ORIGINAL RESEARCH

Treatment and Outcome of Anaphylactic Reactions in Emergency Medical Services of Dresden/Germany: A 5-Year Analysis

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Abbreviations:
AMWF: Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. [Association of the Scientific Medical Societies]
EAACI: European Academy of Allergy and Clinical Immunology
H1: Histamine-H1
H2: Histamine-H2
ICD: International Classification of Diseases

Abstract

Introduction: Anaphylactic reactions can lead to life-threatening situations. Therefore, a rapid diagnosis and therapy are indicated. Various guidelines recommend immediate treatment with intramuscular adrenaline in severe anaphylaxis. Based on study data from different countries, it has been shown that therapy of anaphylaxis is often not carried out according to existing guidelines.

Study Objective: The aim of the study was an analysis of the emergency treatment and outcome of anaphylaxis in children and adults according to its severity. Focus was placed on the recommended first-line therapy with adrenaline in cases of severe reactions. Further demographic data, triggers, symptoms, and hospitalization rates of anaphylaxis were analyzed.

Methods: Data from Emergency Medical Services from Dresden/Germany in cases of anaphylaxis from the start of 2012 through the end of 2016 were retrospectively analyzed. The data of the air rescue were not considered. The severity of the anaphylaxis, the therapy, the further monitoring, and the outcome were analyzed.

Results: A total of 1,131 adults and 223 children with anaphylactic reactions (Grade I-IV) were analyzed. Overall, 591 adults and 102 children showed a severe anaphylaxis. The most common trigger for severe anaphylactic reactions was food in children (61%) and medication in adults (33%). Seven percent of adults and eight percent of children with Grade II or higher anaphylactic reactions received adrenaline. There is a significant correlation between adrenaline therapy and improved condition/outcome in adults and children. Sixty-six percent of adults and 83% of children with severe anaphylaxis were hospitalized. Twenty-one percent of the adults and 13% of the children did not receive further medical observation despite a severe reaction.

Conclusion: The guideline-compliant first-line therapy with adrenaline was not carried out in the majority of the cases analyzed. However, the study shows that treatment with adrenaline for anaphylaxis leads to a significant improvement in the patients' condition.

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Introduction

Anaphylactic reactions are potentially life-threatening, acute systemic reactions caused by an immediate-type allergic response. Anaphylactic reactions are mostly of acute onset and can progress rapidly. Anaphylaxis may cause dermatologic, gastrointestinal, pulmonary, and/or cardiovascular symptoms of varying severity. There is no internationally standardized

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	Symptoms of Anaphylactic Reactions			
Grade	***Skin***	***Gastrointestinal***	***Respiratory***	***Cardiovascular***
I	Flush, Itch, Urticaria, Angioedema	–	–	–
II	Flush, Itch, Urticaria, Angioedema	Nausea, Cramps	Rhinorrhea, Dyspnea, Hoarseness	Tachycardia
III	Flush, Itch, Urticaria, Angioedema	Vomitus, Defecation	Laryngeal Edema, Bronchospasm, Cyanosis	Shock, RR_{syst}-Changes > 20 mmHg
IV	Flush, Itch, Urticaria, Angioedema	Vomitus, Defecation	Respiratory Arrest	Cardiac Arrest

Table 1. Severity Grading of Anaphylaxis According to the Classification of Ring and Messmer

definition of anaphylaxis. Based on symptoms and severity, anaphylaxis can be classified into severity Grades I to IV according to the classification of Ring and Messmer (Table 1).[1] This classification is commonly used in German-speaking countries. In some cases, contact with the allergen leads only to mild allergic symptoms such as erythema. However, anaphylaxis can also lead to more severe symptoms (Grades II-IV), and in the worst case, to cardiopulmonary arrest. There is a smooth transition between the different grades of severity. The dynamics of anaphylaxis are unpredictable, highly variable, and can lead to death in certain circumstances.[2–4] Patients may progress from mild symptoms such as urticaria to severe cardiovascular symptoms without respiratory or gastrointestinal impairment. Anaphylaxis therefore does not necessarily develop in stages. Due to this fact, the rigid classification according to Ring and Messmer from 1977 is often criticized. In this paper, anaphylactic reactions are nevertheless categorized according to this classification, as the German-language guideline recommends the management and treatment of anaphylaxis on the basis of the Ring and Messmer severity grades. Even after therapy and complete remission of symptoms, a biphasic progression of anaphylaxis is possible. Therefore, in-patient monitoring for 24 hours until safe and complete resolution of allergic symptoms is recommended.[5]

The incidence of anaphylaxis is seven to 50 per 100,000/year.[6–8] Anaphylactic reactions account for 0.2% to 1.0% of all emergency department consultations.[9] However, it is assumed that the number of unreported cases is high.

The evidence for the treatment of anaphylaxis remains mostly at a very low level. There are several guidelines world-wide that strongly recommend an evidence-based approach to diagnosis and treatment of anaphylaxis. In the following, the focus of consideration is on therapy with adrenaline.

A guideline for the diagnosis and treatment of anaphylactic reactions has been published by the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. [AMWF]) in 2007[10] and has been updated in 2021.[5] This guideline recommends an immediate therapy depending on the severity of anaphylaxis. For Grade I reactions, therapy with Histamine-1 (H1)-/Histamine-2 (H2)-receptor antagonists and glucocorticoids are recommended. In case of a severe anaphylactic reaction (Grade II-III), first-line therapy consists of immediate administration of adrenaline, followed by antihistamines and glucocorticoids. In Germany, only emergency physicians are authorized to administer medication during emergency operations. The decision to administer medication is therefore at the discretion of the emergency physician. All medication administrations analyzed for this study were carried out by emergency physicians in the prehospital setting.

The Anaphylaxis Guideline (2021 update)[11] of the European Academy of Allergy and Clinical Immunology (EAACI; Zurich, Switzerland) also recommends early use of intramuscular adrenaline as first-line intervention in case of severe anaphylaxis. In the further course of treatment, glucocorticoids and antihistamines are recommended.

The aim of the present study was an analysis of data from Emergency Medical Services of Dresden/Germany in cases of anaphylactic reactions with focus on the recommended first-line therapy with adrenaline in cases of severe anaphylaxis. Demographic data, triggers, symptoms, severity, therapy, and hospitalization rates of anaphylaxis were also evaluated.

Material and Methods

All data from Emergency Medical Services of Dresden/Germany, collected for anaphylactic reactions from January 1, 2012 through December 31, 2016 were examined retrospectively. The data of the air rescue were not considered in this study.

The medical documentation of the emergencies was done electronically. All protocols were checked for plausibility and completeness and then transferred daily to a central database.

The study was approved by the Ethics Committee "Ethikkommission an der Technischen Universität (TU) Dresden" (Dresden, Germany; Reference Number EK98052006).

All emergency cases from the start of 2012 to the end of 2016 of the Emergency Medical Services of Dresden/Germany, except those of air rescue, were screened for the International Classification of Diseases (ICD) T78 and for the following keywords: "anaphylactic reaction," "anaphylaxis," "allergy," "anaphylactic shock." Screening was performed by two different, well-trained emergency physicians who were well-versed in anaphylaxis. Cross-checking was performed for further quality assurance. These procedures were intended to reduce the possible selection and/or information bias. Complete data documentation was not required for the initial selection.

Data analysis was based on the following inclusion criteria: any patient age (children 0-17 years, adults ≥18 years), presence of an anaphylactic reaction, emergency mission performed by the Emergency Medical Services of Dresden/Germany (except air rescue), from the start of 2012 to the end of 2016, and complete protocol regarding age, gender, symptoms, and treatment. Protocols with incomplete information about trigger, outcome,

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and hospitalization were also analyzed. In case of missing documentation, the data were declared as "unknown."

Exclusion criteria were missing documentation of symptoms, local allergic reactions without documented anaphylactic reaction, and chronic/pre-existing angioedema.

Based on the recorded symptoms, the severity of anaphylaxis was graded according to the classification of Ring and Messmer.[1] Table 1 shows the classification into severity levels Grade I to IV based on the presenting symptoms.

IBM SPSS Statistics 29 (IBM Corp.; Armonk, New York USA) and Excel Microsoft 365, Version 2301 (Microsoft Corporation; Redmond, Washington USA) were used to analyze the results. Statistical analysis was performed using the chi-square-test. Significance level of $P < .05$ was defined for all analyses.

Results

Exclusion of Protocols

In total, protocols of 1,619 adults and 323 children were subjected to the inclusion and exclusion criteria. Protocols from 42 children and 208 adults did not include complete symptom information and therefore had to be excluded. Additional 58 children and 252 adults whose medical documentation showed no symptoms or evidence of anaphylaxis were excluded from data analysis. Overall, this meant that data from 100 children and 460 adults could not be used for further analysis.

In children, the most common causes of these non-anaphylactic complaints were isolated local reactions after insect venom (36.2%), infection-associated exanthema (32.8%), and isolated local allergic symptoms after contact with pollen, cosmetics, and animal hair (17.2%). Figure 1 shows the distribution of causes in children.

The distribution of causes of non-anaphylactic reactions in adults are shown in Figure 2. The most common causes are also isolated local reactions after insect venom (32.5%), isolated local reactions due to pollen/cosmetics/animal hair (16.7%), and infections (9.9%). The variability of triggers for non-anaphylactic reactions was greater in adults than in children. Causes such as anxiety, neurological or cardiovascular disease, chronic discomfort, and toxic effects have been noted more frequently.

Additional 28 adults were excluded because of a pharmacologic-induced chronic angioedema, which was pre-existing in the medical history according to documentation.

After applying the exclusion criteria, the analysis included 1,131 adults and 223 children with anaphylactic reactions.

Results of Anaphylaxis in Children

In total, data from 223 children with anaphylaxis were analyzed (Table 2). The mean age was 7.4 years. There were 58.3% male children. The most common triggers were foods (54.3%), medications (10.3%), and insect venom (6.7%). In 19.7% of all children, no trigger could be named. The average time between the alert and the arrival of the Emergency Medical Services was six minutes (minimum: one minute; maximum: 47 minutes).

In case of children, 73.5% were hospitalized for further observation and 16.1% were left at home in the care of their parents. In 0.9% of cases, parents refused hospitalization despite recommendation; 9.4% of the protocols did not contain any information about hospitalization.

Regarding children, 61.4% received immediate therapy. Glucocorticoids were administered in 50.7%, H1-receptor-antagonists in 45.3%, and H2-receptor-antagonists in 24.2% of all cases; 4.9% of all children with anaphylactic reactions received adrenaline.

According to the protocols, the child's condition improved during treatment in 61.4%. In 35.0%, the condition was constant. Worsening was documented in 0.0%; 3.6% of all protocols did not contain any information about the outcome of the child's condition.

Results According to Severity Grade in Children

Regarding all children, 54.3% showed Grade I reactions. Grade II reactions were found in 38.6%; 7.1% of all children had Grade III reactions. Grade IV reactions were not reported. Table 2 contains the detailed information about the distribution of mean age, gender, and triggers of Grade I to Grade III reactions. Hospitalization rate and outcome were also analyzed for the respective severity level.

Grade I reactions were treated in 59.5% with medication. In this group, 49.6% received glucocorticoids, 40.5% H1-receptor-antagonists, 17.4% H2-receptor-antagonists, and 2.5% adrenaline.

In case of Grade II reactions, medication was administered in 61.6%. Glucocorticoids were given in 50.0%, H1-receptor-antagonists in 47.7%, H2-receptor-antagonists in 27.9%, and adrenaline in 5.8%.

Regarding Grade III reactions, 75.0% received drug therapy. Glucocorticoids were administered in 62.5%, H1-receptor-antagonists in 68.8%, H2-receptor-antagonists in 56.3%, and adrenaline in 18.8%.

Correlation between Severity, Therapy with Adrenaline, Outcome, and Hospitalization in Children

Chi-square test and Spearman-correlation test were used for the analysis of relation between severity/treatment with adrenaline, severity/hospitalization, and treatment with adrenaline/outcome.

Results of the chi-square test showed a significant correlation between severity of anaphylaxis and treatment with adrenaline ($\chi^2(1) = 8.21$; $P = .016$; $\varphi = 0.192$). Correlation Spearman $r = 0.171$; $P = .01$.

After censoring all cases with unknown data (n = 21) and refusal of hospitalization (n = 2), the chi-square analysis of the correlation between severity and hospitalization showed no correlation ($\chi^2(1) = 3.44$; $P = .179$; $\varphi = 0.131$). Correlation Spearman $r = 0.130$ and $P = .068$, also not significant.

For analyzing the correlation between therapy with adrenaline and children's outcome, eight cases had to be excluded because outcome data were not documented. In all these excluded cases, no adrenaline was administered. Ten of the eleven children with adrenaline therapy improved; one child showed a constant condition. There was a significant correlation between adrenaline therapy and improved condition in the chi-square test ($\chi^2(1) = 3.71$; $P = .05$; $\varphi = 0.131$). Correlation Spearman $r = 0.131$; $P = .05$.

Results of Anaphylaxis in Adults

The results of the data evaluation of 1,131 adults with anaphylaxis are shown in Table 3. The mean age in the group of adults was 50.5 years. More female patients were affected (61.8%). The most common triggers were medications (31.3%), foods (28.8%), and insect venom (16.7%). In 20.4% of the cases, no trigger was identified. The average time between the alert and the arrival of the Emergency Medical Services was seven minutes (minimum: one minute, maximum: 60 minutes).

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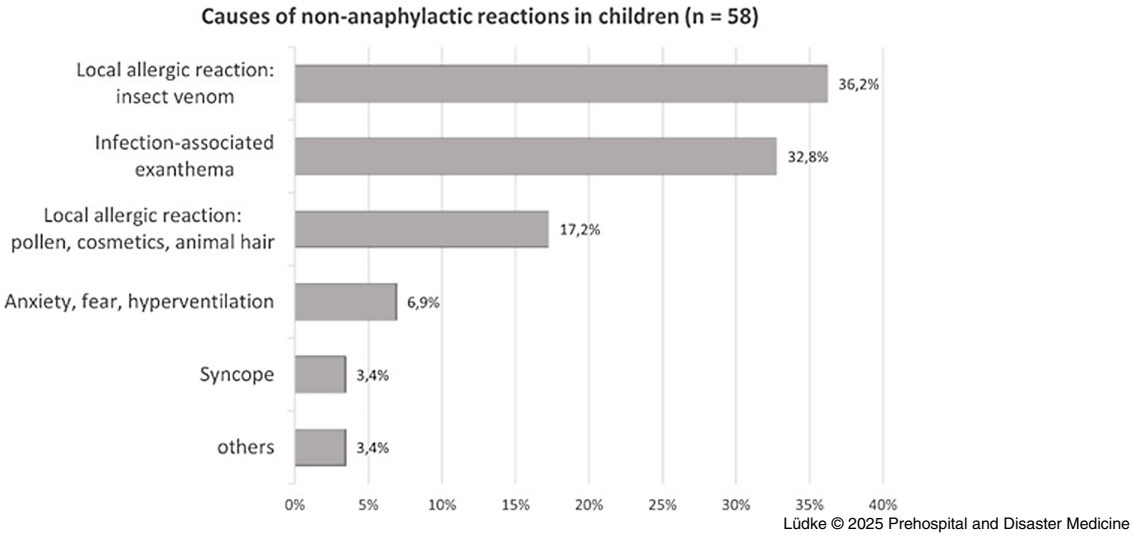

Figure 1. Causes of Non-Anaphylactic Reactions in Children.

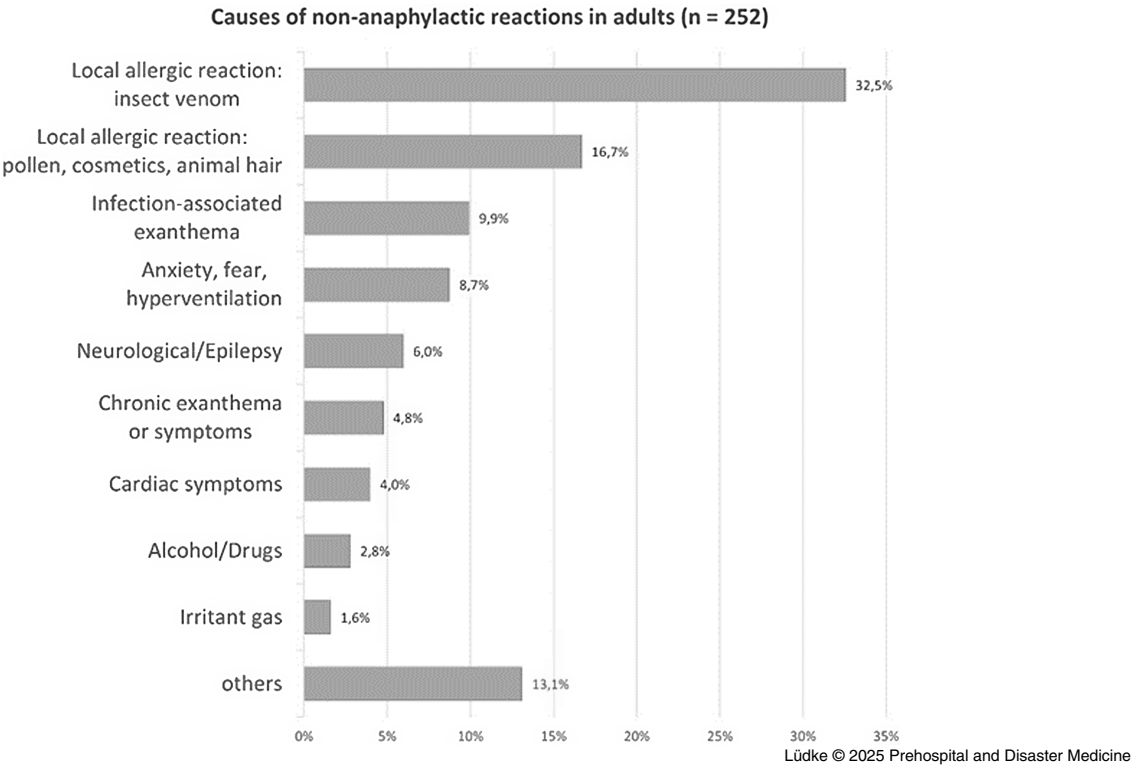

Figure 2. Causes of Non-Anaphylactic Reactions in Adults.

For further observation, 60.3% of all adults with anaphylaxis were admitted to hospital, 25.7% were left at home, and 4.2% denied hospitalization despite recommendation. In 9.8% of the cases, the protocols did not contain any information about the further observation procedure.

Emergency medication was given in 75.2% of all adult cases. Glucocorticoids were administered in 68.3%, H1-receptor-antagonists in 69.2%, and H2-receptor-antagonists in 57.4%; 4.5% of all adults with anaphylaxis were treated with adrenaline.

Under therapy, the patients' condition improved in 66.3%. In 29.1%, it was described as constant; 0.5% worsened despite therapy. In 4.1%, the protocols did not contain any information about the outcome.

Results According to Severity Grade in Adults

Grade I reactions were observed in 47.7%, Grade II reactions in 40.5%, and Grade III reactions in 11.8%. No cases of Grade IV anaphylaxis were reported. Table 3 shows the different distribution of mean age, gender, triggers, hospitalization, and outcome for these subgroups.

In 70.2% of Grade I reactions, immediate medication was given. In this group, 65.0% received glucocorticoids, 64.3% H1-

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		Grade I	Grade II	Grade III	Grade IV	Total
Number (% from total)		121 (54.3%)	86 (38.6%)	16 (7.1%)	0 (0.0%)	**223 (100.0%)**
Mean Age (years)		6.8	8.3	7.4	0.0	**7.4**
Gender (% from category)	Male	69 (57.0%)	53 (61.6%)	8 (50.0%)	0 (0.0%)	**130 (58.3%)**
	Female	52 (43.0%)	33 (38.4%)	8 (50.0%)	0 (0.0%)	**93 (41.7%)**
Trigger (% from category)	Medication	12 (9.9%)	9 (10.5%)	2 (12.5%)	0 (0.0%)	**23 (10.3%)**
	Foods	59 (48.8%)	54 (62.8%)	8 (50.0%)	0 (0.0%)	**121 (54.3%)**
	Insect Venom	10 (8.3%)	4 (4.7%)	1 (6.3%)	0 (0.0%)	**15 (6.7%)**
	Allergen Immunotherapy	1 (0.8%)	8 (9.3%)	2 (12.5%)	0 (0.0%)	**11 (4.9%)**
	Animal Hair, Pollen, House Dust Mites	6 (5.0%)	3 (3.5%)	0 (0.0%)	0 (0.0%)	**9 (4.0%)**
	Unknown	33 (27.3%)	8 (9.3%)	3 (18.8%)	0 (0.0%)	**44 (19.7%)**
Hospitalization (% from category)	Yes	79 (65.3%)	71 (82.6%)	14 (87.5%)	0 (0.0%)	**164 (73.5%)**
	No	23 (19.0%)	12 (14.0%)	1 (6.3%)	0 (0.0%)	**36 (16.1%)**
	Denied	1 (0.8%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	**2 (0.9%)**
	Not Documented	18 (14.9%)	3 (3.5%)	0 (0.0%)	0 (0.0%)	**21 (9.4%)**
Treatment (% from category)	Yes	72 (59.5%)	53 (61.6%)	12 (75.0%)	0 (0.0%)	**137 (61.4%)**
	No	49 (40.5%)	33 (38.4%)	4 (25.0%)	0 (0.0%)	**86 (38.6%)**
	Glucocorticoids	60 (49.6%)	43 (50.0%)	10 (62.5%)	0 (0.0%)	**113 (50.7%)**
	H1-receptor-Antagonist (Fenistil)	49 (40.5%)	41 (47.7%)	11 (68.8%)	0 (0.0%)	**101 (45.3%)**
	H2-receptor-Antagonist (Ranitidin)	21 (17.4%)	24 (27.9%)	9 (56.3%)	0 (0.0%)	**54 (24.2%)**
	Adrenaline	3 (2.5%)	5 (5.8%)	3 (18.8%)	0 (0.0%)	**11 (4.9%)**
Outcome (% from category)	Improved	62 (51.2%)	62 (72.1%)	13 (81.3%)	0 (0.0%)	**137 (61.4%)**
	Constant	53 (43.8%)	23 (26.7%)	2 (12.5%)	0 (0.0%)	**78 (35.0%)**
	Worsened	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0 (0.0%)**
	Not Documented	6 (5.0%)	1 (1.2%)	1 (6.3%)	0 (0.0%)	**8 (3.6%)**

Table 2. Data of Anaphylactic Reactions in Children

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		Grade I	Grade II	Grade III	Grade IV	Total
Number (% from total)		540 (47.7%)	458 (40.5%)	133 (11.8%)	0 (0.0%)	**1,131 (100.0%)**
Mean Age (years)		51.7	48.2	53.6	0.0	**50.5**
Gender (% from category)	Male	198 (36.7%)	176 (38.4%)	58 (43.6%)	0 (0.0%)	**432 (38.2%)**
	Female	342 (63.3%)	282 (61.6%)	75 (56.4%)	0 (0.0%)	**699 (61.8%)**
Trigger (% from category)	Medication	158 (29.3%)	154 (33.6%)	42 (31.6%)	0 (0.0%)	**354 (31.3%)**
	Foods	153 (28.3%)	141 (30.8%)	32 (24.1%)	0 (0.0%)	**326 (28.8%)**
	Insect Venom	73 (13.5%)	84 (18.3%)	32 (24.1%)	0 (0.0%)	**189 (16.7%)**
	Allergen Immunotherapy	5 (0.9%)	8 (1.7%)	3 (2.3%)	0 (0.0%)	**16 (1.4%)**
	Cosmetics, Animal Hair, Pollen, House Dust Mites	6 (1.1%)	7 (1.5%)	2 (1.5%)	0 (0.0%)	**15 (1.3%)**
	Unknown	145 (26.9%)	64 (14.0%)	22 (16.5%)	0 (0.0%)	**231 (20.4%)**
Hospitalization (% from category)	Yes	292 (54.1%)	287 (62.7%)	103 (77.4%)	0 (0.0%)	**682 (60.3%)**
	No	167 (30.9%)	116 (25.3%)	8 (6.0%)	0 (0.0%)	**291 (25.7%)**
	Denied	29 (5.4%)	15 (3.3%)	3 (2.3%)	0 (0.0%)	**47 (4.2%)**
	Not Documented	52 (9.6%)	40 (8.7%)	19 (14.3%)	0 (0.0%)	**111 (9.8%)**
Treatment (% from category)	Yes	379 (70.2%)	365 (79.7%)	107 (80.5%)	0 (0.0%)	**851 (75.2%)**
	No	161 (29.8%)	93 (20.3%)	26 (19.5%)	0 (0.0%)	**280 (24.8%)**
	Glucocorticoids	351 (65.0%)	326 (71.2%)	95 (71.4%)	0 (0.0%)	**772 (68.3%)**
	H1-receptor-Antagonist (Fenistil)	347 (64.3%)	345 (75.3%)	91 (68.4%)	0 (0.0%)	**783 (69.2%)**
	H2-receptor-Antagonist (Ranitidin)	285 (52.8%)	288 (62.9%)	76 (57.1%)	0 (0.0%)	**649 (57.4%)**
	Adrenaline	10 (1.9%)	20 (4.4%)	21 (15.8%)	0 (0.0%)	**51 (4.5%)**
Outcome (% from category)	Improved	318 (58.9%)	326 (71.2%)	106 (79.7%)	0 (0.0%)	**750 (66.3%)**
	Constant	194 (35.9%)	114 (24.9%)	21 (15.8%)	0 (0.0%)	**329 (29.1%)**
	Worsened	2 (0.4%)	3 (0.7%)	1 (0.8%)	0 (0.0%)	**6 (0.5%)**
	Not Documented	26 (4.8%)	15 (3.3%)	5 (3.8%)	0 (0.0%)	**46 (4.1%)**

Table 3. Data of Anaphylactic Reactions in Adults

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receptor-antagonists, 52.8% H2-receptor-antagonists, and 1.9% adrenaline.

In case of Grade II reactions, medication was administered in 79.7%: 71.2% received glucocorticoids, 75.3% H1-receptor-antagonists, 62.9% H2-receptor-antagonists, and 4.4% adrenaline.

Regarding Grade III reactions, 80.5% were treated with medication: 71.4% received glucocorticoids, 68.4% H1-receptor-antagonists, 57.1% H2-receptor-antagonists, and 15.8% adrenaline.

Correlation between Severity, Therapy with Adrenaline, Outcome, and Hospitalization in Adults

The chi-square test showed a significant correlation between severity of anaphylaxis and treatment with adrenaline in the group of adults ($\chi^2(1) = 48{,}18$; $P < .001$; $\phi = 0.206$). Correlation Spearman $r = 0.183$; $P < .001$.

After censoring all cases with unknown data ($n = 111$) and refusal ($n = 47$) of hospitalization, the chi-square test between severity and hospitalization showed a significant correlation ($\chi^2(1) = 36.71$; $P < .001$; $\phi = 0.194$). Correlation Spearman $r = 0.170$; $P < .001$.

For analyzing the correlation between therapy with adrenaline and outcome, 46 cases had to be excluded because outcome data were not documented. In all these excluded cases, no adrenaline was administered. An improvement was observed in 47 of the 51 adults who received adrenaline therapy; four adult patients showed a constant condition after therapy. There was a significant correlation between adrenaline therapy and improved condition in the group of adults in the chi-square test ($\chi^2(1) = 13.32$; $P = .001$; $\phi = 0.111$). Correlation Spearman $r = 0.111$; $P < .001$.

Discussion

The evidence base for the diagnosis and treatment of anaphylaxis is low. There are different classifications for anaphylactic reactions world-wide. The European and German guidelines advocate a harmonized, standardized, and evidence-based approach to anaphylaxis. The retrospective analysis of prehospital emergency missions of the Emergency Medical Services of Dresden/Germany from the start of 2012 to the end of 2016 provided in total data from 1,131 adults and 223 children with anaphylactic reactions. This study provides valuable data on demographics, triggers, severity, treatment, outcome, and hospitalization rates of anaphylaxis.

Demographics, Triggers, and Distribution of Severity

Demographics—Regarding children, 58% with anaphylactic reactions were male and 42% female. As described in literature, boys suffer more frequently from anaphylaxis than girls (70% versus 30%). These gender-associated differences disappear after puberty.[12]

In the group of adults, there were 38% male and 62% female patients. According to the Anaphylaxis Registry of German-speaking countries,[13] 53% of adult patients with anaphylaxis are female and 47% are male.

Triggers—In children (0-17 years), the most common triggers in this study were foods (54%), followed by medication (10%) and insect venom (7%). In 20% of the cases, no trigger was named, or none was known. Food was described as the most common elicitor (60%) of severe anaphylaxis in children.[14]

Regarding adults, most anaphylactic reactions were caused by medication (31%), foods (29%), and insect venom (17%). In 20% of all cases, the elicitors were named as unknown. According to the literature, the most common triggers of severe anaphylaxis in adults are insect venom, medications, and food.[14,15]

For both 20% of the children and 20% of the adults, no triggers were named. Therefore, the number of unreported and/or unknown elicitors was high and can lead to distortions.

Distribution of Severity—In children, Grade I reactions occurred in 54%, Grade II in 39%, and Grade III in seven percent. Grade IV anaphylaxis was not reported in this study. Regarding adults, Grade I reactions were shown in 48%, Grade II reactions in 40%, and Grade III reactions in 12%. Also, no Grade IV anaphylaxis was documented. The average time between alarm and arrival of the Emergency Medical Services was six minutes for children and seven minutes for adults. Therapy was therefore initiated very quickly, which could explain the low number of severe anaphylaxis cases.

Worm, et al published an analysis of 4,000 cases of anaphylaxis in 2014.[15] Around five percent of the adults and children showed Grade I reactions, 50%-60% Grade II, and 35%-45% Grade III reactions. Grade IV anaphylaxis was rarely reported (3.1% in adults; 0.9% in children). For this cited work, data from the Anaphylaxis Registry were evaluated, which almost exclusively records severe anaphylaxis. Therefore, Grade I reactions are underrepresented. The causes of cardiovascular arrests are very diverse, which explains the low number of Grade IV reactions. It is not easy to diagnose anaphylaxis in these cases. Therefore, a certain number of unreported cases can be assumed. The discrepancy between this study data and the literature previously published may be due to a smaller study group and/or local characteristics such as demographic distributions. Furthermore, only severe anaphylactic reactions with cardiovascular and/or pulmonal symptoms are recorded in the Anaphylaxis Registry.

Therapy, Outcome, and Hospitalization

Therapy and Outcome—The present data show that 61% of all children and 75% of all adults with anaphylaxis received emergency drug therapy. In 39% of the children ($n = 86$) and 25% of the adults ($n = 280$), respectively, no medication at all despite the presence of anaphylactic symptoms was given. Treatment rates have been found to increase with increasing severity of anaphylaxis. For Grade III anaphylaxis, 75% of children and 81% of adults received drug treatment. If no therapy could be taken from the evaluated protocols, it was assumed for the analysis that no therapy had taken place. Lack of documentation could therefore be one possible cause for the treatment rates found. Another reason can be insufficient training or insecurity of the health care professionals, especially in children. Here, a strong uncertainty in the emergency treatment of children regarding measures such as the insertion of an indwelling venous catheter and the dosage of medication exists.[16]

Adrenaline—Adrenaline is the first-line therapy in case of severe anaphylaxis.[11] By activating alpha- and beta-receptors and inhibiting histamine release from mast cells, adrenaline functionally antagonizes all relevant pathophysiologic mechanisms of anaphylaxis. It has the fastest onset of action of all anaphylaxis medications.[5] Adrenaline can also reduce the risk of biphasic reactions.[17] The European and German guidelines recommend the immediate administration of intramuscular adrenaline.[5,11] The intravenous use should be restricted to well-trained health care professionals. Due to the challenges of undertaking randomized

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controlled trials in anaphylaxis, the research evidence for the use of adrenaline remains low.

Adrenaline was given in 4.9% of all children and 4.5% of all adults with anaphylactic reactions (Grade I-IV). In case of severe anaphylaxis (Grade II and higher), seven percent adrenaline was administered in the adult group and eight percent in the children group. Ten of the eleven children with adrenaline therapy improved under therapy; one child only showed a constant condition. In the adult group, 51 of the patients received adrenaline. Improvement of the condition was observed in 47 cases; in four adults, the condition remained constant. No worsening of symptoms was observed in either adults or children after therapy with adrenaline.

There is a significant correlation between the severity of anaphylaxis and administered therapy with adrenaline in the group of adults ($P < .001$) and children ($P = .016$). In both groups, therapy with adrenaline had a significant effect on the patients' condition (adults $P = .001$; children $P = .05$).

Based on study data from various countries, it has been shown that therapy of anaphylaxis is often not carried out in accordance with existing guidelines.[18,19] In a previous analysis of anaphylaxis data from Air Rescue Dresden/Germany, it was shown that only 19% of adults and seven percent of children with severe anaphylaxis received adrenaline.[20] Inadequate training of health care professionals regarding the assessment and therapy of anaphylaxis may be one of the reasons.[21] Fear of the side effects of adrenaline or of complications from cardiovascular disease could also be a reason for reluctance to use adrenaline.[22] Especially in children, the uncertainty in the emergency treatment with adrenaline is high.[16]

Antihistamines—Histamine is the central mediator of allergic reactions. The effect of histamine H1-receptor antagonists in acute urticaria and/or rhinoconjunctivitis are undisputed. Their effects on bronchoconstriction and circulation have not been demonstrated.[23] Antihistamines have a slower onset of action than adrenaline. The European and German guidelines recommend the administration of antihistamines once vital functions have been stabilized. There is limited evidence of an effect of histamine H2-receptor antagonists in the therapy of anaphylaxis. A reduction in cutaneous symptoms after the use of ranitidine in combination with H1-receptor antagonists is reported.[24] High doses of cortisone can lead to irritation of the gastric mucosa. H2-receptor antagonists can be administered to protect the gastric mucosa.

In the group of all children, 45% received H1-receptor antagonists and 24% H2-receptor antagonists. Regarding severe anaphylaxis (Grade II and higher), 51% received H1-receptor antagonists and 32% H2-receptor antagonists.

Regarding adults, 69% were treated with H1-receptor antagonists and 57% with H2-receptor antagonists. In severe reactions the rates were higher, 74% H1-receptor antagonists and 62% H2-receptor antagonists.

Glucocorticoids—Glucocorticoids are used in anaphylaxis to prevent protracted symptoms or biphasic reactions. However, the evidence of their effectiveness is limited;[25] their onset of action is slow.[26] Glucocorticoids should be administered in the event of anaphylaxis once vital functions are stabilized and adrenaline has been administered.

Glucocorticoids were administered in 51% of all children and 68% of all adults. Considering only severe anaphylaxis, the rate was slightly higher (children: 52%; adults: 71%).

Hospitalization—Analysis of the data showed that 83% of the children with Grade II or higher reactions were hospitalized. Of the 86 children who did not receive any emergency treatment, 63 children were admitted to hospital for further monitoring. Hospitalization was documented in 66% of the adults with severe anaphylactic reactions; 144 of the 280 adults who did not receive any emergency drug treatment were hospitalized for further observation.

In the group of adults, the analysis of the correlation between severity and hospitalization shows a significant correlation ($P < .001$). This suggests that adults with severe anaphylaxis are more likely to be transferred to hospital for further observation than adults with mild anaphylactic symptoms.

The analysis of correlation between severity and hospitalization in the group of children shows a non-significant correlation trend ($P = .179$). In this analysis, 21 cases had to be excluded because the protocols did not contain information on further observation. In 18 of these cases, Grade I reactions were documented. The incomplete documentation may therefore have led to a bias in the statistical analysis. Nevertheless, there is a positive trend in the correlation between severity and hospitalization in the children's group. It is also conceivable that children with anaphylaxis in general, regardless of severity, are frequently admitted to hospital for further observation. The fears of the parents, but also the insecurity of the emergency professionals, could lead to this decision.

Anaphylaxis may spontaneously cease at any stage of symptoms. But also, a progress in severity despite adequate therapy is possible.[5] In five percent to 20%, a protracted or biphasic course may develop within six to 24 hours after successful therapy.[27] Due to the unclear dynamic and outcome, hospitalization for 24-hour observation is recommended in the case of severe anaphylaxis.[5]

Qualification of Health Care Professionals

Since anaphylaxis has variable presentations and relatively low prevalence, diagnosis may be challenging. The diagnosis of anaphylaxis is still based exclusively on clinical assessment. Anaphylaxis is an emergency that requires a rapid diagnosis and an immediate start of therapy.

In the present study, 58 children and 252 adults whose protocols showed no symptoms or evidence of anaphylaxis were excluded from data analysis. However, in all these cases, anaphylaxis was coded (ICD).

Differential diagnoses are varied and may include chronic skin diseases, respiratory diseases, cardiovascular diseases, toxic reactions, neuropsychiatric diseases, and many more.[11]

Furthermore, a high estimated number of unreported cases of anaphylactic reactions can be assumed. Only protocols in which anaphylaxis was diagnosed and reported were evaluated. Insufficient knowledge in immunology may lead to the high percentage of cases in which the trigger could not be identified or named. In the present investigation, in 20% of all adults and children, the elicitor of anaphylaxis was unknown. The low rate of administration of medication, and especially adrenaline, may be a sign of lack of training or insecurity.

The World Allergy Organization (Milwaukee, Wisconsin USA) Anaphylaxis Guidelines from 2013 recommend that emergency physicians should be trained to recognize anaphylaxis and distinguish it from other diagnoses.[28] The EAACI suggests the use of simulation training and visual prompts to improve health care professionals' recognition and treatment of anaphylactic reactions in emergency situations.[11]

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Another challenge for health care workers is the correct and complete documentation. Protocols from 42 children and 208 adults did not include complete symptom information and therefore had to be excluded. Documentation of outcome and further observation/hospitalization was missing in four percent to ten percent.

Limitations of the Study

The present study focuses on the Emergency Medical Services of Dresden/Germany. Regional or local demographic characteristics or distributions cannot be ruled out.

The quality of the emergency documentation was inconsistent and partly incomplete. Complete data evaluation was therefore not possible. In total, 250 protocols were excluded due to insufficient documentation. A complete description of the application forms and dosages of the medication administered was only partially possible.

The protocols only provide information about the Emergency Medical Services. Therefore, the outcome only describes the dynamics of the patient's condition during the emergency treatment. Long-term data on the further course were not registered and were therefore not part of this study.

Conclusion

The guideline-compliant first-line therapy with adrenaline was not carried out in the majority of the cases analyzed in this study. However, the study shows that treatment with adrenaline for anaphylaxis leads to a significant improvement in the patients' condition.

The literature published to date and the data presented here suggest that there is some uncertainty among prehospital health care professionals about how to recognize and treat anaphylactic reactions. Further studies could help to close the existing medical care gap. However, in the case of emergency treatment of anaphylaxis, double-blind, placebo-controlled, randomized trials are hardly feasible, even though they are needed.

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