



Anaphylaxis in an urban Belgian emergency department: epidemiology and aetiology

Y. Mostmans, M. Blykers, P. Mols, J. Gutermuth, M. Grosber & N. Naeije

To cite this article: Y. Mostmans, M. Blykers, P. Mols, J. Gutermuth, M. Grosber & N. Naeije (2016): Anaphylaxis in an urban Belgian emergency department: epidemiology and aetiology, Acta Clinica Belgica, DOI: [10.1179/2295333715Y.0000000060](https://doi.org/10.1179/2295333715Y.0000000060)

To link to this article: <http://dx.doi.org/10.1179/2295333715Y.0000000060>



Published online: 05 Feb 2016.



Submit your article to this journal [↗](#)



Article views: 13



View related articles [↗](#)



View Crossmark data [↗](#)

Anaphylaxis in an urban Belgian emergency department: epidemiology and aetiology

Y. Mostmans¹, M. Blykers¹, P. Mols², J. Gutermuth¹, M. Grosber¹, N. Naeije³

¹Department of Dermatology, Universitair Ziekenhuis Brussel Brussel, Vrije Universiteit Brussel, Belgium,

²Service des Urgences et du SMUR, C.H.U. Saint-Pierre, Brussels, Belgium, ³Clinic of Immuno-allergology, C.H.U. Brugmann, Brussels, Belgium

Objectives: Anaphylaxis is an emergency condition of which reliable epidemiological data are lacking. This study focusses on epidemiology and aetiology of anaphylactic reactions in an urban Belgian emergency department (ED).

Methods: Patient data were collected from 04/2009 to 04/2013. During this period, emergency doctors completed a questionnaire for adult patients (> 15 years) with anaphylaxis presenting at the ED. Inclusion criteria were based on the Sampson criteria of anaphylaxis. Data were analysed using a Microsoft Excel database.

Results: Anaphylaxis accounted for 0.04% of all emergency visits in this 4-year period. In both women and men, dyspnoea and urticaria were noted most frequently. 51.7% of cases were possibly elicited by foods, 46.1% by drugs and 3.4% by hymenoptera stings. Women more often reported allergic diseases in their personal history. 55.7% of patients, who had a history of allergy, reported a suspected food-related allergy, 24.6% a drug-related allergy and 8.2% a hymenoptera venom-related allergy. In 76.5% of patients who reported a history of food allergy, food was the presumed elicitor of anaphylaxis. For patients with history of drug allergy, 88.2% had a presumed drug anaphylaxis at the time of presentation at the ED. 81% of cases presented with grade 4 or 5 anaphylaxis. With increasing age, the severity of anaphylaxis increased. Higher tryptase levels correlated with a higher grade of anaphylaxis.

Conclusion: In this Belgian urban population, foods and drugs were by far the most common suspected elicitors of anaphylaxis. Personal history of allergic diseases was present in more than half of the cases.

Keywords: Anaphylaxis, Belgium, Emergency department, Epidemiology, Aetiology

Abbreviations

ED	emergency department;
GIT	gastrointestinal tract;
NSAID	nonsteroidal anti-inflammatory drugs;
WAO	World Allergy Organisation

Introduction

Anaphylaxis is defined by Sampson *et al.* as a severe, life-threatening, generalised or systemic hypersensitivity reaction.¹ It is characterised by the development of life-threatening airway and/or breathing and/or circulation problems usually associated with skin and mucosal symptoms. Anaphylaxis is an emergency condition with rapid onset and relatively short duration time of reaction and is therefore often poorly recognised.² Although epidemiological data of anaphylaxis have been reported in several studies,

reliable data and especially data for the Belgian population are lacking.^{2,3}

The diagnosis of anaphylaxis may be difficult in poly-symptomatic patients without a clear positive allergy history. The Sampson criteria of grading and definition of anaphylaxis state that anaphylaxis is probable if one of the following criteria are present: (1) skin and/or mucosal tissue symptoms together with respiratory involvement or severe hypotension (systolic pressure below 90 mmHg) and/or organic dysfunction, (2) the involvement of at least two organ systems after recent exposure to a likely allergen or (3) severe hypotension after exposure to a known allergen.¹

World Allergy Organisation guidelines differentiate cofactors and risk factors in defining the severity of an anaphylactic reaction.⁴ Risk factors include age,⁵⁻⁷ asthma and other respiratory diseases,⁸⁻¹⁰ cardiovascular diseases,¹¹⁻¹³ mastocytosis,¹⁴ clonal mast cell disorders,^{15,16} severe atopic dermatitis (more specifically for food anaphylaxis)¹⁷ and medications, such as beta-adrenergic blockers and

Correspondence to: Y. Mostmans, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, Jette, Brussel 1090, Belgium. Email: Yora.Mostmans@uzbrussel.be; Yora.Mostmans@uzbrussel.be

angiotensin-converting enzyme (ACE) inhibitors.^{12,13,18–20} Furthermore, deficiencies in mediator degradation pathways can lead to more severe anaphylaxis.¹⁷ Pregnancy is not considered to be a risk factor in previous literature, though these patients are more vulnerable and thus more at risk of fatality or hypoxic/ischaemic encephalopathy when anaphylaxis occurs.⁴ The most frequent co-factors that make anaphylaxis more severe are exercise, intake of ethanol or nonsteroidal anti-inflammatory drugs (NSAID).^{21–24}

Food is the most common trigger in children and adolescents. Insect stings and medication are more frequent triggers in adults.^{1,25}

The severity of anaphylaxis can be classified according to several systems. Sampson *et al.* classify anaphylaxis in five grades in contrast to Ring and Messmer who distinguish four grades of anaphylaxis, where Grade I is restricted to skin symptoms only.^{1,26} A recent adjustment was made to these last criteria in order to better distinguish Grade I anaphylaxis of acute urticaria.²⁷

Elevated tryptase levels support the clinical diagnosis of anaphylaxis caused by triggers, such as hymenoptera venom or drugs, in hypotensive patients. However, tryptase alone is not a specific diagnostic tool for anaphylaxis. Usually, normal tryptase levels are found in food-related anaphylaxis.^{27–29}

In this study, we report on the epidemiology, aetiology and clinical features of patients presenting to a Belgian emergency department (ED) over a period of 4 years.

Methods

Data on patients with anaphylaxis were collected prospectively over a period of 4 years (April 2009 to April 2013). During this period, emergency physicians were encouraged to complete a questionnaire for adult patients (age ≥ 15 years) with anaphylaxis presenting at the emergency room. Over this period, 230,878 patients visited the ED of the Sint-Pieters Hospital, Brussels, and 100 cases were diagnosed with anaphylaxis.

Diagnosis of anaphylaxis was based on the Sampson criteria of grading and definition of anaphylaxis.¹ Grade I anaphylaxis includes skin symptoms, such as localised pruritus, flushing, urticaria, angioedema and gastrointestinal tract (GIT) symptoms, such as oral pruritus, oral ‘tingling’, mild lip swelling. Grade II is probable if any of the following symptoms are present: (1) skin symptoms, such as generalised pruritus, flushing, urticaria and angioedema, (2) GI symptoms, such as oral pruritus, oral ‘tingling’, mild lip swelling, nausea and/or emesis, (3) respiratory tract symptoms, such as nasal congestion and/or sneezing, (4) neurological symptoms, such as change in activity level. Grade III is probable if any of the

following criteria are present: (1) skin symptoms as described above, (2) GI symptoms as described above plus repetitive vomiting, (3) respiratory tract symptoms, such as rhinorrhoea, marked congestion, sensation of throat pruritus or tightness, (4) neurological symptoms, such as change in activity level plus anxiety, (5) cardiovascular symptoms, such as tachycardia (increase > 15 beats/minute). Grade IV is probable if any of the following criteria are present: (1) skin symptoms as described above, (2) GI symptoms as described above plus diarrhoea, (3) respiratory tract symptoms, such as any of the above plus hoarseness, ‘barky’ cough, difficulty swallowing, dyspnoea, wheezing, cyanosis, (4) neurological symptoms, such as ‘Light headedness’, feeling of ‘pending doom’, (5) cardiovascular symptoms, such as described above, plus dysrhythmia and/or mild hypotension.

Grade V is probable if any of the following criteria are present: (1) skin symptoms as described above, (2) GI symptoms as described above plus loss of bowel control, (3) respiratory tract symptoms, such as any of the above plus respiratory arrest, (4) neurological symptoms, such as loss of consciousness, (5) cardiovascular symptoms, such as severe bradycardia and/or hypotension or cardiac arrest.

Presence of all symptoms mentioned in the grading system is not mandatory. The severity score should be based on the organ system most affected, e.g., if grade III respiratory symptoms are present but only grade I GI symptom, then the anaphylaxis severity score would be ‘grade III’.

To prevent over-diagnosis of anaphylaxis, grade I anaphylaxis cases according to the classification of Sampson were not included in this database.³⁰ Data collection was based on emergency records combined with the completed questionnaire. Collected data were incorporated as standard operating procedure in the ED during the study period. Study adherence was continually controlled by administrative staff. Collected data elements from the questionnaire and medical files included age and sex, medical history (including other allergic diseases), risk factors and co-factors, such as presence of asthma or cardiopathy, use of beta blocking agents, ACE-inhibitors, intake of alcohol or NSAID drugs. Clinical symptoms, blood pressure and pulse and possible elicitors of anaphylaxis were included. Follow-up was not planned, since this study aimed to find the incidence rates in the ED without follow-up in an allergy department.

Blood mast cell tryptase levels were measured with an immunocap Tryptase Phadia 1000 with a limit of quantification at 1 $\mu\text{g/l}$ (measuring range: 1–200 $\mu\text{g/l}$). Levels below 11.4 $\mu\text{g/l}$ were considered normal according to the manufacturer’s cut-off for peak tryptase. All data were processed and analysed using a Microsoft

Excel database. Relationships between (encoded) categorical variables were determined using the Pearson's Chi-square test or Fisher exact test (for expected cell count lower than 5). We defined a significance level $\alpha = 0.05$ for all examined cases.

Results

Epidemiology

Over a period of 4 years, 0.04% of all emergency visits in adults presented with anaphylaxis. Forty-five per cent were males and 55% were females.

The distribution of the incidence of anaphylaxis differed with age, showing higher numbers in patients below the age of 50 years. Seventy-nine per cent of all patients included in the study are of age < 50 (Table 1).

Symptoms classified by organ affected and their correlation with sex

In general, urticaria and dyspnoea were the most frequently noted symptoms. Respectively, 82% and 61% of all patients noted these symptoms. Twenty-six out of 48 patients with pharynx and larynx oedema (54.2%) were men. Thirty-five patients of 58 patients with gastrointestinal complaints (60.3%) were women (Table 1).

Vital parameters

Blood pressure and pulse were measured during management in the emergency room. Forty per cent of

patients had a systolic blood pressure under 100 mmHg. Men with anaphylaxis had a decrease of their systolic pressure with increasing age, while in women this trend was not observed. Furthermore, 57% of patients had a normal heart rate. Two per cent had a bradycardia while 39% were tachycardia. Two per cent needed to be resuscitated. There were no cases of death registered (data not shown).

Etiology

In 89%, a possible elicitor could be suspected for the anaphylaxis, while in 11% of cases, no specific aetiology was suspected. Table 2 shows that 51.7% of cases had a possible aetiology of food, 46.1% of drugs and 3.4% hymenoptera venom. In 4.5%, ED-specialists indicate other causes, such as exercise, cat contact or partial rupture of a hydatid cyst (Echinococcosis).

History of allergy comparing with recurrence

A total of 68% of patients reported a personal history of allergic diseases. Table 3 shows that women indicated more allergy in their history compared to men. Furthermore, with increasing age, the number of reported previous allergies increased. 55.7% of patients who reported having an allergy in the past had a suspected food-related allergy in their history, 24.6% a suspected drug-related allergy and 8.2% had a suspected hymenoptera venom-related allergy.

Table 1 Age distribution and symptoms classified by organ affected.

Sex	Age group	Count of dyspnoea	Count of pharynx and/or larynx oedema	Count of bronchospasm	Count of facial oedema	Count of urticaria	Count of digestive symptoms	Count of palmo plantar prurigo
Men (n = 45)	16–30 (n = 11)	8	6	3	4	11	6	5
	31–40 (n = 14)	10	7	6	5	12	8	6
	41–50 (n = 12)	7	7	3	3	11	6	6
	51–60 (n = 7)	5	5	3	3	5	2	3
	61–70 (n = 1)	1	1	1	0	1	1	1
	Men total	31	26	16	15	40	23	21
Women (n = 55)	< 16 (n = 2)	1	1	0	0	1	2	0
	16–30 (n = 16)	9	7	4	6	15	9	8
	31–40 (n = 12)	6	4	4	7	10	8	8
	41–50 (n = 12)	7	5	5	4	7	7	3
	51–60 (n = 9)	6	3	1	5	7	6	4
	61–70 (n = 2)	0	1	0	0	1	2	1
	71–80 (n = 2)	1	1	0	1	1	1	1
	Women total	30	22	14	23	42	35	25
Grand total (n = 100)		61	48	30	38	82	58	46

Counts are defined as absolute numbers of individuals.

Table 2 Suspected elicitors of anaphylaxis.

Sex	Suspected aetiology			
	Foods	Drugs	Hymenoptera venom	Others
Men (<i>n</i> = 38)	21 (55.3%)	15 (39.5%)	2 (5.3%)	2 (5.3%)
Women (<i>n</i> = 51)	25 (49.0%)	26 (51.0%)	1 (2.0%)	2 (3.9%)
Grand total (<i>n</i> = 89)	46 (51.7%)	41 (46.1%)	3 (3.4%)	4 (4.5%)

Data are given as total patient count and sex-specific percentage of suspected elicitors.

Table 3 Previous history of allergy.

Sex	History of allergy			
	Food	Drugs	Hymenoptera venom	Respiratory allergens
Men (<i>n</i> = 24)	13 (54.2%)	5 (20.8%)	2 (8.3%)	2 (8.3%)
Women (<i>n</i> = 37)	21 (56.8%)	10 (27.0%)	3 (8.1%)	7 (18.9%)
Grand total (<i>n</i> = 61)	34 (55.7%)	15 (24.6%)	5 (8.2%)	9 (14.8%)

Data are given as total patient count and sex specific percentage of suspected elicitors.

14.8% reported an allergy towards respiratory allergens (mostly hayfever). Nineteen per cent reported asthma in the past (without specifying which type of asthma).

76.5% of patients who reported a history of food allergy had a suspected (recurrent) food elicitor when presenting at the Sint-Pieters Hospital. For patients with a history of drug allergy, 88.2% had a suspected recurrence of a drug elicitor for the presenting anaphylaxis (data not shown).

Classification of anaphylaxis

Eighty-one per cent of all patients presented with grade 4 or 5 anaphylaxis according to the Sampson criteria of grading and definition of anaphylaxis (Fig. 1).

As age increased, severity of anaphylaxis increased. When further analysed, this relationship was not significant ($P = 0.756169$). Thirty-four of 41 patients (82.9%) having a suspected drug-related anaphylaxis were classified as a grade 4 or 5 anaphylaxis. Thirty-seven of 46 patients (80.4%) having a supposable food-related anaphylaxis and two of three patients (66.7%) having a suspected hymenoptera anaphylaxis were classified as a grade 4 or 5 anaphylaxis (data not shown).

Risk factors for severe anaphylaxis and co-factors that amplify anaphylaxis

In total, 42% of patients had been exposed to at least one well-established risk factor or co-factor for anaphylaxis. In men, asthma (22.2%) and alcohol intake (20%) were the most frequent risk factor and co-factor. In women, asthma also was the most frequent risk factor (16.4%)

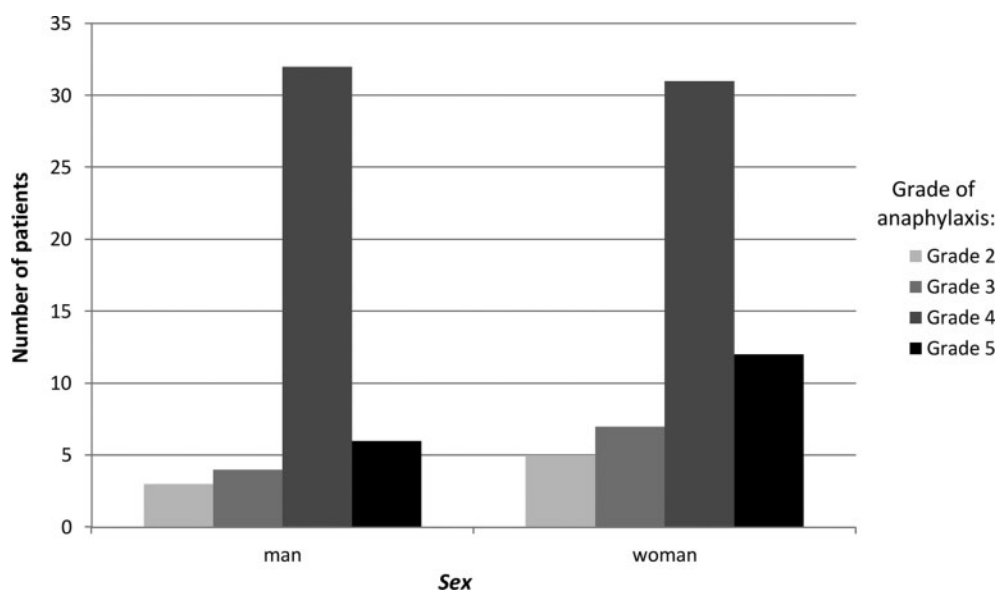


Figure 1 Classification of anaphylaxis. Data are shown as total patient count and sex and sorted by grade of severity of anaphylaxis.

Table 4 Risk factors for severe anaphylaxis and cofactors that amplify anaphylaxis.

Sex	Risk/co-factor						
	Cardio-logic history	Beta-blocking agent	Angiotensin-converting enzyme (ACE) inhibitor	Asthma	Non-steroidal anti-inflammatory drugs (NSAID)	Alcohol consumption	Pregnancy
Men (n = 45)	5 (11.1%)	2 (4.4%)	1 (2.2%)	10 (22.2%)	7 (15.6%)	9 (20%)	0 (0%)
Women (n = 55)	4 (7.3%)	3 (5.5%)	3 (5.5%)	9 (16.4%)	7 (12.7%)	1 (1.8%)	1 (1.8%)
Grand total (n = 100)	9 (%)	5 (%)	4 (%)	19 (%)	14 (%)	10 (%)	1 (%)

Data given as number of patients reporting risk factors and cofactors and the respective sex-specific percentages.

but NSAID the most frequent co-factor (12.7%). Only 1.8% of all women reported alcohol consumption prior to the anaphylaxis. Nineteen per cent of all patients reported asthma (Table 4).

Tryptase values

Generally, tryptase was measured in 81% of all patients diagnosed with anaphylaxis following initial evaluation of the patient. A trend of higher median tryptase levels was observed in cases of higher severity of anaphylaxis (Fig. 2A). Though, this relation was statistically not significant ($P = 0.101504$). Although men seemed to have higher median tryptase levels than women in case of severe anaphylaxis (Fig. 2B), this gender difference was not significant ($P = 0.745203$). 43.2% of patients (35/81) had elevated tryptase levels (cut-off 11.4 µg/l). Furthermore, the highest average value of tryptase levels was detected in patients with suspected drug-related anaphylaxis (19.45 µg/l). An average tryptase level of 12.97 µg/l was calculated for suspected food-related anaphylaxis (data not shown).

Discussion

This is the first large prospective study on the epidemiology of anaphylaxis in adults in a Belgian ED. 0.04% of all ED visits were diagnosed as anaphylaxis. The age distribution of anaphylaxis showed a higher incidence in patients below the age of 50 years. Age distribution numbers of Brussels in 2008 contribute to these findings. In 2008, 70% of all people living in Brussels were younger than 50 years, therefore implicating that a higher prevalence in patients below age of 50 is to be expected.³¹ Second, this article shows the distribution of symptoms accompanying anaphylaxis in a Belgian urban population. In both men and women, dyspnoea and urticaria were the most frequently noted symptoms. Investigating the vital parameters, 2% had bradycardia at admission on the emergency room. One of these two patients had a daily antihypertensive treatment with a beta-blocking agent. Another explanation for this bradycardia could be the occurrence of a neurocardiogenic reflex, triggered by cardiac mechanoreceptors and enhanced by increased levels of serotonin, catecholamines, prostaglandins and nitric oxide that are known to potentiate this reflex are elevated during anaphylaxis.³²

In our study, the two most common elicitors of anaphylaxis were food (51.7%) and drugs (46.1%). The urban localisation of our hospital may account for the low incidence of hymenoptera venom anaphylaxis in our study.

The majority of patients (83%) with a drug-related anaphylaxis were classified as a grade 4 or 5 anaphylaxis. This confirms previous studies indicating that drug-related anaphylaxis is associated with more severe clinical symptomology.^{33,34}

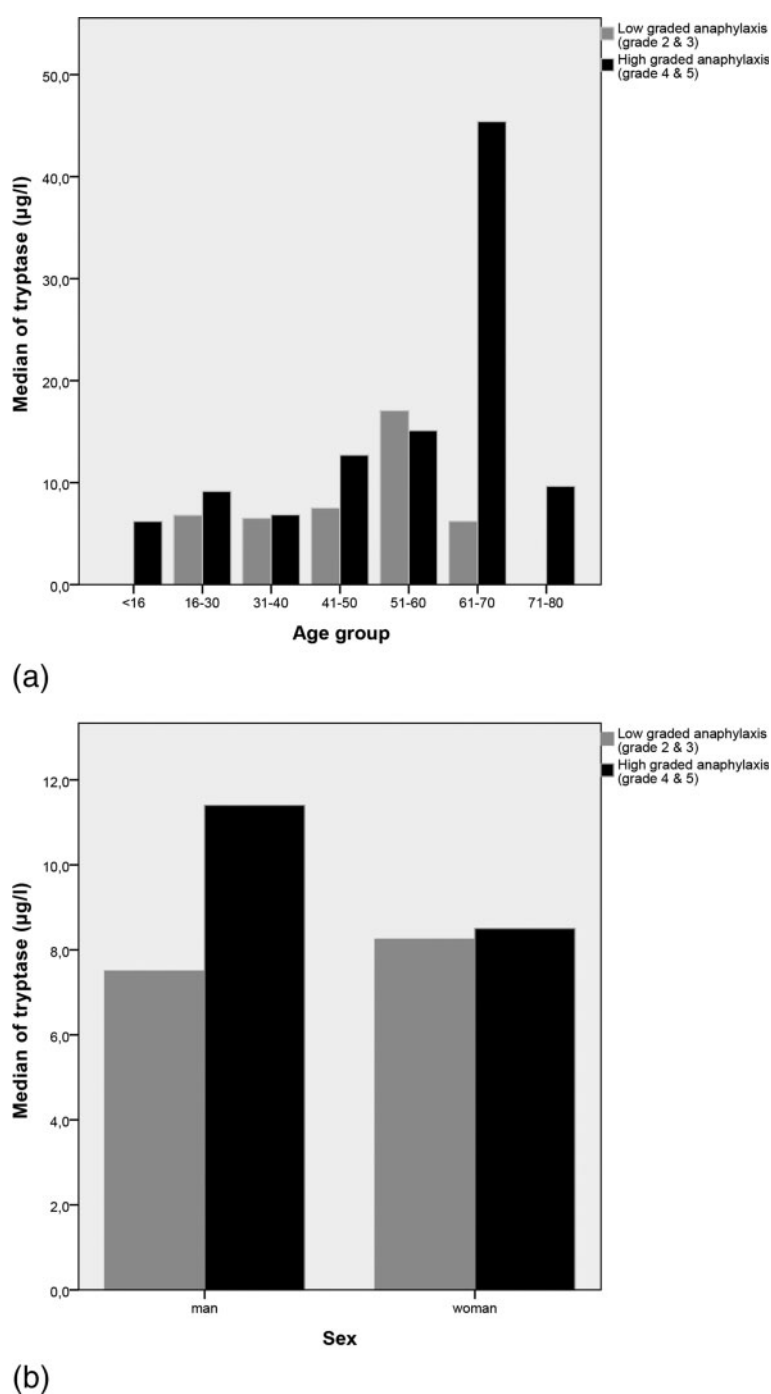


Figure 2 (A) Tryptase levels and grade of severity. Data are shown as median of tryptase levels of different age groups, and sorted by severity of anaphylaxis. **(B) Higher tryptase levels in men in case of high graded anaphylaxis.** Data are shown as median of tryptase levels and sex, and sorted by severity of anaphylaxis.

In 76.5% of patients who reported a history of food allergy, again food was the presumed elicitor of anaphylaxis. For patients with history of drug allergy, 88.2% had a presumed drug anaphylaxis at the time of presentation at the ED. Nonetheless, these data should be interpreted with caution. This study does not elucidate whether re-exposure with a previous elicitory allergen or a presumably second food or drug allergen was the cause of this incident. Indeed, a limitation of this study is that aetiology was based on ED assessments and medical records

rather than on allergical diagnoses with confirmatory skin testing, specific IgE analysis or provocation testing when necessary.

In general, the reported risk factors and cofactors are quite similar comparing men and women, except for alcohol consumption. 20% of men reported having alcohol intake before onset of anaphylaxis, in contrast to 1.8% of women.

To prevent over-diagnosis of anaphylaxis, grade I anaphylaxis patients according to the classifications of Ring and Sampson were not included

in our database. The majority of patients presented with grade 4 or 5 anaphylaxis according to the Sampson criteria of grading and definition of anaphylaxis. With increasing age, a statistically non-significant increase of severity of anaphylaxis was observed. The finding that age correlated with reaction severity is consisted with previous literature.^{32–35}

Tryptase levels were measured and classified according to grade of anaphylaxis. As expected, elevated tryptase levels correlated with a higher grade of anaphylaxis confirming what we would expect from previous literature.³⁶ Furthermore, in case of high-graded anaphylaxis, men had higher median tryptase levels than women. Due to the relative small study cohort per category of severity, these correlations did not reach statistical significance. Nevertheless, tryptase levels were not measured consistently for all patients. In 81% of all cases, tryptase levels were measured. 45.7% of those patients had tryptase levels above 11.4 µg/l. On a general note, the measured values were frequently lower than expected from previous studies. Furthermore, in this study, no baseline tryptase value was measured. Thus, we could not apply the 20%+2 ng/ml over baseline rule that is nowadays recommended to evaluate mast cell activation.³⁷ Additionally, mastocytosis or other causes of an elevated total tryptase level could not be excluded.³⁸ In our study, the highest average of tryptase levels was detected when a drug-related anaphylaxis was suspected. The average tryptase level in suspected food-related anaphylaxis was significantly lower as to be expected from previous literature.^{4,39}

Conclusion

This is the first large prospective study on incidence of anaphylaxis in an ED in the Belgian population. Generally, the inner city population displayed the same characteristics, concerning symptoms, tryptase levels, risk factors and frequent elicitors, as previous cohorts from Spain, the UK, Australia and Canada.^{2,3,32–36} Food and drugs proved to be by far the most common elicitors of anaphylaxis. Personal history of allergic diseases was present in more than half of the cases, thus identifying allergic patients as a population at risk.

Acknowledgements

We thank Prof. Dr med. Dr phil. Johannes Ring for fruitful discussions.

Disclaimer statements

Contributors MG and NN contributed equally to this work.

Funding

Conflict of interest There is no conflict of statement.

Ethics approval No ethics approval was required.

References

- 1 Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, *et al*. Second symposium on the definition and management of anaphylaxis: summary report - Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Ann Emerg Med*. 2006;117(2):391–7.
- 2 Gibbison B, Sheikh A, McShane P, Haddow C, Soar J. Anaphylaxis admissions to UK critical care units between 2005 and 2009. *Anaesthesia*. 2012;67(8):833–9.
- 3 Moro Moro M, Tejedor Alonso MA, Esteban Hernandez J, Mugica Garcia MV, Rosado Ingelmo A, Vila Albelda C. Incidence of anaphylaxis and subtypes of anaphylaxis in a general hospital emergency department. *J Investig Allergol Clin Immunol*. 2011;21(2):142–9.
- 4 Simons FE, Arduoso LR, Bilo MB, El-Gamal YM, Ledford DK, Ring J, *et al*. World Allergy Organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J*. 2011;4(2):13–37.
- 5 Simons FE. Anaphylaxis in infants: can recognition and management be improved? *Ann Emerg Med*. 2007;120(3):537–40.
- 6 Alves B, Sheikh A. Age specific aetiology of anaphylaxis. *Arch Dis Child*. 2001;85(4):348.
- 7 Chaudhuri K, Gonzales J, Jesurun CA, Ambat MT, Mandal-Chaudhuri S. Anaphylactic shock in pregnancy: a case study and review of the literature. *Int J Obstet Anesth*. 2008;17(4):350–7.
- 8 Greenberger PA, Rotskoff BD, Lifschultz B. Fatal anaphylaxis: postmortem findings and associated comorbid diseases. *Ann Allergy Asthma Immunol*. 2007;98(3):252–7.
- 9 Gonzalez-Perez A, Aponte Z, Vidaurre CF, Rodriguez LA. Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. *J Allergy Clin Immunol*. 2010;125(5):1098–1104e1.
- 10 Iribarren C, Tolstykh IV, Miller MK, Eisner MD. Asthma and the prospective risk of anaphylactic shock and other allergy diagnoses in a large integrated health care delivery system. *Ann Allergy Asthma Immunol*. 2010;104(5):371–7.
- 11 Triggiani M, Patella V, Staiano RI, Granata F, Marone G. Allergy and the cardiovascular system. *Clin Exp Immunol*. 2008;153(Suppl 1):7–11.
- 12 Lieberman P. Use of epinephrine in the treatment of anaphylaxis. *Curr Opin Allergy Clin Immunol*. 2003;3(4):313–8.
- 13 Mueller UR. Cardiovascular disease and anaphylaxis. *Curr Opin Allergy Clin Immunol*. 2007;7(4):337–41.
- 14 Shen Y, Li L, Grant J, Rubio A, Zhao Z, Zhang X, *et al*. Anaphylactic deaths in Maryland (United States) and Shanghai (China): a review of forensic autopsy cases from 2004 to 2006. *Forensic Sci Int*. 2009;186(1–3):1–5.
- 15 Bonadonna P, Perbellini O, Passalacqua G, Caruso B, Colarossi S, Dal Fior D, *et al*. Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum tryptase levels. *J Allergy Clin Immunol*. 2009;123(3):680–6.
- 16 Metcalfe DD, Schwartz LB. Assessing anaphylactic risk? Consider mast cell clonality. *J Allergy Clin Immunol*. 2009;123(3):687–8.
- 17 Summers CW, Pumphrey RS, Woods CN, McDowell G, Pemberton PW, Arkwright PD. Factors predicting anaphylaxis to peanuts and tree nuts in patients referred to a specialist center. *J Allergy Clin Immunol*. 2008;121(3):632–638e2.
- 18 TenBrook JA Jr, Wolf MP, Hoffman SN, Rosenwasser LJ, Konstam MA, Salem DN, *et al*. Should beta-blockers be given to patients with heart disease and peanut-induced anaphylaxis? A decision analysis. *J Allergy Clin Immunol*. 2004;113(5):977–82.
- 19 Rueff F, Przybilla B, Bilo MB, Muller U, Scheipl F, Aberer W, *et al*. Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum tryptase—a study of the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity. *J Allergy Clin Immunol*. 2009;124(5):1047–54.
- 20 Caviglia AG, Passalacqua G, Senna G. Risk of severe anaphylaxis for patients with Hymenoptera venom allergy: are angiotensin-receptor blockers comparable to angiotensin-converting enzyme inhibitors? *J Allergy Clin Immunol*. 2010;125(5):1171.
- 21 Robson-Ansley P, Toit GD. Pathophysiology, diagnosis and management of exercise-induced anaphylaxis. *Curr Opin Allergy Clin Immunol*. 2010;10(4):312–7.

- 22 Baek CH, Bae YJ, Cho YS, Moon HB, Kim TB. Food-dependent exercise-induced anaphylaxis in the celery-mugwort-birch-spice syndrome. *Allergy*. 2010;65(6):792–3.
- 23 Sanchez-Borges M, Iraola V, Fernandez-Caldas E, Capriles-Hulett A, Caballero-Fonseca F. Dust mite ingestion-associated, exercise-induced anaphylaxis. *J Allergy Clin Immunol*. 2007;120(3):714–6.
- 24 Matsuo H, Kaneko S, Tsujino Y, Honda S, Kohno K, Takahashi H, *et al*. Effects of non-steroidal anti-inflammatory drugs (NSAIDs) on serum allergen levels after wheat ingestion. *J Dermatol Sci*. 2009;53(3):241–3.
- 25 Simons FE. Anaphylaxis. *J Allergy Clin Immunol*. 2010;125(2 Suppl 2):S161–81.
- 26 Ring J, Brockow K, Behrendt H. History and classification of anaphylaxis. *Novartis Found Symp*. 2004;257:6–16, [discussion 24, 45–50, 276–85].
- 27 Ring J, Beyer K, Biedermann T, Bircher A, Duda D, Fischer J, *et al*. Guideline for acute therapy and management of anaphylaxis. *Allergo J Int*. 2014;23(3):96–112.
- 28 Valent P, Sperr WR, Sotlar K, Reiter A, Akin C, Gotlib J, *et al*. The serum tryptase test: an emerging robust biomarker in clinical hematology. *Exp Rev Hematol*. 2014;7(5):683–90.
- 29 Simons FE, Frew AJ, Ansotegui IJ, Bochner BS, Golden DB, Finkelman FD, *et al*. Risk assessment in anaphylaxis: current and future approaches. *J Allergy Clin Immunol*. 2007;120(1):S2–24.
- 30 Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet*. 1977;1(8009):466–9.
- 31 Belgian Federal Government, Department Economics [internet]. Bevolking per geslacht, leeftijdsgroep en -klasse 1990–2008. België en gewesten. Brussels Hoofdstedelijk gewest 2011.
- 32 van der Linden PW, Hack CE, Struyvenberg A, van der Zwan JK. Insect-sting challenge in 324 subjects with a previous anaphylactic reaction: current criteria for insect-venom hypersensitivity do not predict the occurrence and the severity of anaphylaxis. *J Allergy Clin Immunol*. 1994;94(2 Pt 1):151–9.
- 33 Brown SG. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol*. 2004;114(2):371–6.
- 34 Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy*. 2000;30(8):1144–50.
- 35 Brown SG, Franks RW, Baldo BA, Hedde RJ. Prevalence, severity, and natural history of jack jumper ant venom allergy in Tasmania. *J Allergy Clin Immunol*. 2003;111(1):187–92.
- 36 Vadas P, Perelman B, Liss G. Platelet-activating factor, histamine, and tryptase levels in human anaphylaxis. *J Allergy Clin Immunol*. 2013;131(1):144–9.
- 37 Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, *et al*. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol*. 2012;157(3):215–25.
- 38 Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. *Immunol Allergy Clin North Am*. 2006;26(3):451–63.
- 39 Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med*. 1992;327(6):380–4.