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Patterns of anaphylaxis after diagnostic work-up: a follow-up study of 226 patients with suspected anaphylaxis.

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Abstract

Background: Most published studies on anaphylaxis are retrospective or register based. Data on subsequent diagnostic work-up are sparse. We aimed to characterize patients seen with suspected anaphylaxis at the emergency care setting (ECS), after subsequent diagnostic work-up at our Allergy Center (AC).

Methods: Prospective study including patients from the ECS, Odense University Hospital, during May 2013–April 2014. Possible anaphylaxis cases were daily identified based on a broad search profile including history and symptoms in patient records, diagnostic codes and pharmacological treatments. At the AC, all patients were evaluated according to international guidelines.

Results: Among 226 patients with suspected anaphylaxis, the diagnosis was confirmed in 124 (54.9%) after diagnostic work-up; 118 of the 124 fulfilled WAO/EAACI criteria of anaphylaxis at the ECS, while 6 were found among 46 patient with clinical suspicion but not fulfilling the WAO/EAACI criteria at the ECS. The estimated incidence rate of anaphylaxis was 26 cases per 100,000 person years and the one year period prevalence was 0.04%. The most common elicitor was drugs (41.1%) followed by venom (27.4%)

and food (20.6%). In 13 patients (10.5%) no elicitor could be identified. Mastocytosis was diagnosed in 7.7% of adult patients and was significantly associated with severe anaphylaxis. Atopic diseases were significantly associated only with food-induced anaphylaxis. Co-factors were present in 58.1% and were significantly associated with severe anaphylaxis.

Conclusion: A broad search profile in the ECS and subsequent diagnostic work-up is important for identification and classification of patients with anaphylaxis. Evaluation of co-morbidities and co-factors are important.

Key words: anaphylaxis, co-factors, co-morbidities, epidemiology, mastocytosis.

Conflicts of interest: The authors declare that they have not competing interests.

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Authors Contributions: ARO, CGM, CBJ and AL designed the study. ARO, CGM, CBJ, HFK, SBO and HV evaluated the patients. ARO performed the analysis and interpretation of the data supported by CBJ, SBO, AL and CGM. TK performed the *KIT* D816V mutation analysis. MBM performed the analysis of pathology and flow cytometry data in mastocytosis patients. ARO reviewed the literature and drafted the manuscript. CBJ, SBO, TK, MBM, HV, AL, HFK, SH and CGM revised it critically and participated in the discussion and interpretations of the results. All approved the final version to be published.

INTRODUCTION

Anaphylaxis is defined as a severe allergic reaction that is rapid in onset and may be fatal (1). During the last 10 years diagnostic criteria for anaphylaxis have been published from the World Allergy Organization (WAO) (2) and subsequently from the European Academy of Allergy and Clinical Immunology (EAACI) (3), and several scoring systems have been developed to graduate the severity of anaphylaxis (4-6). Anaphylaxis is estimated to occur in up to 2% of the population at least once during life (7), with a variable incidence rate depending on the population and study design, ranging from 1.5 to 42 cases per 100,000 person years (8, 9). The profile of elicitors varies depending on age, sex and geographical area (2, 3, 7, 10).

Co-morbidities such as asthma or cardiovascular disease have been described to increase the severity of anaphylactic reactions (11-13). Similarly, in patients with mastocytosis there is a clearly increased risk for anaphylaxis and severe reactions (14-17), and this heterogeneous disease may easily be overlooked if appropriate diagnostic tools are not applied (18, 19). Co-factors such as exercise, infection, use of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or alcohol consumption are described to play an important role in up to 30% of anaphylactic reactions as they may increase the severity and probably lower the threshold for the allergen dose needed to elicit the reaction (20, 21).

The diagnosis of anaphylaxis is based on clinical findings (1-3), but an increase in serum tryptase within 6 hours of onset of the reaction can be helpful to verify the diagnosis. However, this dynamic increase in tryptase is not a highly sensitive parameter, since it is, for instance, often not seen in food-induced anaphylaxis (22-24).

Most data on anaphylaxis originate from retrospective/register based studies at the Emergency Care Setting (ECS) (7, 9, 11, 12), while data on subsequent diagnostic work-up are sparse (25).

Here, we describe diagnostic findings after diagnostic work-up at our specialized Allergy Center (AC) in a patient cohort with suspected anaphylaxis identified at the ECS according to broad inclusion criteria. We aimed to describe the incidence rate (IR) and the period prevalence of anaphylaxis, elicitors, co-morbidities and self-reported co-factors.

METHODS

Study design and settings

We conducted a prospective, non-interventional, follow-up study at the AC including patients with suspected anaphylaxis identified at the Emergency Care Setting (ECS); Emergency Department (ED) and Acute Pediatric Ward (APW), Odense University Hospital (OUH), during 1st May 2013–30th April 2014. The patient cohort in the ED and APW has been described previously (26). Odense University Hospital is a 1000-bed hospital with all medical specialties represented. The population served by the ED and APW consists of four well-defined municipalities with a mixed rural–urban population of 288,587 persons (adults n= 240,070; children n= 48,517). The ED attends patients > 15 years of age and the APW children (0–14 years old), with a 24-hour acute medical care.

Population and diagnostic work-up

At the ECS, the cases were eligible if any clinical suspicion of anaphylaxis and/or a diagnosis related to anaphylaxis according to the International Classification of Diseases 10 (ICD-10), and/or if treated with adrenaline, antihistamines or glucocorticoids at the ECS or at prehospital level (26). We applied very

broad criteria for inclusion in order not to miss eligible cases, e.g. we included angioedema or urticaria as a single sign although knowing, that these would not fulfill the inclusion criteria based on international guidelines. Exclusions criteria were: patients treated with glucocorticoid for other medical diseases e.g. Chronic Obstructive Pulmonary Disease (COPD), patients with physical or mental incapacity of giving consent, patients without Danish personal identification number, patients residing outside the hospital's catchment area at the time of contact and inpatients developing anaphylaxis (26).

At the AC a careful clinical history was obtained including a standardized interview regarding symptoms, possible elicitors, co-morbidities and co-factors in relation to the anaphylactic reaction. Objective findings and pharmacological treatment during the reaction were obtained from the medical files from ECS. In all patients, the reaction at the ECS was classified according to WAO/EAACI (3) diagnostic criteria for anaphylaxis. The severity of the anaphylactic reaction at the ECS was graded according to Sampson's severity score (4).

All patients were evaluated according to international guidelines: Challenge tests were conducted depending on the history, and findings in skin tests including Skin Prick Test (SPT) and Intra Cutaneous Test (ICT), specific Immunoglobulin E (IgE), Component Resolved Diagnostics (CRD) and Basophil Histamine Release (BHR) test. Baseline serum tryptase (ImmunoCAP Tryptase, Thermo Fisher, USA) was determined in all patients at the first visit at the AC and it was compared to the value during the suspected anaphylactic episode at the ECS, if available. All adults were screened for mastocytosis by sensitive *KIT* D816V mutation analysis of peripheral blood as previously described (19). Cases with β -lactam antibiotics as suspected elicitor were evaluated according to the European Network for Drug Allergy (ENDA) guidelines (27) including specific IgE, SPT, ICT and if negative a titrated penicillin challenge. For other drugs, the diagnosis was verified by a titrated drug challenge (28). Food allergy was evaluated according to EAACI guidelines (29) with food challenge being the gold standard for the

diagnosis. In a few cases, mostly patients with severe anaphylaxis or presence of co-morbidity, challenges were not performed, but the diagnosis was based on a clear cut history with only one obvious allergen and sensitization pattern. For venom allergy the diagnosis was based on history and sensitization pattern (30). In case of suspicion on Food Dependent Exercise Induced Anaphylaxis (FDEIA), exercise was included in the challenges (31).

After diagnostic work-up, cases with confirmed anaphylaxis were included in the study for further analysis (**Figure 1**). Patients with an unclear history, who did not complete the diagnostic work-up, were excluded, as well as patients diagnosed with other medical diagnosis than anaphylaxis after the diagnostic work-up.

The registered co-morbidities included current or previous history with asthma, allergic rhinitis and atopic dermatitis, previous history of urticaria and/or angioedema and cardiovascular diseases. Self-reported co-factors in relation to the anaphylactic reaction included: infection, acetylsalicylic acid (ASA) and NSAIDs, exercise and alcohol (11-13, 20, 21).

A significant increase in acute serum tryptase was defined as an increase of at least 20% plus 2 µg/L above basal serum tryptase level, in line with previous reports (22, 32).

Statistical analysis

Baseline characteristics are presented as numbers and percentages. Adults were defined as persons over 18 years of age. Age is given as median with 25-75 percentiles (IQR). The Incidence Rate (IR) of anaphylaxis was calculated as the number of patients having anaphylaxis for the first time per 100,000 person-years. The period prevalence was calculated as the number of patients having anaphylaxis per the total numbers of habitants in the hospital's catchment area during the study period. Data on the population living in the hospitals catchment area during our study period were collected at the StatBank

Denmark website (<http://www.statistikbanken.dk>; accessed November 2016). Both the IR and the period prevalence were calculated with the correspondent 95% confidence interval based on a poisson distribution (CI 95%). Comparisons were made by χ^2 -based table analysis. Statistical analysis was performed with Stata IC 14.0 (Stata Corporation LP®, College Station, Texas, USA). Statistical significance was defined as $p < 0.05$.

Ethics

The study was approved by the Data Protection Agency (J. no. 12/26172) and the Regional Scientific Ethics Committee for Southern Denmark (J. no. S-20120203). The patients were included after informed consent.

Results

Applying broad inclusion criteria at the ECS based on symptoms, diagnostic codes and treatment, the subsequent evaluation at the AC confirmed anaphylaxis in 124 (54.9%) of the 226 cases. The WAO/EAACI criteria of anaphylaxis were applied to classify the reaction at the ECS in all 226 cases. Using these criteria excluded 46 of the 226 patients, whereas 180 fulfilled the criteria. Results from the ESC have been published previously (26). Among the 46 patients not fulfilling the WAO/EAACI criteria of anaphylaxis at the ECS, 6 (13.0%), ended up with an anaphylaxis diagnosis after diagnostic work-up. By contrast, 118 of the 180 cases fulfilling the WAO/EAACI criteria at the ECS (65.6%) were verified after diagnostic work-up. Of the 124 (6+118) with confirmed anaphylaxis, 16.1% ($n = 20$) were children with a median age of 6 years and 83.9% ($n = 104$) were adults with a median age of 49.5 years. There was an

equal gender distribution (64 females/60 males). A flow diagram of the patients is presented in **Figure 1**.

Suspected elicitors at the ECS and confirmed elicitors after diagnostic work-up in the AC are shown in **Table 1**.

Baseline characteristics for patients with confirmed anaphylaxis distributed by age group and elicitors are shown in **Table 2**.

In 93 patients anaphylaxis was excluded after diagnostic work-up and 9 patients did not complete the diagnostic work-up (40 males (39.2%) and 62 females (60.8%); 6 (5.9%) were children with a median age of 15.5 years (IQR, 11.5–17) and 96 (94.1%) were adults with a median age of 47 years (IQR, 33–64) (**Figure 1**). These patients were excluded from further analysis. The most common diagnosis in this group of patients was urticaria/angioedema (n= 46), most of them in relation to infection and concomitant penicillin treatment, followed by ACE-inhibitor angioedema (n= 18).

Incidence and prevalence of anaphylaxis after diagnostic work-up (n= 124)

First time anaphylaxis was found in 76 of the 124 patients (children n= 13, adults n= 63). The IR of anaphylaxis in children was estimated to 26.8 cases per 100,000 person years (95% CI: 14.3-45.8) and in adults 26.2 cases per 100,000 person years (95% CI: 20.2-33.6).

The period prevalence of anaphylaxis in the hospitals catchment area during 2013-14 was estimated in children to 0.04% (95% CI: 0.02-0.06) and in adults to 0.04% (95% CI: 0.03-0.05).

Elicitors

Drugs (41.1%), venom (27.4%) and food (20.6%) were the most often observed elicitors in our study group. Food was the most common elicitor among children compared to adults ($p<0.001$), while drugs ($p<0.01$) and venom ($p<0.003$) were more prevalent in adults compared to children (**Table 2**).

After diagnostic work-up, the suspected elicitors of anaphylaxis in the ECS were confirmed in 85.5% (106/124) of cases with anaphylaxis; in 97.1% of cases suspected to be elicited by venom, 94.3% by drugs and 84.6% by food. In only 4.0% of the cases ($n=5$) an unexpected elicitor was identified. In 10.5% of the cases ($n=13$) an elicitor was not identified (**Figure 1, Table 1**).

Drugs ($n=51$)

The most common drugs among adults ($n=48$) were: β -lactam antibiotics ($n=24$, 50.0%), followed by ASA and NSAIDs ($n=10$, 20.8%). Other drugs ($n=14$, 29.2%) were radio contrast media ($n=5$), Metronidazole ($n=2$), and 7 individual cases elicited by Pantoprazole, Chlorhexidine, Camphorated opium tincture, Acyclovir, Roxithromycin, Miconazole and Gabapentin. Among children we found three cases elicited by drugs; Valerian root, Lamotrigine and Codeine, respectively.

β -lactam antibiotics were confirmed as elicitor according to guidelines in 20/24 cases (positive specific IgE $n=9$, positive SPT $n=0$, positive ICT $n=4$, positive challenge $n=7$) and in further 4 cases the diagnosis was based on a clear cut history. ASA/NSAIDs were confirmed as elicitor based on challenge in 5/10 cases and in 5/10 the diagnosis was based on clear cut history. Radio contrast media as elicitor of anaphylaxis was based on case history in all cases. In the group of other drugs, Chlorhexidine allergy was confirmed by positive SPT and specific IgE and Pantoprazole was confirmed as elicitor by challenge. In the other 10 cases the diagnosis was based on history.

Food (n= 26)

Among children (n= 13) the most common eliciting food allergens were: Tree nuts (n= 5, 38.5%) and peanuts (n= 3, 23.1%) while allergy to egg, milk, sesame, mango and almond (FDEIA) was found in one case each. One child with a history of FDEIA to almond, were challenge negative to almond but positive when combining almond with exercise. The most common eliciting food allergens among adults (n= 13) were: Wheat (Wheat Dependent Exercise Induced Anaphylaxis – WDEIA n= 5, 38.5 %) and tree nuts (n= 4, 30.7%), while one case was found for peanuts, celery, avocado, and tomato, respectively. In the group with WDEIA all patients were eating conventional wheat on a daily basis but had a history of anaphylaxis only when combining intake of a wheat product with exercise within 4 hours. Omega-5-gliadine was positive in 3 of the 5 patients.

The diagnosis of food allergy was based on food challenge in 14 patients, food challenge combined with exercise in 5 patients (WDEIA n= 4, almond n= 1) and by a clear cut history and sensitization pattern in 8 patients.

Venom (n= 34)

The insects registered in this group were wasp (n= 26, 76.5%), bee (n= 6, 17.6%), bumblebee and gadfly (n=2, 5.9%). The diagnosis of wasp and bee anaphylaxis was based on case history and specific IgE and CRD, while diagnosis in the 2 cases with other insects as elicitor was based on the history and a negative specific IgE to wasp and bee.

Unknown elicitor (n= 13)

In a total of 10.5% of patients (n= 13; 9 adults, 4 children) no elicitor could be identified after diagnostic work-up. A history of atopic diseases was observed in 69.2% (n= 9) of the cases and the presence of one or more cofactors were registered in 61.5% (n= 8). Two of the patients were subsequently diagnosed

with mastocytosis. The severity of the reactions was distributed as: grade 2; n= 2, grade 3; n= 1, grade 4; n= 7 and grade 5; n= 3.

Co-morbidities

Atopic diseases were observed in 47.6% (n= 59) of all cases, more often in children (65.0%) compared to adults (44.2%). Rhinitis was found in 21.8% (n= 32), atopic dermatitis in 18.5% (n= 23) and asthma in 17.7% (n= 22) of the patients. Previous history of urticaria and/or angioedema was found in 30.6% (n= 38) of all cases. Among the adults, 25.0% (n= 26) had cardiovascular diseases and Kounis syndrome (33) was described in a 70 years old man in relation to wasp sting. The distribution of the evaluated co-morbidities according to elicitors and age group is listed in **Table 2**. Atopic diseases were significantly associated with food-induced anaphylaxis ($p=0.04$) both in children and adults, whereas this was not seen in anaphylaxis caused by drugs or venom.

Mastocytosis

Mastocytosis was diagnosed in 7.7% of adults (2 females, 6 males) all with positive *KIT* D816V mutation analysis, of whom 4 have been included in a previous publication from our center (18). All 8 patients had indolent systemic mastocytosis fulfilling WHO diagnostic criteria. Median value of basis serum tryptase for this group of patients was 9.4 µg/l (range 5.35-15). Symptoms suggestive of mastocytosis such as urticaria pigmentosa (UP) skin lesions or mast cell-mediator related symptoms were absent in all patients except for one who had discrete UP. Mastocytosis was significantly associated with grade 5 anaphylaxis at the initial reaction ($p=0.046$). Elicitors related to anaphylactic reactions among mastocytosis patients were: venom (3 wasp, 1 gadfly), drugs (1 β-lactam antibiotic and 1 camphorated opium tincture) and in two no elicitor could be identified.

Co-factors

At least one co-factor was reported in 58.1% (n=72) of the anaphylaxis cases. Among the registered self-reported co-factors the most frequent observed were infection 29.8% (n= 37; 3 children, 34 adults), exercise 20.9% (n= 26; 3 children, 23 adults) and ASA/NSAID 16.1% (n= 20; 2 children, 18 adults, excluding cases with ASA/NSAIDs as elicitor). Alcohol was registered in 13.7% (n= 17) of the adults. Detailed distribution of co-factors by elicitors is shown in **Table 3**. Exercise as co-factor was proven by challenge in five cases (wheat n= 4, almond n= 1). Presence of one or more co-factors in connection with the initial reaction was significantly associated with severe anaphylaxis (grade 4-5, $p=0.042$).

Serum tryptase increase during reaction

Acute serum tryptase was measured at the ECS in 40.3% (50/124) of all cases, while basis serum tryptase measurement was performed in 95.9% (115/124). Both measurements were present in 39.5% (49/124) of the patients. Increased acute serum tryptase was found in only 46.9% (23/49) of the patients, mostly with severe reactions (grade 5) ($p < 0.005$) and elicited by venom.

Discussion

This is the first prospective follow-up study, describing findings after diagnostic work-up at a specialized Allergy Center (AC) in patients with suspected anaphylaxis identified at the Emergency Care Setting (ECS) according to broad inclusions criteria.

We found that anaphylaxis was confirmed in half of the patients identified by a broad search profile at the ECS. Among patients fulfilling the WAO/EAACI criteria at the ECS, anaphylaxis was verified in 65.6% after diagnostic work-up. The WAO/EAACI diagnostic criteria of anaphylaxis have previously been

evaluated showing a high sensitivity (>95%) and a slightly lower specificity (>71%) (34, 35). In our study, 13.0% of the cases that did not fulfill the anaphylaxis criteria at the ECS were diagnosed with anaphylaxis after diagnostic work-up. All these cases had localized or generalized skin and mucosal symptoms but no symptoms from other organ systems. On the other hand, 34.4% of the cases fulfilling the anaphylaxis criteria received other medical diagnosis after diagnostic work-up. Nevertheless, at the ECS the higher sensitivity is preferred over specificity in order to have a low risk to overlook cases with anaphylaxis.

The estimated IR in our study of 26.2 and 26.8 cases per 100,000 person years in children and adults respectively is within the previous described incidence rates in the literature ranging from 1.5 to 42 cases per 100,000 person years (8, 9). The IR is higher than the latest estimates from Denmark (2012) on 10.57 cases per 100,000 person year based on register data (36). However, compared with our estimates from the ECS before diagnostic work up the incidence is lower (26). The period prevalence of anaphylaxis in the general population of Odense was estimated to 0.04%, higher than Beyer's estimates of 0.004% in the general population of Berlin (37), but in line with Bohlke's estimates of 0.03% in children and adolescents in Washington state (38). We consider, that our results may reflect the real occurrence of anaphylaxis in our population as they are based on confirmed cases after diagnostic work-up in contrast to the referred studies.

Our results regarding elicitors of anaphylaxis and their age distribution are in line with previous epidemiological studies (2, 3, 7, 39). Tree nuts and peanuts were the most common elicitors of anaphylaxis in children in agreement with data from Germany, Austria, Switzerland and Sweden, probably due geographical dietary habits (10, 40) and the age of the children in this group (median 3 years) (40, 41). In adults, drugs, especially β -lactam antibiotics and ASA/NSAIDs, were the most common elicitors followed by venom, supporting previous reported findings (7, 8, 12, 25).

In our study, the proportion of cases with unknown elicitor of anaphylaxis was 10.5% compared to 13-20% reported in other studies (3, 25) and only 5.3% reported by Helbling (12). Mastocytosis was diagnosed in 2/13 patients in this group, probably reflecting a spontaneous mast cells activation (42).

Co-factors were reported in 61.5% of patient with unknown elicitor. In the future it could be interesting to challenge these patients with presence of co-factors to evaluate if this has an impact.

As expected, increased acute serum tryptase levels were significantly associated with the most severe cases of anaphylaxis (22, 23, 43) and were observed mostly in the group of venom induced anaphylaxis. However, a limitation is that acute serum tryptase was measured in only 40.3% of our study population.

The prevalence of atopic diseases among anaphylaxis patients has been described to be 20-39% (12, 25, 44), lower than the 47.6% reported in our study. Our findings support that atopic diseases are prevalent in children and adolescents and are closely related to cases with food induced anaphylaxis (38). It is known that cardiovascular diseases are associated with more severe anaphylactic reactions both because of pathophysiological reasons and because of treatment with ACE inhibitors and β -blockers (2, 13). In our study, 25.0% of adults had a cardiovascular disease, a higher frequency as compared to 18.5% reported among patients from the anaphylaxis registry in German-speaking countries (44).

In our study, exercise was the only confirmed co-factor in five patients, who consumed the suspected allergen (almonds and wheat) conventionally, but by the concomitant presence of physical activity anaphylaxis was elicited both in the history and by challenge. These results are in line with the literature (31, 45). The frequency of self-reported co-factors in this study is higher than the reported from anaphylaxis registers from Europe (20). In addition, we found a significant association between the presence of one or more co-factors and severe anaphylactic reactions, supporting the important role that they may play in the development of allergic reactions (20, 21).

Mastocytosis was significantly associated with the most severe anaphylactic reactions, supporting previous findings in the literature (14, 16, 17). However, it was diagnosed in 7.7% of adults in our study group (including 2 patients with unknown elicitor of anaphylaxis) representing a high frequency among anaphylaxis patients compared with 0.4-2.7% reported in other studies (12, 25). This finding is related to the screening of adults in our study population with the sensitive *KIT* D816V mutation analysis of peripheral blood (19). This diagnostic test has clinical relevance in patients with anaphylaxis since mastocytosis may easily be missed applying standard tools for recognizing the disease (18, 32). Here, none of the eight diagnosed patients had an elevated level of baseline serum tryptase ($>20 \mu\text{g/l}$) and in 7 out of 8 no UP skin lesions or other symptoms indicative of mastocytosis were present. The sensitive *KIT* D816V mutation analysis of peripheral blood has a very high diagnostic sensitivity and specificity and is readily available (19), and the present study supports the inclusion of this diagnostic screening tool when evaluating patients with anaphylaxis.

The strength of this study is that all patients with possible anaphylaxis at the ECS underwent subsequent diagnostic work-up in a specialized AC, giving estimates of verified anaphylaxis including elicitors.

Furthermore, the prospective inclusion of the patients at the ECS with a broad search profile based on any clinical suspicion of anaphylaxis and/or a diagnosis related to anaphylaxis according to the International Classification of Diseases 10 (ICD-10), and/or if treated with adrenaline, antihistamines or glucocorticoids at the ECS or at prehospital level made it possible to identify all possible anaphylaxis cases.

Limitations of this study include that co-factors were self-reported and only in few cases they were confirmed by challenge. Even though all patients with suspected anaphylaxis at the ECS were studied at the AC, we cannot rule out that some patients with anaphylaxis living in OUH's catchment area may have attended other hospitals during our study period.

In conclusion, a broad search profile at the ECS, including patients fulfilling diagnostic criteria for anaphylaxis but also with milder symptoms, followed by diagnostic work-up is important not to overlook anaphylaxis cases and thereby prevent further incidents. Mastocytosis was diagnosed in 7.7% of adults with anaphylaxis; half of the mastocytosis patients had venom anaphylaxis. Atopic diseases were significantly associated with food-induced anaphylaxis, but not anaphylaxis elicited by drug and venom. Co-factors were reported in more than half of the patients and were significantly associated with severe anaphylaxis. It is important to take these factors into consideration when evaluating patients with anaphylaxis since they may play a role for future anaphylactic reactions.

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Table 1. Elicitors of anaphylaxis distributed according to primary suspicion in the emergency care setting and the final diagnosis after diagnostic work-up at the Allergy Center

Emergency Care Setting		Allergy Center						
Suspected elicitors		Confirmed elicitors of anaphylaxis				Other conditions		
Elicitors	Total	Drugs	Food	Venom	Unknown elicitor	ACE inhibitor angioedema	Other medical diagnosis	Diagnostic work-up not completed
Drugs	108	50	0	0	3	16	30	9
Food	47	1	22	0	3	1	20	0
Venom	41	0	0	34	1	0	6	0
Unknown	30	0	4	0	6	1	19	0
Total	226	51	26	34	13	18	75	9

Table 2. Characteristics of patients with confirmed anaphylaxis distributed by age group and elicitors ^a

Variables	Drugs n (%)	Food n (%)	Venom n (%)	Unknown elicitor n (%)	Total n (%)
Adults (> 18 years)					
N (%)	48 (46.1)	13 (12.5)	34 (32.7)	9 (8.7)	104 (100)
Age in years, Median (IQR)	51.5 (27.5-66.8)	39 (25.5-54.0)	54 (42.8-68.3)	41 (28.0-63.5)	49.5 (30.8-66.0)
Sex (%)					
Male	15 (31.2)	5 (38.5)	25 (73.5)	2 (22.2)	47 (45.2)
Female	33 (68.7)	8 (61.5)	9 (26.5)	7 (77.8)	57 (54.8)
Co-morbidities					
Atopic diseases	20 (41.7)	7 (53.8)	13 (38.4)	6 (66.7)	46 (44.2)
Asthma	10 (20.8)	4 (30.8)	2 (5.9)	2 (22.2)	18 (17.3)
Rhinitis	11 (22.9)	6 (46.1)	8 (23.5)	5 (55.6)	30 (28.8)
Atopic Dermatitis	5 (10.4)	3 (23.1)	3 (8.8)	3 (33.3)	14 (13.5)
History of Urticaria and/or Angioedema	14 (29.2)	4 (30.8)	8 (23.5)	4 (44.4)	30 (28.8)
Cardiovascular diseases	13 (27.1)	0	10 (29.4)	3 (33.3)	26 (25.0)
Mastocytosis	2	0	4	2	8 (7.7)
Serum-Tryptase ^b ↑	5/17	4/7	9/13	1/3	19/40
Children (0-18 years)					
N (%)	3 (15.0)	13 (65.0)	0	4 (20.0)	20 (100)
Age in years, Median (IQR)	13 (11.0-17.0)	3 (1.5-10.0)	-	8.5 (5.0-11.25)	6 (2.3-11.8)
Sex (%)					
Male	2 (66.7)	8 (61.5)	-	3 (75.0)	13 (65.0)
Female	1 (33.3)	5 (38.5)	-	1 (25.0)	7 (35.0)
Co-morbidities					
Atopic diseases	0	10 (76.9)	-	3 (75.0)	13 (65.0)
Asthma	0	4 (30.8)	-	0	4 (20.0)
Rhinitis	0	5 (38.5)	-	2 (50.0)	7 (35.0)
Atopic Dermatitis	0	7 (53.9)	-	2 (50.0)	9 (45.0)
History of Urticaria and/or Angioedema	0	6 (46.1)	-	2 (50.0)	8 (40.1)
Cardiovascular diseases	0	0	-	0	0
Mastocytosis	-	-	-	-	-
Serum-Tryptase ^b ↑	1/2	2/4	-	1/3	4/9

^a Values expressed as total number (fraction) and median [25-75 percentile] as appropriate.^b Serum-Tryptase increase was calculated in patients with both acute and basis tryptase values according to the formula = (1.2 x basis tryptase value) + 2

Table 3. Co-factors in the group of patients with confirmed anaphylaxis distributed by elicitor group

Elicitors	Co-factors			
	Infection n (%)	ASA/NSAIDs n (%)	Exercise n (%)	Alcohol n (%)
Drugs				
B-lactam antibiotics n= 24	24 (100)	6 (25)	5 (20.8)	2 (8.3)
ASA/NSAIDs n= 10	1 (10)	N/A	1 (10)	2 (20)
Other drugs ^a n= 17	7 (41.2)	5 (29.4)	1 (5.9)	1 (5.9)
Food				
Tree nuts, Peanut and Almond n= 14	0	2 (14.3)	3 ^c (21.4)	0
Wheat (WDEIA) n= 5	0	0	5 ^c (100)	1 (20)
Other ^b n= 7	1 (14.3)	0	0	1 (14.3)
Venom				
Wasp n= 26	0	4 (15.4)	8 (30.8)	9 (34.6)
Bee n= 6	0	0	1 (16.7)	0
Other ^d n= 2	0	0	0	0
Unknown n= 13				
	4 (30.8)	3 (23.1)	2 (15.4)	1 (7.7)
Total n= 124	37 (29.8)	20 (16.1)	26 (20.9)	17 (13.7)

^a**Drugs:** Radio contrast media n= 5, Metronidazole n= 2, Proton pump inhibitor n= 1, Chlorhexidine n= 1, Camphorated opium tincture n= 1, Acyclovir n= 1, Macrolides n= 1, Miconazole n= 1, Gabapentin n= 1, Valerian root n= 1, Lamotrigine n= 1 and Codeine n= 1.

^b**Food:** Celery, avocado, tomato, egg, milk, sesame and mango

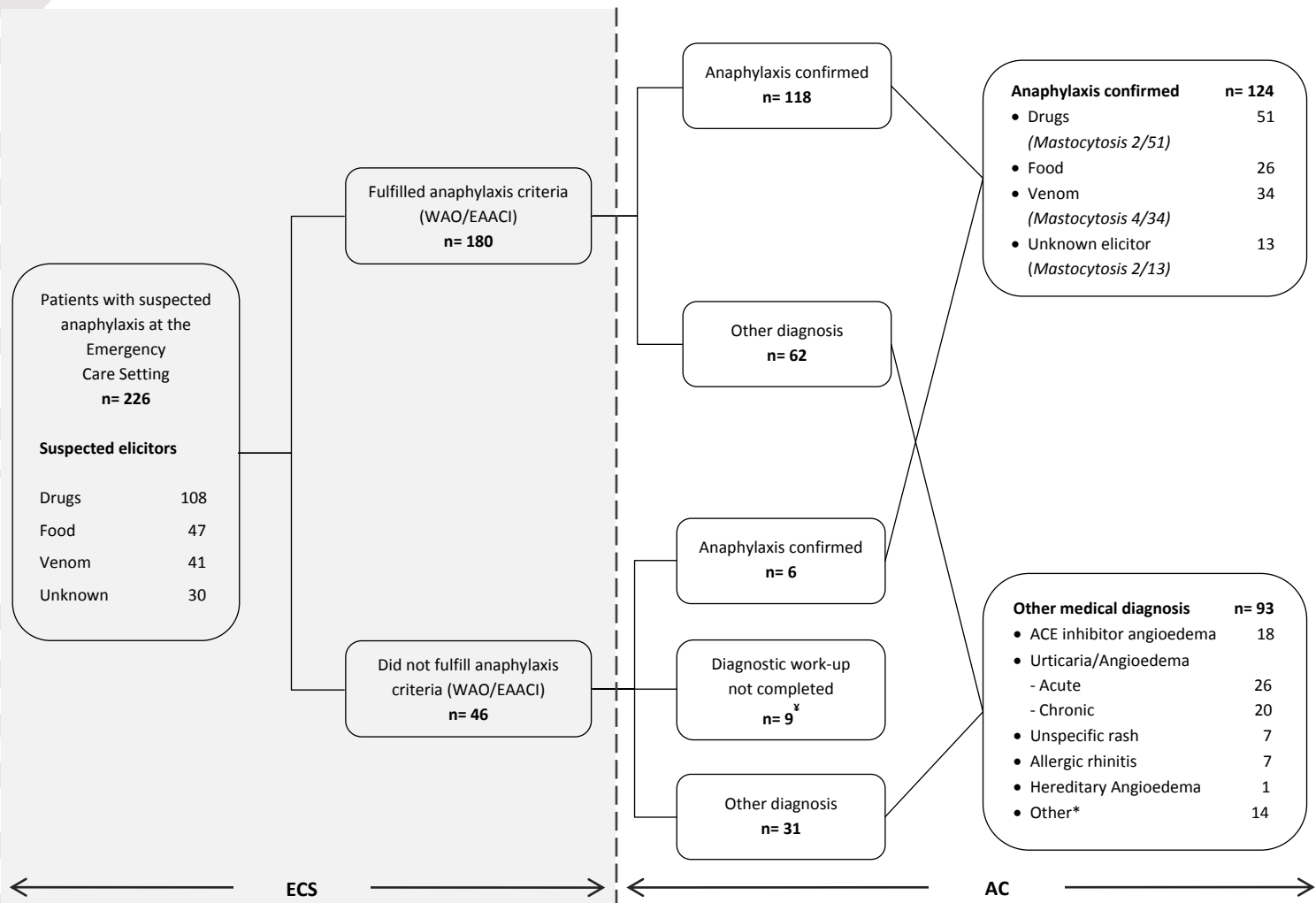
^c**Food:** Food Dependent Exercise Induced Anaphylaxis (FDEIA) was concluded in 6 patients in relation with following food products: wheat n= 5 and almond n= 1

^d**Venom:** Bumblebee and gadfly

Legend to Figure 1:

Flowchart of patients identified at the Emergency Care Setting with suspected anaphylaxis and referred to the Allergy Center for diagnostic work-up distributed according to WAO/EAACI criteria for the diagnosis of anaphylaxis and final diagnosis

Figure 1



*Noxious substance eaten as food, unspecified n= 1; toxic effect of unspecified seafood n= 1; local reaction after insect sting n= 3; hyperventilation n= 3; infection n= 5; transient cerebral ischemic attack n= 1

[‡] Patients who declined further investigation or challenge n= 9;