

Systemic reactions and anaphylaxis with an acute serum tryptase ≥ 14 $\mu\text{g/L}$: retrospective characterisation of aetiology, severity and adherence to National Institute of Health and Care Excellence (NICE) guidelines for serial tryptase measurements and specialist referral

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ABSTRACT

Aims To characterise patients with systemic reactions and anaphylaxis with an acute serum tryptase of ≥ 14 $\mu\text{g/L}$ against recently published World Allergy Organisation (WAO) diagnostic criteria. To also perform a clinical audit to assess adherence to National Institute of Health and Care Excellence (NICE) guideline recommendations regarding serial tryptase measurements and specialist referral.

Methods A systematic retrospective survey (2006–2010) was carried out ($n=171$; males=86; mean age $\pm$ SD 48 $\pm$ 20 years) and data were extracted from emergency department and specialist allergy clinic records.

Results 34 patients (20%) had a grade 1 reaction, 61 (36%) grade 2, 46 (27%) grade 3 and 6 patients (4%) grade 4 (24 patients (13%) could not be graded due to lack of adequate clinical details) and 6% developed a biphasic response. Serial tryptase measurements were not available in 117 (69%) of the cohort. 97 (57%) patients were referred for specialist assessment, and 72 (74%) attended. 50% of cases were diagnosed with idiopathic systemic reactions/anaphylaxis and 28%, 14% and 8% triggered by drugs, foods and other allergies including disorders of mast cell overload, respectively. A weak positive correlation was detected between acute serum tryptase and severity.

Conclusions The correlation between acute serum tryptase and severity of anaphylaxis/systemic reactions is weak. A significant proportion of patients with raised acute serum tryptase had mild reactions which did not meet WAO criteria for anaphylaxis and this may reduce the specificity of the test. The commonest aetiology in this cohort was idiopathic followed by drug and food allergies. NICE guidelines relating to serial tryptase measurements and specialist referral were not followed, and there is an urgent need to raise the awareness among clinicians involved in the management of anaphylaxis.

INTRODUCTION

Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction characterised by rapidly developing signs and symptoms involving the airway (pharyngeal or laryngeal oedema) and/or breathing (bronchospasm with tachypnoea) and/or circulation (hypotension and/or tachycardia). In most cases, there are associated skin and mucosal

changes. The true prevalence is not known, but previous studies have suggested that 1 in 2300 people may be affected in the UK and there has been a sevenfold increase in prevalence in little over a decade.^{1,2}

The aetiology of anaphylaxis varies depending on age. While food allergy is a common cause in children, drugs and insect stings account for the majority in adults.³ Prompt and early administration of adrenaline is vital to a successful outcome, and the diagnosis of anaphylaxis is made on clinical grounds.⁴ The gold standard laboratory test involves serial serum tryptase measurements, but there is no currently agreed standardised method for its interpretation. Previous studies involving anaphylaxis have either used a 'peak acute level' or 'relative change' from a baseline measurement (≥ 24 h following the episode) with different 'cut-off' points and reported varying sensitivity and specificity.^{5–7} However, these studies have shown that serum tryptase measured during an acute episode is a useful adjunct to the diagnosis and a raised level is highly specific, that is, suggests that anaphylaxis has occurred.⁸ Previous studies reporting on the aetiology of anaphylaxis have been based on the clinical diagnosis per se, that is, data specifically on acute serum tryptase measurements were not presented in conjunction and there are scarce data on characterisation of systemic reactions and anaphylaxis associated with raised acute serum tryptase.

In this retrospective survey, we analysed patients presenting with systemic reactions and anaphylaxis who had a raised acute serum tryptase (≥ 14 $\mu\text{g/L}$ —current upper end of the reference range in our local laboratory) and report data on aetiology, severity of reactions (with correlation with acute serum tryptase) and rate of biphasic reactions. Furthermore, we also conducted a clinical audit to assess adherence of clinical practice to National Institute of Health and Care Excellence (NICE) guidelines⁸ relating to tryptase measurements and specialist referral.

METHODS

This retrospective study was performed at The Heart of England NHS Foundation Trust (HoEFT).

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This NHS Trust has three emergency departments located in Birmingham Heartlands Hospital and Solihull Hospital covering the catchment area of East Birmingham and Solihull and Good Hope Hospital located in Sutton Coldfield covers North Birmingham and South Staffordshire. This study was registered with the clinical governance department in HoEFT as a clinical audit.

Patient selection

An electronic search was carried out using our laboratory database between 1 January 2006 and 8 August 2010 in order to identify patients with a tryptase level of ≥ 14 $\mu\text{g/L}$. This list was further refined by selecting only those patients whose blood samples were obtained during the acute phase of a systemic reaction or anaphylaxis. The cohort included a combination of patients from the emergency department as well as those who developed these reactions as an inpatient.

Data collection

Demographic and clinical details were obtained from ambulance sheets, emergency department/inpatient records and allergy clinic notes. Age, gender, vital parameters, signs and symptoms, whether a biphasic reaction occurred and aetiology were entered on an Excel (2007) spreadsheet (Microsoft, Redmond, Washington, USA).

Reactions were graded according to Ring and Messmer criteria^{9 10} and compared with the World Allergy Organisation (WAO) diagnostic criteria³ for anaphylaxis. Severity grading is summarised as follows:

Grade 1: included pruritis, flushing, urticaria and angioedema.

Grade 2: grade 1 features plus additional gastrointestinal (GI) nausea, cramping), respiratory (rhinitis, hoarseness, dyspnoea) and cardiovascular (tachycardia and >20 mm Hg systolic blood pressure drop) symptoms.

Grade 3: has more severe GI (vomiting, defecation and diarrhoea), respiratory (laryngeal oedema, bronchospasm and cyanosis) and cardiovascular symptoms (shock).

Grade 4: is respiratory or cardiac arrest.

The timing of tryptase samples was recorded. A biphasic reaction was defined as described previously¹¹—as an initial reaction with a period of resolution for ≥ 1 h, during which there were no new symptoms or treatment administered, followed by a second phase and where it was due to an allergy without re-exposure to the same antigen.

Allergy investigations

All patients with a diagnosis of systemic reactions/anaphylaxis should be referred to the allergy clinic for further assessment as per the HoEFT 'anaphylaxis pathway' and the NICE guidelines. A detailed history was obtained by an allergy specialist, and relevant investigations were undertaken as clinically indicated. Allergy skin tests were performed in accordance with previously published guidelines^{12 13} using commercial extracts for relevant allergens (aero-allergens, foods and venoms) (ALK Abelló, (Hørsholm, Denmark), Alyostal ST-IR (Stallergenes S.A. France)) and where relevant 'prick-prick tests' with fresh food/s were also performed.

Investigations for drug allergy were carried out as per British Society for Allergy and Clinical Immunology (BSACI)^{13 14} and European Network for Drug Allergy (ENDA)¹⁵ guidelines.

Serum specific IgE and tryptase measurements were performed by fluoroenzyme immunoassay (Immuno CAP-FEIA) method on ImmunoCAP (Phadia Thermo-Fisher Scientific, Uppsala, Sweden) platform.

Statistical analysis

Statistical analyses were performed on graphpad Prism V5.0c (Graphpad Software, San Diego, California, USA). Since data were not normally distributed, Spearman's rank correlation was employed to assess correlation between acute serum tryptase and severity. The Mann-Whitney U test was used to compare differences between acute peak serum tryptase and underlying aetiology. A p-Value of <0.05 was considered statistically significant.

RESULTS

A summary of results is shown in [figure 1](#).

Demography

There were 86 males and 85 females. The largest number of cases (18.7%, $n=32$) were in the 61–70 years age group, 11% ($n=19$) of the cases were under 20 years of age.

The frequency distribution of age is shown in [figure 2](#).

Acute serum tryptase measurement and aetiology

The median peak tryptase was 22 (IQR 17–39.5) $\mu\text{g/L}$.

The p-value was 0.245, suggesting that there were no significant differences between acute serum tryptase levels and underlying aetiology ([figure 3](#)).

There were 74 (43% of total, ie, 74 out of 171) patients reviewed in the allergy clinic. Two of these patients had been to another specialist centre and hence already had a known diagnosis while 72 were reviewed in our clinic.

Of the 74 patients, the most common aetiology was spontaneous or 'idiopathic' (50%; $n=37$) followed by drug (28%; $n=21$) and food (14%; $n=10$) allergies. Wasp venom and hair dye were diagnosed as the culprit agents in one patient each and wheat-dependent exercise-induced allergy was also diagnosed in one patient. Three patients were found to have disorders of mast cell overload. There were 11 patients who were children (16 years or younger), the most common trigger was food (5 patients) with 4 of these being due to peanut and 1 due to cow's milk, 2 patients suffered from spontaneous reactions, 3 were not diagnosed and 1 was due to wasp venom.

In five patients, the culprit allergen was a neuromuscular blocking agent used in general anaesthesia. One patient had a reaction to radiocontrast medium. These patients did not go through the emergency department.

Severity grading and biphasic reactions

Thirty-four patients (20%) had grade 1 systemic reactions, 61 (36%) grade 2, 46 (27%) grade 3 and 6 patients (4%) grade 4. Twenty-four patients (13%) could not be graded due to lack of adequate clinical details about the reaction. The patients with grade 1 reactions did not meet the WAO diagnostic criteria for anaphylaxis despite having an acute tryptase level of ≥ 14 $\mu\text{g/L}$. Ten patients (6%) were diagnosed with biphasic anaphylaxis.

There was a weak positive correlation between acute serum tryptase and the severity of anaphylaxis ($r=0.29$; $p<0.001$) ([figure 4](#)). There were no cases of fatal anaphylaxis.

Adherence to NICE guidelines

The NICE guideline recommendations state that serum tryptase should be measured during the acute phase as soon as possible following stabilisation of the patient and two further samples should be taken 1–2 h (but not later than 4 h) and ≥ 24 h after (baseline sample). Twenty-five patients (14.6%) had two acute tryptase measurements, and only one patient had the

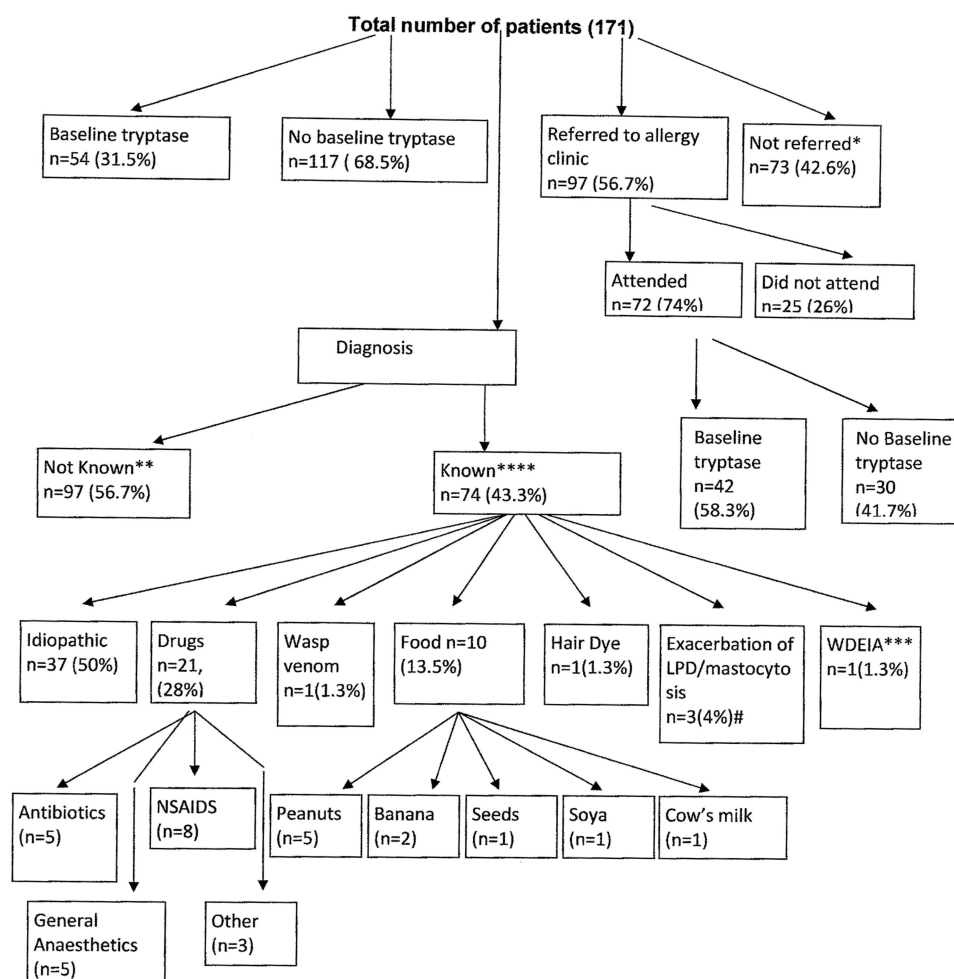


Figure 1. Results algorithm. *One patient was referred to another clinic (haematology), **did not attend, no information, investigation ongoing in allergy clinic, ***wheat-dependent exercise induced anaphylaxis, #exacerbation of lymphoproliferative disease/mastocytosis and ****two patients had a previous definitive diagnosis by an allergy specialist at another centre.

recommended three timed samples including a baseline sample. The timing of tryptase samples was documented on the request form of 60% (n=102) of patients. One hundred and seventeen patients (68.4%) did not have a baseline tryptase measurement.

Baseline tryptase was checked in 42 patients (58.3%) who attended allergy clinic for review. Patients in whom baseline

tryptase was not measured during clinic review were contacted following data analysis and 11 (36.7%) responded. Two patients had an elevated baseline tryptase of 26.0 and 14.4 µg/L and are currently being followed up in clinic. They did not have 'B symptoms' or other signs/symptoms of haematological malignancy and bone marrow studies were not pursued.

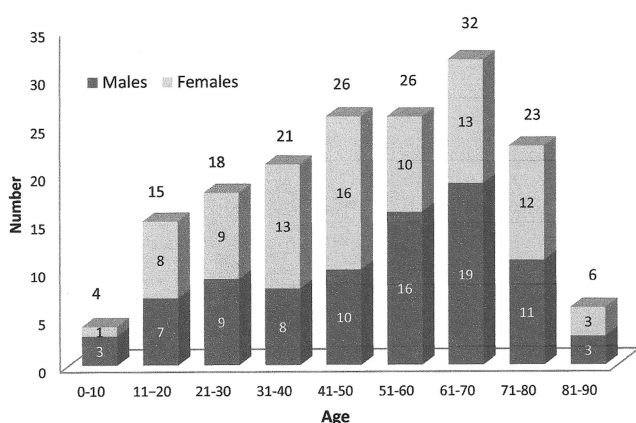


Figure 2 Bar chart showing the age distribution of the population studied.

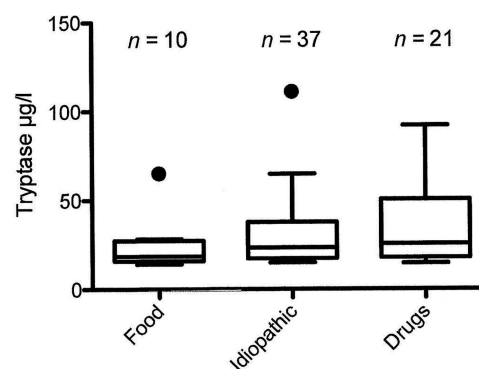


Figure 3 Box plots showing the correlation between tryptase level and allergen. Single data points are outliers. Food—the median peak tryptase was 18.5 (IQR 15.9–27.3) µg/L. Idiopathic—the median peak tryptase was 23.4 (IQR 17.3–37.8) µg/L. Drugs—the median peak tryptase was 25.6 (IQR 17.8–50.5) µg/L.

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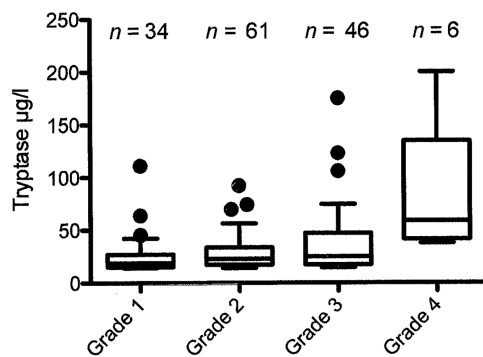


Figure 4 Box plots showing the correlation between acute serum tryptase level and severity of anaphylaxis ($r=0.29$, $p<0.001$). Single data points are outliers.

Seventy-three (42.6%) patients were not referred to an allergy specialist, and 25 (26%) of those who were referred did not attend their appointment following a formal referral.

Effect of introduction of 2008 UK Resuscitation Guidelines on 'emergency treatment of anaphylactic reactions' on tryptase measurement and specialist referral

Since these guidelines¹⁶ were released in 2008, data from patients that had their tryptase sample taken before (2006–2007) and after (2009–2010) the introduction of the 2008 UK resuscitation guidelines were compared to assess whether these had had any effect on tryptase measurements and specialist referral rates (figure 5A,B). These figures show no improvement in these parameters.

DISCUSSION

Our data have shown a weak correlation between acute serum tryptase measurement and severity of systemic reactions. These results are

similar to those recently reported in a Canadian cohort.¹⁷ Their study was prospective, cross-sectional and included a small cohort ($n=41$) of patients presenting to the emergency department with acute allergic reactions. They used a different severity grading system and found a weak correlation for histamine, tryptase and platelet activation factor in patients with mild, moderate and severe reactions.

In our cohort, the most common grade was 2 (36%), followed by 3 (27%), 1 (20%) and a minority with 4 (4%). The most common aetiology was 'spontaneous' (idiopathic), followed by drug and food allergies. Acute serum tryptase levels were not influenced by underlying aetiology. There was poor adherence to NICE guidelines for serial tryptase measurements, and a significant proportion of patients were not referred and even fewer reviewed by an allergy specialist.

It has been previously reported that raised acute serum tryptase carries high specificity for anaphylaxis. Patients in this study with relatively mild cutaneous systemic reactions (grade 1 (20%)) had acute tryptase measurements of $\geq 14 \mu\text{g/L}$ but did not fulfil WAO criteria for anaphylaxis. The sensitivity and specificity for acute serum tryptase in the diagnosis of anaphylaxis from previous studies is difficult to interpret since the definition was not standardised until 2011, and different approaches were employed for interpretation including absolute values with various 'cut-off' points as well as 'relative change' from baseline. The positive predictive value of an acute serum tryptase level of $\geq 14 \mu\text{g/L}$ for the diagnosis of anaphylaxis as per the WAO criteria in this cohort of patients is 76.9%.

Our data suggest that if WAO criteria are applied for interpretation of acute serum tryptase measurement, the specificity of the test for anaphylaxis is likely to decline for measurements $\geq 14 \mu\text{g/L}$. Preliminary studies^{17–19} have shown that other biomarkers including platelet activation factor, carboxypeptidase A3 and dipeptidylpeptidase I (DPPI) may be superior and confer a greater advantage for risk assessment in anaphylaxis.

Following on from this, grades 1 and 2 of the Ring and Messmer severity scale have not been universally accepted as consistent with anaphylaxis.^{3 16} Grade 1 symptoms and/or an

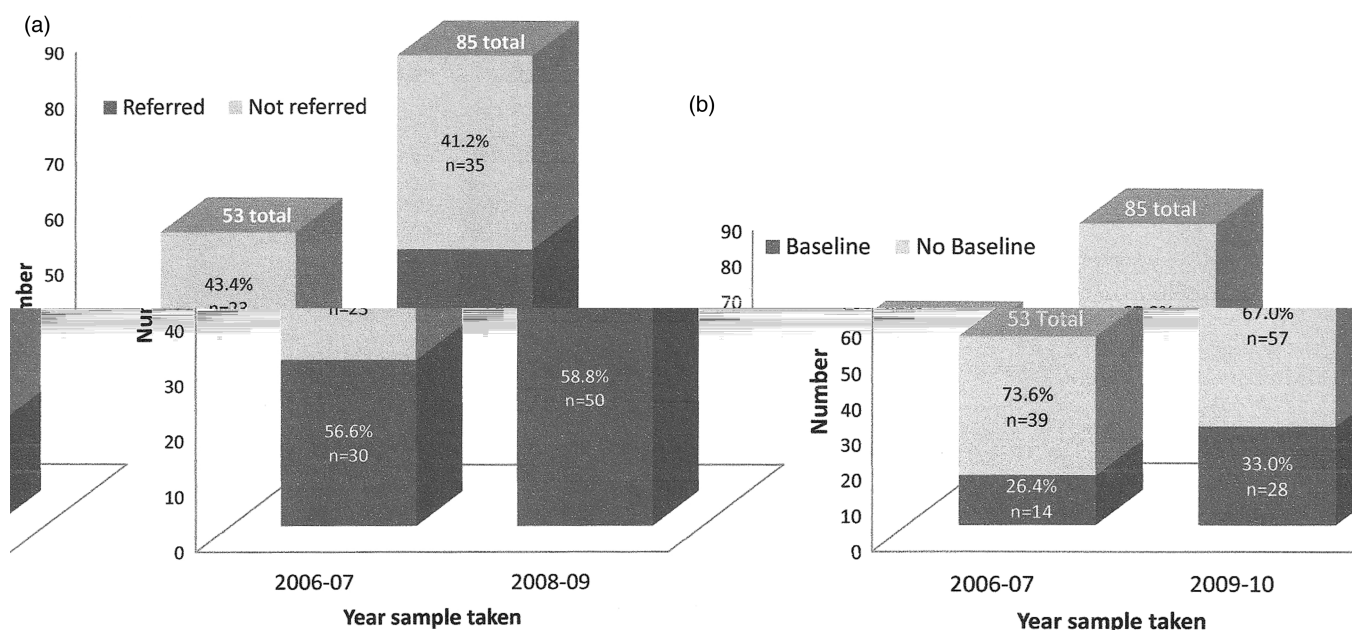


Figure 5 (A) Bar chart showing the number of patients referred to an allergy specialist before (2006–2007) and after (2009–2010) the 2008 UK Resuscitation Guideline¹⁶ introduction. (B) Bar chart showing the number of patients who had a baseline serum tryptase checked before (2006–2007) and after (2009–2010) the 2008 UK Resuscitation Guidelines¹⁶ were introduced.

elevated tryptase may not be enough in isolation to diagnose anaphylaxis. In view of the WAO anaphylaxis guideline criteria,³ it could be argued that this severity scale is no longer applicable for diagnosis. However, this grading enables systemic reactions to be documented consistently in a standardised manner. Use of both Ring and Messmer grading and recent WAO guideline criteria is subject to interpretation and could potentially result in both an under-reporting or over-reporting of reactions.

The commonest aetiology of reactions in our cohort was idiopathic. This is in contrast to other studies where data were analysed on the basis of clinical presentation per se^{20–22}—foods being the commonest trigger in children and drugs and hymenoptera (bee and wasp) stings in adults. Food-induced anaphylaxis is usually not associated with raised acute serum tryptase.²³ However, this was the third most common trigger (14%) in our cohort (the range of acute tryptase level in these patients was between 14.1 and 28.2 µg/L with an outlier at 65 µg/L; [figure 3](#)).

Only 97 patients (57%) were referred to the allergy clinic for further assessment and 72 patients (74%) attended their appointment. To address this, we plan to raise awareness of NICE guidelines among clinicians involved in the care of these patients as well as other factors known to decrease guideline usage, such as ease of access to the guidelines, coexistent workload, etc. There may also be a need to emphasise to patients about the importance of attending their hospital appointments. This is important for further tests and counselling regarding the relevant avoidance measures and self-management plans for the treatment of acute allergic reactions as this has been shown to reduce recurrence rates, particularly with food-induced anaphylaxis.²⁴

The implementation of serial tryptase measurements raises some important practical issues since patients are often discharged from UK emergency departments following stabilisation, particularly those with mild-moderate reactions who have responded well to treatment and those with severe reactions may be transferred to intensive care or high dependency units. Obtaining further blood samples may be challenging in a busy clinical environment. However, having a complete dataset of the three measurements would be valuable in those with paucity of cutaneous signs, special groups including children, the elderly or inpatients with hearing/visual impairment or underlying psychiatric disorders where the diagnosis may not be straightforward. Measurement of baseline tryptase is an important aspect in the management plan since this is a useful surrogate marker for disorders of mast cell overload (mastocytosis, urticaria pigmentosa), which usually remain 'silent' in a majority of patients and have important implications with respect to susceptibility to anaphylaxis to various drugs, insect stings as well as development of osteopenia/osteoporosis.²⁵

This study has some limitations. It is a retrospective analysis and with selection bias. While data were collected on standardised proforma, the source documents were completed by different clinicians. Serial tryptase measurements were not available in a significant proportion of patients and the diagnosis of anaphylaxis was based on clinical grounds. However, these data were carefully scrutinised by an allergy specialist in order to validate the diagnosis. It is plausible that some patients with systemic reactions/anaphylaxis may not have had their acute tryptase measurement checked and thus not have been included in our analysis. Furthermore, this study did not include those patients that presented with disorders masquerading as anaphylaxis and in whom acute serum tryptase was ≤ 14 µg/L.

In conclusion, we have shown a weak positive correlation between acute serum tryptase and the severity of systemic reactions/anaphylaxis. A significant proportion of patients with an

acute tryptase ≥ 14 µg/L did not meet the WAO criteria for anaphylaxis. The commonest aetiology in this cohort was 'idiopathic', followed by drug and food allergies. NICE guidelines were not followed, and there is a need to increase the uptake of the guidelines by clinicians involved in the management of anaphylaxis as well as raise the awareness of patients about the importance of further specialist assessment.

Take home messages

- The correlation between acute serum tryptase and severity of anaphylaxis/systemic reactions is weak.
- A significant proportion of patients with an acute tryptase ≥ 14 µg/L did not meet the WAO criteria for anaphylaxis, and this may reduce the specificity of the test.
- The commonest aetiology in this cohort was 'idiopathic', followed by drug and food allergies.
- NICE guidelines regarding tryptase measurements and specialist referral were not followed, and there is a need to increase the uptake of the guidelines by clinicians involved in the management of anaphylaxis.

Contributors SS planned the study with MTK and collected and analysed the data. SS and MTK wrote the manuscript. MTK planned the study, assessed and managed patients in the allergy clinic and provided critiques on the manuscript. APH and SH assessed and managed patients in the allergy clinic and reviewed the manuscript. MWC and SD managed patients in the emergency department and provided critiques of the manuscript.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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