**Anaphylaxis in 1165 patients aged 65 or more: Data from European Anaphylaxis Registry**

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**Abstract**

Background and aim: Anaphylaxis in children and adults differs with regard to elicitors and clinical picture. Little is known about anaphylaxis in elderly patients. We aimed at characterizing typical features of anaphylaxis in this group of patients.

Methods:Data fromthe Network for Online Registration of Anaphylaxis (NORA) were analyzed for Europe. We compared data from patients aged ≥ 65 (elderly) with data from patients aged 18-40 (younger adult group) and patients aged ≥41-64 in terms of elicitors, clinical symptoms, comorbidities and emergency treatment.

Results:Between July 2007 and March 2017, anaphylaxis was registered in 1165 elderly, and 4665 of other adult patients. Insect venom was the most frequent trigger in all groups (elderly: 60% vs. adults: 52%), followed by drugs (24% vs. 21%) and food items (10% vs. 17%). Within the group of insects yellow jacket (72% vs. 73%) and in the group of drugs analgesics (38% vs. 40%) were the most common elicitors. For food anaphylaxis hazelnut (16%) was the most frequent elicitor in the elderly, and wheat (16%) in younger adults. Cardiovascular symptoms were slightly more prevalent in the elderly (77% vs. 73%) and the reactions are more severe with 46% (36% compared to other adults) experiencing a grade III/IV reaction. Noteworthy, 60% of the elderly had a preexisting cardiovascular comorbidity compared with 18% of the other adults. First line treatment by professionals included mainly corticosteroids (89%) and antihistamines (82%) in both groups. Epinephrine was only used in 24% (elderly) versus 19% (other adults).

Discussion and conclusion:Compared to adults aged below 65 years, the symptom pattern in the elderly was characterized by cardiovascular symptoms and more severe reactions but not fatal. Epinephrine was used more frequently in the elderly compared to younger adults but was still only used in less than one out of four patients.

**Clinical Implications or Key Messages**

**Capsule summary**

**Keywords (MeSH terms)**

Anaphylaxis

Drug Hypersensitivity

Elderly

Epinephrine

Arthropod Venoms

**Abbreviations:**

sIgE; specific Immunglobulin E

SIT; specific immunotherapy

CVD; cardiovascular disease

**Introduction**

Anaphylaxis occurs in all ages, but little is known about the characteristics of anaphylaxis in elderly patients. In general, the incidence of anaphylaxis seems to be rising [Decker WW, Campbell RL, Manivannan V, Luke A, St Sauver JL, Weaver A, Bellolio MF, Bergstralh EJ, Stead LG, Li JT. The etiology and incidence of anaphylaxis in Rochester, Minnesota: A report from the Rochester Epidemiology Project. J Allergy Clin Immunol. 2008;122:1161-5.; Tejedor Alonso MA1, Moro Moro M, Múgica García MV, et al. Incidence of anaphylaxis in the city of Alcorcon (Spain): a population-based study. Clin Exp Allergy. 2012;42:578-89.] and above all life expectancy of the population is increasing. It is estimated that people more than 65 years old will reach 20% in the year 2030 [Cardona V, Guilarte M, Luengo O, et al. Allergic diseases in the elderly. Clin Transl Allergy 2011; 1:11.]. Like there are differences in children and adults in terms of elicitor, cofactors and clinical presentation of anaphylaxis, there are also differences in elderly patients more than 65 years old [González-de-Olano D, Lombardo C, González-Mancebo E. The difficult management of anaphylaxis in the elderly. Curr Opin Allergy Clin Immunol. 2016 Aug;16(4):352-60.].

The demographic distributions are changing over the last years and the percentage of patients aged above 80 years will increase disproportionately [Ventura MT, Scichilone N, Gelardi M, Patella V, Ridolo E. Management of allergic disease in the elderly: key considerations, recommendations and emerging therapies. Expert Rev Clin Immunol. 2015;11(11):1219-28.]. The prevalence of allergic diseases, in the elderly is estimated around 5-10% [Mathur SK: Allergy and asthma in the elderly. Semin Respir Crit Care Med 2010, 31(5):587-95.]. Less is known about the anaphylaxis in such an aging population. The elderly patients are not the group of higher frequencies of anaphylaxis, but the group with a higher risk of fatal reactions [Ventura MT, Scichilone N, Gelardi M, Patella V, Ridolo E. Management of allergic disease in the elderly: key considerations, recommendations and emerging therapies. Expert Rev Clin Immunol. 2015;11(11):1219-28.; Ring J, Beyer K, Biedermann T, et al. Guideline for acute therapy and management of anaphylaxis: S2 Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Association of German Allergologists (AeDA), the Society of Pediatric Allergy and Environmental Medicine (GPA), the German Academy of Allergology and Environmental Medicine (DAAU), the German Professional Association of Pediatricians (BVKJ), the Austrian Society for Allergology and Immunology (OGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Anaesthesiology and Intensive Care Medicine (DGAI), the German Society of Pharmacology (DGP), the German Society for Psychosomatic Medicine (DGPM), the German Working Group of Anaphylaxis Training and Education (AGATE) and the patient organization German Allergy and Asthma Association (DAAB). Allergo J Int 2014; 23:96–112.]

In general population, insect venoms are main elicitor of anaphylaxis, followed by drugs and food items [Worm M, Moneret-Vautrin A, Scherer K, et al. First European data from the network of severe allergic reactions (NORA). Allergy. 2014 Oct;69(10):1397-404.]. This differs due to age group, in children and young adults food items are predominant [Grabenhenrich LB, Dölle S, Moneret-Vautrin A, et al. Anaphylaxis in children and adolescents: The European Anaphylaxis Registry. J Allergy Clin Immunol. 2016 Apr;137(4):1128-37.e1.], whereas drug anaphylaxis is more common in older patients. The higher consumption of drugs in elderly patients is probably one reason. Patients more than 65 years old are more likely to develop cardiovascular symptoms. It is unclear whether more cardiovascular diseases or limited cardiovascular reserves are the reasons [Lieberman P, Simons FE. Anaphylaxis and cardiovascular disease: therapeutic dilemmas. Clin Exp Allergy. 2015 Aug;45(8):1288-95.].

Cofactors like exercise, drugs, ethanol and stress are known to reduce the threshold of allergic reactions [Simons FE, Ebisawa M, Sanchez-Borges M, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organ J. 2015 Oct 28;8(1):32]. Especially, older patients have an increased drug consumption, which may be the reason for drugs as main elicitor but also for severe reactions [Ring J, Beyer K, Biedermann T, et al. Guideline for acute therapy and management of anaphylaxis. Allergo J Int 2014; 23:96–112.].

Emergency treatment is similar in all age groups and supported by current guidelines [Muraro, A., et al., Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy, 2014. 69(8): p. 1026-45.] but some considerations and adaptions should be made in elderly patients. For example, the administration of adrenaline in patients with known or suspected CVD is no contraindication, but can be difficult due to increased coronary blood flow especially in patients with acute coronary syndrome [Lieberman P, Simons FE. Anaphylaxis and cardiovascular disease: therapeutic dilemmas. Clin Exp Allergy. 2015 Aug;45(8):1288-95.]

In this survey, we aimed to analyze data from xx European countries concerning severe allergic reactions, with focus to patients 65 years and older regarding elicitors, symptoms, comorbidities, emergency treatment and longterm-treatment. The population is increasing, especially the proportion of the elderly, thus the prevalence of allergic diseases is raising, too. Therefore, we need to know the impact of comorbidities, co-medication to anaphylactic reactions. It might also influence the management of anaphylaxis. The aim was to characterize anaphylaxis in patients aged 65 or above….

**Methods**

**Setting and Design**

The European Anaphylaxis Registry collected information on anaphylactic reactions through a web based data entry system. It aims to document cases of severe anaphylaxis. Participation of study centers was voluntary and could be declined at any time. Data for the current analysis were provided by tertiary referral centers specialized in allergology and/or dermatology in Germany, France, Switzerland, Ireland, Greece, Austria, Spain, Bulgaria , Italy and Poland. The study was approved by the Ethics Committee at Charité – Universitätsmedizin Berlin (the coordinating center) and by the local Ethics Committees in all participating countries.

Only countries with >100 cases were considered.

**Participants**

After treatment of a severe anaphylactic reaction, patients were referred for further diagnostics up to specialized centers for evaluation, education and counselling, and specific immunotherapy. Patients were asked to give written informed consent to allow the use of their data on medical history and diagnostic workup within this study. We aimed to enter most severe cases preferably, usually with circulatory or respiratory symptoms, but milder anaphylaxis could be recorded as well.

**Data source and handling**

After completion of diagnostics, patients’ data were retrieved from medical treatment, laboratory measurements, emergency protocols as available. Using a pseudonym, the data were entered by trained study personnel into online questionnaire in each study center. The online data entry system comprised a German questionnaire for Germany, Austria and

Switzerland, which was translated for international use. Raw study data were stored on a central server at Charité – Universitätsmedizin Berlin ([www.anaphylaxie.net](http://www.anaphylaxie.net)). The questionnaire was refined through yearly updates, with new items introduced based on expert judgment. Data collected through questionnaire versions 2 to 6 (n=134, 219, 167, 689, and 761) with entry dates from July 2007 to March 2017 were used.

**Variables**

Specific areas covered have been reported earlier [22], the online version can be accessed through www.anaphylaxie.net. Age at reaction was categorized in three groups: patients aged 18-40 years, patients aged 41-64 years, and elderly patients 65 years and older. Most variables were assessed as answers by item (comorbidities, cofactors, details of previous reactions, elicitors, symptoms and severity, emergency treatment, and long-term management). The Elicitors were grouped into typical foods, insect venoms, drugs, and other less-frequently expected causes of allergic reaction, such as latex or allergen immunotherapy (AIT). Rare food items could be specified by free text entries within the group of elicitors. Based on local allergy specialist´s appraisal the elicitor was documented as known or highly suspicious. Symptoms were assessed through closed questions, categorized via organ system involvement including detailed options. Further symptoms were documented via free text and were manually assigned to default answer categories. Severity was graded retrospectively in four levels of symptom profiles using the classification proposed by Ring [Ring, J. and K. Messmer, Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet, 1977. 1(8009): p. 466-9.]: grade II with involvement of at least two organ systems; grade III with signs of circulatory and/or respiratory failure/shock; grade IV with circulatory or respiratory arrest. Time between allergen exposure and occurrence of symptoms were assessed in six categories (<10 min, 10–30 min, 30– 60 min, 1–2 h, 2 –4 h and >4 h).

**Statistics**

The analysis of the data was carried out using the…. As a cross-sectional approach, the analysis was used to describe documented variables. Missing data were attempted to reduce in individual queries to study centers. A minimum set of information (age at reaction, date of birth and sex) were needed as inclusion criteria. Other variables are allowed to remain missing by item. …

223 cases are not-unique, but were included in the analysis.

**Results**

**Study centers and participants**

The European Anaphylaxis Registry collected data on 7136 patients >18 years from xx study centers in xx countries: Germany (n=xxx), France (n=xxx), Switzerland (n=xxx), Ireland (n=xx), Greece (n=xx), Austria (n=xx), Spain (n=xx), Bulgaria (n=xx), Italy (n=x), and Poland (n=x).

Of the 7136 patients > 18 years, 2360 are 18-40 years (adult group 1), 3611 are 41-64 years (adult group 2) and 1165 are > 65 years. Xxx (56%) were female in the group of the elderly, with a higher female distribution in young adults (63%). The mean age in patients > 65 years was 71+5 years.

The recent medical history in patients > 65 years mainly includes cardiovascular diseases (60%) (18-40 4%, 41-64 27%) and thyroid diseases (17%). In In the age group 18-40 allergic diseases with RKA, AA, AD (36%) were predominant. Other diseases like urticaria (??? In Table 1 mit aufnehmen!), mastocytosis were not dependent on age.

In general, co-factors influencing the allergic reaction were more prevalent in elderly patients (76%). There was a strong relation of age and medication (80%). 32% of elderly patients reported of an occurrence of an allergic reaction to this elicitor before. Only xx % reported of a milder reaction, xx % with a similar or even more severe reaction. Most reactions occurred in private home (xx%) and outdoor locations (xx%).

**Elicitors**

The main cause for severe allergic reactions were insect venoms in 2987 (53%) of 5601 (78%) patients, followed by drugs (1227 (22%)) and food items (904 (16)). Insect venom anaphylaxis appeared slightly more prevalent in patients > 40 years (n= , xx%), with yellow jacket 2176 (overall n=2556) and bee stings 344 (overall n=564) responsible for the majority of cases. Drugs were across all ages > 18 a main causative agent of anaphylaxis, slightly more prevalent in elderly patients (24%). Analgesics [metamizole (n=xx, xx%), diclofenac (n=xx, xx%), ibuprofen (n=xx, xx%)] and antibiotics [penicillin (n=xx, xx%), cephalosporins (n=xx, xx%), gyrase inhibitors/ quinolones (n=xx, xx%)] were the most frequent elicitors of drug anaphylaxis. Cardiovascular drugs were primarily causative agent in patients > 65 years (3%). Foods were predominant elicitors in younger adults (26%), especially wheat (16%), in the elderly only 10% of reactions were caused by foods, here hazelnut is predominating elicitor reported (16%). Food items reported <10 times in the whole study are not listed in detail.

In elderly patients, only three cases (0,3%) of anaphylaxis are due to allergen specific immunotherapy (SIT) whereas in younger patients 27 cases (1,5%) are caused by SIT.

There is a slight shift of elicitors, predominating food items in younger adults to insect venoms and drug in elderly adults (figure 1).

In the group of 18-40 years only in 1658 (91%) the elicitor is known or suspected whereas in 95% it is known/suspected in adults (41-64) and elderly (> 65).

**Symptoms**

The following specific skin symptoms occurred similarly across all ages (overall percentages): angioedema (xx%), urticaria (xx%), pruritus (xx%), and erythema/flush (xx%,).

Gastrointestinal system was affected by xx% of the patients with vomiting (?) in younger adults and nausea (?) in elderly patients (figure 2, left panel). Respiratory system was involved in xx%, mainly as dyspnea (xx%), cough was more prevalent in younger adults (figure 2, middle panel). Cardiovascular symptoms occurred mainly in elderly patients, predominated by dizziness, hypotension, and collapse (figure 2, right panel). These symptoms were more common in reactions caused by drugs and insect stings. Cardiac arrest occurred in … cases, of these … cases in the elderly patients. In xx% Grade III and xx% grade IV anaphylaxis was registered, predominant in patients > 65 (xx% Grad III/IV reaction).

The time between occurring of first symptoms and allergen exposure usually was less than 10 minutes similarly across all ages (….%). Oder gibt es Unterschiede?! Delayed reactions were reported in xx% of patients, with a reaction onset of more than one hour after allergen exposure. Comparing groups of elicitors, this was mainly seen in food-induced anaphylaxis (?).

Biphasic reactions were in xx% of patients prevalent. gibt es Unterschiede in den Gruppen?! Auslöser?

**Emergency treatment**

First-line treatment was carried out by emergency physicians in xxx (xx%) of xxx patients, in xxx patients through lay- or self-administered drugs. The administration of epinephrine by professionals in elderly patients was 24% (across all severity grades) and hospital administration 59%, of whom 19 % were treated in intensive care unit (ICU) (table 3). Epinephrine by professionals was mainly applied intramusculary (xx%), in all groups. Further medical treatment by professionals included in all groups corticosteroids (xx%), antihistamines (xx%) and beta-2-agonists (xx%).

Xxx patients carried out emergency treatment by a lay person (self-treated xx% and other lay person xx%). The adrenaline auto-injector was more often used by patients aged xxx (xx%) and by lay persons (mostly family members, colleagues) in patient group xxx (xx%). Xx% of patients with an adrenaline auto-injector prescription failed to use it because of not carrying it with them or not applying it. gibt es Unterschiede in den Gruppen?! Unterschiede in prescriptions of auto-injector? Vllt ältere Patienten seltener Adrenalin-Pen?

**Fatal reactions**

12 patients experienced a fatal anaphylactic reaction, xx of them in the patient group 41-64 years, only xx were older than 64 years. Most frequently reported elicitor was insect venom and analgesics (table 4). In xx patients it was a repeated reaction to the same allergen, usually with milder symptoms (ist doch wahrscheinlich so?). In xx patients first treatment was carried out by a lay person. A second dose adrenaline was applied in xx patients. Co-diseases included among others mastocytosis (n=x), atopic diseases (n=x) and maligne disease (n=x).

**Discussion**

**Key results**

This is the first large-scale description of anaphylaxis in patients 65 years old or older, with 1165 patients. The European anaphylaxis registry covers a heterogonic sample of patients across all age groups, a wide range of elicitors and various symptom severities. Although the group of elderly patients have been described as group with more cardiovascular diseases and more co-medication [Lieberman P, Simons FE. Anaphylaxis and cardiovascular disease: therapeutic dilemmas. Clin Exp Allergy. 2015 Aug;45(8):1288-95.], the use of adrenaline in patients aged 65 years or older is higher than in patients 18 to 64 years.

Elicitors – younger adults food items more prevalent than in elderly patients. Drugs are frequent elicitors in the elderly probably due to higher consumption. Usually drugs are reported to be the most common cause of fatal reactions [Jerschow E, Lin RY, Scaperotti MM, McGinn AP. Fatal anaphylaxis in the United States, 1999-2010: temporal patterns and demographic associations. J Allergy Clin Immunol. 2014 Dec;134(6):1318-1328.e7.], in our study insect venoms are much more frequent as cause for fatal reactions. But the fatality rates reported in our data do not represent actual fatality rates.

Cardiovascular symptoms appeared more frequently in elderly patients, mostly with dizziness, hypotension, and collapse. Cyanosis, syncope and dizziness are highly predictive for shock development [Park HJ, Kim SH. Factors associated with shock in anaphylaxis. Am J Emerg Med. 2012 Nov;30(9):1674-8.], and thus need a fast adequate treatment. Most patients (xx%) with cardiovascular symptoms presented with hypotension. In the literature, this is associated with a biphasic course of anaphylaxis [Simons FE, Ebisawa M, Sanchez-Borges M, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organ J. 2015 Oct 28;8(1):32.] also shown in our data.

Professional first aid treatment – adrenaline

Treatment by lay person

Prescription of adrenalin auto-injector

**Strength and limitations**

Usually, more severe and fatal reactions are reported in older patients [Clark S, Wei W, Rudders SA, Camargo CA Jr. Risk factors for severe anaphylaxis in patients receiving anaphylaxis treatment in US emergency departments and hospitals. J Allergy Clin Immunol. 2014 Nov;134(5):1125-30.], this is not represented in our data, the reported fatalities in our data is not an estimated fatality rate since not all fatal reactions are reported to an allergy tertiary center. The actual fatality rate is probably higher. In general, those data not reflect the general population measures of frequency cannot be estimated from this registry.

A quantitative comparison is not possible due to different participation of countries/regions/centers.

**Conclusion**

In this large scale-description of anaphylaxis in patients aged 65 years and older, we report about typical age-dependent elicitors, comorbidities, symptoms and emergency treatment. This study is one of the first major analysis exploring data concerning with anaphylaxis in patients older 65 years and can serve as base for further investigations in this patient group, especially in an aging population. The data confirms adrenaline as treatment of choice in anaphylaxis even in patients with CVD, there are no contraindications for its use.

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**Tables**

**Table 1: Baseline characteristics.** In total 7.224 cases were analyzable until April 2016, 1623 (22%) were <18 years old and 5.601 (78%) were ≥18 years old.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Young adults** | **Adults** | **Elderly** | **All adults** |  |
|  | **18-40 y**  **n (%)** | **41-64 y**  **n (%)** | **≥ 65 y**  **n (%)** | **≥ 18 y**  **n (%)** | ***Chi² test*** |
| **Total** | **1809 (25)** | **2856 (40)** | **936 (13)** | **5604 (78)** |  |
| Age in years±SD | 30±6.6 | 52±6.8 | 71±4.6 | 48±15.5 |  |
| Female | **1138 (63)** | 1630 (57) | 524 (56) | 3292 (59) | *p<0.001* |
| **Co-morbidities** | | | | |  |
| Atopic disease | **607 (36)** | 681 (25) | 167 (19) | 1455 (28) | *p<0.001* |
| Cardiovascular disease | 75 (4) | **726 (27)** | **538 (60)** | 1339 (25) | *p<0.001* |
| Mastocytosis | 27 (2) | **93 (3)** | **37 (4)** | 157 (3) | *p<0.001* |
| Thyroid disease | 112 (7) | 319 (12) | **151 (17)** | 582 (11) | *p<0.001* |
| **Cofactors** | | | | |  |
| involved in general | 785 (58) | 1535 (65) | **651 (76)** | 2971 (53) | *p<0.001* |
| drugs | 95 (13) | 726 (50) | **510 (80)** | 1331 (24) | *p<0.001* |
| Physical exercise | 513 (70) | 778 (55) | 230 (40) | 1521 (27) | *NS* |
| Psychological stress | 138 (18) | 192 (13) | 55 (8) | 385 (7) | *NS* |
| Alcohol | 91 (16) | 127 (11) | 35 (6) | 253 (5) | *NS* |
| Mensis | **49 (23)** | 22 (5) | 0 (0) | 71 (1.3) | *p<0.001* |
| Acute Infection | **75 (10)** | 69 (5) | 22 (3) | 166 (3) | *p=0.001* |
| **Repeated reaction** | | | | |  |
| yes | 534 (33) | 821 (32) | 259 (32) | 1614 (29) | *NS* |

**Table 2: Specific elicitor by age group.**   
The elicitor was not specified in 352 (6%) patients. Rare elicitors are not reported in detail.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Young adults** | **Adults** | **Elderly** | **All adults** |  |
|  | **18-40 y**  **n (%)** | **41-64 y**  **n (%)** | **≥ 65 y**  **n (%)** | **≥ 18 y**  **n (%)** | ***Chi² test*** |
| **Total** | 1809 (25) | 2856 (40) | 936 (13) | 5601 (78) |  |
| Elicitor known | **1198 (66)** | 2134 (75) | 711 (76) | 4043 (72) | *p<0.001* |
| Elicitor suspected | **460 (25)** | 567 (20) | 179 (19) | 1206 (22) | *p<0.001* |
| **Drugs** | 375 (21) | 625 (22) | 227 (24) | 1227 (22) | *NS* |
| analgesics | 144 (38) | 254 (41) | 86 (38) | 484 (39) | *NS* |
| antibiotics | 97 (26) | 137 (22) | 46 (20) | 280 (23) | *NS* |
| Local anesthetics | 38 (10) | 65 (10) | 20 (9) | 123 (10) | *NS* |
| x-ray (contrast agent) | 12 (3) | 31 (5) | 19 (8) | 62 (5) | *NS* |
| PPI | 15 (4) | 14 (2) | 7 (3) | 36 (3) | *NS* |
| Cardiovascular drugs | 1 (0.3) | 5 (0.8) | **7 (3)** | 13 (1.1) | *p=0.005* |
| **Insects** | **756 (42)** | 1672 (59) | 559 (60) | 2987 (53) | *p<0.001* |
| Yellow jacket | 523 (69) | 1248 (75) | 405 (72) | 2176 (73) | *NS* |
| Bee | 179 (24) | 266 (16) | 88 (16) | 533 (18) | *NS* |
| Hornet | 30 (4) | 83 (5) | 37 (7) | 150 (5) | *NS* |
| **Food** | **468 (26)** | 343 (12) | 93 (10) | 904 (16) | *p<0.001* |
| wheat | 76 (16) | 57 (17) | 13 (14) | 146 (16) | *NS* |
| hazelnut | 37 (8) | 28 (8) | **15 (16)** | 80 (9) | *p=0.009* |
| soy | 28 (6) | 41 (12) | 5 (5) | 74 (8) | *NS* |
| celery | 27 (6) | 29 (8) | 7 (8) | 63 (7) | *NS* |
| shellfish | 33 (7) | 23 (7) | 6 (6) | 62 (7) | *NS* |
| peanut | 33 (7) | 13 (4) | 1 (1) | 47 (5) | *NS* |
| **Immunotherapy (SIT)** | 27 (1.5) | 25 (0.9) | 3 (0.3) | 55 (1.0) | *NS* |

**Table 3: First line treatment by professionals depending on severity grade according to Ring&Messmer.**YA – young adults, A – adults, E – Elderly

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | I | | | II | | | III | | | IV | | | Total | | |
|  | YA,  18-40 y | A,  41-64 y | E,  > 65 y | YA,  18-40 y | A,  41-64 y | E,  > 65 y | YA,  18-40 y | A,  41-64 y | E,  > 65 y | YA,  18-40 y | A,  41-64 y | E,  > 65 y | YA,  18-40 y | A, 41-64 y | E,  > 65 y |
|  | n=121 | n=163 | n=57 | n=1138 | n=1603 | n=449 | n=523 | n=997 | n=394 | n=27 | n=93 | n=36 | n=1809 | n=2856 | n=936 |
| First line Treatment | 84 (70)) | 105 (64)) | 34  (60)) | 859 (75)) | 1229 (77)) | 354  (79)) | 397 (76)) | 831 (83)) | 328  (83)) | 25  (93)) | 86  (92)) | 35  (97)) | 1501 (83)) | 2429 (85)) | 792  (84)) |
| Epinephrine | 2  (4)) | 4  (6)) | 0 | 81  (14)) | 113 (14)) | 46 (19)) | 55 (19)) | **147 (28))\*** | **51 (26))\*** | 13  (72)) | 41  (64)) | 19  (79)) | 151 (16)) | 305 (21)) | **116 (24))\*\*\*** |
| Corticosteroids | 49 (88)) | 63 (88)) | 19 (79)) | 528 (89)) | 719 (91)) | 209 (87)) | 248 (87)) | 476 (92)) | 182 (94)) | 15  (83)) | 52 (81)) | 18  (75)) | 840 (88)) | 1310 (90)) | 428 (89)) |
| Antihistamines | 45 (80)) | 57 (79)) | 21 (88)) | 495 (83)) | 655 (83)) | 189 (79)) | 240 (85)) | 430 (83)) | 166 (86)) | 12  (67)) | 45  (70)) | 18  (75)) | 792 (83)) | 1187 (82)) | 294 (82)) |
| Admitted to hospital | 21 (40)) | 20 (28)) | 7 (30)) | 193 (48)) | 226 (14)) | 81 (53)) | 97 (55)) | 203 (66)) | 77 (70)) | 6  (67)) | 232 (91)) | 13  (93)) | 317 (50)) | 481 (52)) | **178 (59))\*** |
| Intensive Care Unit | 4  (7)) | 3  (4)) | 0 | 28  (7)) | 50 (10)) | 17 (11)) | 27 (16)) | 61 (21)) | 25 (24)) | 4  (44)) | **29 (94))\*\*\*** | **13 (93))\*\*\*** | 63 (10)) | 143 (16)) | **55 (19))\*\*\*** |
| Chi² test; p-values calculated for the 3 patient groups in the same severity grade, \* p<0.05, \*\* p<0.01, \*\*\* p<0.001 | | | | | | | | | | | | | | | |

Tab 4: Fatal reactions (n=7) in order of increasing age. All grade IV according to Ring and Messmer severity grading

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Year of reaction** | **Age** | **Sex** | **Elicitor** | **Repeated reaction** | **Interval** | **Co-Factors** | **Codisease** | **Therapy** | **2nd dose adrenalin** |
| 2010 | 81 | F | Analgesics (metamizole) | Yes | n.a. | stress | maligne disease | Clinic, adrenalin i.v., corticosteroid i.v., AH i.v., O2, volume | unknown |
| 2016 | 53 | M | Bee | Yes | n.a. | Exercise (moderate) | asthma | Lay person +emergency doctor, AAI, adrenalin i.m., AH i.v., corticosteroid i.v., volume | yes |
| 2014 | 50 | M | Bee | unknown | n.a. | Exercise (mild),  concomitant drugs unknown | CVD | No treatment | no |
| 2012 | 49 | M | Yellow jacket | Yes | 0-10 min | Exercise (mild) | mastocytosis | Lay person +emergency doctor, AAI, adrenalin i.v., other drugs not specified, reanimation | yes |
| 2010 | 47 | M | Yellow jacket | No | n.a. |  |  | Emergency doctor, adrenalin i.v., AH i.v., corticosteroid i.v., O2,volume, reanimation | unknown |
| 2007 | 44 | M | Yellow jacket | Yes | n.a. | stress | mastocytosis | Clinic, adrenalin i.v., AH i.v., corticosteroid i.v., volume, reanimation | unknown |
| 2014 | 35 | F | Analgesics (metamizole) | unknown | 11-30 min | thyroxin | asthma, thyroid disease | Clinic, adrenalin i.v., corticosteroid i.v., O2 | yes |

**Figure Legends**

**Registered cases between   
July 2007 and March 2017**

**n = 10.000**

**Cases categorized according to Ring&Messmer’s  
 severity grading system**

**n = 9.758**

**children&adolescent**

**n = 2622 (27%)**

**adults ≥18 years**

**n = 7136 (73%)**

**Elderly**

**≥64 y**

**n = 1165 (12%)**

**Adults**

**41-64 y**

**n = 3611 (37%)**

**Young adults**

**18-40 y**

**n = 2360 (24%)**

**Figure 1: Flow chart of study cohort**

Note method part statistics:

*Chi² test for overall analysis with further testing. Multiple test correction with Bonferroni with cellwise residue analysis.*

