

The Etiology, Clinical Features, and Severity of Anaphylaxis in Childhood by Age Groups

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Keywords

Anaphylaxis · Pediatric · Infant · Adolescent · Preschoolers · School-age children · Adrenaline · Drug anaphylaxis · Food anaphylaxis · Anaphylaxis severity

Abstract

Introduction: Anaphylaxis is a severe, potentially fatal systemic hypersensitivity reaction with an acute onset. Etiology, clinical presentation, risk factors, comorbidities of pediatric anaphylaxis may vary depending on the age of the child. **Objective:** The aim of this study was to investigate the etiology, clinical features, management of anaphylaxis in infants, preschoolers, school-age children, and adolescents. **Methods:** The patients presenting with anaphylaxis between January 2015 and December 2018 in a single pediatric tertiary hospital were evaluated retrospectively. Demographic data, the triggers, sign-symptoms, severity, and the management of anaphylaxis were recorded. **Results:** 239 patients were included in the study, 62.3% of whom were boys. The median age was 6.7 (IQR 2.33–12.83) years. 23.8% of the patients were infants, 15.5% were preschoolers, 33.5% were

school-age children, and 27.2% were adolescents. Anaphylaxis mostly occurred at home. The most common causative agents were foods (39.3%), drugs (30.1%), and venoms (15.9%) of all cases. Main food allergens were cow's milk and hen's eggs in infants, cow's milk and tree nuts in preschoolers, and tree nuts and legumes in school-age children. Cases of drug-induced anaphylaxis (DIA) were recorded mostly with antibiotics (40.3%), followed by NSAIDs (23.6%). The primary trigger of anaphylaxis was foods in infants and preschoolers and drugs in school-age children and adolescents. There was no difference between age groups in terms of the system involved and severity. Severe anaphylaxis was more common with DIA. Adrenaline was used in 69.8% of all cases with no significant difference between age groups. **Conclusion:** Etiology and symptoms of anaphylaxis may differ between age groups. Raising awareness, educating patients and their parents on anaphylaxis and its management is essential.

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Introduction

Anaphylaxis is defined as a severe, potentially fatal generalized or systemic hypersensitivity reaction with an acute onset [1]. Pediatric anaphylaxis differs from adult anaphylaxis with regard to etiology, clinical presentation, risk factors, and comorbidities. These features may also vary depending on the age of the child [2]. In infants, it is not always easy to notice the symptoms of anaphylaxis as they cannot express themselves verbally and some symptoms of anaphylaxis can overlap with certain normal infant behaviors [3]. On the other hand, adolescence is a transition period during which the child goes through major physical, psychological, social, and cognitive changes in terms of independence [4]. Since risk-taking behaviors increase during this period, adolescent anaphylaxis should also be evaluated separately from anaphylaxis seen in other age groups.

Studies examining childhood anaphylaxis by age groups are limited. The aim of this study was to evaluate the etiology, signs, symptoms, severity, and management of pediatric anaphylaxis cases presenting to a pediatric tertiary hospital according to age groups.

Methods

Study Design and Data Collection

Medical records of the pediatric patients who were diagnosed with anaphylaxis in a single pediatric tertiary hospital between January 2015 and December 2018 were reviewed retrospectively. Patients with anaphylaxis who were evaluated by the pediatric allergists and immunologists were included in the study.

Demographic data, the triggers of anaphylaxis, detailed information on the signs and symptoms as well as system(s) involved, severity of anaphylaxis, requirement for hospitalization at the pediatric intensive care unit (PICU), the management of anaphylaxis, laboratory data, diagnostic allergy work-up to confirm triggers, and comorbidities were recorded. The institutional ethics committee approved the study protocol (E1-20-388).

Definition of Anaphylaxis

The diagnosis of anaphylaxis and severity classification was based on the criteria recommended by the European Academy of Allergy and Clinical Immunology Taskforce for the management of anaphylaxis in childhood [5].

Age Groups

The patients were divided into 4 groups according to their age at the time of anaphylaxis: 0–2 years (infants), 3–5 years (preschoolers), 6–12 years (school-age children), and over 12 years of age (adolescents).

Tests Used to Confirm Triggers in Anaphylaxis

Skin prick tests (SPTs) and/or serum-specific IgE results confirming the trigger(s) of anaphylaxis were recorded if available. SPTs were considered positive when the diameter of the wheal was >3 mm greater than the negative control, with surrounding erythema appearing within 20 min. Specific IgE levels were measured by UniCAP (up to April 2015) and IMMULITE (after April 2015) techniques. Written informed consent was obtained from parents prior to all procedures. When a proven causative agent could not be identified, the reactions were labeled as idiopathic anaphylaxis.

Statistical Analysis

Statistical analyses were performed using the SPSS Statistics for Windows, version 25.0 (IBM Corporation, Armonk, NY, USA). Categorical variables were expressed as percentages. Continuous variables showing a normal distribution were presented as mean and standard deviation, and those with a non-normal distribution were summarized as median and interquartile range. Differences among the groups were compared using the Student's *t* test, Mann-Whitney U test, or χ^2 test, as appropriate. Logistic regression analyses were done to determine the risk factors for severe anaphylaxis. Variables with a *p* value of <0.2 in the univariate analysis were included in the multivariate logistic regression models. A backward elimination (likelihood ratio) modeling strategy was used. The odds ratios, and their associated 95% confidence intervals, were presented for the effect size of each of the risk factors. A *p* value of <0.05 was considered statistically significant.

Results

Between January 2015 and December 2018, 239 patients were diagnosed with anaphylaxis. The median age of the study population was 6.7 (IQR 2.33–12.83) years, of whom 62.3% were boys. 23.8% (*n* = 57) of anaphylaxis cases observed in infants. Thirty-seven (15.5%) of the patients were preschoolers, 80 (33.5%) were school-age children, 65 (27.2%) were adolescents. Anaphylaxis occurred at home in 55.2% (*n* = 132) patients, 25.5% (*n* = 61) in hospital, 17.6% (*n* = 42) during outdoor activities, and 1.7% (*n* = 4) at school.

The most common causative agents of anaphylaxis were foods (*n* = 94, 39.3%), drugs (*n* = 72, 30.1%), and venoms (*n* = 38, 15.9%). Other triggers were blood products (*n* = 10), horse hair (*n* = 2), vaccination, latex, and cold (*n* = 1, each). Idiopathic anaphylaxis was recorded in twenty (8.4%) patients.

When anaphylaxis cases which occurred in hospital and out of hospital were analyzed separately, foods (52.8%), venoms (21.3%), and drugs (12.9%) were identified as the most common causative agents for anaphylaxis developing out of hospital. There was no difference between the 2 groups in terms of median age and sex (Table 1).

Table 1. General information on the study sample

	All patients (<i>n</i> = 239) (%)	Anaphylaxis out of hospital (<i>n</i> = 178) (%)	Anaphylaxis in hospital (<i>n</i> = 61) (%)	<i>p</i> value*
Male sex	149 (62.3)	116 (65.2)	33 (54.1)	0.124
Median age at anaphylaxis, year, IQR	6.7, IQR 2.33–12.83	7.21, IQR 1.91–13	6.09, IQR 2.36–11.67	0.428
<i>Age groups</i>				
Infants	57 (23.8)	46 (25.8)	11 (18)	
Preschoolers	37 (15.5)	21 (11.8)	16 (26.2)	
School-age children	80 (33.5)	59 (33.2)	21 (34.5)	
Adolescents	65 (27.2)	52 (29.2)	13 (21.3)	
<i>Trigger</i>				
Food	94 (39.3)	94 (52.8)	–	
Drug	72 (30.1)	23 (12.9)	49 (80.3)	
Venom	38 (15.9)	38 (21.3)	–	
Idiopathic	20 (8.4)	20 (11.2)	–	
Blood products	10 (4.2)	–	10 (16.4)	
Other	5 (2.1)	3 (1.7)	2 (3.3)	
<i>Severity of anaphylaxis</i>				
Mild	36 (15.1)	31 (17.4)	5 (8.2)	
Moderate	151 (63.2)	122 (68.5)	29 (47.5)	0.000
Severe	52 (21.7)	25 (14)	27 (44.3)	

* Statistical analyses were performed between outpatients and inpatients.

Main food allergens were cow's milk (CM), tree nuts, hen's eggs, and legumes (39.4%, 16%, 14.9%, and 12.8%, respectively). Drug-induced anaphylaxis (DIA) was recorded mostly with antibiotics, followed by NSAIDs and chemotherapy drugs (40.3%, 23.6%, and 19.4%, respectively). DIA occurred most commonly by intravenous administration of drugs (*n* = 38, 52.8%). 68.1% of DIA occurred in the hospital setting. DIA in outpatients (*n* = 23) recorded mostly with NSAIDs (65.2%) and beta-lactam antibiotics (21.7%).

Triggers of Anaphylaxis by Age Groups

Infants

Foods were the most common causative agents (*n* = 45, 78.9%) in infants. Anaphylaxis was mostly triggered by CM (*n* = 24, 53.3%) and hen's eggs (*n* = 10, 22.2%), followed by legumes (*n* = 5, 11.1%) and tree nuts (*n* = 4, 8.9%).

Preschoolers

Foods (*n* = 17, 45.9%) were also the most common triggers in preschoolers, followed by drugs (*n* = 11, 29.7%). The primary culprit food allergen was CM (*n* = 9). DIA was caused mostly during intravenous infusion of che-

motherapy drugs. Causative antibiotics were beta-lactams.

School-Age Children

In school-age children, drugs (*n* = 27, 33.8%) accounted for the majority of anaphylaxis cases, followed by venoms (*n* = 22, 27.5%) and foods (*n* = 21, 26.3%). The most common causative drugs were beta-lactam antibiotics (*n* = 13, 48.1%); anaphylaxis was triggered by ceftriaxone in 7 patients and cefdinir and cefepime in 1 patient each. Tree nuts and legumes were the most common causative foods (23.8%, each).

Adolescents

Drugs (*n* = 26, 40%) were the most frequent triggers in adolescents. DIA cases were mostly caused by NSAIDs (*n* = 11, 42.3%). Thirteen patients had idiopathic anaphylaxis. The other causative agents were venoms (*n* = 13) and foods (*n* = 11).

General characteristics of the study population, triggers of anaphylaxis are presented in Table 1. Detailed triggers of food-induced anaphylaxis (FIA) and DIA by age groups are summarized in Table 2.

Table 2. Detailed triggers of anaphylaxis by age groups

	All, <i>n</i> (%)	Infants, <i>n</i> (%)	Preschoolers, <i>n</i> (%)	School-age children, <i>n</i> (%)	Adolescents, <i>n</i> (%)
Food anaphylaxis	<i>n</i> = 94	<i>n</i> = 45	<i>n</i> = 17	<i>n</i> = 21	<i>n</i> = 11
CM	37 (39.4)	24 (53.3)	9 (52.9)	4 (19)	–
Hen's eggs	14 (14.9)	10 (22.2)	1 (5.9)	2 (9.5)	1 (9.1)
Tree nuts	16 (17)	4 (8.9)	4 (23.5)	5 (23.8)	3 (27.3)
Walnut	3	2	–	1	–
Hazelnut	6	1	1	1	3
Pistachio	4	1	2	1	–
Almond	2	–	1	1	–
Cashew	1	–	–	1	–
Legumes	12 (12.8)	5 (11.1)	1 (5.9)	5 (23.8)	1 (9.1)
Lentil	10	4	1	4	1
Chickpea	1	1	–	–	–
Haricot bean	1	–	–	1	–
Fish	3 (3.2)	–	1 (5.9)	2 (9.5)	–
Fruit	4 (4.3)	–	1 (5.9)	1 (4.8)	2 (18.2)
Peach	2	–	1	–	1
Kiwi	1	–	–	–	1
Banana	1	–	–	1	–
Potato	3 (3.2)	2 (4.4)	–	–	1 (9.1)
Seeds (hashish)	1 (1.1)	–	–	1 (4.8)	–
Sumac	1 (1.1)	–	–	1 (4.8)	–
Red pepper	1 (1.1)	–	–	–	1 (9.1)
Mushroom	1 (1.1)	–	–	–	1 (9.1)
Corn	1 (1.1)	–	–	–	1 (9.1)
Drug anaphylaxis	<i>n</i> = 72	<i>n</i> = 8	<i>n</i> = 11	<i>n</i> = 27	<i>n</i> = 26
Antibiotics	29 (40.3)	4 (50)	3 (27.3)	14 (51.9)	8 (30.8)
Penicillins	7	–	1	4	2
Cephalosporins	16	2	2	9	3
Meropenem	1	–	–	–	1
TMP-SMX	2	1	–	–	1
Vancomycin	1	1	–	–	–
Azitromycin	1	–	–	1	–
Metronidazole	1	–	–	–	1
NSAIDs	17 (23.6)	–	1 (9.1)	5 (18.5)	11 (42.3)
Ibuprofen	4	–	–	3	1
Flurbiprofen	2	–	–	–	2
Dexketoprofen	2	–	–	–	2
Paracetamol	5	–	1	1	3
ASA	4	–	–	1	3
Chemotherapy drugs	14 (19.4)	1 (12.5)	5 (45.5)	5 (18.5)	3 (11.5)
Asparaginase	12	1	3	5	3
Etoposide	2	–	2	–	–
Enzyme repl. drugs	4 (5.6)	2 (12.5)	1 (9.1)	1 (3.7)	–
Sebelipase alfa	1	1	–	–	–
Alglucosidase alfa	2	1	1	–	–
Elsulfonase	1	–	–	1	–
Octreotide	1 (1.4)	1 (12.5)	–	–	–
Cyclosporine	1 (1.4)	–	1 (9.1)	–	–
Steroid	1 (1.4)	–	–	1 (3.7)	–
Monoclonal ab (rituximab)	1 (1.4)	–	–	1 (3.7)	–
Proton pump inh	1 (1.4)	–	–	–	1 (3.8)
H2 res antagonist	1 (1.4)	–	–	–	1 (3.8)
Parenteral iron	1 (1.4)	–	–	–	1 (3.8)
Local anesthetic	1 (1.4)	–	–	–	1 (3.8)

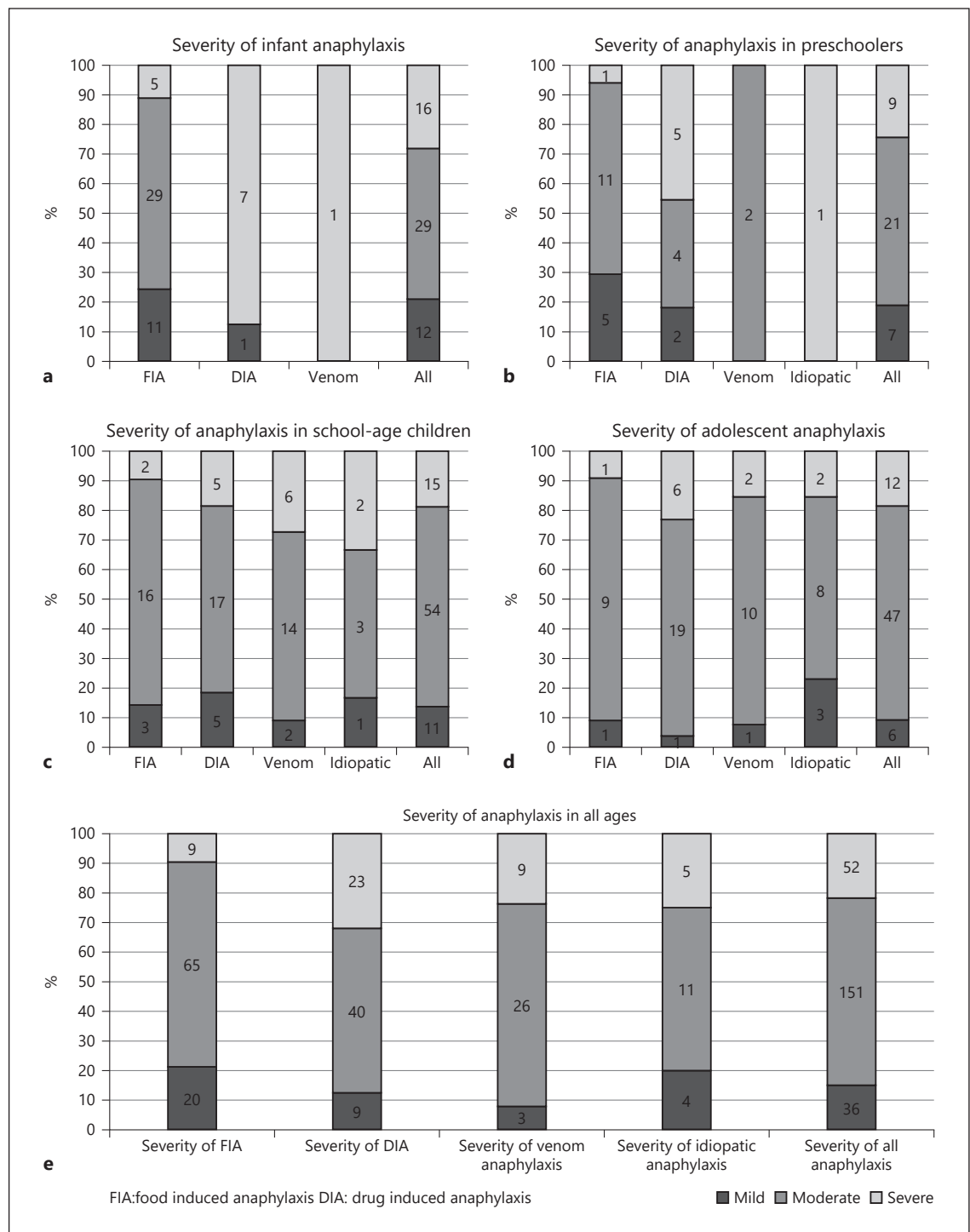


Fig. 1. **a** Severity of infant anaphylaxis. **b** Severity of anaphylaxis in preschoolers. **c** Severity of anaphylaxis in school-age children. **d** Severity of adolescent anaphylaxis. **e** Severity of anaphylaxis in all ages.

Table 3. Risk factors for severe anaphylaxis in childhood

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p value	OR	95% CI	p value
Male sex	1.04	0.55–1.96	0.89			
Young age	1.58	0.8–3.13	0.19			
IV exposure	4.02	2.02–8	0.000	3.4	1.96–6.8	0.001
Having asthma	1.47	0.67–3.25	0.34			
Having AR	9.36	1.24–70.4	0.03	6.64	0.87–50.7	0.69
Having AD	1.6	0.53–4.87	0.41			
Having CD	3.73	1.85–7.52	0.000			

AD, atopic dermatitis; AR, allergic rhinitis; CD, chronic disease; IV, intravenous.

Severity of Anaphylaxis

Of the anaphylaxis cases, 36 (15.1%) were classified as mild, 151 (63.1%) as moderate, and 52 (21.8%) as severe. There was no significant sex-related difference among the severity groups ($p = 0.228$). The severity groups were classified as mild-to-moderate and severe, and age groups were categorized as infants and older age groups to allow for better statistical analysis. The severity of FIA was not significantly different among infants and older age groups ($p = 0.628$), but severe DIA was significantly more prevalent in the infant group ($p = 0.001$). Anaphylaxis severity by age groups and triggers are shown in Figure 1.

The frequency of severe anaphylaxis was significantly higher in the DIA cases compared to cases triggered by foods ($p = 0.000$). Venom-induced anaphylaxis cases were more severe than FIA cases ($p = 0.032$). However, there was no significant difference in terms of severity between cases triggered by venoms and DIA ($p = 0.364$). Of the severe anaphylaxis cases, 44.3% occurred in the hospital, 12.1% at home, 21.4% during outdoor activity.

In univariate logistic regression analysis, younger age, intravenous exposure to causative agent, having allergic rhinitis (AR) and having a chronic disease (CD) were identified as significant risk factors and in multivariate logistic regression analysis, intravenous exposure to causative agent was the only significant risk factor for severe anaphylaxis (Table 3).

Seventeen patients (7.1%) required PICU monitoring. There was no significant difference with regard to mean age ($p = 0.89$), frequencies of asthma ($p = 0.28$), AR ($p = 0.14$), and atopic dermatitis ($p = 0.7$) between the patients who were treated in PICU and those who were not. Comorbidities were significantly more prevalent among patients followed in the PICU ($p = 0.02$). Causative agents were foods ($n = 3$), drugs ($n = 7$), venoms ($n = 3$), blood

products ($n = 3$), and vaccination in patients who were treated in PICU. Four near-fatal reactions occurred, no deaths were recorded. 2.1% ($n = 5$) of anaphylaxis cases were biphasic which was idiopathic in 3 cases and venom associated in 2 cases.

Signs and Symptoms

There was no difference between the age groups in terms of the system involved (Table 4). System involvement by triggers is shown in Figure 2. Persistent vomiting, sneezing, cough, wheezing, and cyanosis were significantly more common in infants than in older age groups ($p = 0.023$, $p = 0.009$, $p = 0.036$, $p = 0.013$, and $p = 0.045$, respectively). Irritability was recorded only in infant anaphylaxis. Generalized pruritus, itchy throat, uvular edema, and dyspnea were significantly more frequent in adolescents compared to younger age groups ($p = 0.000$, $p = 0.017$, $p = 0.012$, $p = 0.007$ respectively).

153 patients (64%) had 2 system involvements. The most common combination was cutaneous and respiratory system involvement which was observed in 69.9% of patients. Seventy patients (29.3%) had 3 system involvement (systems mostly involved were cutaneous, respiratory, and gastrointestinal), 14 patients (5.9%) had 4 system involvement, 2 patients had 5 system involvement.

Concomitant Allergic and CDs

Concomitant allergic and CDs are detailed in Table 5. Children with FIA had a significantly higher rate of asthma and atopic dermatitis than children with non-FIA ($p = 0.000$). There was no difference in AR frequency between food and nonfood triggered anaphylaxis cases ($p = 0.201$). 40.3% ($n = 29$) of patients with DIA had comorbidities.

Table 4. Signs and symptoms during anaphylaxis

	All (n = 239) (%)	Infants (n = 57) (%)	Preschoolers (n = 37) (%)	School-age (n = 80) (%)	Adolescents (n = 65) (%)
Cutaneous	218 (91.2)	52 (91.2)	30 (81.1)	74 (92.5)	62 (95.4)
Urticaria	160 (66.9)	46 (80.7)	18 (48.6)	57 (71.3)	39 (60)
Angioedema	115 (48.1)	22 (38.6)	18 (48.6)	40 (50)	35 (53.8)
Rash	86 (36)	29 (50.9)	10 (27)	27 (33.8)	20 (30.8)
Generalized pruritus	42 (17.6)	3 (5.3)	3 (8.1)	15 (18.8)	21 (32.3)
Itching of eyes/nose/mouth	17 (7.1)	5 (8.8)	1 (2.7)	6 (7.5)	5 (7.7)
Uvular edema	22 (9.2)	2 (3.5)	4 (10.8)	5 (6.3)	11 (16.9)
Respiratory	190 (79.5)	46 (80.7)	28 (75.7)	62 (77.5)	54 (83.1)
Nasal congestion	4 (1.7)	1 (1.8)	–	–	3 (4.6)
Rhinorrhea	11 (4.6)	5 (8.8)	3 (8.1)	1 (1.3)	2 (3.1)
Sneezing	13 (5.4)	7 (12.3)	1 (2.7)	1 (1.3)	4 (6.2)
Throat pruritus	7 (2.9)	–	–	2 (2.6)	5 (7.7)
Dyspnea	139 (58.2)	22 (38.6)	19 (51.4)	51 (63.8)	47 (72.3)
Cough	41 (17.2)	15 (26.3)	10 (27)	14 (17.5)	2 (3.1)
Mild wheezing	23 (9.6)	11 (19.3)	3 (8.1)	7 (8.8)	2 (3.1)
Moderate wheezing	26 (10.9)	7 (12.3)	5 (13.5)	7 (8.8)	7 (10.8)
Hoarseness	9 (3.8)	1 (1.8)	1 (2.7)	2 (2.5)	5 (7.7)
Difficulty swallowing	7 (2.9)	2 (3.5)	1 (2.7)	1 (1.3)	3 (4.6)
Stridor	1 (0.4)	1 (1.8)	–	–	–
Respiratory arrest	3 (1.3)	1 (1.8)	1 (2.7)	–	1 (1.5)
Cyanosis	24 (10)	10 (17.5)	5 (13.5)	5 (6.3)	5 (7.7)
Laryngospasm	1 (0.4)	–	1 (2.7)	–	–
Gastrointestinal	95 (39.7)	22 (61.4)	16 (56.8)	33 (58.8)	24 (63.1)
Nausea and vomiting	78 (32.6)	21 (36.8)	13 (35.1)	25 (31.3)	19 (29.2)
Abdominal pain	25 (10.5)	1 (1.8)	4 (10.8)	13 (16.3)	7 (10.8)
Recurrent vomiting	9 (3.8)	5 (8.8)	–	2 (2.5)	2 (3.1)
Diarrhea	7 (2.9)	1 (1.8)	2 (5.4)	4 (5)	–
Cardiovascular	38 (15.9)	10 (17.5)	5 (13.5)	12 (15)	11 (16.9)
Tachycardia	14 (5.9)	5 (8.8)	2 (5.4)	4 (5)	3 (4.6)
Hypotension/collapse	27 (11.3)	5 (8.8)	3 (8.1)	10 (12.5)	9 (13.8)
Dysrhythmia	1 (0.4)	–	1 (2.7)	–	–
Bradycardia	5 (2.1)	–	1 (2.7)	2 (2.5)	2 (3.1)
Cardiac arrest	3 (1.3)	1 (1.8)	2 (5.4)	–	–
Neurological	41 (17.2)	9 (15.8)	9 (24.3)	12 (15)	11 (16.9)
Change in activity level	14 (5.9)	4 (7)	6 (16.2)	1 (1.3)	3 (4.6)
Irritability	3 (1.3)	3 (5.2)	–	–	–
Altered consciousness	16 (6.7)	3 (5.2)	3 (8.1)	5 (6.3)	5 (7.7)
Convulsion	2 (0.8)	1 (1.8)	–	1 (1.3)	–
Dizziness	5 (2.1)	–	–	3 (3.8)	2 (3.1)
Fear of death	2 (0.8)	–	–	2 (2.5)	–

Laboratory Data

Allergy work-up to confirm triggers (SPT and/or specific IgE) was performed in 71.5% ($n = 171$) of all cases: 96.8% of FIA, 86.8% of venom anaphylaxis, and 34.7% of DIA. Tryptase values measured at the time of reaction were available only for 56 patients. Fourteen patients had a tryptase value exceeding the normal range ($>11.4 \mu\text{L}$). Median tryptase value was $7.3 \mu\text{L}$ (IQR 3.36–11.6) (min: $1.26 \mu\text{L}$ to max: $105 \mu\text{L}$) (Table 5).

Treatment of Anaphylaxis

Adrenaline was given as first-line treatment in 69.8% ($n = 157$, data available for 225) of the patients and 83.6% of the patients who developed an anaphylactic reaction in the hospital received adrenaline. There was no significant difference between the age groups in terms of adrenaline administration ($p = 0.504$). 55.6% of patients with mild anaphylaxis, 66.7% of patients with moderate anaphylaxis, and 88.2% of patients with severe anaphylaxis received

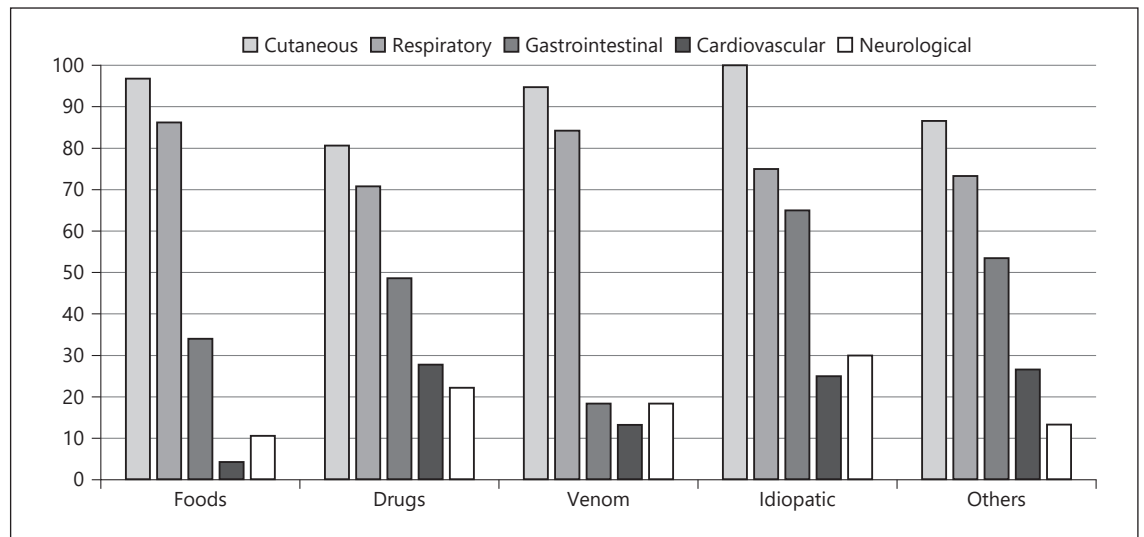


Fig. 2. System involvement by triggers.

Table 5. Concomitant diseases, laboratory data, and treatment of anaphylaxis by age groups

	All, n (%)	Infant, n (%)	Preschoolers, n (%)	School-age children, n (%)	Adolescents, n (%)
Concomitant allergic diseases	90 (37.7)	27 (47.4)	13 (35.1)	28 (35)	22 (35.5)
Asthma/recurrent wheezing	53 (22.2)	12 (27)	10 (23.8)	19 (18.5)	12 (22.2)
AD	26 (10.9)	19 (33.3)	3 (8.1)	4 (5)	–
AR	30 (12.6)	–	4 (10.8)	13 (16.3)	13 (20)
Chronic urticaria	1 (4.2)	–	–	–	1 (1.5)
Concomitant CD	43 (18)	9 (15.8)	13 (35.1)	11 (13.8)	10 (15.4)
Hematologic-oncologic disease	22 (9.2)	2 (3.5)	10 (27)	7 (8.8)	3 (4.6)
Immune deficiency disease	7 (2.9)	3 (5.3)	1 (2.7)	1 (1.3)	2 (3.1)
Metabolic disease	4 (1.7)	2 (3.5)	1 (2.7)	1 (1.3)	–
Neurological disease	4 (1.7)	1 (1.8)	1 (2.7)	–	2 (3.1)
Nephrological disease	4 (1.7)	–	–	1 (1.3)	3 (4.6)
Hypercholesterolemia	1 (0.4)	–	–	1 (1.3)	–
Protein losing enteropathy	1 (0.4)	1 (1.8)	–	–	–
Laboratory					
Median eosinophil count (IQR)	200 (100–400)	350 (200–725)	200 (0–500)	200 (0–300)	100 (0–200)
Median eosinophil % (IQR)	1.95 (0.73–4.48)	3.95 (1.8–6.25)	3.32 (1.2–4)	1.8 (0.6–4.5)	1 (0.2–1.98)
Median IgE (IQR)	143.5 (28.8–407.8)	69.1 (19.3–409.3)	305 (138.3–1,292)	144 (39–429.5)	119 (50.2–235.8)
Tryptase (IQR)	7.3 µL (IQR 3.36–11.6)	7.9 µL (IQR 4.7–11.1)	4.8 µL (IQR 2.8–8.1)	7.8 µL (IQR 2.9–13.8)	10.2 µL (IQR 3.2–12.3)
Treatment (data available in 225)					
Adrenaline	157/225 (69.8)	32/51 (62.7)	25/35 (71.4)	53/77 (68.8)	47/62 (75.8)
Steroid	157/225 (69.8)	37/51 (72.5)	23/35 (65.7)	52/77 (67.5)	42/62 (67.7)
H1 antihistamines	151/225 (67.1)	35/51 (68.6)	23/35 (65.7)	53/77 (68.8)	45/62 (72.6)
Fluid replacement therapy	22/225 (9.8)	6/51 (11.8)	2/35 (5.7)	9/77 (11.7)	5/62 (8.1)
β2 mimetics	15/225 (6.7)	2/51 (3.9)	3/35 (8.6)	3/77 (3.9)	7/62 (11.3)
Oxygen	12/225 (5.3)	2/51 (3.9)	3/35 (8.6)	4/77 (5.2)	3/62 (4.8)
Cardiopulmonary resuscitation	4/225 (1.7)	1/51 (1.9)	2/35 (5.7)	1/77 (1.3)	–

AD, atopic dermatitis; AR, allergic rhinitis; CD, chronic disease

adrenaline as first-line treatment. Adrenaline administration was significantly more common in the severe anaphylaxis group ($p = 0.002$). Other drugs and supportive measures used during anaphylactic reactions are summarized in Table 5.

Discussion

In this study, we evaluated anaphylaxis cases according to age groups in a large pediatric tertiary hospital over a period of 4 years. Foods were the most common cause of anaphylaxis in younger age groups; drugs were the most common offenders in older age groups. The frequencies of persistent vomiting, sneezing, cough, wheezing, and cyanosis were significantly higher in infants whereas uvular edema, itchy throat, and dyspnea were more prevalent in adolescents. The severity of anaphylaxis was not different among age groups but severe anaphylaxis was more common with DIA. Adrenaline was used in 69.8% of all anaphylaxis cases with no significant difference among age groups.

Vezir et al. [6] reported the frequency of anaphylactic triggers (in descending order) as venoms, foods, drugs in their study which was conducted at the same institution between 2010 and 2012. The most common triggers were foods, followed by drugs and venoms in the current study. However, when the triggers were analyzed according to age groups, foods were the most common culprit agents in the infants and preschool children, while drugs were the primary trigger in the school-age children and adolescents.

Although there are studies reporting foods as the main trigger of anaphylaxis in all age groups [7, 8], in a Latin American study, foods were the main triggers until 12 years of age and drugs were the most frequent culprit agents in adolescents [9]. Foods were the main triggers in all age groups in the European Anaphylaxis Registry, but it was underscored that there was a continuous shift from food to venom and DIA up to the age of 10 [10].

In the present study, the most common food allergens were CM and hen's eggs in infants, CM and tree nuts in preschoolers, and tree nuts and legumes in school-age children. In the studies from the USA, tree nuts and peanuts were reported to be the key triggers of FIA [7, 11]. In the European Anaphylaxis Registry, peanut was the most common trigger in all age groups, but it was stated that CM and hen's eggs were primarily responsible for anaphylactic reactions in infants and tree nuts in preschoolers [10]. In a Turkish study, Kahveci et al. [12] reported

that the main food allergens responsible for anaphylaxis were CM in infants and tree nuts among toddlers and preschoolers. It is noteworthy that there was no case of peanut anaphylaxis in our study. This may be explained by the nutritional habits of our country which is located in the Eastern Mediterranean region, where peanut consumption is not as common as in western countries.

In former studies on anaphylaxis in children, the DIA prevalence varied widely from 5% to 33% of all cases [6, 7, 9, 10, 13–15]. In the current study, drugs were the most common causative agents in school-age children and adolescents and accounted for 30% of anaphylaxis cases. Antibiotics, especially beta-lactams, have been reported as the primary trigger of DIA in several pediatric studies [6–8, 16, 17]. On the other hand, NSAIDs were found to be the most frequent culprit drugs in a Latin American study [9], and ibuprofen was reported as the primary cause of DIA in a Singapore study [13]. The majority of DIA cases were attributed to antibiotics, most commonly with cephalosporins in our study but in adolescents, DIA occurred mostly with NSAIDs.

Presentation of infant anaphylaxis may differ from that observed in older children who are able to verbalize their symptoms and certain anaphylaxis symptoms may be considered as part of normal infant behavior. Therefore, a high index of suspicion is required for the recognition of infant anaphylaxis [3]. Hoarseness, drooling, hypotonia, faintness, continuous crying, irritability, persistent vomiting, and somnolence were reported as nonspecific symptoms for infant anaphylaxis in previous reports from our country [18, 19]. Pouessel et al. [20] reported that, in addition to hives and neurologic symptoms, hypotension was more common in infants with FIA than preschoolers. In the present study, persistent vomiting, sneezing, cough, wheezing, and cyanosis were significantly common among infants and irritability was reported only in infants.

In the European Anaphylaxis Registry cohort, 6% of patients were treated in PICU [10]. Hoffer et al. [21] reported that 7.6% of hospitalized pediatric patients with anaphylaxis required intensive care. In our study, 7.1% of all patients were treated at PICU, 41.2% of whom were DIA cases. On the other hand, peanut was identified as the most common trigger of anaphylaxis among children who were admitted to PICU in North America and Mexico [22].

Underuse of adrenaline in anaphylaxis treatment has been reported in several pediatric studies [6, 23–25]. Although it has been reported that the use of adrenaline in anaphylaxis has increased gradually over the years, it is

still not at the desired level [26, 27]. In the current study, 69.8% of patients received adrenaline as the first-line treatment. The frequency of adrenaline use was 44.4% in the study conducted in the same pediatric tertiary hospital between 2010 and 2012 [6]. Although it was reported that adrenaline use for the management of infant anaphylaxis was significantly less common when compared with older age groups [12], there was no difference between age groups in terms of adrenaline administration in our study.

Limitations of Our Study

Confirmatory allergy work-up could not be performed for all patients. Anaphylaxis triggers were identified through compatible story in some patients. Our hospital is a large tertiary pediatric institution where hematology-oncology patients are frequently referred and receive care. Therefore, we may have detected more DIA cases in our study population than in the general population.

In conclusion, the etiology and symptoms of anaphylaxis may differ among age groups. Foods are the most common triggers of anaphylaxis in younger age groups. In addition to foods, drugs account for the majority of anaphylactic reactions in older age groups. It may be difficult to recognize symptoms of anaphylaxis in younger age groups. Raising awareness of anaphylaxis among patients and their parents and educating them about the prevention and management of anaphylaxis are essential.

Statement of Ethics

Subjects have given their written informed consent, and the study protocol was approved by the institute's committee on human research.

References

- 1 Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T, et al. A revised nomenclature for allergy. An EAACI position statement from the EAAACI nomenclature task force. *Allergy*. 2001; 56(9):813–24.
- 2 Chipps BE. Update in pediatric anaphylaxis: a systematic review. *Clin Pediatr*. 2013;52(5): 451–61.
- 3 Greenhawt M, Gupta RS, Meadows JA, Pistiner M, Spergel JM, Camargo CA Jr, et al. Guiding principles for the recognition, diagnosis, and management of infants with anaphylaxis: an expert panel consensus. *J Allergy Clin Immunol Pract*. 2019;7(4):1148–56.e5.
- 4 Zimmer-Gembeck MJ, Collins WA. Autonomy development during adolescence. *Blackwell handbook of adolescence*. 2006. p. 174–204.
- 5 Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G, et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. *Allergy*. 2007;62(8): 857–71.
- 6 Vezir E, Erkokoglu M, Kaya A, Toyran M, Ozcan C, Akan A, et al. Characteristics of anaphylaxis in children referred to a tertiary care center. *Allergy Asthma Proc*. 2013;34(3):239–46.
- 7 Anvari S, Blackman AC, Anagnostou A. Insights from 275 cases of childhood anaphylaxis in the United States. *J Allergy Clin Immunol Pract*. 2019;7(5):1696–9.e2.
- 8 Lee SY, Ahn K, Kim J, Jang GC, Min TK, Yang HJ, et al. A multicenter retrospective case study of anaphylaxis triggers by age in Korean children. *Allergy Asthma Immunol Res*. 2016; 8(6):535–40.
- 9 Sole D, Ivancevich JC, Borges MS, Coelho MA, Rosario NA, Arduoso L, et al. Anaphylaxis in Latin American children and adolescents: the online Latin American survey on anaphylaxis (OLASA). *Allergol Immunopathol*. 2012;40(6):331–5.
- 10 Grabenhenrich LB, Dolle S, Moneret-Vautrin A, Kohli A, Lange L, Spindler T, et al. Anaphylaxis in children and adolescents: the European anaphylaxis registry. *J Allergy Clin Immunol*. 2016;137(4):1128–37.e1.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Irem Turgay Yagmur, Emine Dibek Mısırlıoğlu, İlknur Kulhas Celik, Ozge Yilmaz Topal, Muge Toyran, Can Naci Kocabas, and Ersoy Civelek made substantial contributions to design of the study, acquisition of data, analysis and interpretation of data; drafted the article and reviewed it critically for important intellectual content; gave final approval of the version to be published and agrees to be accountable for all aspects of the study related to its accuracy or integrity. Betül Karaatmaca made substantial contributions to acquisition of data, drafted the article, gave final approval of the version to be published and agrees to be accountable for all aspects of the study related to its accuracy or integrity.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author [E.D.M.].

- 11 Motosue MS, Bellolio MF, Van Houten HK, Shah ND, Campbell RL. National trends in emergency department visits and hospitalizations for food-induced anaphylaxis in US children. *Pediatr Allergy Immunol*. 2018;29(5):538–44.
- 12 Kahveci M, Akarsu A, Koken G, Sahiner UM, Soyer O, Sekerel BE. Food-induced anaphylaxis in infants, as compared to toddlers and preschool children in Turkey. *Pediatr Allergy Immunol*. 2020;31(8):954–61.
- 13 Liew WK, Chiang WC, Goh AE, Lim HH, Chay OM, Chang S, et al. Paediatric anaphylaxis in a Singaporean children cohort: changing food allergy triggers over time. *Asia Pac Allergy*. 2013;3(1):29–34.
- 14 Manuyakorn W, Benjaponpitak S, Kamchaisatian W, Vilaiyuk S, Sasisakulporn C, Jotikasthira W. Pediatric anaphylaxis: triggers, clinical features, and treatment in a tertiary-care hospital. *Asian Pac J Allergy Immunol*. 2015;33(4):281–8.
- 15 Gaspar A, Santos N, Faria E, Pereira AM, Gomes E, Camara R, et al. Anaphylaxis in children and adolescents: the Portuguese anaphylaxis registry. *Pediatr Allergy Immunol*. 2021;32(6):1278–86.
- 16 Xing Y, Zhang H, Sun S, Ma X, Pleasants RA, Tang H, et al. Clinical features and treatment of pediatric patients with drug-induced anaphylaxis: a study based on pharmacovigilance data. *Eur J Pediatr*. 2018;177(1):145–54.
- 17 Cavkaytar O, Karaatmaca B, Cetinkaya PG, Esenboga S, Arik Yilmaz E, Sahiner UM, et al. Characteristics of drug-induced anaphylaxis in children and adolescents. *Allergy Asthma Proc*. 2017;38(5):56–63.
- 18 Dibek Misirlioglu E, Vezir E, Toyran M, Capanoglu M, Guvenir H, Civelek E, et al. Clinical diagnosis and management of anaphylaxis in infancy. *Allergy Asthma Proc*. 2017;38(1):38–43.
- 19 Topal E, Bakirtas A, Yilmaz O, Ertoyl Karagol IH, Arga M, Demirsoy MS, et al. Anaphylaxis in infancy compared with older children. *Allergy Asthma Proc*. 2013;34(3):233–8.
- 20 Pouessel G, Jean-Bart C, Deschildre A, Van der Brempt X, Tanno LK, Beaumont P, et al. Food-induced anaphylaxis in infancy compared to preschool age: a retrospective analysis. *Clin Exp Allergy*. 2020;50(1):74–81.
- 21 Hoffer V, Scheuerman O, Marcus N, Levy Y, Segal N, Lagovsky I, et al. Anaphylaxis in Israel: experience with 92 hospitalized children. *Pediatr Allergy Immunol*. 2011;22(2):172–7.
- 22 Ramsey NB, Guffey D, Anagnostou K, Coleman NE, Davis CM. Epidemiology of anaphylaxis in critically ill children in the United States and Canada. *J Allergy Clin Immunol Pract*. 2019;7(7):2241–9.
- 23 Wright CD, Longjohn M, Lieberman PL, Lieberman JA. An analysis of anaphylaxis cases at a single pediatric emergency department during a 1-year period. *Ann Allergy Asthma Immunol*. 2017;118(4):461–4.
- 24 de Silva IL, Mehr SS, Tey D, Tang ML. Paediatric anaphylaxis: a 5 year retrospective review. *Allergy*. 2008;63(8):1071–6.
- 25 Sidhu N, Jones S, Perry T, Thompson T, Storm E, Melguizo Castro MS, et al. Evaluation of anaphylaxis management in a pediatric emergency department. *Pediatr Emerg Care*. 2016;32(8):508–13.
- 26 Cohen N, Capua T, Pivko-Levy D, Ben-Shoshan M, Rimon A, Benor S. Improved diagnosis and treatment of anaphylaxis in a pediatric emergency department (2013–2018). *J Allergy Clin Immunol Pract*. 2019;7(8):2882–4.e2.
- 27 Rueter K, Ta B, Bear N, Lucas M, Borland ML, Prescott SL. Increased use of adrenaline in the management of childhood anaphylaxis over the last decade. *J Allergy Clin Immunol Pract*. 2018;6(5):1545–52.