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

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

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

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4 **Tryptase et anaphylaxie: de l'aire de jeux au centre de vaccination COVID, deux prélèvements sont**  
5 **nécessaires en toutes circonstances**

6  
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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

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

25 Adequate timing refers to paired acute (sAT) and baseline (sBT) serum tryptase determination, with sAT  
26 sample optimally taken 30-120 min after the onset of signs or symptoms and sBT sample drawn at least  
27 24 hours after the complete resolution of all signs and symptoms. The current international consensus  
28 states that a transient elevation of sAT greater than  $[2 + (1.2 \times \text{sBT})]$  is indicative of mast cell  
29 degranulation [3]. This algorithm allows calculating an individual cut-off for each patient, based on sAT  
30 and sBT values: sAT exceeding  $[2 + (1.2 \times \text{sBT})]$   $\mu\text{g/L}$  supports mast cell degranulation, even in cases when  
31 sAT remains in the normal reference range.

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

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

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

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

54 To summarize, taking two tryptase samples at adequate times for acute and baseline serum tryptase  
55 assessment and interpretation is the current state of the art recommendation for anaphylaxis. This  
56 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**

