

Clinical Communications

Postmortem tryptase cutoff points and main causes of fatal anaphylaxis

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Clinical Implications

- Our results suggest that the best cutoff point for postmortem tryptase in anaphylaxis is 40-60 µg/L, particularly for anaphylaxis due to drugs and hymenoptera, but may be lower for anaphylaxis due to food.

TO THE EDITOR:

The utility of postmortem tryptase is controversial, because increased tryptase values have been reported in other causes of death (trauma, heart disease, asphyxia, heroin overdose, intracranial hemorrhage, and sudden infant death syndrome). Values can be increased for several reasons (postmortem interval, sampling site, hemolysis, trauma, prolonged agonal asphyxia, and external cardiac massage),¹⁻⁸ and the range of tryptase cutoff points varies widely (10-110 µg/L).¹⁻⁸

In this study, we investigated the optimal cutoff point for postmortem tryptase in a series of 39 cases of fatal anaphylaxis from the database of the Spanish National Institute of Toxicology and Forensic Science (INTCF). To our knowledge, ours is the largest series of postmortem tryptase values published to date.

In Spain, possible fatal anaphylaxis is investigated in the laboratory of the INTCF, where cases of suspected anaphylaxis are assessed by a forensic physician. A total of 122 such cases were recorded between 1998 and 2015. After death, blood was collected within 24 hours under cold chain conditions until processing. Serum tryptase was measured, at least in duplicate, 1-3 days later using an enzyme immunofluorescent assay (ImmunoCAP, Thermo Fisher Scientific, Uppsala, Sweden).

The 122 cases were later analyzed by 2 researcher-allergists, who used forensic data to establish whether anaphylaxis was the most probable cause of death. The characteristics used to establish a diagnosis of anaphylaxis have been published elsewhere.⁹ Receiver operating characteristic curves and the Youden index were used to calculate the best tryptase cutoff points that classified cases as anaphylaxis or not.

The 2 allergists considered 46 cases to be fatal anaphylaxis (37.7%). The allergists disagreed on only 6 cases, which were ruled out following the criterion of maximal specificity. The rate of agreement was 95.08% (kappa index = 0.90; $P < .0001$).

Postmortem serum tryptase was measured in 85 cases (41, 89.1% for anaphylaxis and 44, 57.9% for nonanaphylaxis) (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). This low percentage of tryptase measurement in nonanaphylaxis cases was probably due to the low degree

of suspicion of anaphylaxis. Two cases of anaphylaxis were not included in the study because the patients died 3 days after onset. Tables E2 and E3 in this article's Online Repository at www.jaci-inpractice.org show postmortem tryptase values in cases with and without anaphylaxis for different causes of deaths. The heart involvement was present in 8 cases (bradycardia, 1; hypotension, 1; collapse/syncope, 6). Tryptase values were high in 5 of these cases, in 2 tryptase was not sampled, and finally low values were recorded in 1 case with syncope and upper airway edema (21 µg/L) (Table E4, available in this article's Online Repository at www.jaci-inpractice.org).

The Kruskal-Wallis test did not reveal statistically significant differences in postmortem serum tryptase levels between causes of anaphylaxis. However, tryptase values in deaths due to hymenoptera or drugs were more than double of those deaths due to foods (Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

In our sample, the optimal cutoff point was 64 µg/L for all types of anaphylaxis (Table 1). The sensitivity of this cutoff was 74.4%, with a specificity of 95.5%. In the case of fatal food anaphylaxis, the area under the curve 95% confidence interval included 0.5. In the case of fatal anaphylaxis due to drugs and hymenoptera stings, the results were similar for the whole group (Table 1 and Figure 1). Tryptase values were higher than 64 µg/L (>201 µg/L) in only 2 of the 44 cases classified as non-anaphylactic death by the 2 allergists. For each case, the logistic regression model revealed that the probability of being classified as anaphylactic death was 0.034 and 0.0007. Drugs taken before death were recorded in both cases. In the first case, the drugs were metamizole and local and general anesthetic and in the second case heparin and omeprazole. However, both cases were ruled out owing to the absence of a temporal reference in the clinical reports of both cases between administration and anaphylaxis. In 10 of the 39 cases classified as fatal anaphylaxis, values were lower than 64 (66.7% food, 21.4% drugs, 1/1 unknown cause, and 14.3% hymenoptera) (Table E4, available in this article's Online Repository at www.jaci-inpractice.org).

The higher number of cases of fatal anaphylaxis in our study increased the accuracy of our estimated cutoff point (64 µg/L), owing to the higher number of available intermediate values. Our cutoff was highly specific but poorly sensitive. Our sensitivity, specificity, and LR+ were similar to those reported by McLean-Tooke et al,⁶ although these authors reported a higher LR+ and lower cutoff point and we reported a higher number of cases of fatal anaphylaxis.⁶ Our cutoff point is also closer to that recommended by Edston et al,³ Xiao et al,⁸ and Tse et al.⁷ All previous studies used a small number of anaphylaxis cases (10 or less), except the study of Xiao et al.⁸ In the other 3 studies, comparisons were not possible, given that the method of tryptase testing was not reported or methods other than fluorescence enzyme immunoassay were used (Table E5, available in this article's Online Repository at www.jaci-inpractice.org).

In 92.9% of cases of fatal anaphylaxis where tryptase values and length of survival were available, death occurred between minutes and 4 hours after onset, and tryptase values were high (median >130 µg/L). The optimum time to measure tryptase in living individuals is between 30 minutes and 2 hours after onset

TABLE I. ROC curve results of postmortem tryptase values for classification of cases of anaphylaxis and nonanaphylaxis in the series of the INTCF (1998-2015), where allergic-immunologic and toxicological assessment due to the suspicion of anaphylaxis was required

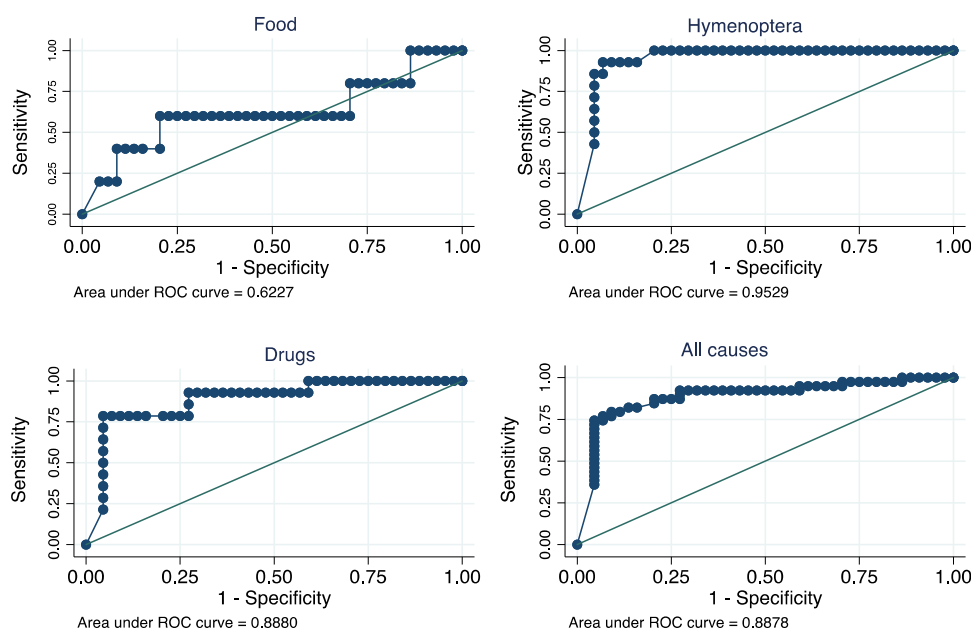
Cause of anaphylaxis	ROC		Asymptotic normality		Cutoff point				
	N (anaphylaxis/ nonanaphylaxis)	Area	Standard error	95% confidence interval	Cutoff point, $\mu\text{g/L}$	Sensitivity	Specificity	Correctly classified	LR+ LR–
All anaphylaxis*	44/39	0.89	0.04	0.81-0.97	≥ 64	74.4%	95.5%	85.5%	16.4 0.3
Anaphylaxis due to food†	44/5	0.63	0.17	0.28-0.96	≥ 54.4	20.00%	93.2%	85.7%	2.9 0.9
Anaphylaxis due to drugs	44/14	0.89	0.05	0.79-0.99	≥ 81.7	78.6%	95.5%	91.4%	17.3 0.2
Anaphylaxis due to hymenoptera*	44/14	0.95	0.03	0.90-1.00	≥ 64	85.7%	95.5%	93.1%	18.9 0.2

INTCF, National Institute of Toxicology and Forensic Science; ROC, receiver operating characteristic.

*Two values were classified as better than the rest (46.5 and 64), but the value with the best specificity (64) was chosen.

†Cutoff point >201 was ruled out because of the large interval between the 2 highest values 54.4 and >201 and to consider >201 as an outlier value.

ROC curves for postmortem tryptase in anaphylaxis

**FIGURE 1.** Receiver operating characteristic (ROC) curves for postmortem tryptase cutoff points in the different causes of deaths due to anaphylaxis in the series of the National Institute of Toxicology and Forensic Science (1998-2015).

of anaphylaxis. Therefore, the survival time of a high number of episodes was close to this optimum time.

In this group of 10 cases of fatal anaphylaxis defined according to our study criteria but with tryptase values lower than $64 \mu\text{g/L}$, most deaths were due to food anaphylaxis (66.7%). These low values in fatal food anaphylaxis are due to the fact that parenteral allergens preferentially trigger cutaneous human tryptase- and chymase-containing mast cells, which harbor approximately 3-fold more tryptase than human tryptase-containing mast cells from the small bowel mucosa and the lungs.¹ Therefore, a low tryptase value does not rule out food-triggered mast cell-dependent anaphylaxis as the cause of death.

In summary, we found that a tryptase cutoff point of $64 \mu\text{g/L}$ confirmed anaphylaxis as the cause of death with high specificity and low sensitivity. For fatal food anaphylaxis, these values are

probably not as useful for the diagnosis of fatal anaphylaxis, given the lower values of postmortem tryptase found in fatal food anaphylaxis.

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TABLE E1. Demographic variables for anaphylaxis cases and nonanaphylaxis cases in the series of the INTCF

Year	Death	N	Males		Age, y		
			Percentage	P and OR Mantel-Haenszel odds ratio test, adjusted for 5 age groups	Median	Interquartile range (p25-p75)	Wilcoxon rank sum test
0-15	Anaphylactic	3	37.5	.4	52	27 (42-69)	0.01
	Nonanaphylactic	5	62.5	1.51 (0.6-3.8)			
16-45	Anaphylactic	5	23.8				
	Nonanaphylactic	16	76.2				
46-65	Anaphylactic	14	48.3				
	Nonanaphylactic	15	51.7				
66-85	Anaphylactic	12	66.7				
	Nonanaphylactic	6	33.3				
>85	Anaphylactic	1	100				
	Nonanaphylactic	0	100				

INTCF, National Institute of Toxicology and Forensic Science; OR, odds ratio.

TABLE E2. Comparison of postmortem tryptase values between cases of anaphylaxis from the INTCF series and causes of death for INTCF cases where anaphylaxis was ruled out

Tryptase values for pathologic/symptoms/causes in anaphylactic and nonanaphylactic deaths	N	Median, µg/L	IQR (p25-p75)	Wilcoxon rank sum test	Benjamini-Hochberg significance False discovery rate = 0.25	Benjamini-Hochberg P value
Anaphylactic deaths	39	151	154.5 (46.5-201)			
Nonanaphylactic deaths	44	6.85	14.2 (3.25-17.45)	<0.0001	Significant	.0009
Pulmonary findings in nonanaphylactic deaths	16	8.54	14.24 (5.4-19.6)	<0.0001	Significant	.004
Cardiac findings in nonanaphylactic deaths	9	6.86	7.88 (6.6-14.5)	0.0004	Significant	.004
Unknown causes in nonanaphylactic deaths	9	6.08	10.80 (3.3-14.1)	0.002	Significant	.01
Infection in nonanaphylactic deaths	4	4.92	4.67 (2.5-7.2)	0.004	Significant	.01
Upper airway angioedema in nonanaphylactic deaths	7	3.86	9.67 (2.3-12.6)	0.006	Significant	.01
Syncope in nonanaphylactic deaths	4	5.61	8.19 (4.1-12.3)	0.008	Significant	.01
Asthma in nonanaphylactic deaths	4	17.45	10.7 (13.1-23.8)	0.026	Significant	.07
Arrhythmias in nonanaphylactic deaths	2	6.88	0.03 (6.86-6.89)	0.053	Nonsignificant	
Intracranial hemorrhage	1			Not applicable		
Heroin overdose	1			Not applicable		
Thoracic trauma	1			Not applicable		

INTCF, National Institute of Toxicology and Forensic Science; IQR, interquartile range.

TABLE E3. Age and tryptase values for causes of anaphylaxis in the INTCF series (1998-2015)

Cause of anaphylaxis	Summary of age					Summary of tryptase				
	Median, µg/L	Percentile 25	Percentile 75	N	Probability (Kruskal-Wallis test)	Median, µg/L	Percentile 25	Percentile 75	N	Probability (Kruskal-Wallis test)
Food	11.5	7	18	6	$P = .0001$	18.7	3.65	40.3	5	$P = .09$
Hymenoptera	55	42	71	15		168.5	75.9	201	14	
Drugs	54	49	68	18		127.5	81.7	191	14	

Comparison between causes of anaphylaxis					
	Age			Tryptase	
	Wilcoxon rank sum test	Benjamini-Hochberg P value False discovery rate = 0.25		Wilcoxon rank sum test	Benjamini-Hochberg P value False discovery rate = 0.25
Food-drug	$P = .12$	$P = .19$	Food-drug	$P = .2$	$P = .3$
Food-hymenoptera	$P = .003$	$P = .09$	Food-hymenoptera	$P = .08$	$P = .2$
Drug-hymenoptera	$P = .4$	$P = .4$	Drug-hymenoptera	$P = .8$	$P = .8$

Differences between 2 causes were estimated using the Wilcoxon rank sum test and corrected with the Benjamini-Hochberg procedure for multiple tests.
 INTCF, National Institute of Toxicology and Forensic Science.

TABLE E4. Individual clinical characteristics and individual tryptase values in case series

	Cause of anaphylaxis	Duration of episode before death	Tryptase value, $\mu\text{g/L}$	Cause of death	Cardiac mechanisms involved
1	Food	<1 h	3.65	Pulmonary edema and food in the bronchi	No
2	Food	4-24 h	40.3	Asthma, angioedema of the glottis	No
3	Food	<1 h		Bradycardia, asthma, acute pulmonary edema, and upper airway angioedema	Yes
4	Food	<1 h	18.7	Angioedema of the glottis, angioedema and mucus affecting the trachea, food in the lower respiratory tract, asthma, vomitus	No
5	Food		2.34	Asthma, hyperinflated lungs, congestive laryngeal and tracheal mucosa, degranulated eosinophils in the bronchial wall, egg in the stomach	No
6	Hymenoptera sting	<1 h	176	Syncope, pulmonary congestion, upper and lower airway dyspnea	Yes
7	Drugs	<1 h		Eosinophils in the lung, rapid death (min)	No
8	Unknown	1-4 h	201	Angioedema of glottis and tonsillar area, mucus in the trachea and bronchi, eosinophils in the bronchial mucosa	No
9	Hymenoptera sting		161	Pulmonary edema, mucus in the bronchial branches, angioedema of the trachea and larynx, congestion of the larynx	No
10	Drugs		124	No data	No
11	Hymenoptera sting	4-24 h	16.3	Angioedema of the uvula, glottis, and epiglottis and dyspnea	No
12	Insect sting	<1 h	201	Syncope	Yes
13	Hymenoptera sting	<1 h	21	Syncope, angioedema of the glottis, epiglottis, and oropharynx, upper airway congestion	Yes
14	Unknown		201	Mucus plugs with eosinophils in the bronchi, asthma, dyspnea	No
15	Drugs		201	No data	No
16	Hymenoptera stings	1-4 h	75.9	Pulmonary edema and angioedema of the subglottis	No
17	Hymenoptera sting	<1 h	201	Angioedema in the pharynx and epiglottis	No
18	Unknown		201	Pulmonary edema and congestion in the larynx	No
19	Drugs	<1 h		Mucus in the trachea, congestion of the laryngeal-tracheal mucosa	No
20	Drugs	1-4 h	5.91	Asthma, angioedema of the uvula, inspiratory stridor, angioedema of the glottis, and larynx	No
21	Hymenoptera sting	<1 h	201	Mucus in the bronchi with edema, eosinophil infiltration of the lung, increased mast cells in lungs	No
22	Drugs	<1 h	14.8	No data	No
23	Drugs	<1 h	1.38	Angioedema of the glottis and pharynx, inspiratory stridor, chemical colitis	No
24	Drugs	<1 h	100	Collapsed lungs, sudden dyspnea	No
25	Drugs	<1 h	128	Angioedema of the tongue, hemorrhagic gastroenteritis	No
26	Hymenoptera sting	<1 h	64	Hyperinflated lungs, angioedema of the epiglottis, glottis, supraglottis, and trachea, congestion of the trachea and pharynx	No
27	Hymenoptera sting	<1 h	201	No data	No
28	Drugs	<1 h	14.9	Sudden death	No
29	Drugs	1-7 d		Syncope, dizziness, pulmonary edema and congestion, emphysema, angioedema of the vocal cords and larynx, dyspnea, lower respiratory diseases, death due to cerebral anoxia	Yes
30	Hymenoptera sting	1-4 h	201	Angioedema of the aryepiglottic folds, angioedema of the glottis	No
31	Hymenoptera sting		110	No data	No

(continued)

TABLE E4. (Continued)

	Cause of anaphylaxis	Duration of episode before death	Tryptase value, $\mu\text{g/L}$	Cause of death	Cardiac mechanisms involved
32	Drugs		151	Bradycardia, angioedema of the glottis, mucus plugs in the bronchi	Yes
33	Drugs	<1 h	201	Dyspnea	No
34	Food	<1 h	201	No data	No
35	Unknown			Emphysema	No
36	Drugs	<1 h	191	Syncope and asthma	Yes
37	Drugs	<1 h	127	No data	No
38	Hymenoptera sting	<1 h	201	Syncope	Yes
39	Drugs	<1 h	201	Angioedema of the larynx and supraglottis	No
40	Hymenoptera sting	<1 h	46.5	Pulmonary edema, mucus and congestion in the bronchial branches, trachea, and glottis	No
41	Hymenoptera sting		103	No data	No
42	Drugs		153	No data	No
43	Hymenoptera sting		201	Deterioration of consciousness, dyspnea, pulmonary edema, mast cells in the lungs with positive staining for tryptase	No
44	Unknown		30	Angioedema of the epiglottis, glottis, and tongue	No
45	Hemodialysis	1-4 h	170	Hypotension and pulmonary edema	Yes
46	Drugs		81.7	No data	No

TABLE E5. Results of ROC curves for the best postmortem tryptase cutoff points in published series

Author, year	N	Time of extraction	Method of tryptase test	Values of tryptase, ng/mL or µg/L
Yunginger, 1991 ^{E1}	19	1-24 h	Sandwich enzyme-linked immunosorbent assay. The authors did not describe the forms of tryptase detected	<2.5 to 150,000
	• 9 hymenoptera • 8 food • 2 drugs			• Hymenoptera 40-150.0 • Food 2.5-150,000 • Drugs 1038 and 6000
Edston, 1998 ^{E2}	7 anaphylaxis, 58 controls	No correlation between tryptase and postmortem sample ($r = 0.11$, linear regression)	β-Tryptase (Pharmacia Tryptase RIACT, Pharmacia Diagnostics, Uppsala, Sweden)	Cutoff value: 10
				• Anaphylaxis: sensitivity 86%, specificity 88%, 1 case of food anaphylaxis <10 • 7% heart disease • 5% suicide • 35% trauma • 32% heroin overdose • 40% sudden infant death syndrome
Edston, 2007 ^{E3}	5 anaphylaxis, 55 controls (16 asphyxia, 5 acute aortic dissection, 24 sudden cardiac deaths)	Time between death and autopsy 3 to 5 d	Reference values for tryptase (α and β). Tryptase was measured using a commercial fluorescence enzyme immunoassay (FEIA) method (Pharmacia Diagnostics AB)	Cutoff value: 44.3 ± 5 (standard distribution), assuming a gamma distribution in the group of sudden cardiac deaths
				No statistically significant differences in tryptase concentrations according to the prone position, petechiae on face and conjunctiva, or resuscitation efforts by cardiac massage
Low, 2008 ^{E4}	15		Not described the method	>20: 8 cases 8-12.8: 5 cases
				• Hymenoptera ○ 1 from 2: 5 to 9.9 ○ 1 from 2: >200 • Food ○ 1 from 2: 5 to 99.9 ○ 1 from 2: >200 • Drugs ○ 3 from 8: 5 to 9.9 ○ 3 from 8: 50 to 99.9
Shen, 2009 ^{E5}	28		Serum tryptase (α and β isoforms) was tested using FEIA	3.3 to 200
				• >10: 9 cases • Hymenoptera: >200 (2 cases) • Food, median: 8.25 (6 cases)

(continued)

TABLE E5. (Continued)

Author, year	N	Time of extraction	Method of tryptase test	Values of tryptase, ng/mL or µg/L
				• Drugs, median: 18 (83 cases)
McLean-Tooke, 2014 ^{E6}	10 anaphylaxis, 189 controls		Serum tryptase was measured using FEIA (ImmunoCAP, Phadia, now Thermo Fisher Scientific, Sweden)	Cutoff value (ROC curve):110
				• Anaphylaxis: ○ PPV 34.9%, NPV 98.9%, sensitivity 80%, specificity 92.1%, LR+ 10.1 ○ 2 cases below 110 (peanut 43.3 and unknown cause 31.6)
Xiao, 2017 ^{E7}	20 anaphylaxis, 44 controls	12-72 h	Tryptase (α and β isoforms) testing using a commercial FEIA method	Cutoff value (ROC curve) 43
				• Sensitivity of 90%, and specificity of 98%
Tse, 2018 ^{E8}	9 anaphylaxis, 45 controls	Within 6 h	Total tryptase (α and β isoforms)	Cutoff value (ROC curve) 54.8
				• Sensitivity of 89% and specificity of 93%
Tejedor-Alonso, 2018 ^{E9}	44 anaphylaxis, 41 controls		Tryptase (α and β isoforms) testing using a commercial FEIA	Cutoff value (ROC curve) 64.1
				• Sensitivity 70.73% • Specificity of 95.45% • Percentage of correctly classified cases of 83.53% • Positive likelihood ratio of 15.56 • Negative likelihood ratio of 0.31

NPV, Negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.

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