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Evaluation of the triggers and the treatment models of anaphylaxis in pediatric patients

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ABSTRACT

OBJECTIVE: Anaphylaxis is an acute, life-threatening systemic hypersensitivity reaction. We aimed to evaluate the demographic and clinical characteristics of patients presenting with anaphylaxis, as well as triggers and risk factors, and to determine the rate of adrenaline auto-injector (AAI) usage.

METHODS: The study was planned in the pediatric allergy outpatient clinic over a 1-year period. The data of children diagnosed with anaphylaxis were evaluated retrospectively; demographic characteristics, causes of anaphylaxis, and treatment modalities were recorded in the created study form.

RESULTS: Eighty children (29 females) with a median age of 6.5 years (range: 1 month-17 years) were evaluated. The most common triggers were foods under 2 years of age (73%), and drugs (70%) above 2 years of age. Nearly half of the anaphylaxis episodes (n=41, 51.3%) occurred at home. Cutaneous and respiratory symptoms were the most commonly reported complaints (98.8%). The median age of the patients at the first attack with severe anaphylaxis (n=29, 36.3%) was significantly higher than the rest (p:0.007). The age at onset of the reaction (p:0.006) and occurrence of the reaction in hospital conditions (p<0.001) were determined to be significant risk factors for severe anaphylaxis. Most of them received antihistamines (95.7%) and corticosteroids (91.3%), while 78.3% received adrenaline. Only 9.5% of patients with recurrent episodes of anaphylaxis used AAIs.

CONCLUSION: Foods in infants and drugs in older children were the leading causative allergens of anaphylaxis. The most common clinical manifestations were respiratory and cutaneous symptoms. The older age at onset of the reaction and the occurrence of the reaction in hospital conditions were determined to be significant risk factors for severe anaphylaxis. It was determined that the frequency of AAI use was low among patients and their families.

Keywords: Adrenaline; anaphylaxis; child; drug; food.

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Anaphylaxis is an acute, life-threatening, systemic hypersensitivity reaction in which clinical presentations vary widely depending on the organ involved [1]. The estimated lifetime prevalence of anaphylaxis in the general population is approximately 1.6–5.1%, and its prevalence is increasing both in children and in adults, particularly in developed countries [2–4]. The majority of new cases occur in the younger age group [2], and the incidence ranges from 1 to 761/100.000 person-years [5]. Triggers vary according to the age of the patients. In addition, characteristics of anaphylaxis in children, such as risk factors and clinical course, may be different from those in adults [6]. Foods are the most common causes of anaphylaxis in children, whereas medications

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and stinging insect venom are the leading etiologic factors in adults [7]. It is important to identify the triggers and risk factors for anaphylaxis to prevent the recurrence of episodes as well as educate patients about avoiding known allergen exposures.

Adrenaline (epinephrine) is recommended as the first-line treatment for anaphylaxis, and delayed administration has been associated with a fatal outcome [4, 7]. Therefore, it should be administered promptly when anaphylaxis is suspected. Despite its pivotal role in the management of anaphylaxis, adrenaline use remains suboptimal [8]. Similarly, self-treatment of anaphylaxis by auto-injectors has an important role in providing early treatment for patients with a history of anaphylaxis. For this reason, it is important to prescribe an adrenaline auto-injector (AAI) to patients who have experienced anaphylaxis and to educate them on how to use it [9].

The aim of this study was to evaluate the demographic and clinical characteristics of patients who experienced anaphylaxis, as well as the triggers and risk factors of the anaphylactic episodes. The secondary aim was to determine the rate of proper use of adrenaline by physicians and patients/parents.

Highlight key points

- Triggers of anaphylaxis vary according to the age of patients.
- Adrenaline (epinephrine) is recommended as first-line treatment for anaphylaxis, and delayed administration has been associated with a fatal outcome.
- Self-treatment of anaphylaxis by epinephrine auto-injectors has an important role in providing early treatment in patients with a history of anaphylaxis.
- The most common triggers were foods under 2 years of age, and drugs above 2 years of age.
- Adrenaline it has not been used adequately either by doctors as first-line therapy or as an auto-injector by patients in the self-treatment of anaphylaxis.

MATERIALS AND METHODS

Patients

We conducted a retrospective study, including patients who were referred with a diagnosis of anaphylaxis to our pediatric allergy clinic over a 1-year period. The diagnosis of anaphylaxis was confirmed according to the clinical criteria of the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network in all patients [10]. The severity of anaphylaxis was classified as mild, moderate, and severe according to the position paper of the European Academy of Allergy and Clinical Immunology [11].

Data Collection

Demographic and clinical data such as age, gender, age at onset of reactions, presence of underlying allergic diseases, family history of allergy, triggers of reactions, symptoms, and involved systems during reactions, the interval between exposure and the onset of reaction, setting of anaphylaxis, number of anaphylactic episodes, treatments that have been done, self-treatment of patients with AAIs, and laboratory values were collected from the patients' medical records. In cases of missing data in the records, the parents were called. The children were categorized as 0–2, 3–5, and >6 years based on the age groups.

Diagnostic Evaluation

Etiologic factors were determined by clinical history. Diagnostic tools such as skin prick tests (SPTs) and allergen-specific immunoglobulin (Ig) E for the suspected triggers were performed on patients whose parents had given informed consent. SPTs were performed with commercial extracts of suspected foods as well as inhalant allergens at least 4 weeks after the last anaphylactic episode. Tests were evaluated 20 min after the procedure and considered positive if the wheal diameter was at least 3 mm or larger than the negative control. Skin pricks and intradermal tests with culprit drugs could not be performed due to the lack of informed consent. In these patients, drugs were determined to be the triggering factor based on a strong clinical history. Allergen-specific IgE levels for suspected foods, drugs, and venom were measured using the immunoCAP system (Pharmacia Diagnostic AB, Uppsala, Sweden). Values >0.35 kU/L were considered positive. Patients with no identified specific triggers were considered to have idiopathic anaphylaxis.

The study was approved by the Ethics Committee of our university (Number 2021/236) and conducted in accordance with the Helsinki Declaration.

Statistical Analysis

IBM Statistical Package for the Social Sciences (SPSS) for Windows Version 21.0 statistics package program (IBM SPSS Corp.; Armonk, NY, USA) was used for the analysis of data. Descriptive statistics of categorical

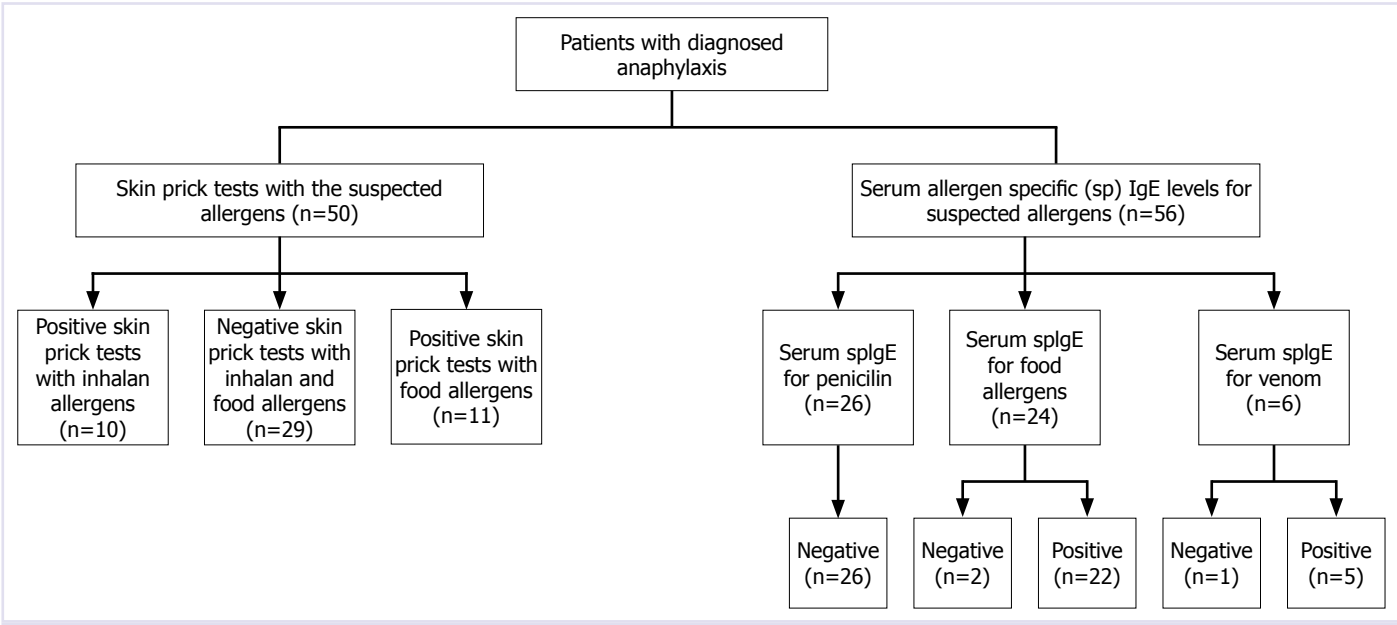

FIGURE 1. Diagnostic evaluation of patients. Skin prick tests and/or serum allergen-specific IgE measurement for the suspected triggers were performed to patients whose parents had given informed consent.

variables were presented as frequency (n) and percentage (%), and numeric variables were presented as means with a standard deviation or median value based on the normality of distribution. The Fisher Exact Test was used to compare the differences in categorical variables, and the Mann–Whitney U test was applied for the comparison of continuous variables between two independent groups. Regression analysis was used to predict severe anaphylaxis. A value of $p<0.05$ was considered statistically significant.

RESULTS

Demographic Data and Atopic Status

We evaluated 80 children (51M, 29F) diagnosed with anaphylaxis. The median age of patients at the onset of anaphylaxis was 6.5 years (range: 1 month-17 years). Fifty-three patients (66.3%) had a history of allergic diseases: 22 had asthma, 14 had a food allergy, 5 had chronic urticaria, 4 had atopic dermatitis, 4 had allergic rhinitis, 2 had drug allergies, and 2 had asthma and allergic rhinitis. In addition, 34 (42.5%) children had a family history of atopy. SPTs were performed on 50 patients, and the rates of sensitization to inhalant and food allergens were similar (20% and 22%, respectively). The serum-specific IgE for the suspected foods and venoms was detected in 22 and 5 patients, respectively (Fig. 1). The demographic and clinical characteristics of the children are shown in Table 1.

Triggers and Symptoms of Anaphylaxis

In all age groups, the most commonly reported etiological agents were drugs (52.5%), followed by food allergens (28.8%) and insect stings (10%). When patients were evaluated according to age, food allergens were the most common triggers in the 0–2 years of age range, whereas drugs were the leading triggers above 2 years of age. The most common triggers of anaphylaxis according to age groups are shown in Figure 2. Among patients with drug-induced anaphylaxis, antibiotics, especially penicillin, were the most common causes of anaphylaxis (n=33, 41.3%), followed by nonsteroidal anti-inflammatory drugs (n=13, 16.3%). The main food allergens in 23 patients with food-induced anaphylaxis were milk and dairy products (n=15, 18.8%). In 7.5% of patients, no causative agent could be identified. The triggers of anaphylaxis are presented in Table 2.

Among the patients who had experienced anaphylaxis, cutaneous and respiratory symptoms were the most commonly reported presenting complaints (98.8%). The symptoms of anaphylaxis are presented in Table 3.

Course of Anaphylaxis

Most patients (81.3%) reported that the interval between exposure to allergens and the onset of symptoms was <30 min. Twenty-one of the patients (26.3%) had a history of recurrent anaphylaxis. Among them, 7 (33.3%) had severe

Table 1. Demographic and clinical characteristics of the patients diagnosed with anaphylaxis

Characteristics	n=80 (%)
Gender	
Male	63.8
Female	36.2
Age (years)	
Median (range)	6.5 (1 month-17 years)
Age range (years)	
0–2	32.5
3–5	17.5
≥6	50
History of allergic disease	66.3
Asthma	27.5
Allergic rhinitis	5
Asthma and allergic rhinitis	2.5
Chronic urticaria	6.3
Food allergy	17.5
Atopic dermatitis	5
Drug allergy	2.5
Familial history of allergic disease	42.5
Setting of reaction	
Home	51.3
Hospital	33.7
Outdoors	13.7
School	1.3
Severity of reaction	
Mild/moderate	63.8
Severe	36.2
Interval between exposure and symptoms	
Unknown	2.5
0–30 min (m)	81.3
>30 m	16.2
History of recurrent anaphylaxis	26.3
Treatment	
Antihistamine	95.7
Systemic corticosteroid	91.3
Adrenaline	78.3
Nebulized beta2-agonist	23.2
Skin prick tests	
Negative	36.2
Positive	26.3
Not applied	37.5
Serum total IgE (IU/mL)	
Median (lower-upper limit)	68.5 (2–1061)
Serum eosinophilia (%)	
Median (lower-upper limit)	2.4 (0–20.5)

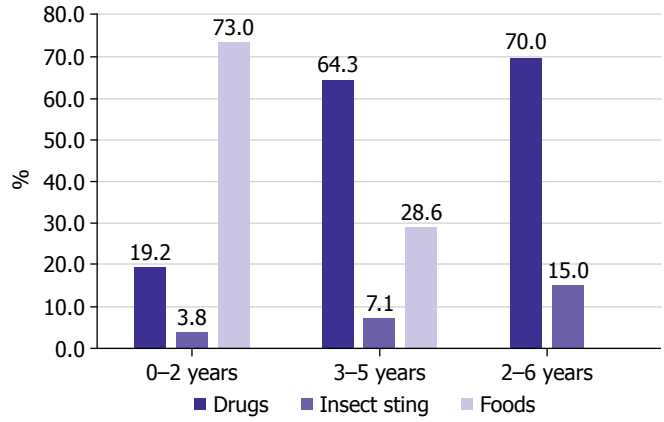

Figure 2. The most common triggers of anaphylaxis according to age groups. Food allergens were the most common triggers in the 0–2 years, whereas drugs were the leading triggers above 2 years of age. In patients over 6 years old, food allergens did not detect as triggers.

anaphylaxis. However, only two of the patients used AAI during the reactions. Trigger factors were medications in 12 (57.1%) patients, foods in 7 (33.3%) patients, and venom in 1 (4.8%) patient. The causative allergen could not be identified in only one patient. Most of the recurrent anaphylaxis episodes (n=9, 42.8%) occurred in hospital settings. The most common clinical manifestations were cutaneous and respiratory (95.2%), followed by cardiovascular (33.3%), gastrointestinal (14.3%), and neurological (4.8%) symptoms. Nearly half of the anaphylaxis episodes (n=41/80, 51.3%) occurred at home. The hospital was the most common second setting with 27 cases (33.7%), followed by outdoors with 11 cases (13.7%).

Management of Anaphylaxis

Information about the medical treatment in the hospital setting could be obtained from 69 patients. Of them, 66 (95.7%) received antihistamines, 63 (91.3%) received corticosteroids, and 54 (78.3%) received adrenaline (Table 1). Fourteen patients were treated with only antihistamines without adrenaline administration. Although AAIs had been prescribed for 20 children with a previous history of anaphylaxis, only two of them used the device during the anaphylaxis episode.

Clinical Characteristics of Patients with Severe Anaphylaxis

Among 80 patients, 29 (36.2%) had severe anaphylaxis, and 10 (12.5%) required observation at the intensive care

Table 2. Triggers of anaphylaxis

Triggers	n	%
Drugs	42	52.5
Antibiotics	33	41.3
Nonsteroidal anti-inflammatory drugs	13	16.3
Anesthesia medication	1	1.3
Foods	23	28.8
Milk	15	18.8
Hen's egg	5	6.3
Hazelnut	2	2.5
Walnut	2	2.5
Pistachio nut	1	1.3
Fish	1	1.3
Wheat	1	1.3
Insect sting	8	10
Hymenoptera venom	5	6.3
Mosquito bites	3	3.8
Idiopathic	6	7.5
Measles Vaccine	1	1.3

Table 3. Clinical manifestations of the patients during anaphylaxis

Clinical manifestations	n=80 (%)
Cutaneous	98.8
Urticaria	10
Angioedema	18.8
Urticaria and angioedema	68.8
Flushing	10
Pruritus	1.3
Respiratory	98.8
Dyspnea	85
Stridor	6.3
Wheezing	10
Cough	32.5
Cyanosis	11.3
Cardiovascular	27.5
Hypotension	23.8
Syncope	10
Neurologic	2.5
Seizures	2.5
Gastrointestinal	6.3
Abdominal pain	2.5
Vomiting	5
Diarrhea	1.3

unit. Their median age was 9 years. Seventeen of them had an allergic disease. The most common triggering factors were drugs; the etiological agent could not be determined in one patient. Seven of the 29 patients had a history of recurrent anaphylaxis episodes, and only one used AAI during the reaction.

Comparison of Patients According to the Severity of Anaphylaxis

When the patients were classified according to the severity of anaphylaxis as mild-to-moderate or severe, the median age of patients at the onset of anaphylaxis was significantly higher in the severe group (p=0.007). However, gender, family history of atopy, number of anaphylaxis episodes, total serum IgE levels, and eosinophil counts did not differ significantly between the severe and mild-to-moderate groups (Table 4). The interval between exposure to allergens and the onset of symptoms was also similar in both groups.

In univariate analysis, age at onset of reaction (Odds Ratio [OR]: 1.12, 95% Confidence Interval [CI]: 1.02–1.23, p=0.012), occurrence of the reaction in a hospital setting (OR: 13.96, 95% CI: 4.55–42.82, p<0.001), and drug reaction (OR: 2.92, 95% CI: 1.11–7.66, p=0.029) were associated with severe anaphylaxis. Concomitant asthma and the onset of symptoms within 0–30 min were not significant risk factors. When multivariate regression analysis was performed, age at onset of reaction (OR: 1.20, 95% CI: 1.05–1.38, p=0.006) and occurrence of the reaction in hospital settings (OR: 47, 95% CI: 6.54–342–70, p<0.001) were determined as significant risk factors for severe anaphylaxis (Table 5).

DISCUSSION

In the present study, we evaluated 80 children diagnosed with anaphylaxis and determined the characteristics of the patients and the anaphylactic reactions. In our study, more than half of the cases (63.8%) were male, in accordance with previous studies conducted on children [12, 13]. Most of them (66.3%) had a history of allergic disease. Although the results of our study are compatible with studies conducted by Lee et al. [14] and Serbes et al. [12], there are also studies reporting a lower frequency of allergic disease in anaphylaxis [6, 15]. Hence, the exact role of atopy in anaphylaxis is not well defined.

Table 4. Comparison of the clinical characteristics of the patients with mild to moderate and severe anaphylaxis

	Mild/moderate (n=51) (%)	Severe (n=29) (%)	p
Gender			
Male	64.7	18 (35.3)	0.81*
Female	62	11 (38)	
Age (years) median (range)	5.3 (4 months-17 years)	9 (2 months-17 years)	0.005†
Age at onset of reactions (years) median (range)	3 (4 months-17 years)	8 (1 month-17 years)	0.007†
Serum total IgE (IU/mL) median (lower- upper limit)	87 (2.75-1061)	60 (2-674)	0.41†
Serum eosinophilia (%) median (lower- upper limit)	2.9 (0–20.5)	2 (0–11.9)	0.19†
History of allergic disease (%)	68	32	0.27*
Familial history of allergic disease	64.7	35.3	0.87*
History of recurrent anaphylaxis	66.7	33.3	0.74*

*: Fisher Exact Test was applied; †: Mann–Whitney U test was applied.

Table 5. Risk factors related to severe anaphylaxis

	Univariate regression			Multivariate regression[a]		
	OR	95% CI	p	OR	95% CI	p
Age at onset of reactions (years)	1.12	1.02–1.23	**0.012**	1.20	1.05–1.38	**0.006**
Trigger (drug)	2.92	1.11–7.66	**0.029**	0.156	0.02–1.09	0.061
Setting of reaction (hospital)	13.96	4.55–42.82	**<0.001**	47	6.54–342.70	**<0.001**
History of asthma	1.08	0.40–2.90	0.879	1.61	0.42–6.21	0.483
Interval between exposure and symptoms (0–30 minutes)	2.08	0.52–8.31	0.298	0.8	0.14–4.57	0.080

[a]Variables included in the entered method: Age at onset of reactions, trigger (drug), setting of reaction (hospital), history of asthma, interval between exposure and symptoms (0-30 min). OR: Odds ratio; CI: Confidence interval; Negelkerke R^2:0.425; Prediction percentage: 79.5%.

According to our results, drugs (52.5%) were the leading cause of anaphylaxis in all age groups and especially in children above 2 years of age. On the other hand, when we evaluate our patients according to age groups, food-induced anaphylaxis was observed more commonly in the 0–2 age group. Similar to our results, Hsin et al. [16] reported drugs to be the main cause of anaphylaxis in children. Furthermore, Alves and Sheikh demonstrated a rising trend in drug-induced anaphylaxis with increasing age [17]. However, food was reported as the most common causative agent in all age groups in plenty of studies [3]. This discrepancy can be explained by the higher median age of our patients and the referral of drug allergy cases to our clinic, as it is a tertiary university hospital. However, all of these results were consistent with the knowledge of age-varying triggers and food-induced anaphylaxis, a hallmark of young children [18].

Antibiotics were the main causal agents in patients with drug-induced anaphylaxis. These results were in line with previous studies conducted on children [6, 19]. The food allergens that induce anaphylaxis may differ according to ethnic cultures, dietary habits, and geographic areas. Cow's milk, hen's eggs, and tree nuts are the most common foods causing anaphylaxis [20, 21]. In our study, the main food allergens were cow's milk and dairy products, followed by tree nuts and hen's eggs. Our results are consistent with a recent multicentric study involving 227 patients performed in our country [22]. Similarly,

another study from Turkiye reported that the main food allergens causing anaphylaxis in infants were cow's milk, tree nuts, and hen's egg, respectively [18]. However, in another pediatric study from Turkiye, the main causative agents of food-induced anaphylaxis were reported as peanut and tree nuts, cow's milk, and egg white, respectively [19]. This discrepancy may be attributable to the older age of the study population.

In our study, the cutaneous and respiratory systems were involved in 98.8% of patients. In a retrospective study evaluating 123 pediatric patients with anaphylaxis, the most common clinic manifestations were reported as respiratory and cutaneous symptoms with similar frequency (97%) [13]. Besides, some authors reported that the most prevalent clinical findings involve the cutaneous system, followed by the respiratory, cardiovascular, and gastrointestinal systems [9], while others observed respiratory system involvement more frequently than other organ symptoms [6, 20]. The variability in the symptoms might be caused by the differences in the study population and methodology.

In the present study, 36.2% of patients experienced severe anaphylaxis with intensive care unit admission. In other previous reports, the rate of severe anaphylaxis varied between 1% and 34% [3, 15, 23] This discrepancy may be due to differences in the classification of reaction severity.

Our study showed that drugs were the main causative factor in patients with severe anaphylaxis. This was compatible with the previous reports [15, 23]. Moreover, we have not identified any food allergen as a trigger of severe reactions, in contrast to the study of Grabenhenrich et al. [3], which reported that food allergens were the most frequent causes of severe reactions. This result can be explained by the fact that the median age of our patients with severe anaphylaxis was older.

In our study, older age at onset of reaction was identified as a significant risk factor for severe anaphylaxis. Similarly, severe anaphylaxis was found to be more likely in older patients in a recent study by Kim et al. [15] Although a history of asthma was found to be a risk factor for severe anaphylaxis in previous pediatric studies [14, 15, 24, 25], concomitant asthma was not found to be a significant risk factor in our study. Besides, family history of allergic disease, total serum IgE levels, and eosinophil counts were not significantly associated with severe anaphylaxis, similar to the previous study by Kim et al. [15]. Additionally, we identified that the occurrence of the reaction in a hospital setting was a significant risk factor for severe anaphylaxis. This finding can be explained by the fact that parenteral administrations of drugs in hospital settings might have increased the probability of severe anaphylactic reactions. Drug use as a trigger was found to be a significant risk factor in the univariate analysis, whereas it disappeared in the multivariate analysis.

Although delayed administration of adrenaline has been suggested to be associated with fatal anaphylaxis, it is inadequately used as a first-line treatment [8]. In our study, adrenaline was administered to 78.3% of patients. Moreover, antihistamines were the most commonly used medications for the treatment of anaphylaxis, even though they are considered second-line treatment. Similarly, Huang et al. [26] reported that antihistamines and corticosteroids are given more frequently than adrenaline to children in the pediatric emergency department. Furthermore, our results were compatible with the previous studies conducted in our country [12, 19, 22]. There have been numerous studies evaluating the knowledge of physicians about the diagnosis and management of anaphylaxis, and it was observed that most of the physicians did not indicate adrenaline as a first-line treatment or could not choose the correct dose or administration route [27, 28]. In a recent study that evaluated the knowledge of pediatricians about anaphylaxis, it was reported that most pediatricians use adrenaline as a first-line treatment; however, only 48% of them indicate it correctly. Besides, the authors observed that the proper administration of adrenalin was significantly correlated with the experience of the physicians [29]. However, it is important to know that adrenaline is the only drug that prevents a fatal outcome. Hence, the education of physicians and health-care providers to promote the use of adrenaline in the management of anaphylaxis is essential.

Self-usage of adrenaline by patients is very important, as is prompt treatment by health-care providers to prevent severe outcomes. Hence, patients who experience anaphylaxis should be prescribed AAIs and educated about how to use them. However, previous studies indicated that the prescription of AAIs by physicians is insufficient and that AAIs are still underused by patients with recurrent episodes of anaphylaxis [30, 31]. Consistently, in our study, only 9.5% of patients with recurrent episodes of anaphylaxis used their device. The data from the European Anaphylaxis Registry revealed that 12% of patients with a history of anaphylaxis used AAIs before admission to the hospital [3]. In a recent study from

Turkiye, Esenboga et al. [32] reported that nearly one-third (30%) of 190 patients who were prescribed AAIs used them, and among these patients, only three-quarters used AAIs correctly during recurrent episodes. The inadequate usage of AAIs may be due to the device-related concerns of patients as much as a lack of knowledge.

There were some limitations to this study. One of them was the failure to measure serum tryptase levels in patients diagnosed with anaphylaxis. This limitation is due to the retrospective design of the study. Also, the small number of study groups was an additional limitation.

Conclusion

In conclusion, foods in the first 2 years of age, and drugs in older age were the leading causative allergens of anaphylaxis. However, drugs were the main causative factor in severe anaphylaxis. Most of the reactions occurred at home. The older age at onset of the reaction and the occurrence of the reaction in hospital conditions were determined to be significant risk factors for severe anaphylaxis. Although adrenaline is the first choice in the treatment of anaphylaxis, it has not been adequately used either by doctors in emergency departments as first-line therapy or as an auto-injector by patients in the self-treatment of anaphylaxis. More training programs about the management of anaphylaxis should be planned for patient families and physicians.

Ethics Committee Approval: The Istanbul University, Istanbul Faculty of Medicine Ethics Committee granted approval for this study (date: 19.02.2021, number: 2021/236).

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Authorship Contributions: Concept – SSC, ZT; Design – SSC, ZT; Supervision – SSC, ZT, NG; Data collection and/or processing – SSC, AS, EY; Analysis and/or interpretation – SSC, AS, EY, ZT, NG; Literature review – SSC, AS, EY; Writing – SSC, ZT, NG; Critical review – ZT, NG.

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