anaphylaxis?

When a child or young person has an IgE-mediated allergy they and their parents may be concerned as to the risk of future anaphylaxis. Deciding which children should carry an adrenaline autoinjector and how stringent allergen avoidance should be, is difficult. There is fledgling research into the use of a baseline tryptase as a predictor of future anaphylaxis. There are two exclusively paediatric studies exploring the role of baseline tryptase levels in predicting future anaphylaxis risk in children with venom and food-mediated IgE allergies.^{17 18}

In a study by Yavuz *et al* 128 children were recruited;¹⁸ 55 of these children had severe reactions to venom (defined as 'anaphylactic shock, cardiac arrest or apnoea'), the remainder were children with large local reactions to venom ($n=18$) or matched controls ($n=55$).¹⁸ In that study the authors found that there was a statistically significant positive correlation between baseline tryptase level and the likelihood of severe anaphylaxis.¹⁸ They describe the "best cut-off" value as $4.8 \mu\text{g/L}$ with a positive predictive value for anaphylaxis of 87.1%.¹⁸ Unfortunately this value only has a sensitivity of 45.8% and the authors comment that there was significant overlap between groups with baseline tryptase values ranging from $1.3 \mu\text{g/L}$ to $14.5 \mu\text{g/L}$ in the severe reaction group and $1.0 \mu\text{g/L}$ to $6.1 \mu\text{g/L}$ in the control group.¹⁸

There is only one paediatric study looking at the association between baseline tryptase levels and IgE-mediated anaphylaxis to foods.¹⁷ In that study by Sahiner *et al* 167 children were recruited with IgE-mediated food allergies to milk, egg and nuts along with 113 healthy controls.¹⁷ Of the 167 allergic children 79 had previous anaphylaxis and 88 had IgE-mediated food allergies without anaphylaxis.¹⁷ The median baseline tryptase levels were significantly different between groups; with controls, allergy without anaphylaxis and allergy with anaphylaxis having median baseline tryptase levels of $3.3 \mu\text{g/L}$ (2.4–4.4), $3.6 \mu\text{g/L}$ (2.3–4.5) and $4 \mu\text{g/L}$ (2.8–5.8), respectively, (p value for trend=0.016).¹⁷ In addition median baseline tryptase levels were also significantly higher in those children with nut allergies ($4.7 \mu\text{g/L}$ (3.0–6.7)) when compared with milk allergy ($3.5 \mu\text{g/L}$

Topics for further research

- ▶ Research is required in the paediatric population to determine whether diagnostic cut-offs for tryptase can be identified to confirm anaphylaxis post mortem.
- ▶ More research is required to understand the role of tryptase in stratifying risk of anaphylaxis in children with food allergy.
- ▶ There needs to be a greater understanding of the effect of common diseases on tryptase levels. The existing 'normal ranges' are derived from healthy atopic individuals and we do not understand how common disease may affect the specificity of tryptase testing.

Clinical bottom line

- ▶ Anaphylaxis is a clinical diagnosis.
- ▶ When there is clinical uncertainty whether anaphylaxis has occurred tryptase measurements may be useful. Low levels do not rule out anaphylaxis (especially to food) but a high level which returns to normal within 24 hours is very suggestive of anaphylaxis.
- ▶ Tryptase levels are difficult to interpret post mortem but a very high level $>110 \mu\text{g/L}$ is highly suggestive of anaphylaxis occurring prior to death.
- ▶ Systemic mastocytosis cannot be confidently diagnosed or ruled out using only a tryptase level without other confirmatory tests.

(2.5–4.3)) and egg allergy ($3.8 \mu\text{g/L}$ (2.4–5.5) ($p=0.022$)).¹⁷ This may however, reflect that those with nut allergies were more likely to have a more severe phenotype with more cases of moderate to severe anaphylaxis with a greater degree of respiratory distress/hypotension and collapse when compared with egg or milk allergic children ($p=0.005$).¹⁷ In this study the authors suggest using 'cut-off values' of $5.7 \mu\text{g/L}$ and $14.5 \mu\text{g/L}$ predict a 50% and 90% risk of anaphylaxis, respectively.¹⁷ The authors do not however, provide details on sensitivity and again there is overlap in the range of tryptase values seen between groups.¹⁷

From these two small paediatric studies it is clear that there is a positive correlation between baseline tryptase levels and the risk of anaphylaxis.^{17 18} From these studies we can also see however, that baseline tryptase levels show significant variability between individuals and although a high baseline tryptase level confers an increased risk of anaphylaxis a low baseline tryptase level cannot be used to reassure the clinician,

or patient, of a low future risk of anaphylaxis. More research is needed to better understand the role of baseline tryptase levels in predicting anaphylaxis risk before the test can be used reliably to counsel children and their families.

In a child with suspected mastocytosis can a tryptase level be used to confirm or rule out the diagnosis?

Mastocytosis is a haematological disorder of clonal proliferation of abnormal mast cells. It can have both systemic and cutaneous features, and it is these cutaneous features that are more common in childhood. Typical lesions consist of red-brown macules, papules or plaques, often on the trunk and they can be associated with pruritus and blister formation. Histological examination of the lesions will demonstrate an accumulation of mast cells within the papillary dermis with potential extension into the reticular dermis and subcutaneous fat. There may also be systemic features, and in these cases there are often bone marrow changes. These features include flushing, abdominal pain, bone pain, headaches, peripheral blood abnormalities, lymphadenopathy and hepatosplenomegaly.

Mastocytosis is usually spontaneous rather than inherited and if the onset is in childhood it tends to be limited to cutaneous rather than extracutaneous (systemic) mastocytosis, and to resolve spontaneously by adulthood. Raised serum tryptase levels of $>20 \mu\text{g/L}$ are currently a minor diagnostic criterion for systemic mastocytosis (table 3). Using the WHO criteria a patient requires either one major and one minor criterion or three minor criteria before a diagnosis of systemic mastocytosis can be made.¹⁹ Therefore tryptase measurements alone are not sufficient to confirm or refute a diagnosis of suspected mastocytosis.

Table 3 WHO criteria for systemic mastocytosis¹⁹

Major criterion	Minor criterion
Multifocal, dense aggregates of mast cells (15 or more) detected in sections of bone marrow and confirmed by tryptase immunohistochemistry or other special stains.	In biopsy section, more than 25% of the mast cells in the infiltrate have atypical morphology, or, of all the mast cells in the aspirate smear, more than 25% are immature or atypical.
	Mast cells coexpress CD117 with CD2 and/or CD25.
	Detection of <i>KIT</i> point mutation at codon 816 in bone marrow, blood, or other extracutaneous organs.
	Serum total tryptase persistently $>20 \mu\text{g/L}$ (not a valid criterion in cases of systemic mastocytosis with associated clonal haematological non-mast-cell lineage disease).

Search strategy and selection criteria

Information was obtained from Medline and PubMed searches for years between 1960 and 2015. Using the MESH search terms 'Tryptase, allergy, allergic reaction, anaphylaxis, mastocytosis, leukaemia, malignancy, acute myeloid leukaemia', original articles in English relating to tryptase were retrieved and their references searched for relevant clinical studies.

Test your knowledge

- Mast cells are predominantly found in the following tissues? (Select all that are correct)
 - Gut
 - Brain
 - Skin
 - Respiratory tract
- In cases of suspected anaphylaxis tryptase levels should be recorded at the following times?
 - As soon as possible, 1 hour and 24 hours
 - 1 hour and 24 hours
 - 24 hours only
 - At 1 hour only
- Tryptase levels are measured in a child with suspected anaphylaxis to venom (but with ongoing diagnostic uncertainty). Which of the following tryptase levels is most supportive of a diagnosis of anaphylaxis?
 - $5 \mu\text{g/L}$
 - $1.2 \times$ baseline
 - $1.2 \times$ baseline $+2 \mu\text{g/L}$
 - Baseline $+ 2 \mu\text{g/L}$
- In which type of malignancy is tryptase a useful tumour marker?
 - Acute lymphoblastic leukaemia
 - Acute myeloid leukaemia
 - Nephroblastoma
 - None
- Which of the following are minor diagnostic features of mastocytosis?
 - Mast cells coexpress CD117 with CD2 and/or CD25
 - Detection of *KIT* point mutation at codon 816 in bone marrow, blood, or other extracutaneous organs
 - Serum total tryptase persistently $>20 \mu\text{g/L}$
 - All of the above

The answers are after the references.

In a child with suspected or confirmed leukaemia can a tryptase level be used as a reliable tumour marker?

Currently tryptase measurements have no role in paediatric oncology except in research settings. There are

Interpretations

very little data on the usefulness of tryptase as a tumour marker. One study of 914 adult and paediatric patients with haematological conditions (including mastocytosis) found that no patients with lymphoid leukaemias had an elevated tryptase level whereas 34% of patients with acute myeloid leukaemia (AML) did demonstrate an elevated tryptase level ($>15 \mu\text{g/L}$).²⁰ It is worth noting however that none of the 317 cases of AML were in children under the age of 16 years.²⁰

In summary tryptase currently has no role in the diagnosis or management of paediatric haematological malignancies.

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Competing interests None declared.

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Answers to the multiple choice questions

- A, C, D
- A
- C
- D
- D



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