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Serum Baseline Tryptase Level as a Marker for the Severity of Anaphylaxis

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Keywords

Anaphylaxis · Tryptase · Allergy · IgE · Epinephrine

Abstract

Background: Anaphylaxis is a severe and potentially fatal allergic disease or hypersensitivity reaction with variable clinical presentation. Biomarkers in anaphylaxis could be useful to improve diagnosis, to allow endotyping of patients, and to predict risk. **Objective:** To investigate the role of serum basal tryptase (sBT) levels in the management of patients with anaphylaxis. **Methods:** Patients with at least 1 episode of anaphylaxis were selected among those who attended the Allergy Clinics of the Clinical Hospital of the Ribeirão Preto Medical School, University of São Paulo, Brazil, upon evaluation by allergy/immunology specialists of our medical staff. Demographic and clinical data were obtained using a structured questionnaire. sBT levels were determined using the ImmunoCAP Tryptase immunoassay. **Results:** 57 patients (56.1% female) with a median age of 35 years (range 7–87 years) participated in the study. sBT levels ranged from 2.57 to 21.19 ng/mL (mean 5.17 ng/mL), with no significant differences in patients with anaphylaxis due to different triggers. Mean levels were 4.93; 5.2; 5.41, and 5.24 ng/mL for

patients who had anaphylaxis due to *Hymenoptera* venom ($n = 17$), foods ($n = 13$), drugs ($n = 13$), and idiopathic disease ($n = 14$), respectively. Significantly higher sBT levels were observed in patients with severe anaphylaxis (grade IV) than in patients with mild-moderate disease (grades II/III) (mean levels 6.61 vs. 4.71 ng/mL, respectively). **Conclusion:** High sBT levels may help to identify patients at increased risk of more severe anaphylaxis, prompting physicians to initiate immediate therapy to avoid further acute episodes.

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Introduction

Anaphylaxis is a severe and potentially fatal allergic disease or hypersensitivity reaction with variable clinical presentation, which usually occurs suddenly after contact with a triggering antigen. IgE-mediated reactions frequently underlie the development of anaphylaxis; however, other pathways have also been described [1]. Due to the lack of universally accepted clinical criteria for the diagnosis of

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anaphylaxis, this condition is often underrecognized, underdiagnosed, and, consequently, undertreated [2–5]. Prevalence of anaphylaxis is increasing, with estimates of 0.3–5.1% depending on the definition used [6].

Currently, anaphylaxis phenotypes have been defined as type-I-like reactions, when classical allergic symptoms due to the release of inflammatory mediators from mast cells and basophils are present, including flushing, pruritus, urticaria, angioedema, dyspnea, wheezing, nausea, vomiting, diarrhea, hypotension, and cardiovascular collapse; cytokine storm-like reactions and mixed reactions, which are frequently provoked by chemotherapy or monoclonal antibodies and induce atypical symptoms such as chills, fever, or pain, in addition to classical symptoms, and reactions mediated by complement, which can be caused by contrast dyes or dialysis membranes, and often induce hypotension and oxygen desaturation [1, 7, 8]. Endotypes underlying these clinical presentations include IgE and non-IgE-mediated mechanisms, cytokine release, direct mast cell and basophil activation, complement activation with generation of anaphylatoxins C3a and C5a, contact system activation with bradykinin release, IgG-mediated cell activation which is still debatable in humans, and mixed reactions [1, 7, 8].

In keeping with precision medicine concepts, biomarkers in anaphylaxis would be very useful to improve diagnosis, particularly if point-of-care diagnostic biomarkers could be developed, to allow endotyping of patients, to propose new therapies based on the stratification of severity, and to predict risk [7, 8]. To date, serum tryptase levels are the best-characterized biomarker of anaphylaxis and have been included as part of institutional protocols [9–15]. Tryptase is a serine protease produced and released in large amounts by mast cells and to a lesser extent by basophils. Baseline tryptase levels have been shown to increase after mast cell activation in anaphylaxis [9, 10], but specificity may be limited by the fact that it can be increased in other conditions, particularly mast cell disorders such as systemic mastocytosis [9]. Serum tryptase concentrations >11.4 ng/mL indicate mast cell/basophil activation, and during anaphylaxis, levels correlate with severity. In patients with low baseline tryptase levels, levels may increase during anaphylaxis but still remain in the normal range; therefore, levels of 2 ng/mL plus 1.2 times baseline have been considered significantly increased [1]. Measurements of the histamine metabolite methylhistamine; prostaglandin D₂ and its metabolite 9 α -11 β prostaglandin F₂; and leukotrienes E₄ and C₄ have also been investigated; however, difficulties in obtaining 24-h urine samples in the scenario of ana-

Table 1. Signs and symptoms (*n*) reported by patients (*n* = 57) during their first episode of anaphylaxis

Cutaneous/mucosal signs/symptoms	
Skin rash	44 (77.2%)
Itching	44 (77.2%)
Angioedema	42 (73.7%)
Urticaria	33 (57.9%)
Respiratory signs/symptoms	
Dyspnea	51 (89.5%)
Glottis edema	45 (78.9%)
Dysphagia	34 (59.6%)
Nasal pruritus	30 (52.6%)
Cough	26 (45.6%)
Wheezing	26 (45.6%)
Stridor	22 (38.6%)
Hoarseness	22 (38.6%)
Cyanosis	20 (35.1%)
Gastrointestinal signs/symptoms	
Nausea	26 (45.6%)
Vomiting	16 (28.1%)
Abdominal pain	11 (19.3%)
Diarrhea	7 (12.3%)
Fecal incontinence	2 (3.5%)
Cardiovascular signs/symptoms	
Sweating	34 (59.6%)
Tachycardia	34 (59.6%)
Palpitation	32 (56.1%)
Hypotension	31 (54.4%)
Pallor	31 (54.4%)
Presyncope	20 (35.1%)
Chest pain	16 (28.1%)
Arrhythmia	9 (15.8%)
Shock	5 (8.8%)
Cardiopulmonary arrest	3 (5.3%)
Bradycardia	2 (3.5%)
Neurological signs/symptoms	
Dizziness	25 (43.9%)
Fatigue	22 (38.6%)
Mental confusion	21 (36.8%)
Headache	19 (33.3%)
Behavior changes	12 (21.1%)
Seizure	2 (3.5%)
Genitourinary signs/symptoms	
Uterine cramping	6 (10.5%)
Urinary incontinence	5 (8.8%)

Reported symptoms were in keeping with those described in the comprehensive review article on anaphylaxis by Castells [1].

phylaxis may hamper their practical use [7, 8]. Elevated IL-6 levels have been proposed as a marker of cytokine storm-type anaphylaxis [1].

In the present study, we aimed to investigate the role of serum basal tryptase (sBT) in the management of patients

with anaphylaxis and to establish its possible use in daily routine care by evaluating associations of sBT levels with the severity of anaphylactic episodes in a way that the findings could be used to predict a greater risk of new and potentially worse events. We also wanted to know whether sBT levels would vary among patients with anaphylaxis triggered by different factors, and whether sBT would be useful to screen our patients who had anaphylaxis for systemic mastocytosis and other mast cell disorders.

Patients and Methods

Patients

Patients participating in the present study were selected among those who attended the Allergy Clinics of the Clinical Hospital of the Ribeirão Preto Medical School, University of São Paulo, Brazil (HCFMRP-USP). Patients were evaluated by allergy/immunology specialists of our medical staff and included in the study if they fulfilled the criterion of having had at least 1 episode of anaphylaxis based on their medical interview and analysis of medical records. Although it would be desirable that all patients who had an acute anaphylactic reaction would be promptly transferred to an allergy consultation from the emergency department, in our public system patients need a referral from their primary care doctors to allow for consultation at our specialty clinic. However, we issue high priority allergy consultation to all patients referred to us for evaluation of anaphylaxis.

Anaphylaxis was defined as a serious systemic allergic or hypersensitivity reaction following exposure to a known or unknown trigger involving 2 or more organs, or associated with hypotension/upper respiratory symptoms, that can be life-threatening or fatal [16–18]. Patients were divided into 4 groups according to the trigger factor responsible for their first episode of anaphylaxis: foods, drugs, venom of *Hymenoptera* insects, and idiopathic disease when the trigger could not be identified.

All patients or patients' caregivers agreed to participate in the present study and signed a written informed consent. Ethical approval was obtained from the HCFMRP-USP Ethics Committee and from Brazil's Platform of Ethics (protocol No. 3773/2016).

Questionnaire

Each patient completed a questionnaire addressing clinical and epidemiological aspects focusing on signs and symptoms during their first episode of anaphylaxis, treatment received, treatment beyond the anaphylactic reaction, including having or not self-injectable epinephrine, and simultaneous comorbidities. Signs and symptoms assessed in our questionnaire are outlined in Table 1. After data collection, the severity of the first anaphylaxis episode was defined according to Ring and Messmer [19]: grade I, only cutaneous symptoms; grade II, mild symptoms; grade III, moderate-severe symptoms; and grade IV, cardiac and/or respiratory arrest.

Serum Baseline Tryptase Levels

sBT levels were determined using the ImmunoCAP Tryptase immunoassay (Thermo Fisher Scientific, Uppsala, Sweden). Levels >11.4 ng/mL were considered elevated [20], and levels >20 ng/mL led to further investigation for systemic mastocytosis [21]. Tryptase

Table 2. Demographic and clinical characteristics of the patients with anaphylaxis ($n=57$) enrolled in the study

Median age (range), years	35 (7–87)
At the first episode	29 (1–82)
Gender, males/females	25/32
Mean tryptase levels (range), ng/mL	5.17 (2.57–21.19)
Severity of the first episode, n (%)	
Grade II	4 (7.0%)
Grade III	40 (70.2%)
Grade IV	13 (22.8%)
Trigger factors, n (%)	
<i>Hymenoptera</i> venom	17 (29.8%)
Food	13 (22.8%)
Drugs	13 (22.8%)
Idiopathic disease	14 (24.6%)
Anaphylactic episodes, n (%)	
1–5 episodes	41 (71.9%)
6–10 episodes	9 (15.8%)
11–20 episodes	6 (10.6%)
>20 episodes	1 (1.7%)

Anaphylaxis grades were defined using the criteria proposed by Ring and Messmer [19]: grade I, cutaneous symptoms; grade II, mild symptoms; grade III, moderate-severe symptoms; grade IV, cardiac and/or respiratory arrest.

Table 3. Types of acute and preventive therapies reported by patients with anaphylaxis

Therapy modality	Patients, n
<i>Acute treatment</i>	
Epinephrine	36 (65.5%)
Antihistamines	43 (78.2%)
Corticosteroids	42 (75.0%)
β_2 -Agonists	18 (31.6%)
Oxygen	24 (42.1%)
Intubation	5 (8.8%)
Cardiopulmonary resuscitation	1 (1.7%)
<i>Preventive therapy</i>	
Allergen-specific immunotherapy	15 (26.3%)
Exclusion diet	13 (22.8%)
Desensitization	2 (3.5%)
Anti-IgE	6 (10.5%)
Epinephrine auto-injector	16 (28.0%)
None	21 (36.9%)

Although all patients had prescriptions for epinephrine auto-injectors, only 16 were successful in fulfilling the prescription due to lack of availability and/or financial constraints. We provided epinephrine ampules to 3 of the patients who could not obtain epinephrine auto-injectors after weighing risks and benefits.

tase levels during the acute event(s) of anaphylaxis were not available in the present study. Most patients received care for their acute events in other hospitals or health care facilities before being referred to our specialty clinic at a reference tertiary hospital for investigation, so we could not obtain information on tryptase measurement accurately from the patients or from medical records. In addition, tryptase measurement is usually not part of the routine protocol in emergency departments in our country, in most cases due to financial constraints.

Statistical Analysis

Means, medians, standard deviations, and quartiles were calculated for each group, and Bayesian linear regression models were fitted to estimate differences in means, with respective 95% credible intervals (95% CrI), using the software OpenBugs.

Results

Clinical and Epidemiological Characterization

A total of 57 patients participated in our study, and 32 (56.1%) were female. Their median age was 35 years (ranging from 7 to 87 years), including 10 children (7–16 years old). Seven of the 57 patients (12.2%) had >10 episodes.

The age at the first anaphylaxis episode varied from 1 to 82 years, with a median of 29 years. Triggers of the first anaphylaxis episode were *Hymenoptera* venom in 17 patients; foods in 13 patients; and drugs in 13 patients. Fourteen patients were characterized as having idiopathic anaphylaxis. The most relevant triggers in the *Hymenoptera* venom group were wasp/hornet, bee, and fire ant, in decreasing order of frequency. Among foods, shrimp, fish, peanut, and milk/dairy foods were the most frequent triggers. Within the drug group, antibiotics (cefazolin and sulfadiazine) and anti-inflammatory nonsteroidal drugs (ibuprofen, parecoxib, and dipyron) were the dominant triggers. Moderate reactions (grade III in 40 patients) were most commonly found, followed by severe reactions (grade IV in 13 patients), and mild reactions (grade II in 4 patients). These data are summarized in Table 2.

Regardless of the severity of anaphylaxis episodes, the majority of patients had cutaneous/mucosal and respiratory symptoms simultaneously (55/57 patients, 96.4%). Next in frequency, patients presented cardiovascular (52/57 patients, 91.2%), neurological (44/57 patients, 77.1%), gastrointestinal (27/57 patients, 47.3%), and genitourinary symptoms (9/57 patients, 15.7%). Some patients reported unusual symptoms, including hypothermia, metallic taste, neck pain, peeling skin on hands and feet, sore throat, fluorescent vision, mouth ulcers, leg pain, paresthesia, and anasarca.

Table 4. Concurrent conditions and medications reported by patients with anaphylaxis

Asthma	21 (36.8%)
Rhinitis	34 (59.6%)
Atopic dermatitis	5 (8.8%)
Urticaria	16 (28.1%)
Hypothyroidism	5 (8.8%)
Use of β -blockers	1 (1.7%)
ACE inhibitor use ¹	1 (1.7%)
Food allergy (not the primary trigger of anaphylaxis)	28 (49.1%)
Eosinophilic gastrointestinal disease	2 (3.5%)

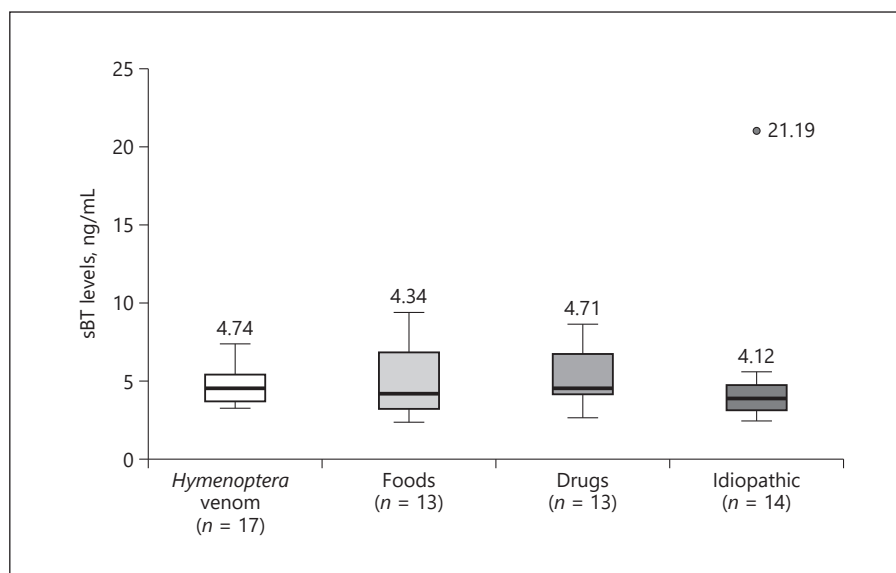
¹The same patient used a β -blocker and angiotensin-converting enzyme (ACE) inhibitor due to multiple comorbidities, including high blood pressure, diabetes mellitus type II, dyslipidemia, chronic renal disease, and previous stroke. The patient also had a pacemaker for atrioventricular blockade. There were no alternative pharmacological options suitable for his conditions.

Most patients were treated in the hospital/emergency room (50/57 patients, 87.7%), including 2 patients who needed treatment in the intensive care unit. However, 3 patients received care at a primary care unit (3/57, 5.3%), 3 patients self-administered medication at home (3/57, 5.3%), and 1 patient received treatment at a physician's office (1/57, 1.7%).

Regarding treatment received during this first episode of anaphylaxis, patients reported the use of antihistamines (75.4%) and corticosteroids (73.6%) most often. Epinephrine and β_2 -agonists were used in 63.1 and 31.5% of the patients, respectively. Twenty-four patients (42.1%) reported need of oxygen supplementation by nasal cannula or face mask, and 5 patients (8.8%) were intubated. One patient had cardiac arrest and was resuscitated by cardiopulmonary resuscitation protocol (Table 3).

Beyond the acute treatment, preventive treatment included subcutaneous allergen-specific immunotherapy in 15/17 (88.2%) patients with *Hymenoptera* venom-induced anaphylaxis; elimination diets for all patients with food-induced anaphylaxis; and desensitization for 2 patients with drug-induced anaphylaxis. In addition, 6 patients received anti-IgE therapy with the monoclonal antibody omalizumab, whereas 21 patients did not receive any kind of preventive treatment. Only 16/57 (28%) patients had epinephrine auto-injectors for reasons including financial constraints and previous advice to not use the medication. Three patients were given epinephrine ampules (Table 3).

Fig. 1. Serum baseline tryptase (sBT) levels in patients with anaphylaxis due to different triggers. Median values and 25th and 75th percentiles are represented. Median values are expressed above the boxes, as well as 1 outlier (21.19); this patient underwent further investigation of mastocytosis. Mean values of 4.93, 5.20, 5.41, and 5.24 ng/mL were found in patients who had anaphylaxis due to *Hymenoptera* venom, foods, drugs, and idiopathic disease, respectively.



Concurrent conditions and medications reported included asthma, rhinitis, atopic dermatitis, urticaria, hypothyroidism, and use of angiotensin-converting enzyme inhibitors and β -blockers. Allergy to foods not identified as the trigger of anaphylaxis was reported by 28 patients, and eosinophilic gastrointestinal disease was reported by 2 patients (Table 4).

Serum Baseline Tryptase Levels

sBT levels ranged from 2.57 to 21.19 ng/mL (mean 5.17 ng/mL), with no significant differences among patients who had anaphylaxis due to different triggers. Mean levels of 4.93, 5.2, 5.41, and 5.24 ng/mL were found in patients who had anaphylaxis due to *Hymenoptera* venom, foods, drugs, and idiopathic disease, respectively (Fig. 1). In the idiopathic group, there was 1 patient with an sBT level of 21.19 ng/mL (Fig. 1). At her initial evaluation for the study in July 2017, at the age of 40 years, this patient had had 8 episodes of anaphylaxis with no identifiable triggers, starting at the age of 23 years. She also presented with chronic urticaria refractory to antihistamines, leading to treatment with 300 mg omalizumab every 4 weeks. After the start of omalizumab therapy, her chronic urticaria was controlled, and the frequency and severity of anaphylactic episodes showed a marked decrease. Levels of sBT obtained in August 2017 (1 week after omalizumab injections) and repeated in September 2017 (4 weeks after omalizumab injections) were 21.17 and 13.25 ng/mL, respectively. She was promptly investigated for systemic mastocytosis at the Hematology Clinics in our

Hospital and underwent bone marrow biopsy, which was negative for mast cell disease.

Regarding the severity of anaphylaxis, mean sBT levels were 5.06, 4.67, and 6.61 ng/mL for patients with grade II, III, and IV anaphylaxis, respectively. Significantly higher sBT levels were observed in patients with severe anaphylaxis (grade IV) than in patients with more moderate disease (grades II/III), with mean levels of 6.61 and 4.71 ng/mL, respectively (mean difference = -1.92 ; 95% CrI -3.55 to -0.37) (Fig. 2).

Discussion

The use of tryptase measurement for the diagnosis of anaphylaxis is well established [13, 15, 22]. However, one single acute measurement of the tryptase level may not be decisive to establish the correct diagnosis of anaphylaxis. Baseline measurements are useful for allowing comparison to acute measurements, therefore enhancing diagnostic capacity. Although anaphylactic reactions to intravenous drugs have been shown to elicit greater increases in tryptase levels than oral triggers such as foods [13], our observational study has not identified significant differences in sBT levels and the types of triggers involved, but sBT levels were significantly higher among patients with more severe anaphylaxis. Our results are in keeping with those of Sahiner et al. [23], who showed the relevance of sBT levels in predicting the risk of anaphylaxis in food allergy: a cutoff of 5.7 ng/mL was associated with a 50%

probability of moderate-severe anaphylaxis. The work by Dua et al. [24] reinforced the importance of sBT levels as a tool for the comparison with acute measurements in food-allergic reactions, and showed a correlation of sBT levels with the severity of symptoms in food allergy. Yavuz et al. [25] reported similar findings in children with insect venom allergy, demonstrating that sBT levels ≥ 4.8 ng/mL were a significant risk factor for severe systemic reactions, supporting the role of sBT measurements as an instrument to help in deciding when to indicate preventive treatment with venom immunotherapy.

sBT measurements play also an important role in the investigation of mast cell-related diseases, particularly systemic mastocytosis [26, 27]. In the present study, only 1 patient presenting with multiple severe idiopathic anaphylactic episodes had sBT levels which prompted us to investigate mastocytosis. Although systemic mastocytosis was unlikely after bone marrow biopsy showing no abnormalities in mast cells, we could not exclude a mast cell activation syndrome (MCAS) as the underlying cause of symptoms in this patient. According to WHO criteria, additional findings including mast cells expressing CD2 and/or CD25 and presence of the *KIT* D816V mutation would help in the diagnosis of clonal MCAS [7, 28]. Nonclonal MCAS could also be suspected; however, we could not find common features of this condition in our patient, including IgE-mediated allergy, inflammatory and autoimmune diseases, neoplasms, Ehlers-Danlos syndrome, postural orthostatic tachycardia syndrome, bone abnormalities, or osteomuscular and central nervous symptoms, as described [7]. On the other hand, the elevated sBT level in conjunction with the clinical presentation of this patient was fundamental to indicate treatment with omalizumab, leading to clinical improvement, as previously described [28–31]. In addition, sBT levels have also been shown to be helpful to assess the risk for anaphylaxis in patients with confirmed systemic mastocytosis [32].

Recognition of the acute reaction and prompt epinephrine administration remain crucial issues in anaphylaxis. Results of our study indicate that there is room for improving anaphylaxis management. Epinephrine is recommended as first-line treatment for anaphylaxis, and its no-use is related to a greater occurrence of fatal outcomes [33–35]. There are strong reasons for that recommendation, since epinephrine reaches its maximal pharmacological effect within 10 min of intramuscular administration into the thigh, while antihistamines and corticosteroids have a delayed peak of action, and may not prevent respiratory and/or cardiovascular arrest [33]. In our study, the most common treatment modalities reported

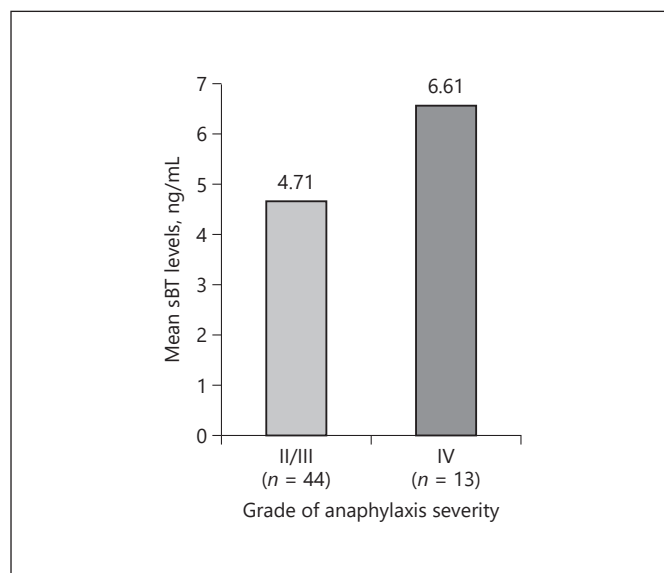


Fig. 2. Serum baseline tryptase (sBT) levels according to the severity of anaphylaxis. sBT levels were significantly higher in patients with severe anaphylaxis (grade IV reactions, $n = 13$) than in those who had mild-moderate anaphylaxis (grades II and III reactions: $n = 4$ and $n = 40$, respectively). Mean levels are represented above the bars (mean difference = -1.92 ; 95% CrI -3.55 to -0.37).

by our patients were antihistamines and corticosteroids; epinephrine was used in only 65.5% of the patients during the acute episode of anaphylaxis. This observation is in accordance with other studies in the literature [33–35]. Most of our patients failed to fulfill one of the fundamental recommendations for anaphylaxis follow-up: to carry an epinephrine auto-injector all the time. There are many barriers for appropriate use of epinephrine auto-injectors [36], but in our country, the main factors are availability only through importation and financial barriers.

Our study has some limitations, including the small number of patients evaluated, and possibly the fact that more severe cases could have been selected, as a result of being a reference public hospital in the field. However, we tried to minimize these effects by choosing a diverse group of patients, comprising male and female subjects, as well as children and adults, and different triggers of anaphylaxis implicated, and our findings were in accordance with other studies. In addition, it was not possible to investigate the *KIT* mutation D816V in the peripheral blood of our patients, particularly in those with idiopathic anaphylaxis and *Hymenoptera* venom-induced anaphylaxis with normal sBT level in order to recommend a bone marrow biopsy appropriately [37].

In conclusion, our study showed that sBT levels were significantly higher among patients with more severe anaphylaxis, independent of the timing between sBT level measurement and anaphylaxis occurrence. Although the measurement of tryptase levels in the emergency setting has previously been identified as a suitable biomarker for anaphylaxis, high sBT levels may identify patients at increased risk of more severe anaphylaxis. Therefore, sBT should be routinely measured in all patients with a previous anaphylactic reaction. This is not usually performed, and it would be helpful to evaluate future risks.

Acknowledgment

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Statement of Ethics

All subjects or their parents or guardians have given their written informed consent.

Approval for the study protocol was obtained by the HCFMRP-USP Ethics Committee and Brazil's Platform of Ethics (protocol No. 3773/2016).

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

V.A. applied the questionnaires, collected clinical data, and prepared the first draft of the manuscript; M.M.D. carried out the tryptase measurements in the laboratory; J.M.L.M. selected patients and collected clinical data; O.T.-N. collected clinical data; D.C.A. helped with the design of the study and performed statistical analysis; L.S.M.M. collect blood samples and helped with tryptase measurements; A.S.M. supervised all the experiments in the laboratory and revised the manuscript; L.K.A. designed the study, supervised collection of clinical data, participated in the analysis of the data, and revised the manuscript to its final version. All authors approved of the final version of the manuscript and agreed with its submission.

References

- Castells M. Diagnosis and management of anaphylaxis in precision medicine. *J Allergy Clin Immunol*. 2017 Aug;140(2):321–33.
- Loprinzi Brauer CE, Motosue MS, Li JT, Hagan JB, Bellolio MF, Lee S, et al. Prospective validation of the NIAID/FAAN criteria for Emergency Department diagnosis of anaphylaxis. *J Allergy Clin Immunol Pract*. 2016 Nov - Dec;4(6):1220–6.
- Reber LL, Hernandez JD, Galli SJ. The pathophysiology of anaphylaxis. *J Allergy Clin Immunol*. 2017 Aug;140(2):335–48.
- LoVerde D, Iweala OI, Eginli A, Krishnaswamy G. Anaphylaxis. *Chest*. 2018 Feb;153(2):528–43.
- Solé D, Ivancevich JC, Cardona V. Knowledge of anaphylaxis among Ibero-American physicians: results of the Ibero-American Online Survey for Physicians on the management and treatment of anaphylaxis (IOSPTA) - Latin American Society of Allergy, Asthma & Immunology (LASAAI). *J Investig Allergol Clin Immunol*. 2013;23(6):441–3.
- Tejedor Alonso MA, Moro Moro M, Múgica García MV. Epidemiology of anaphylaxis. *Clin Exp Allergy*. 2015 Jun;45(6):1027–39.
- Jimenez-Rodriguez TW, Garcia-Neuer M, Alenazy LA, Castells M. Anaphylaxis in the 21st century: phenotypes, endotypes, and biomarkers. *J Asthma Allergy*. 2018 Jun;11:121–42.
- Sala-Cunill A, Guilarte M, Cardona V. Phenotypes, endotypes and biomarkers in anaphylaxis: current insights. *Curr Opin Allergy Clin Immunol*. 2018 Oct;18(5):370–6.
- Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T. Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. *N Engl J Med*. 1987 Jun;316(26):1622–6.
- Vitte J. Human mast cell tryptase in biology and medicine. *Mol Immunol*. 2015 Jan;63(1):18–24.
- Payne V, Kam PC. Mast cell tryptase: a review of its physiology and clinical significance. *Anaesthesia*. 2004 Jul;59(7):695–703.
- Dzingina M, Stegenga H, Heath M, Jones D, Rogers G, Kleijnen J, et al; Guideline Development Group. Assessment and referral after emergency treatment of a suspected anaphylactic episode: summary of NICE guidance. *BMJ*. 2011 Dec;343:d7595.
- Sala-Cunill A, Cardona V, Labrador-Horrillo M, Luengo O, Estes O, Garriga T, et al. Usefulness and limitations of sequential serum tryptase for the diagnosis of anaphylaxis in 102 patients. *Int Arch Allergy Immunol*. 2013;160(2):192–9.
- Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernández Rivas M, et al; EAACI Food Allergy and Anaphylaxis Guidelines Group. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy*. 2014 Aug;69(8):1026–45.
- Buka RJ, Knibb RC, Crossman RJ, Melchior CL, Huissoon AP, Hackett S, et al. Anaphylaxis and clinical utility of real-world measurement of acute serum tryptase in UK emergency departments. *J Allergy Clin Immunol Pract*. 2017 Sep - Oct;5(5):1280–1287.e2.
- Simons FE, Arduoso LR, Dimov V, Ebisawa M, El-Gamal YM, Lockey RF, et al; World Allergy Organization. World Allergy Organization Anaphylaxis Guidelines: 2013 update of the evidence base. *Int Arch Allergy Immunol*. 2013;162(3):193–204.
- Simons FE, Arduoso LR, Bilò MB, Cardona V, Ebisawa M, El-Gamal YM, et al. International consensus on (ICON) anaphylaxis. *World Allergy Organ J*. 2014 May;7(1):9.
- Lieberman P, Nicklas RA, Randolph C, Oppenheimer J, Bernstein D, Bernstein J, et al. Anaphylaxis—a practice parameter update 2015. *Ann Allergy Asthma Immunol*. 2015 Nov;115(5):341–84.

- 19 Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet*. 1977 Feb;1(8009):466–9.
- 20 Fellinger C, Hemmer W, Wöhrl S, Sesztak-Greinecker G, Jarisch R, Wantke F. Clinical characteristics and risk profile of patients with elevated baseline serum tryptase. *Allergol Immunopathol (Madr)*. 2014 Nov-Dec; 42(6):544–52.
- 21 Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. *N Engl J Med*. 2015 Nov;373(19):1885–6.
- 22 De Schryver S, Halbrich M, Clarke A, La Vieille S, Eisman H, Alizadehfar R, et al. Tryptase levels in children presenting with anaphylaxis: temporal trends and associated factors. *J Allergy Clin Immunol*. 2016 Apr;137(4):1138–42.
- 23 Sahiner UM, Yavuz ST, Buyuktiryaki B, Cavkaytar O, Yilmaz EA, Tuncer A, et al. Serum basal tryptase may be a good marker for predicting the risk of anaphylaxis in children with food allergy. *Allergy*. 2014 Feb;69(2):265–8.
- 24 Dua S, Dowey J, Foley L, Islam S, King Y, Ewan P, et al. Diagnostic value of tryptase in food allergic reactions: a prospective study of 160 adult peanut challenges. *J Allergy Clin Immunol Pract*. 2018 Sep - Oct;6(5):1692–1698.e1.
- 25 Yavuz ST, Sackesen C, Sahiner UM, Buyuktiryaki B, Arik Yilmaz E, Sekerel BE, et al. Importance of serum basal tryptase levels in children with insect venom allergy. *Allergy*. 2013 Mar;68(3):386–91.
- 26 Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. *Immunol Allergy Clin North Am*. 2006 Aug;26(3):451–63.
- 27 Schuch A, Brockow K. Mastocytosis and anaphylaxis. *Immunol Allergy Clin North Am*. 2017 Feb;37(1):153–64.
- 28 Gülen T, Hägglund H, Sander B, Dahlén B, Nilsson G. The presence of mast cell clonality in patients with unexplained anaphylaxis. *Clin Exp Allergy*. 2014 Sep;44(9):1179–87.
- 29 Christensen MJ, Bindslev-Jensen C. Successful treatment with omalizumab in challenge confirmed exercise-induced anaphylaxis. *J Allergy Clin Immunol Pract*. 2017 Jan - Feb; 5(1):204–6.
- 30 Heffler E, Fichera S, Nicolosi G, Crimi N. Anaphylaxis due to progesterone hypersensitivity successfully treated with omalizumab. *J Allergy Clin Immunol Pract*. 2017 May - Jun; 5(3):852–4.
- 31 Constantine GM, Bressler PB, Petroni D, Metcalfe DD, Carter MC. Twelve-year follow-up of omalizumab therapy for anaphylaxis in 2 patients with systemic mastocytosis. *J Allergy Clin Immunol Pract*. 2018 Aug. pii: S2213-2198(18)30517-8.
- 32 Gülen T, Ljung C, Nilsson G, Akin C. Risk factor analysis of anaphylactic reactions in patients with systemic mastocytosis. *J Allergy Clin Immunol Pract*. 2017 Sep - Oct;5(5): 1248–55.
- 33 Song TT, Lieberman P. Epinephrine in anaphylaxis: doubt no more. *Curr Opin Allergy Clin Immunol*. 2015 Aug;15(4):323–8.
- 34 Cardona V, Ferré-Ybarz L, Guilarte M, Moreno-Pérez N, Gómez-Galán C, Alcoceba-Borràs E, et al; AdreSCAIC Research Group. Safety of adrenaline use in anaphylaxis: a multi-centre register. *Int Arch Allergy Immunol*. 2017;173(3):171–7.
- 35 Grabenhenrich LB, Dölle S, Ruëff F, Renaudin JM, Scherer K, Pföhler C, et al. Epinephrine in severe allergic reactions: the European Anaphylaxis Register. *J Allergy Clin Immunol Pract*. 2018 Nov - Dec;6(6):1898–1906.e1.
- 36 Song TT, Worm M, Lieberman P. Anaphylaxis treatment: current barriers to adrenaline auto-injector use. *Allergy*. 2014 Aug;69(8): 983–91.
- 37 Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. *Blood*. 2017 Mar;129(11):1420–7.