

# Tryptase and anaphylaxis: The case for systematic paired samples in all settings, from the playground to the COVID-19 vaccination center

Joana Vitte, C. Gonzalez, Caroline Klingebiel, Moïse Michel

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1 2 Tryptase and anaphylaxis: the case for systematic paired samples in all settings, from the playground 3 to the COVID-19 vaccination center 4 5 Joana Vitte \*1,2,3, Constance Gonzalez 1,2, Caroline Klingebiel 4, Moïse Michel 1,2,5 6 7 1 Aix-Marseille Univ, IRD, MEPHI, Marseille, France 8 2 IHU Méditerranée Infection, Marseille, France 9 3 IDESP, INSERM UMR UA11, University of Montpellier, Montpellier, France 10 4 Laboratoire Synlab Provence 11 5 Laboratoire d'Immunologie, CHU de Nîmes, Nîmes, France 12 13 \*Corresponding author 14 Dr Joana Vitte 15 IHU Méditerranée Infection 16 19-21 bd Jean Moulin 17 13005 Marseille, France 18 joana.vitte@inserm.fr 19 20 21 4090 characters; 1 figure; 8 references 22 23 **ORCID** numbers 24 Joana Vitte: 0000-0002-3344-9408 25 Caroline Klingebiel: 0000-0002-9069-6931 26 Moïse Michel: 0000-0002-0460-9898 27 28 29

1	Tryptase and anaphylaxis: the case for systematic paired samples in all settings, from the playground
2	to the COVID-19 vaccination center
3	
4	Tryptase et anaphylaxie: de l'aire de jeux au centre de vaccination COVID, deux prélèvements sont
5	nécessaires en toutes circonstances
6	
7	
8	Keywords
9	anaphylaxis; hypersensitivity; mast cell; tryptase
10	
11	Mots clés
12	anaphylaxie; hypersensibilité; mastocyte; tryptase
13	
14	Abbreviations
15	sAT, serum acute tryptase; sBT, serum baseline tryptase

Anaphylaxis is an immediate and potentially life threatening systemic reaction [1], associated with significant morbidity, mortality, and much too frequent suboptimal management. Serum tryptase is the main and most widely available mast cell biomarker available for in vitro diagnostics. In the clinical setting, tryptase determination is commonly performed using the "total tryptase assay" (ImmunoCAP Tryptase, Thermo Fisher Scientific, Uppsala, Sweden), which has received significant technical improvement and related changes in median and upper limit values since its first release in 1995 [2]. Taking two tryptase samples with adequate timing has been recommended for the diagnosis of anaphylaxis and may also add mechanistic information. Indeed, anaphylaxis by itself does not provide clues for the underlying mechanism [2].

Adequate timing refers to paired acute (sAT) and baseline (sBT) serum tryptase determination, with sAT sample optimally taken 30-120 min after the onset of signs or symptoms and sBT sample drawn at least 24 hours after the complete resolution of all signs and symptoms. The current international consensus states that a transient elevation of sAT greater than [2 + (1.2x sBT)] is indicative of mast cell degranulation [3]. This algorithm allows calculating an individual cut-off for each patient, based on sAT and sBT values: sAT exceeding  $[2 + (1.2 \text{ x sBT})] \, \mu\text{g/L}$  supports mast cell degranulation, even in cases when sAT remains in the normal reference range.

Paired sAT and sBT determination increases both the sensitivity and the specificity of anaphylaxis diagnosis [2], assists with severity grading [4] and since recently help identify patients at increased risk of severe reactions due to the hereditary alpha-tryptasemia genetic trait [5]. In fact, proper interpretation of both sAT and sBT can only be done using paired samples. For example, recent data on hereditary alpha tryptasemia have provided further support for systematic testing of paired sAT and sBT. With a prevalence of up to 8% in general population and most studies showing an increased risk of severe hypersensitivity reactions, no clinician should take the risk of overlooking hereditary alpha-tryptasemia, which can only be suspected through sBT determination and confirmed with digital droplet PCR in specialized laboratories. Missing other mast cell-related disorders, such as mastocytosis, often discovered as an elevated sBT, may lead to substandard patient management, which would have been avoidable through proper tryptase assessment.

Among other frequent errors, we would like to cite the assumption that the manufacturer's upper limit for serum tryptase (currently 11.0  $\mu$ g/L in Europe) is a reliable cut-off for discriminating mast cell degranulation. This assumption has been abundantly demonstrated as false by large cohort studies on perioperative anaphylaxis, showing that up to 60% of confirmed mast cell degranulation events had sAT lower than the manufacturer's cut-off [2, 6].

In some patients, especially in those with extremely high sAT, serum tryptase levels may not return to baseline after 24h, therefore, if a sample taken after 24 h is higher than 8  $\mu$ g/L or even 7  $\mu$ g/L, a control sBT sample should be taken later, for example during the allergy work-up which must be offered to any patient having experienced anaphylaxis.

Further support for the paired sAT and sBT determination comes from its robust use in populations such as children [7] and pregnant women [8].

To summarize, taking two tryptase samples at adequate times for acute and baseline serum tryptase assessment and interpretation is the current state of the art recommendation for anaphylaxis. This recommendation should be kept in mind and implemented in any case of anaphylaxis or suspicion of

57 immediate hypersensitivity reaction, should it happen at home, at school, in the office, during an 58 anesthetic procedure, while delivering a COVID-19 vaccine, or in any other setting. Proper sampling time 59 is critical for acute tryptase measurement, and baseline sampling must not be overlooked.

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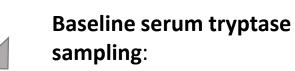
Figure. Paired tryptase sampling in anaphylaxis



Immediate,
potentially lifethreatening systemic
reaction =
anaphylaxis

### **Acute tryptase sampling:**

- 30 min 2 h after onset
- earlier than 30 min: risk of false negative
- up to 4-6 h: acceptable, cautious interpretation, risk of false negative



- >24 h after complete resolution
- repeat if ≥ 8 µg/L

mast cell degranulation confirmed if sAT > [2 + (1.2 x sBT)]



referral to allergist:
mandatory for all patients
having experienced
suspected or confirmed mast
cell degranulation