

Using Baseline and Peak Serum Tryptase Levels to Diagnose Anaphylaxis: a Review

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Abstract

The diagnosis of anaphylaxis relies on a suggestive clinical history after exposure to a potential triggering factor. Serum tryptase concentrations increase on degranulation of mast cells and therefore serum tryptase levels are measured to diagnose anaphylaxis. There is no standardized method for assessing total serum mast cell tryptase (MCT) in anaphylaxis. The Working Conference in 2010 proposed a consensus equation (peak MCT should be $> 1.2 \times$ baseline tryptase + 2 ng/L) to diagnose acute mast cell activation (aMCA). Our objective was to narratively review the literature since the Working Conference in 2010, examining the use of the consensus equation and other equations comparing baseline and peak serum tryptase during anaphylaxis. Computerized bibliographic searches of PUBMED and EMBASE were supplemented with a manual search of reference lists. English-language studies were included. Eleven studies met our inclusion criteria with a total of 4551 participants. However, only four studies with 653 participants used the consensus equation. The other seven studies used other methods to compare peak and baseline serum tryptase concentrations. Measuring serum tryptase levels is valuable in the diagnosis of anaphylaxis but is unable to detect all anaphylactic reactions. Based on our current literature review, the consensus equation is underused in the diagnosis of anaphylaxis. There is also a need for exploration of other biomarkers which could be used in parallel to peak and baseline serum tryptase measurements for further diagnostic certainty. Serum tryptase is the most studied biomarker in anaphylaxis but is still far from being the ideal biomarker for this. There is a need to identify new potential useful biomarkers. Serum tryptase levels are valuable in the diagnosis of anaphylaxis, but are unable to detect all anaphylactic reactions. Additionally serial tryptase measurements are laborious in daily clinical practice.

Keywords Anaphylaxis · Baseline and peak serum tryptase · Mast cell activation · Mast cell tryptase

Abbreviations

AT	Absolute tryptase
BMI	Body mass index
BT	Basal tryptase
ED	Emergency department
IHR	Immediate hypersensitivity reaction
aMCAS	Acute mast cell activation syndrome
MCT	Mast cell tryptase
PC	Percentage change.
PPV	Positive predictive value
ST	Serum tryptase

Introduction

Tryptase is a serine protease released from mast cells during an acute allergic reaction. [1] Anaphylaxis is a systemic life-threatening allergic reaction, typically caused by an IgE-mediated response to an allergen with resulting degranulation of mainly mast cells. This degranulation results in a range of symptoms including respiratory distress secondary to bronchospasm and/or hemodynamic collapse secondary to vasodilatation, capillary leak, and direct cardiac effects of mast cell mediators. [2]

Anaphylaxis is defined by the World Allergy Organization as the acute appearance of an illness with two or more of the following symptoms: (a) involvement of the skin mucosal tissue, (b) reduced blood pressure, (c) respiratory compromise, and (d) gastrointestinal signs. Anaphylaxis is an extreme form of immediate hypersensitivity reaction (IHR) or Type I hypersensitivity reaction; these are mediated through allergic and non-allergic mechanisms. [3] The diagnosis of

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anaphylaxis is primarily a clinical diagnosis, based on suggestive clinical symptoms after exposure to a potential triggering agent. The diagnosis remains difficult in some cases, for example, in a post mortem examination following an unwitnessed out-of-hospital collapse, or when under anesthesia. [2] Anaphylaxis remains under-recognized, undertreated, and poorly understood due to the lack of biomarker providing an unambiguous diagnosis. [4] It is an ongoing clinical issue that a reliable test is needed to confirm or refute the diagnosis of anaphylaxis. [2]

Tryptase levels have been proved to be an indicator of mast cell activation in anaphylaxis and systemic mastocytosis. [5] Many centers consider the normal range of basal serum tryptase as being < 11.4 ng/mL in accordance with the manufacturer Thermo Fisher. However, the use of upper limits of normal ranges as wide-ranging as 8.23 ng/mL [6] and 14 ng/mL [7] have also been reported. In September 2010, a Working Conference was held to discuss standardizing the method for assessing total serum mast cell tryptase (MCT) and to validate an upper limit of normal, providing a cut-off point for the diagnosis of anaphylaxis. Eighty percent of the members present agreed that for a diagnosis of mast cell activation, the acute total serum tryptase level should be at least 120% of the baseline tryptase level plus 2 ng/mL (peak MCT $\geq (1.2 \times \text{baseline tryptase} + 2 \text{ ng/mL})$). For example, in an individual with suspected anaphylaxis, a peak tryptase value of 8 ng/mL and a baseline value of 5 ng/mL confirm mast cell activation. [8] When applying this criterion, it is important to measure the basal serum tryptase level at least 24 h after total resolution of all signs and symptoms in order to: (a) confirm the transient nature of the reaction and (b) exclude an elevated baseline level of tryptase (> 20 ng/mL) which would be highly suggestive of systemic mastocytosis and therefore warrant further investigation. [8]

Questions remain regarding the applicability in clinical practice of this equation and other equations evaluating baseline and peak serum tryptase levels during anaphylaxis. There is a need for further research in this area [9] and for this purpose a narrative review of the published literature was conducted.

Methods

Literature Search Strategy and Selection Criteria

This systematic review was implemented according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. [10] A search was started on 01.08.2018 and finished in June 2019. It was performed via two different databases: Pubmed and Embase. We searched for articles written since the Working Conference of 2010, up until June 2019 which employ the algorithm: $1.2 \times \text{baseline}$

tryptase + 2 ng/mL. Articles that study the relationship between baseline and peak serum tryptase in the diagnosis of anaphylaxis but without using the consensus equation have also been included in this review.

We first performed a search in Pubmed, the exact search criteria were: “Tryptase” [MeSH] AND “Mastocytosis” [MeSH], “Tryptases” [MeSH] AND “Anaphylaxis” [MeSH], “Tryptases” [MeSH] AND “Hypersensitivity” [MeSH], “Biomarkers” [MeSH] AND “Anaphylaxis” [MeSH], “Biomarkers” [MeSH] AND “Mastocytosis” [MeSH]. Using this method, we found 1036 articles in *PubMed*.

The exact search that we performed in Embase was: “biological marker” AND “anaphylaxis” AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [humans]/lim AND [english]/lim AND [abstracts]/lim AND [embase]/lim AND [2010–2019]/py, “biological marker” AND “mastocytosis” AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [humans]/lim AND [english]/lim AND [abstracts]/lim AND [embase]/lim AND [2010–2019]/py, “tryptase” AND “anaphylaxis” AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [humans]/lim AND [english]/lim AND [abstracts]/lim AND [embase]/lim AND [2010–2019]/py, “tryptase” AND “hypersensitivity” AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [humans]/lim AND [english]/lim AND [abstracts]/lim AND [embase]/lim AND [2010–2019]/py, “tryptase” AND “mastocytosis” AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [humans]/lim AND [english]/lim AND [abstracts]/lim AND [embase]/lim AND [2010–2019]/py. Using this method, we found 1324 articles in Embase.

We screened these articles by title and abstract and when these met the inclusion criteria, the full text of the article was read to assess eligibility. Furthermore, the references of these reviewed articles were also screened to pick up other relevant studies. The search was mainly limited to studies written in English.

The statistical evaluation was descriptive. Specified concentrations in microgram/liter were converted to nanogram/milliliter.

Critical Appraisal

Most appraisal tools for diagnostic studies were designed for those that compare a reference standard with an index test. This was not the focus of this article as there is no standard reference equation. Therefore, it was decided to use a modified version of the 2015 STARD criteria (<http://www.equator-network.org/reporting-guidelines/stard>). The articles were scored on 13 items that included population background, the rationale behind the study, the quality of the analysis, and general completeness. If four or more of the included items were found to be missing, completeness of reporting was considered inadequate.

Results

We identified 11 studies with 4551 participants. However, only four studies used the proposed consensus equation after the Working Conference in 2010 for MCT in IHR. [8] The flow chart in Fig. 1 graphically displays the process used in searching for data.

The Consensus Equation Proposed by the Working Conference in 2010

Four studies with a total of 653 participants used the proposed equation of the Working Conference in 2010 (Table 1).

De Schryver et al. published a study in 2016 using the consensus eq. ($1.2 \times \text{baseline tryptase} + 2 \text{ ng/mL}$) which included 203 pediatric patients presenting to the emergency department (ED) with anaphylaxis. Thirty-nine children showed an elevated post-reaction tryptase level. The equation was more sensitive with increasing severity of the reaction; there was 100 and 80% sensitivity in severe and mild reactions, respectively. Similarly, the

sensitivity of the absolute difference (at least 2 ng/mL) increased to 100% (95% CI, 46.3 to 100%) and 80% (95% CI, 29.9 to 98.9%) in severe and mild reactions, respectively. Nevertheless, in moderate reactions, the sensitivity decreased for both the consensus equation and the absolute difference (52.4%; (95% CI, 30.3 to 73.6%), and 57.1%; (95% CI, 34.4 to 77.4%), respectively). The authors conclude that tryptase levels are particularly useful for the diagnosis of severe and/or milk-induced anaphylaxis and that assessing the difference between tryptase levels during the reaction and post-reaction may improve diagnostic sensitivity regardless of the trigger. [11]

Baretto et al. published a study in 2017 in which they validated the consensus equation in cases of suspected peri-operative anaphylaxis during general anesthesia. They recruited 82 patients during a period of 4 years. In this study, age distribution and gender was not described. A rise in acute MCT greater than defined by the equation had high specificity (91%) and a positive predictive value (98%) with a moderate negative predictive value (44%) and sensitivity (78%) in peri-operative anaphylaxis. [12]

Fig. 1 Flow chart of the article selection process

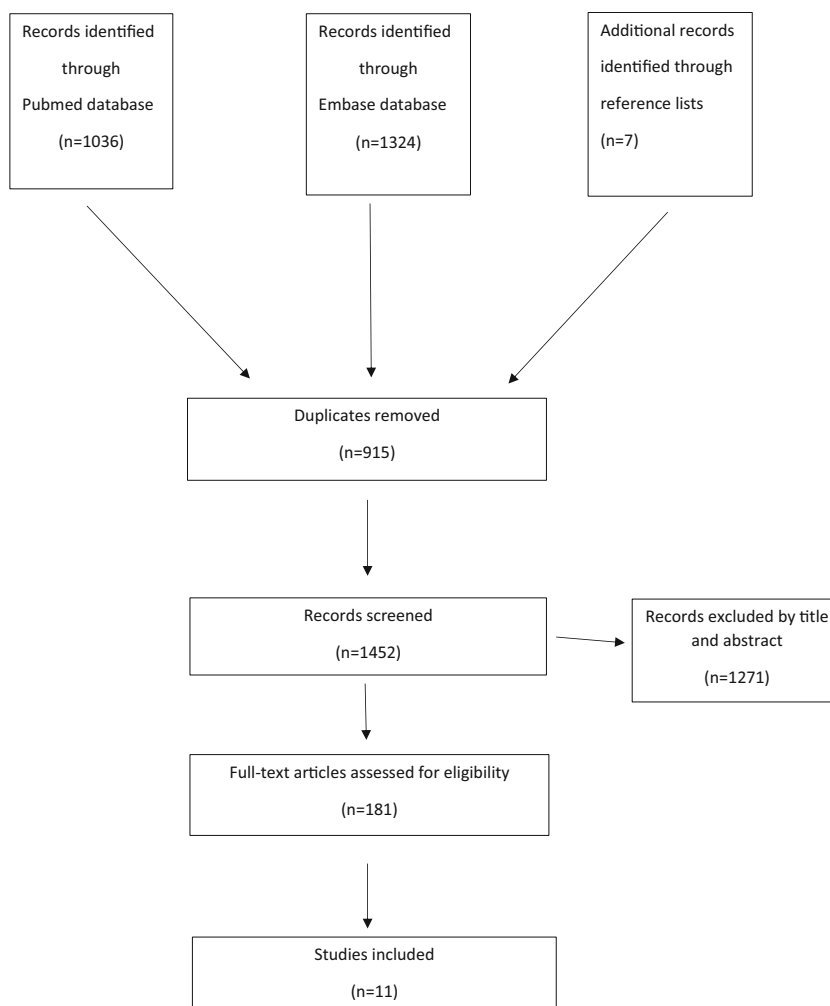


Table 1 Data extractions, studies using the eq. 1.2x baseline+2 ng/mL

Author, year, country of publication	Type of study	Study population	Sample size	Etiology of anaphylaxis	Timepoint peak tryptase	Timepoint baseline tryptase	Studied comparison of tryptase ^a	Severity of anaphylaxis	General comments
De Schryver, 2016, Canada [11]	Prospective, monocentric	Children with anaphylaxis in ED ^b , April 2011–April 2015	203	Food, hymenoptera venom, drug, other, and unknown	T1: 30–120 min after onset of reaction	At least 24 h after resolution of event	1.2x baseline tryptase +2 ng/mL	Mild to severe, according grading system by Brown ^c	Tryptase level exceeding threshold 1.2x baseline tryptase +2 ng/mL or difference of 2 ng/mL will detect most of the anaphylaxis reactions Sensitivity 78%, specificity 91%, PPV 98%, NPV 44%
Baretto, 2017, UK [12]	Prospective, monocentric	Adverse anesthetic drug reactions, 2013–2017	82	Perioperative anaphylaxis	T1: as soon as possible after resuscitation T2: 1–2 h after onset of reaction	≥ 24 h after onset	>1.2x baseline tryptase +2 ng/mL	n.a. ^d	
Egner, 2018, UK [13]	Retrospective, multicentric	Pediatric and adult population, November 2015–November 2016	266	Perioperative anaphylaxis	T1: Within first 1 h after onset of reaction T2: 32% within 2 h after onset of reaction (only 32%) T3: 43% within 3 h after onset of reaction T4: 71% within 6 h after onset of reaction	≥ 24 h after onset (73%) < 20 h after onset (12%)	Anaphylaxis with peak tryptase < 14 µg/L: 1.2x baseline tryptase +2 ng/mL	Grades 3–5 included, according to grading system of WAO definitions ^e	
Vitte, 2019, France [14]	Retrospective, monocentric	Adult population (aged ≥ 18), November 2011 to May 2017	102	Perioperative anaphylaxis	T1: 0.5–2 h after onset of reaction T2: Resolution + 24 h	Work-up before start of reaction or at least 24 h after resolution of all signs and symptoms	>1.35x sBT >1.2x sBT + 2 ng/mL >sBT + 3 ng/mL	Grades 1–4 adapted from Ring and Messmer ^f	94% PPV, 53% NPV, 75% sensitivity, 86% specificity

PPV positive predictive value, NPV negative predictive value

^a Specified concentrations in microgram/liter were converted to nanogram/milliliter

^b Emergency Department

^c Brown SG. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 2004;114:371–6

^d Not available

^e Harper NJN, Cook TM, Garcez T, Lucas DN, Thomas M, Kemp H, et al. Anaesthesia, surgery, and life-threatening allergic reactions: management and outcomes in the 6th National Audit Project (NAP6). *British journal of anaesthesia*. 2018;121 [1]:172–88

^f Ring and Messmer scale, fatal cases considered as grade 5 (Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* (London, England). 1977;1(8009):466–9)

Egner et al. published data from the NAP6 cohort in 2018. In this study, age distribution and gender was not specified. In total, 266 cases of perioperative anaphylaxis were included between November 2015 and 2016 in the UK. Peak tryptase (PT) threshold was defined as being above 14 ng/mL and was seen in 71% of cases. They used the term “dynamic tryptase” (DT) which referred to the calculation of serial rises and falls of tryptase suggesting acute release within the reference range. Two hundred twenty-nine cases with two or more tryptase measurements were analyzed. DT was associated with acute tryptase (AT) release if the PT exceeded ($1.2 \times$ baseline + 2 ng/mL), even within the references range. DT detected an additional 37 (16%) cases where PT was lower than 14 ng/mL. DT was also useful for thresholds lower than 11.4 ng/mL. [13]

Vitte et al. published the results of a retrospective monocentric study in 2019, including 102 adult patients who had experienced a perioperative anaphylactic reaction. The diagnostic performances of three algorithms including the consensus equation $> (1.2 \times \text{serum baseline tryptase} + 2 \text{ ng/mL})$, other paired baseline and peak comparisons $> (1.35 \times \text{serum baseline tryptase})$, or $> (\text{serum baseline tryptase} + 3 \text{ ng/mL})$ and $> 11.4 \text{ ng/mL}$ (manufacturer’s upper reference value) were compared. Overall, adequate paired acute serum tryptase and baseline tryptase values were available in 85 of 102 patients. The consensus equation was the most effective algorithm in diagnosing perioperative anaphylaxis with 0.94 PPV, 0.53 NPV, 0.75 sensitivity, and 0.86 specificity. It was also useful in those patients with an AT level less than 11.4 ng/mL. [14]

Other Methods of Comparing Peak and Baseline Serum Tryptase Concentrations since the Working Conference in 2010

Seven studies used other methods to compare baseline and peak tryptase concentrations in anaphylaxis (Table 2).

Borer-Reinhold et al. included 35 patients with hymenoptera venom hypersensitivity; of these, 20 developed hypersensitivity reactions to stings or following venom injections during immunotherapy (considered as reactors), while 15 tolerated re-exposure to stings or venom injections during immunotherapy without hypersensitivity reactions (considered as non-reactors). The authors observed that a relative increase in tryptase of greater than or equal to 135% of the baseline value, during a suspected anaphylactic reaction, indicated mast cell activation, even below 11.4 ng/mL. [15]

Sala-Cunill et al. performed a prospective study of 102 patients attending the ED with clinically confirmed acute anaphylaxis, of which only 61.8% of these patients showed an elevated tryptase level compared to baseline. Tryptase was more frequently elevated in severe anaphylaxis and positively correlated with the severity grading score. Interestingly, food induced anaphylaxis was less likely to result in an elevated

tryptase level when compared with venom or drug-induced anaphylaxis. [16]

Krishna et al. conducted a multi-center retrospective survey in the UK to evaluate serial tryptase measurements in anaphylaxis during general anesthesia in 161 adults. This study showed that the absolute tryptase (AT) increase and the percentage change (PC) from the baseline were comparable. Three serial tryptase measurements were available in 34% of patients, and a ROC analysis of area under the curve (AUC) showed comparable performance for PC and AT. High specificity ($\geq 80\%$) and a PPV $\geq 85\%$ was achieved for a $> 506\%$ increase from baseline or an absolute value of $> 33.6 \text{ ng/mL}$ but this had a low sensitivity value of 53%. [17]

Wongkaewpothong et al. performed a prospective study to investigate the utility of serum tryptase for confirmation of shrimp-induced anaphylaxis. Thirty-nine patients were recruited for shrimp challenges. However, only 3 patients had a peak tryptase level above the cut off (11.4 ng/mL). This study demonstrated that the delta-tryptase (peak minus baseline tryptase level) or the tryptase ratio (peak tryptase divided by baseline tryptase level) should be used for the confirmation of anaphylaxis instead of a single peak tryptase. The tryptase ratio provided a higher sensitivity, specificity, positive likelihood ratio (LR), and lower negative LR compared to a single peak tryptase value. The best cut-off value for the tryptase ratio was ≥ 1.5 with 92% sensitivity, 96% specificity, a positive LR of 23 and a negative LR of 0.08. [18]

Egner et al. studied perioperative anaphylaxis in 3455 patients (3400 patients were included) in the NARCOS database (National Adverse Reactions Advisory Service); this contains laboratory and clinical information on all samples referred to Sheffield, UK. In this study, age distribution and gender was not described. The authors showed that an increase in tryptase of 20% from baseline or a simple increment of 3 ng/mL can detect perioperative allergic reactions in suspected cases, even with peak tryptase concentrations between 5 and 14 ng/mL and in some cases below 5 ng/mL. [19]

Dua et al. carried out a prospective study of mast cell tryptase during allergic reactions to peanuts, including 50 known patients with peanut allergy, recruited from 2013 to 2016. The average peak percentage rise in tryptase concentration for all reactions was 34.8%. In the anaphylaxis group, the average rise was 148.4%, and in the non-anaphylaxis group, 23.9%. Severe reactions correlated with a higher peak/baseline tryptase ratio. The authors conclude that the optimal cutoff to identify a reaction was a 30% rise in tryptase above the baseline, which was associated with a sensitivity of 0.53 and specificity of 0.85. [20]

Gastaminza et al. performed a retrospective study which aimed to compare the diagnostic accuracy of tryptase during reaction (TDR) alone and the TDR/basal tryptase (TDR/BT) ratio for discriminating IgE- from non-IgE-mediated anaphylactic reactions, and to estimate the best numerical diagnostic

Table 2 Data extractions, studies using other baseline and peak serum tryptase comparison methods

Author, year, country of publication	Type of study	Study population	Sample size	Etiology of anaphylaxis	Timepoint peak tryptase	Timepoint baseline tryptase	Studied comparison of tryptase ^a	Severity of anaphylaxis	General comments
Borer-Reinhold, 2011, Switzerland [15]	Prospective, monocentric	Adult patients Hymenoptera venom hypersensitivity, 2007–2009	35	Hymenoptera venom	T1: 2 h after onset of reaction T2: 5 h after onset of reaction T3: 24 h after onset of reaction	Before exposure or at least 72 h after exposure	Relative tryptase increase to $\geq 135\%$	Grades 1–4, according to grading system by HL Mueller ^b	Increase of $\geq 135\%$, even below 11.4 ng/mL indicative of mast cell activation
Sala-Cumill, 2013, Spain [16]	Prospective, monocentric	Adults with anaphylaxis in ED ^c , September 2008–September 2009	102	Drug, food, Anisakis, latex, hymenoptera venom, cold, unknown	T1: 1–2 h after onset of reaction T2: 4–6 h after onset of reaction T3: 12–24 h after onset of reaction	At least 1 week later	Comparison of tryptase level T1, T2, and T3 with TB; T1 with highest increase	Moderate to severe, according to grading system by Brown ^d	Age and coronary risk factors were associated with more severe anaphylaxis. In 36.3% of cases, tryptase was not elevated
Krishna, 2014, UK [17]	Retrospective, multicentric	Adults, adverse anesthetic drug reactions, 2005–2012	161	Perioperative anaphylaxis	T1: as soon as possible after resuscitation T2: 1–2 h after onset of reaction	≥ 24 h after onset	Peak tryptase cut off: 25 ng/mL Peak tryptase and change from the baseline	3, 19, 65, and 13% of patients with grades of severity 1, 2, 3, and 4, respectively, based on Mertes et al. ^e and Ring and Messmer ^f (data on severity were available for 100 patients)	Specificity $\geq 80\%$, sensitivity of 53%, and PPV ^g $\geq 85\%$ for $> 506\%$ increase from baseline or an absolute value of > 33.6 ng/mL
Wongkaewpothong, 2014, Thailand [18]	Prospective, monocentric	Patients over 5 years old, food challenge to shrimps	39	Shrimp allergy	Peak tryptase: 60 min after the onset of symptoms	Before the challenge day	Cut-off for peak and baseline tryptase ratio ≥ 1.5 Cut-off for delta-tryptase (peak –baseline tryptase) ≥ 0.8 ng/mL	Mild to severe reactions, according to the grading system of Brown ^d	Cut-off for tryptase ratio ≥ 1.5 : 92% sensitivity, 96% specificity, 23 PLR, and 0.08 NLR
Egner, 2016, UK [19]	Retrospective, monocentric	Adverse anesthetic drug reactions, NARCOS database, January 1998–May 2015	3400	Perioperative anaphylaxis	T1: immediately T2: 1–6 h after onset of reaction	24 h after reaction	Delta-tryptase: 20% Delta-tryptase: 3 ng/mL	Grades 1–5, $> 70\%$ of the cohort with grades 3–5 reactions, according to the grading system by Ring and Messmer ^f	Increment of 20% would identify additional 14% cases with PT between 5 and 14 ng/mL and a further 15% with PT below 5 ng/mL
Dua, 2018, UK [20]	Prospective, monocentric	Adult patients, food challenge with peanut, 2013–2016	50	Peanut allergy	T1: Pre challenge T2: At the onset of reaction T3: 1 h after onset of reaction	Before challenge	Rise of 30% from baseline tryptase	Grades 2–5, according to the grading system by Ewan and Clark ^g	Rise of 30%: sensitivity 53%, specificity of 85%

Table 2 (continued)

Author, year, country of publication	Type of study	Study population	Sample size	Etiology of anaphylaxis	Timepoint peak tryptase	Timepoint baseline tryptase	Studied comparison ^a of tryptase	Severity of anaphylaxis	General comments
Gastaminza, 2018, Spain [21]	Retrospective, monocentric	Age 3–99 years, 2009–2015	111	Drugs, foods, iodinated contrast media, other causes (hymenopter venom, latex, or physical urticaria), unknown	T4: 2 h after onset of reaction T1 (=TDR): When patient received medical assistance T2: 2 h after the onset of reaction	At least 24 h after total recovery or in previous month before onset	TDR/BT ratio 1.66 discriminative between IgE- and non-IgE-mediated reaction	Milder allergic reactions that did not fulfill clinical anaphylaxis criteria also included	Optimal TDR/BT ratio: 1.66 with 76.4% sensitivity, 76.8% specificity, 76.4 PPV, and 76.8 NPV

PPV positive predictive value; PLR positive likelihood ratio; NLR negative likelihood ratio; NARCOS national service for the laboratory investigation of adverse anesthetic drug reactions based in Sheffield, UK; TDR tryptase during reaction; NPV negative predictive value

^a Specified concentrations in microgram/liter were converted to nanogram/milliliter

^b Mueller HL. Diagnosis and treatment of insect sensitivity. The Journal of asthma research. 1966;3 [4]:331–3

^c Emergency Department

^d Brown SG. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol 2004;114:371–6

^e Mertes PM, Malinovsky JM, Jouffroy L, Working Group of the S, Sfa, Aberer W, et al. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. J Investing Allergol Clin Immunol. 2011;21 [6]:442–53

^f Ring and Messmer scale, fatal cases considered as grade 5 (Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet (London, England). 1977;1(8009):466–9)

^g Ewan PW, Clark AT. Long-term prospective observational study of the outcome of a management plan in patients with peanut and nut allergy referred to a regional allergy center. Lancet 2001;357:111–5;

cut off point. But also milder allergic reactions that did not fulfill clinical anaphylaxis criteria were also included in the study. The TDR/BT ratio showed the greatest ability to discriminate IgE- from non IgE-mediated allergic reactions compared to TDR alone. They conclude that an optimal TDR/BT ratio threshold of approximately 1.66 may be useful in clinical practice to classify allergic reactions as IgE- or non-IgE-mediated. [21]

Critical Appraisal

The results of the critical appraisal can be found in Tables 3 and 4. The reporting of variables was found to be incomplete for 2 out of 4 of the studies using the conference's consensus equation (Table 3) and for 2 out of 7 of the studies using other baseline and peak tryptase comparison methods (Table 4) according to the aforementioned criteria. All articles explained the aim of their research. A rationale for the equation used was often lacking in the methods. Interestingly, population diversity, clinical background, and diagnostic accuracy were often not specified or analyzed in either study group.

Discussion

Anaphylaxis can be a potential life-threatening condition and its rapid diagnosis followed by initiation of emergency therapy is crucial.

Serum tryptase is currently the best studied biomarker for anaphylaxis. There are two major forms of tryptase described, the α -protryptase, which leaks continuously from MCs and is present in normal plasma, and β -tryptase which is stored in the MC granules. Active β -tryptase is released, together with other mediators, on MC activation during hypersensitivity reactions. [3, 15] During acute allergic reactions, increased β -tryptase is released from MCs and this increased concentration correlates with a decrease in arterial blood pressure. Total tryptase (α -protryptase and β -tryptase) concentrations are remarkably stable with time in normal patients, with large inter-individual variations. Commercially, tests measure only total tryptase and cannot discriminate between α -protryptase and β -tryptase. In this context, a baseline serum tryptase level of > 20 ng/mL is considered a minor diagnostic criterion for systemic mastocytosis. [22] Therefore, elevated tryptase levels should be helpful for the diagnosis of anaphylaxis particularly the comparison of baseline and peak levels. Interestingly, the study of Vitte et al. which measured mature forms of α and β tryptases using an in-house method, during perioperative anaphylaxis, failed to show a rise of mature tryptase in samples (total levels below 16 ng/mL). [14]

Nine years after the Working Conference and the creation of the consensus equation (peak MCT should be $> 1.2 \times$ baseline tryptase + 2 ng/mL), there are only a few studies available

which have applied this equation. In total, we identified 11 studies comparing baseline and peak serum tryptase. Four studies [11–14] used the proposed consensus equation of the Working Conference in 2010 [8], and seven studies [15–21] used other methods to compare baseline and peak serum tryptase concentrations. In general, the consensus equation and the other methods of comparing baseline and peak serum tryptase are unable to detect all anaphylactic reactions.

In daily clinical practice, serial measurements of tryptase are laborious. Buka et al.'s retrospective observational study of patients attending British EDs revealed that only 33.1% of suspected anaphylaxis cases had acute serum tryptase levels measured. [23] No patients had serial measurements or baseline serum tryptase taken despite the British guideline recommendations to the contrary. Acute serum tryptase levels higher than 12.4 ng/mL carried a high positive predictive value (0.93) and specificity (88%) for anaphylaxis, but poor sensitivity (28%) and a low negative predictive value (0.17). [23]

Francis et al. performed a study to investigate the utility of mast cell tryptase in differentiating anaphylaxis from other causes of critical illness, also involving mast cell activation. They conclude that, although both median peak-MCT and delta-MCT (the difference between the peak and baseline tryptase values) concentrations are higher in anaphylaxis than in other forms of critical illness, the sensitivity and specificity of these analyses are too low. Therefore, diagnostic thresholds for either peak or delta-MCT cannot be reliably used to establish the diagnosis of anaphylaxis in the ED. While MCT levels are somewhat helpful in identifying individuals with acute anaphylaxis when compared to healthy/non-reacting individuals, they have limited utility for differentiating anaphylactic from non-anaphylactic shock. [24]

Tacquard et al. report the results of the 10th GERAP (Groupe d'Etude des Réactions Anaphylactoides Périopératoires) survey on immediate hypersensitivity reactions during perioperative anesthesia in France between 2011 and 2012. Seven hundred fourteen patients were included in this study and serum tryptase levels were determined at the time of reaction in 64.3% of cases. The optimal serum tryptase threshold for diagnosis of an allergic reaction was 14.75 ng/mL with a sensitivity of 0.74 (CI 0.69–0.79) and a specificity of 0.74 (CI 0.67–0.81). The baseline tryptase levels were only rarely available, as this was not part of the guidelines at the time. [25]

Our review has several limitations: the studies are heterogeneous being both prospective and retrospective in character but also monocentric and multicentric. Furthermore, the investigated populations are different in the studies, with regard to the number of patients, age group (children, adults), setting (emergency, perioperative), and allergen (food, drugs, hymenoptera). Meaningful statistical analyses and statements are not feasible due to this heterogeneity. Other factors such as age, BMI, liver disease, or renal impairment need to be taken

Table 3 Clinical appraisal based on the STARD 2015 criteria, studies using the eq. 1.2x baseline+2 ng/mL

Author, year of publication	Introduction		Methods		Results							Discussion	
	Description of scientific and clinical background	Objective of article explained	Description of whether it is prospective or retrospective	Description of patient eligibility criteria	Inclusion of diverse population	Rationale for included equation in methods	Description of test protocol	Description of clinical background of diagnosed patients	Description of severity of reaction in those with the target condition	Description of the index test	Estimates of diagnostic accuracy (sensitivity, specificity)	Description of study limitations	Description of implications for practice
De Schryver 2016, [11]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Baretto, 2017, [12]	Yes	Yes	Unclear	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Yes
Egner, 2018, [13]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	No	Yes
Vitte, 2019, [14]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table 4 Clinical appraisal based on the STARD 2015 criteria, studies using other baseline and peak serum tryptase comparison methods

Author, year of publication	Introduction		Methods		Results							Discussion	
	Description of scientific and clinical background	Objective of article explained	Description of whether it is prospective or retrospective	Description of patient eligibility criteria	Inclusion of diverse population	Rationale for included equation in methods	Description of test protocol	Description of clinical background of diagnosed patients	Description of severity of reaction in those with the target condition	Description of the index test	Estimates of diagnostic accuracy (sensitivity, specificity)	Description of study limitations	Description of implications for practice
Borer-Reinhold, 2011, [15]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	No	Yes
Sala-Cunill, 2013, [16]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Krishna, 2014, [17]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wongkaewphong, 2014, [18]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Egner, 2016, [19]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	No	No
Dua, 2018, [20]	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Gastaminza, 2018, [21]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes

into consideration as they can influence the serum tryptase levels. Furthermore, up to 29% of the normal population have an alpha-tryptase deficiency, which may limit the rise of in serum tryptase levels. [26]

Due to the limitations, there is interest in exploring alternative biomarkers in anaphylaxis. Nassiri et al. demonstrate that serum levels of 9a,11 β -PGF₂, a metabolite of PGD₂, increase profoundly during anaphylaxis and display a higher sensitivity and specificity for anaphylaxis than tryptase. [27] The study of Wittenberg et al. demonstrates that serum levels of ApoA1 decrease during anaphylaxis. ApoA1 and 9a,11 β -PGF₂ combined have a high diagnostic power as a composite biomarker of anaphylaxis. [28] Apolipoprotein B has also been suggested as a possible biomarker for anaphylaxis. [29] Further studies are needed to determine whether UMH (urinary methyl histamine) can identify mast cell mediator release. [19] Other promising biomarkers include the histamine-degrading enzyme diamine oxidase which is released during severe anaphylaxis in mastocytosis patients but this failed to show reliability in pregnancy. [30]

In conclusion, there is no biomarker that singly allows an unambiguous diagnosis of anaphylaxis but it remains vitally important to have a reliable diagnostic test for this. An ideal biomarker should fulfill the following criteria [31]: (a) there is a relationship between the biomarker and the pathophysiological reaction, (b) the test is viable, (c) the test is reproducible in a routine clinical setting, (d) the test is informative about the disease process and prognosis, (e) the test is inexpensive, (f) there are measurable changes in response to intervention, (g) there is little or no diurnal variation in the biomarker, (h) the test is sensitive and disease-specific, (i) the test has high positive and negative predictive values, (j) there is a simple sampling method, (k) the test and its results are available quickly, and (l) it is acceptable to patients. Currently, serum tryptase is the best candidate which meets the majority of these criteria but it is still far from being an ideal biomarker for anaphylaxis. Further research is still needed.

Conclusion

This systematic review found that the consensus equation, formed by the Working Conference in 2010, is underused for the diagnosis of anaphylaxis in studies performed since then. Based on the current evidence, the consensus equation for the threshold tryptase concentration required for the diagnosis of anaphylaxis has its limitations. Furthermore, serial tryptase measurements or paired measurements of baseline and peak tryptase are laborious and therefore of limited application in daily clinical practice. Nevertheless, serum tryptase remains the best current biomarker for anaphylaxis but there is a need for further evaluation of other biomarkers in anaphylaxis.

Ethical Approval and Informed Consent This article does not contain any studies with human participants or animals performed by any of the authors.

Compliance with Ethical Standards

Conflict of Interest All authors have no conflict of interest including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included in this manuscript.

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