

ORIGINAL ARTICLE

ANAPHYLAXIS

Anaphylaxis in an emergency setting – elicitors, therapy and incidence of severe allergic reactions

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Abstract

Background: Anaphylaxis is a severe potentially life-threatening hypersensitivity reaction with an estimated lifetime prevalence of 0.5–2.0%. The prevalence and incidence of anaphylactic reactions in Germany are unknown. We therefore assessed anaphylactic patients seen by emergency physicians in the Berlin area covering 4 million people.

Methods: A standardised questionnaire was filled from 2008 to 2010 by the emergency physicians.

Results: A total of 333 cases of anaphylaxis were reported. 295 of these met the inclusion criteria for severity and were analysed. 13.9% ($n = 41$) were reactions with respiratory symptoms, 25.4% ($n = 75$) with cardiovascular, and in 60.7% ($n = 179$) of cases, respiratory and cardiovascular symptoms were reported. Two reactions were fatal. The most common elicitors were food products (32.2%), drugs (29.2%) and insect venom (19.3%). The most frequently given drugs were corticoids and antihistamines, but not adrenaline. For 2008, the calculated incidence was 4.5 per 100 000.

Conclusions: Our data show that food products are frequent elicitors of severe allergic reactions in the general population including children and adults. It unravels a strong underuse of adrenaline by emergency physicians, not reflecting treatment protocols according to the current guidelines. As data obtained from allergists reveal a different rank order of elicitors, this study suggests that food-allergic adult patients may present a risk population and should receive more attention by allergists.

The nomenclature for the term ‘anaphylaxis’, revised in 2003, is applied to a severe generalised life-threatening hypersensitivity reaction (1, 2). Criteria to define a hypersensitivity have been determined (3, 4). The severity of a reaction is related to the organ system involved. In German-speaking countries, the classification by Ring and Messmer is often used to indicate severity of hypersensitivity (5). Until to date, the documentation of allergic reactions using the International Classification of Diseases (ICD) has led to inconsistent recording (6–8), hampering the determination of prevalence and incidence of severe allergic reactions. However, several studies calculated the prevalence of anaphylaxis using approaches such as the analysis of data from national registers, ICD codes from emergency departments or the numbers of prescribed adrenaline autoinjectors (6, 7, 9–18).

A previous systematic review conducted by Lieberman et al. estimated a lifetime prevalence of anaphylaxis of about

0.5–2.0% (19). Data from Switzerland and the UK calculated an annual prevalence of 7.9–9.6 per 100 000 and a lifetime prevalence of 0.07%, respectively. Mäkinen-Kiljunen and Haahtela from Finland stated an annual frequency of severe allergic reactions with 0.001% (13, 20, 21).

Data regarding the frequency of anaphylaxis in Germany are not available. The German-speaking anaphylaxis registry, a network on a voluntary basis between allergy units, collects data using an online questionnaire. From July 2007 to August 2011, a total of 3239 cases were reported in the registry (22). Due to the procedure of data collection (not all medical facilities are included and not all patients undergo further diagnostic investigations), a calculation of incidence based on data from the registry is limited.

The aim of this study was to obtain data from emergency physicians who treat anaphylactic patients first line. A standardised short questionnaire was used to gather detailed

information on the symptoms of severe allergic reactions, the proposed elicitors and the emergency treatment given. Our data support an estimation of the annual rate of anaphylaxis in a community of about four million people.

Methods

The questionnaire-based survey was initiated in December 2007. Cases reported from January 2008 to December 2010 were analysed. A total of 18 emergency physician bases were informed during a kick-off meeting and equipped with the standardised form for all patients experiencing a severe allergic reaction. These bases cover all emergencies called via 112 occurring in the area of Berlin 24 h a day. Cases reported from January 2008 to December 2010 were analysed.

The questionnaire is a short, clearly arranged and comprehensible one-page form. The provided information covers sex, age, symptoms, the reaction site, the outcome, the eliciting factors and the applied drugs.

Severity classification was based on the onset of respiratory and cardiovascular symptoms. Reactions involving either severe respiratory (dyspnoea, stridor, apnoea) or severe cardiovascular symptoms (decreased alertness, tachycardia, decrease in blood pressure, loss of consciousness, collapse, cardiac arrest) were classified as level 1 and level 2 reactions, respectively. Reactions with respiratory and cardiovascular symptoms simultaneously were classified as level 3 reactions. Concomitant cutaneous and/or gastrointestinal symptoms were registered as well. Reactions with skin manifestations only were not included into the analysis for they are not considered to resemble severe anaphylaxis.

The assessment of complete symptom details enabled us to apply different classification systems of Muraro et al. and Ring and Messmer in addition to our approach performing a sensitivity analysis.

The incidence of severe allergic reactions was calculated for the population of Berlin where this study was performed. The period-based population for the years 2008–2010 was provided by the State Statistical Institute Berlin-Brandenburg (23).

To support and encourage participation, a newsletter containing information on the current progress of the project was sent out every 3 months to the emergency doctors.

Results

Adults are frequently seen by emergency physicians

From January 2008 to December 2010, 333 cases were reported. Thirty-eight of these reported skin symptoms only and were not included into the further analysis. A total of 269 (91.2%) adults with a mean age of 51.0 years (SD 16.9) and 26 (8.8%) children and young adolescents with a mean age of 9.4 years (SD 5.6) required immediate emergency treatment. Forty-one (13.9%) of the 295 analysed reactions were level 1 reactions. Seventy-five reactions (25.4%) were level 2 and 179 reactions (60.7%) potentially life threatening with the onset

of respiratory and cardiovascular symptoms. Of these, 11 patients had a cardiac arrest with two being fatal.

Food is the most frequent elicitor of severe allergic reactions when reported by emergency physicians

The profile of elicitors varied in an age-dependent manner. The most common allergens in children and young adults were food products (46.2%). In adults, drugs and foods were frequent elicitors of severe allergic reactions (31.2% and 30.9%). Insect venom was a common elicitor in adults (20.4%), but less common in children (7.7%). The rate of reactions where the allergen was unknown was 9.3% in adults and 7.7% in children. Specific immunotherapy (SIT) was reported as a common elicitor of severe allergic reactions in individuals below 18 years of age. 26.8% of reactions in children and adolescents compared with 2.6% of reactions in adults were reported in the context of SIT (Fig. 1).

Among 95 cases in which food products have been suspected to be the elicitor of anaphylaxis, the most common allergens were tree nuts ($n = 20$; most common: almonds, $n = 5$) and animal products ($n = 15$; most common: fish, $n = 4$). Five of twelve reactions (41.7%) in children and young adolescents were triggered by animal products, and 4/12 reactions were triggered by tree nuts (33.3%). In adults, 16 of the 83 reported reactions (19.3%) were elicited by the ingestion of tree nuts and 10 (12.0%) by animal products. Fruit and vegetables were elicitors in 9 (9.5%) and 8 (6.3%) reactions, respectively. Twenty-four (25.3%) reactions were suspected to be induced by an unknown food-related trigger (ingestion of several items at the same time).

Drugs were suspected in 86 cases as an elicitor of anaphylactic reactions; 97.7% ($n = 84$) of these occurred in adults.

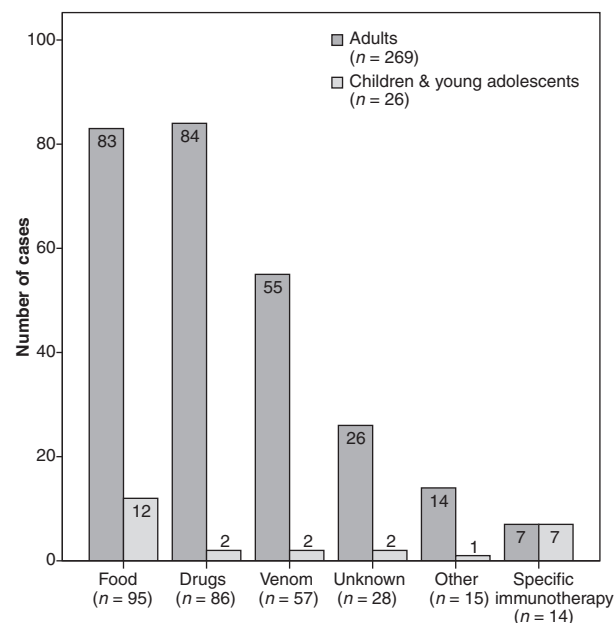


Figure 1 Elicitors of anaphylaxis in adults and children and young adolescents reported by emergency physicians ($n = 295$).

The most common drugs were analgetics ($n = 40$, 48.2%); among these were non-steroidal antiphlogistics (NSAID) ($n = 24$, 60.0%) in general and metamizol in particular ($n = 10$, 25.0%). Antibiotics were suspected as a cause of severe allergic reactions in 18 cases (21.4%). Among these, the group of fluoroquinolones were most common ($n = 10$, 55.6%). Two paediatric cases (2.3%) were related to an antibiotic (cephalosporine) in one case and to an analgetic (ibuprofen) in the other case.

A total of 57 cases were venom-induced and occurred mostly in adults ($n = 55$, 96.5%). Two cases (3.5%) were observed in children and adolescents. The most common suspected insect was wasp ($n = 46$, 80.7%), but also venom of hornet ($n = 5$, 8.8%) and even one case of a biting housefly ($n = 1$, 1.8%) were documented. In five cases (8.8%), the eliciting insect was unknown.

Skin manifestation and hypotension are leading symptoms

A total of 254 reactions (86.1%) involved symptoms of the cardiovascular system, tachycardia and hypotension being the most often reported with 144 (56.7%) and 120 (47.2%), respectively. Hypotension occurred more frequently in adults (48.9%) than in children and adolescents (28.5%). Concomitant symptoms of the skin and mucosal tissue were documented in 240 reactions (81.4%) with generalised erythema (53.7%) and angiooedema (45.8%) being the most frequent cutaneous symptoms besides respiratory and/or cardiovascular symptoms. Interestingly, symptoms like generalised pruritus and urticaria were more often reported in

children and young adults. Respiratory symptoms were present in 220 reactions (74.6%); dyspnoea was the most common single respiratory tract symptom (89.1%). Apnoea was reported in eleven cases; among these, only adults were affected. Gastrointestinal symptoms were reported in 31.5% of cases with nausea being the most frequent symptom (80.6%). Vomiting and diarrhoea occurred more frequently in children and young adults (62.5% and 25.0%) (Table 1).

Treatment

The analysis of the given medication was assessed with respect to the German guideline for the treatment of anaphylaxis (5). Independent from the severity of the reaction, glucocorticosteroids (GC) were applied most often. A total of 285 (96.6%) of the 295 patients received GCs. Also, antihistamines were given frequently (82.0% of cases).

However, adrenaline which is the first-choice drug in anaphylaxis according to the guidelines worldwide (WAO) and also according to the European guidelines (24) was applied in 67 (22.7%) of the 295 cases. 9.8% of patients with a level 1 and 13.3% of patients with a level 2 reaction received adrenaline. 29.6% of patients experiencing a level 3 reaction received adrenaline, and in one of these reactions, noradrenaline was applied additionally to adrenaline. Two reactions were nonetheless fatal. Also, additional drugs (metoclopramide, midazolam, propofol) and fluid support were most frequently given in level 3 reactions. In cases where other drugs were applied, H₂-antihistamines (e.g. cimetidine, ranitidine) were most frequently used (24 of 295 reactions, 8.1%),

Table 1 Symptoms stratified to organ systems (skin, gastrointestinal tract, respiratory and cardiovascular system) by age group (several answers possible, $n = 295$)

Symptoms	Adults ($n = 269$) n (%)	Children and young adults ($n = 26$) n (%)	Total ($n = 295$) n (%)
Skin and mucosa	218 (81.0)	22 (84.6)	241 (81.7)
Generalised erythema	116 (53.2)	13 (59.1)	129 (53.7)
Angiooedema	102 (46.8)	8 (36.4)	110 (45.8)
Generalised pruritus	80 (36.7)	10 (45.5)	90 (37.5)
flush	64 (29.4)	4 (18.2)	68 (28.3)
Generalised urticaria	53 (24.3)	10 (45.5)	63 (26.3)
Respiratory tract	199 (74.0)	21 (80.8)	220 (74.6)
Dyspnoea	178 (89.4)	18 (85.7)	196 (89.1)
Wheezing	57 (28.6)	9 (42.9)	66 (30.0)
Apnoea	11 (5.5)	0 (0.0)	11 (5.0)
Cardiovascular system	233 (86.6)	21 (80.8)	254 (86.1)
Tachycardia	132 (56.7)	12 (57.1)	144 (56.7)
Hypotension	114 (48.9)	6 (28.6)	120 (47.2)
Vertigo	100 (42.9)	6 (28.6)	106 (41.7)
Drop in vigilance	47 (20.2)	5 (23.8)	52 (20.5)
Fainting	40 (17.2)	3 (14.3)	43 (16.9)
Circulatory arrest	9 (3.9)	0 (0.0)	9 (3.5)
Gastrointestinal tract	85 (31.6)	8 (30.8)	93 (31.5)
Nausea	69 (81.2)	6 (75.0)	75 (80.6)
Vomitus	30 (35.3)	5 (62.5)	35 (37.6)
Abdominal pain	19 (22.4)	1 (12.5)	20 (21.5)
Diarrhea	9 (10.6)	2 (25.0)	11 (11.8)

Table 2 Applied drugs by severity of reaction and in comparison using the classifications systems of this study, of Ring and Messmer and Muraro et al. [4, 23]

	Classification of this study			Ring and Messmer				Muraro et al.			Total (n = 295)
	Level 1 (n = 41)	Level 2 (n = 75)	Level 3 (n = 179*)	Grade II (n = 42)	Grade III (n = 242)	Grade IV (n = 11)	Grade 1 (n = 24)	Grade 2 (n = 133)	Grade 3 (n = 138)		
Adrenaline (n = 67)	4 (9.8%)	10 (13.3%)	53 (29.6%)	4 (9.5%)	54 (22.3%)	9 (81.8%)	2 (8.3%)	23 (17.3%)	42 (30.4%)	67 (22.7%)	
Antihistamines (n = 242)	35 (85.4%)	61 (81.3%)	146 (81.6%)	35 (83.3%)	199 (82.2%)	8 (72.7%)	20 (83.3%)	110 (82.7%)	112 (81.2%)	242 (82.0%)	
Corticosteroids (n = 285)	40 (97.6%)	69 (92.0%)	176 (98.3%)	41 (97.6%)	233 (96.3%)	11 (100.0%)	22 (91.6%)	130 (97.7%)	133 (96.4%)	285 (96.6%)	
Fluid support (n = 214)	11 (26.8%)	58 (77.3%)	145 (81.0%)	17 (40.5%)	186 (76.9%)	11 (100.0%)	16 (66.6%)	72 (54.1%)	126 (91.3%)	214 (72.5%)	
Other (n = 61)	6 (14.6%)	13 (17.3%)	42 (23.5%)	6 (14.3%)	51 (21.1%)	4 (36.4%)	2 (8.3%)	21 (15.8%)	38 (27.5%)	61 (20.7%)	

Level 1 = only respiratory symptoms.

Level 2 = only cardiovascular symptoms.

Level 3 = respiratory + cardiovascular symptoms.

*Cardiac arrest = 11 patients.

followed by antiemetics (e.g. metoclopramide, ondansetron) in 14 cases (4.7%).

The proportion of applied drugs according to severity of reactions using the classification systems by Ring/Messmer and Muraro is comparable although the number of reactions within the different grades of severity differ (Table 2).

Estimated frequency rates of anaphylaxis

Based on the data obtained, we wished to calculate the incidence of anaphylaxis although limitations are present due to the design of the study. The calculation revealed a higher rate in 2008, with 4.5 per 100 000 people experiencing a severe allergic reaction, which was slightly lower in 2009 and 2010. The overall rates were in a comparable range during these 2 years of the study. Approximately, 2.5 persons per 100 000 inhabitants experienced a severe anaphylactic reaction for the first time in 2008 (Table 3).

Discussion

The most common elicitor group of anaphylactic reactions requiring emergency physicians' treatment are food products, followed by drugs and insect venom. Regarding the emergency treatment of severe anaphylaxis, adrenaline is underused (22.7% in 295 cases of severe reactions). The incidence of severe anaphylaxis in a large urban area (approx. 3.5 million people) was 4.5 per 100 000 people in 2008.

In our study, the majority of reported cases were adults. Among the adults, (61.3%, $n = 269$) women dominated while in children and adolescents, the majority of patients were male (73.1%, $n = 26$). The finding that a high proportion of adults who experience an anaphylactic reaction are women is supported by other studies (10, 20, 25).

The most common suspected elicitors were food ($n = 95$), drugs ($n = 86$) and insect venom ($n = 57$). In children and adolescents, food products were the leading proposed elicitor. These findings correspond with observations from other studies (3, 25, 26). Interestingly, the most common elicitors seen in adults were also food products and drugs while data from the anaphylaxis registry show that 50% of registered cases are venom, 24% food-induced and 17% were caused by drugs (27). One reason for this discrepancy might be that the majority of patients with food allergy may not present themselves in a specialised allergy centre for further diagnostics as until to date no specific treatment can be offered. Furthermore, the elicitors were recorded by the emergency doctors at the site of reaction without any further diagnostics like specific IgE measurement, skin testing or food challenges. Therefore, these data, especially the food data, should be regarded with caution.

Drugs are another important group among elicitors of anaphylaxis and accounted for 29.2% of the cases in this study. Not only analgetics (47.7%), especially NSAR, but also antibiotics (22.1%) were the most common suspected drugs eliciting a severe reaction. This finding has been reported by others previously (8, 13, 26). However, the relative frequency of the responsible substance varies. Moneret-Vautrin et al.

Table 3 Incidence of anaphylactic reactions in Berlin, Germany [95% confidence interval (CI)]

Year	Population of Berlin	Total cases of anaphylaxis/occurrence for the first time	Calculated Incidence (per 100 000 people)	First onset (per 100 000 people)
2008	3 431 675	155/87	4.5 (CI 3.8–5.3)	2.5 (CI 2.0–3.1)
2009	3 442 675	56/34	1.6 (CI 1.2–2.1)	1.0 (CI 0.7–1.4)
2010	3 460 725	75/45	2.1 (CI 1.7–2.7)	1.3 (CI 1.0–1.7)

identified antibiotics as being the most common eliciting drug in 100 drug-related cases registered by the French Allergy Vigilance Network (26). By contrast, Helbling and Smit (8, 13) likewise in this study identified analgetics as the most common elicitor group in patients requiring an emergency physician.

The venom of hymenoptera are well-known elicitors of severe allergic reactions. The finding of biting housefly (diptera) as an elicitor of a severe reaction has not been reported although anaphylactic reactions to other diptera bites (saliva of mosquitos) have been described (27–29).

The high proportion of anaphylactic reactions during specific immunotherapy, especially in children, might be explained by a higher prevalence of asthma in children, which is an important co-factor for anaphylaxis but also the onset of severe adverse reaction during SIT (30, 31).

According to the WAO guidelines, anaphylaxis should be treated with adrenaline first and second line with antihistamines, beta-2 adrenergic agonists and corticoids. Adrenaline is important because of its alpha-1, beta-1 and beta-2 adrenergic action resulting in an increase in vasoconstriction on most body organ systems, a decrease in mucosal oedema in the airways, bronchodilation, an increase in the heart rate and a decrease in mediator release (2). The data about the first-line treatment indicate a clear discrepancy between current guidelines and real life (12, 32). Adrenaline as the drug of first choice was given in 22.7% of 295 cases only. However, regardless which severity grading system was used, adrenaline was given more frequently in severest cases. In particular, this group of the most severe potentially life-threatening group was best reflected in the Ring and Messmer classification as the drugs given in this group were as recommended. However, given the fact that previous data indicated that an early use of adrenaline can support the positive outcome of a severe allergic reaction (33–35), more data are urgently needed to clarify these findings better, in particular for a European cohort where emergency medicine is largely available for the general population (36).

The calculated frequency of severe allergic reactions of 4.5 per 100 000 people is comparable with findings from other studies (13, 15). However, the slightly lower rates in 2009 and 2010 indicate an annual variance. Factors accounting for this variance are so far not well understood; one explanation might be that the allergenic exposure (e.g. pollen) was higher in 2008 than in 2009 and 2010 in Germany.

The classification of reactions according to symptoms was not performed by the emergency physicians. Therefore, it is possible that the clinical presentation of some of the reac-

tions were not regarded as severe as judged by the emergency physician although proposed by the classification system. This might be an explanation for the underrepresented use of adrenaline and indicates the necessity of a simple, but uniquely used classification system.

Anaphylactic reactions that took place directly in a hospital and cases where patients presented themselves in an emergency room or in a doctor's office without alerting an emergency physician were not covered in this study, therefore potentially leading to an underestimation of incidence rate. The study was designed to catch all emergency physicians called via 112 within the Berlin area; however if patients do not call 112 and go directly to the emergency room, they would not be covered by this survey. The representativeness of this sample is therefore limited. In addition, it cannot be ascertained that all anaphylactic reactions treated by an emergency physician were reported. The determined incidence should therefore be perceived critically.

Conclusion

Taken together, our data reveal an incidence rate of anaphylaxis, which is comparable with those of other European countries. The elicitor profile indicates a high proportion of food-related cases, suggesting a need for better referral practices to specialised allergy clinics but also improvement regarding diagnostic and therapeutic measurements. The very low frequency of adrenaline use in severe anaphylaxis unravels the need to implement existing management guidelines to physicians treating patients with anaphylaxis.

Authors' contributions

M. Worm designed the study. The data were collected by K. Beyer and O. Eckermann. S. Hompes monitored data collection. K. Beyer analysed the data and created the figures. Data evaluation was done by L. Grabenhenrich. K. Beyer wrote the first draft of the article. K. Beyer and M. Worm interpreted the data and drafted the article. The manuscript was revised by O. Eckermann, S. Hompes and L. Grabenhenrich. All authors approved the final report.

Conflict of interest

M. Worm has received consultancy fees from Allergopharma, ALK-Abello and Meda. The other authors declare that they have no competing interests.

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