

Food-induced anaphylaxis in infants, as compared to toddlers and preschool children in Turkey

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Funding information

There is no financial support.

Editor: Motohiro Ebisawa

Abstract

Background: The literature includes scarce data on infants with food-induced anaphylaxis (FIA).

Materials and Methods: Medical records of the patients diagnosed with FIA aged 0-6 years between 2015 and 2020 were retrospectively analyzed.

Results: During the study period, there were 451 instances of FIA in 314 patients, of which 175 (38.8%) occurred in 160 infants (50.9%). The median (IQR) age of infants was 7 months (6-9 months) with a male predominance (67.5%), of which 7.5% had multiple instances (≥ 2) and 60% atopic dermatitis. The most common triggers were cow's milk (51.4%), tree nuts (16.6%), and hen's egg (15.4%), whereas tree nut was the most common trigger in toddlers (35.8%) and preschool children (35.2%). Skin and neurologic symptoms, and nausea-vomiting occurred more frequently ($P = .003$, $P \leq .001$, and $P = .003$, respectively), whereas respiratory symptoms occurred less commonly in infants compared to toddlers and preschool children ($P \leq .001$). In infants, 65 (37.1%) mild, 92 (52.6%) moderate, and 18 (10.3%) severe episodes of anaphylaxis were detected. History of recurrent wheezing (OR: 6.837 [95% CI: 1.940-24.097], $P = .003$) and tree nut allergy (OR: 2.849 [95% CI: 1.056-7.688], $P = .039$) were found to be independent risk factors for moderate-to-severe anaphylactic reactions. 40.6% of the infants received adrenaline, which was lower than the toddlers (49.7%) and preschool children (57.6%) ($P = .005$).

Conclusion: There is no doubt that food-induced anaphylaxis is a medical emergency, specifically in young children. Pediatricians should be aware of the distinct features of infant anaphylaxis, particularly gastrointestinal and neurologic symptoms to provide effective treatment as soon as possible.

KEYWORDS

Epinephrine, food-induced anaphylaxis, infants, preschool children, toddlers

1 | INTRODUCTION

Currently, the incidence of anaphylaxis is increasing, particularly in children.¹ Anaphylaxis can be induced by a variety of agents, but the

food is the most common etiology in children. Cow's milk, hen's egg, and peanut are the most common triggers, but any food can potentially provoke anaphylaxis, including tree nuts, soy and other legumes, fish, vegetables, fruits, and grains;^{2,3} however, the frequency

and distribution of food triggers vary with population-based differences in nutritional preferences.

A major 2006 epidemiological study reported that the lifetime prevalence of anaphylaxis due to all causes is 0.05%-2%,⁴ yet few data are available concerning infant anaphylaxis and its clinical presentation. Moreover, the actual incidence of infant anaphylaxis remains unknown.⁵ The diagnosis of anaphylaxis in infants is especially difficult due to the wide range of clinical presentations and differential diagnoses. Although anaphylaxis is under-diagnosed, it is reported with increasing frequency in infants.⁶ Between 2008 and 2012, there was an annual increase of 27% in Chicago emergency department (ED) visits and hospitalizations due to food-induced anaphylaxis (FIA) among children aged 0-4 years, which highlights the potential vulnerability of infants and toddlers.⁷ More recent studies indicate that infants constitute 3%-22% of anaphylaxis cases admitted to EDs;⁸ as such, clinician knowledge and awareness of infant FIA must be improved in order to promote its clinical diagnosis and treatment. The present study aimed to document the clinical characteristics of FIA and food triggers in infants compared to those in toddlers and preschool children.

2 | MATERIALS AND METHODS

2.1 | Participants

This retrospective study included patients with a history of FIA aged 0-6 years who admitted to Hacettepe University Ihsan Doğramacı Children's Hospital, Ankara, Turkey, between January 01, 2015, and January 01, 2020. Age at FIA was categorized as follows: infants (age: 0-12 months), toddlers (age: 13-36 months), and preschool children (age: 37-72 months). The clinical characteristics and food triggers of FIA in the infant group were compared to the toddler and preschool children groups. The FIA was defined according to the Anaphylaxis Guidelines from the European Academy of Allergy and Clinical Immunology⁹. According to organ systems, symptoms were categorized as skin, mucosal, gastrointestinal, respiratory, cardiovascular, and/or neurologic. Hives, flushing, redness, and pruritus were considered as a skin symptom and angioedema as a mucosal symptom. Also, cough, wheezing, stridor, dyspnoea, and rhinitis were deemed to be respiratory symptoms. Nausea-vomiting, abdominal pain, and diarrhea were defined as gastrointestinal symptoms, and persistent crying, restlessness, decrease in activity (hypotonia), and/or convulsions were defined as neurologic symptoms. Hypotension (anaphylactic shock) at any time was defined as a cardiovascular symptom. Hypotension was a systolic blood pressure <70 mm Hg in the infant group and <70 mm Hg + [2 × age] in the toddler and preschool children groups^{9,10}. The severity of anaphylaxis was classified as mild, moderate, and severe, according to European Academy of Allergology and Clinical Immunology Task Force Management of Anaphylaxis in Childhood Position Paper criteria¹¹.

Key message

The findings of the study showed that food-induced anaphylaxis (FIA) in Turkish children aged <6 years were associated with unique triggers. In the infant group cow's milk, tree nuts, hen's egg, and wheat were the most common food triggers. Interestingly, almost half of the instances of food-induced anaphylaxis (FIA) occurred during the first year of life, usually during initial exposure to the food. In the infant group, the symptom distribution of anaphylaxis was different than the other age groups and anaphylaxis mostly affected skin, gastrointestinal system, and neurological systems which resulted in less severe forms of anaphylaxis.

2.2 | Data source and handling

Patient's medical history and features of hypersensitivity reactions were recorded using a standard survey that included gender, age, history of atopic disease, symptoms of anaphylaxis, trigger foods, the time between exposure and onset of symptoms, location of reaction, pediatric intensive care unit (PICU) admission, medications used at home and hospital, availability and use of an auto-injector by parents, and cofactors such as infections or drugs, biphasic reaction, and family history of atopy. Skin prick test (SPT) and sIgE results for the food that caused anaphylaxis were recorded. A mean wheal diameter of 3 mm larger than the control was considered a positive SPT, and the test was performed 4-6 weeks after anaphylaxis in patients that were not previously diagnosed with a food allergy. The sIgE level was measured in serum using a Pharmacia CAP system (ImmunoCAP; Pharmacia & Upjohn, Uppsala, Sweden); a value ≥ 0.35 kUA L⁻¹ was considered positive. Complete blood cell count, the eosinophil percentage, the absolute eosinophil count (AEC), and total serum IgE, if available, were noted. The study protocol was approved by the Hacettepe University School of Medicine Ethics Committee.

2.3 | Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, USA). Descriptive analysis was used to characterize the patients. Pearson's chi-square test or Fisher's exact test was used for between-group comparisons. Values are shown as the median and inter-quartile range for data not normally distributed. The Mann-Whitney U test or Kruskal-Wallis test was used to compare values. Uni- and multivariate analyses were performed to predict potential associations between clinical and/or laboratory parameters, and anaphylactic reaction severity. Factors that were significant based on univariate regression analysis ($P < .2$)

were then included as covariates in multiple regression analysis. The odds ratio (OR) with relevant 95% confidence interval (CI) was calculated via uni- and multivariate analyses. All statistical tests were 2-sided, and the level of statistical significance was set at $P < .05$.

3 | RESULTS

There were 451 FIA reactions recorded in patients aged 0-72 months, of which 175 (38.8%) occurred in infants, 151 (33.5%) in toddlers, and 125 (27.7%) in preschool children. Among the patients, 29.9% experienced ≥ 2 anaphylactic reactions: 2 reactions ($n = 62$), 3 reactions ($n = 25$), 4 reactions ($n = 6$), and 8 reactions ($n = 1$). The median time (IQR) between multiple anaphylactic reactions was 10 months (3-23 months).

3.1 | Characteristics of the infant group

The infant group consisted of 160 infants who experienced the first anaphylactic reaction at the median (IQR) age of 7 months (6-9 months) with a male predominance (67.5%). In total, 12 infants (7.5%) experienced ≥ 2 anaphylactic reactions as follows: 2 reactions ($n = 9$) and 3 reactions ($n = 3$), and there were 175 instances of FIA. Multiple food allergies were noted in 61.9% of the infants ($n = 99$) and 2,

3, and ≥ 4 food allergies in 28.1%, 17.5%, and 16.9%, respectively. Among the infants, 111 (69.4%) had a concomitant allergic disease, most commonly atopic dermatitis (60%), and a history of recurrent wheezing (16.3%). Some of the infants ($n = 38$) had already been diagnosed as food allergy before the occurrence of FIA. Whereas 25 (15.6%) of them experienced FIA in response to previously known food allergens, 13 (8.1%) had FIA in response to previously unknown food allergens. Nearly, one-sixth of infants ($n = 24$) established FIA at initial exposure during complementary feeding. The primary characteristics of the infants, as compared to the toddlers and preschool children, are detailed in Table 1.

3.2 | Triggers and symptoms of anaphylaxis in the infant group

The main food allergens responsible for 175 anaphylactic reactions in the infant group were cow's milk (51.4%), tree nuts (16.6%), hen's egg (15.4%), wheat (5.7%), lentil (5.1%), sesame (4.6%), and chickpea (0.6%) (Figure 1). Among tree nuts, hazelnut was the most common etiology in the toddler and preschool children groups. In contrast, pistachio was the most common in the infant group, followed by hazelnut, walnut, and cashew. None of the patients in the infant group had peanut-induced anaphylaxis (Figure 2). The most common food allergy in the infant group was cow's milk (51.4%), whereas the most

TABLE 1 Characteristics of the three study groups

	All n = 314	Infants n = 160	Toddlers n = 95	Preschoolers n = 59	P
Male (n, %)	198 (63.1)	108 (67.5)	54 (56.8)	36 (61)	.285
The age at first anaphylaxis (months)*	12 (6-28.5)	7 (6-9)	21 (18-27)	51 (40-60)	<.001
Comorbidities (medical history)					
Allergic rhinitis (n, %)	8 (2.5)	-	-	8 (13.6)	.215
History of recurrent wheezing (n, %)	67 (21.3)	26 (16.3)	20 (21.2)	24 (40.7)	.001
Atopic dermatitis (n, %)	185 (58.9)	96 (60)	64 (67.4)	25 (42.4)	.182
Previously known food allergy (n, %)	155 (49.4)	38 (23.8)	64 (67.4)	53 (89.8)	<.001
Multiple FA (n, %)	203 (64.6)	99 (61.9)	65 (68.4)	39 (66.1)	.126
Number of allergens					
1	111 (35.4)	60 (37.5)	30 (31.6)	21 (35.6)	
2	77 (24.5)	45 (28.1)	19 (20)	13 (22)	
3	61 (19.4)	28 (17.5)	20 (21.1)	13 (22)	
≥ 4	65 (20.7)	27 (16.9)	26 (27.4)	12 (20.3)	
Family history of atopy (n, %)	87 (27.7)	39 (24.4)	29 (30.5)	19 (32.2)	.141
Location of the first exposure (n, %)					
Home	253 (80.6)	152 (95)	70 (73.7)	31 (52.5)	<.001
Hospital, during OFC	40 (12.7)	5 (3.1)	19 (20)	16 (27.1)	
Outdoors	21 (6.7)	3 (1.9)	6 (6.3)	12 (20.3)	

*Median, IQR, inter-quartile range; OFC, oral food challenge; SPT, skin prick test.

common food allergy in the toddler and preschool children groups was tree nuts ($P < .001$).

The median time from allergen exposure to onset of symptoms was 10 min (IQR: 5-15 min), and 95% of the episodes of anaphylaxis occurred at home. The clinical manifestations of FIA were skin (90.9%) [primarily hives (68%)], respiratory (58.9%) [primarily cough (31%)], gastrointestinal (56%) (nausea and vomiting), and mucosal (45.1%). Neurologic symptoms of FIA were observed in 14.9% of the patients. None of the infants had cardiovascular manifestations. Skin (especially redness and pruritus), nausea-vomiting, and neurologic symptoms were noted more frequently in the infant group, whereas respiratory symptoms were less common compared to toddlers and preschool children groups (Table 2). Respiratory symptoms and angioedema were the most frequent symptoms of FIA in cases of tree nut-triggered FIA, as compared to cow's milk and hen's egg (80.3%, 67.8%, and 64.5%, and 60.6%, 45%, and 45.2, respectively).

In the infant group, six of 175 anaphylactic instances occurred in the hospital during the oral food challenge (OFC). Only persistent crying and restlessness were more frequent in the OFC group than in the non-OFC group ($P = .014$). Comparison of the reaction characteristics of non-OFC and OFC groups is shown in Supplementary Table 1. The eosinophil count and percentage were similar in all three groups, but total IgE was higher in the preschool children group. Additionally, although the rate of SPT positivity for food triggers was significantly lower in the infant group, there was not a difference in the sIgE values between the infant group, and the toddler and preschool children groups (Table 2). In total, there were 65 (37.1%) mild, 92 (52.6%) moderate, and 18 (10.3%) severe anaphylaxis reactions in the infant group (Table 2). Tree nuts were the most common etiology (38.9%) in cases of severe anaphylaxis in the infant group, followed by cow's milk (27.7%), hen's egg (22.2%), sesame (5.6%), and wheat (5.6%). Tree nut-induced anaphylaxis caused 5 episodes of mild reactions, and 17 instances of moderate and 7 instances of severe reactions. Multivariate analysis showed that a history of recurrent wheezing (OR: 6.837 [95% CI: 1.940-24.097], $P = .003$) and tree nut allergy (OR: 2.849 [95% CI: 1.056-7.688] $P = .039$) were risk factors for moderate-to-severe versus mild anaphylactic reactions

in the infant group (Table 3). A biphasic anaphylactic reaction was observed in a 6-month-old infant with hen's egg allergy who developed vomiting and cutaneous rash after 4 hours. No fatality was observed. As potential cofactors, three infants were using antibiotics at the time of FIA of whom two had otitis media and one had urinary tract infection. Two had an upper respiratory viral infection.

3.3 | Treatment and follow-up in the infant group

Of all, 71 (40.6%) of the infants were administered adrenaline. Only one infant was given ≥ 2 doses of intramuscular adrenaline, and none of the infants required an intravenous infusion of adrenaline. Adrenaline auto-injectors (AAls) were prescribed to 18 (10.3%) of the infants because of anaphylaxis history, but none used them. The rate of adrenaline use in the infant group was significantly lower than the groups of toddler and preschool children ($P = .005$). Other medications used to treat FIA were as follows: H1 antihistamines ($n = 150$ [85.7%]), corticosteroids ($n = 124$ [70.9%]), β_2 -agonist inhalers ($n = 25$ [14.3%]), and IV fluid ($n = 12$ [6.9%]). ED visits were noted in 153 (87.4%) of the infants, which was a higher rate than in the toddler and preschool children groups ($P < .001$). In total, 36 (16%) of the infants were hospitalized, of whom 2 (1.1%) were treated in a PICU (Table 4).

In terms of the relationship between FIA treatment and food triggers, adrenaline and corticosteroid use and hospitalization were more common in the patients with tree nut allergy than in those with allergy to cow's milk and hen's egg (63.8%, 38.6%, and 46.5%; 85%, 74.3%, and 69.4%; and 24.4%, 12.9%, and 16.1%, respectively). Tree nut-induced anaphylaxis in comparison with cow's milk- and hen's egg-induced anaphylaxis resulted in the more frequent use of adrenaline (63.8%, 38.6%, and 46.5, respectively) and corticosteroids (85%, 74.3%, and 69.4%, respectively).

4 | DISCUSSION

The present study documented infants compared to toddlers and preschool children with FIA, so as to disseminate knowledge of

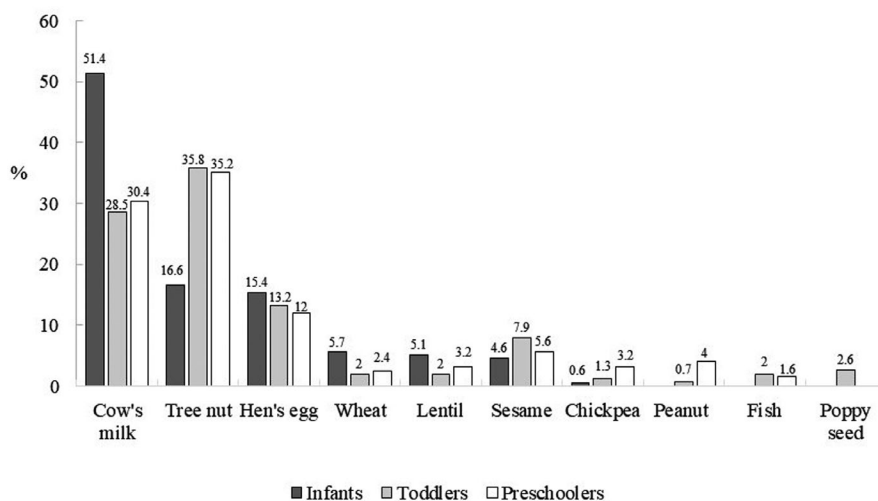
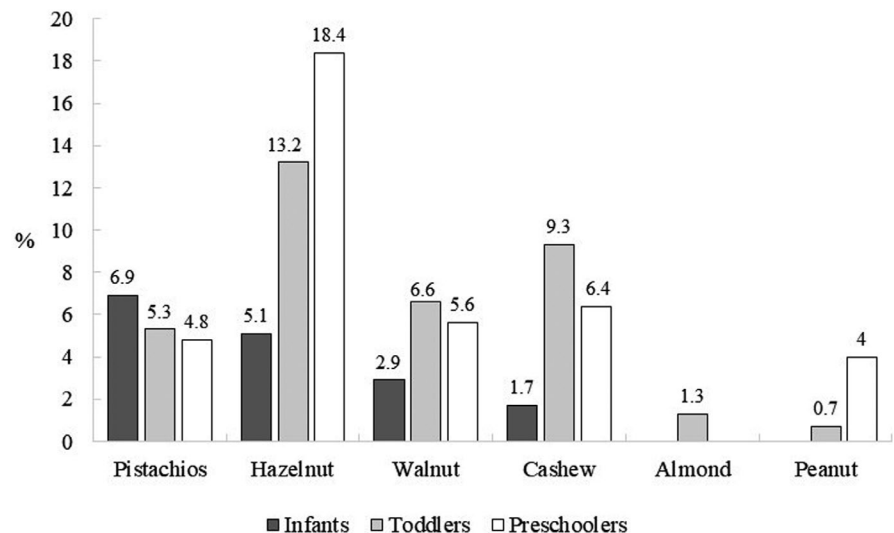


FIGURE 1 Food triggers according to age-groups

FIGURE 2 Tree nut and peanut as trigger according to age-groups



anaphylaxis in this age-group and improve its clinical diagnosis and treatment. The findings of the study showed that FIA in Turkish children aged <6 years was associated with unique triggers. In the infant group, cow's milk, tree nuts, hen's egg, and wheat were the most common food triggers, whereas tree nuts, cow's milk, hen's egg, and sesame were the most common food triggers in the toddler and preschool children groups. Interestingly, almost half of the instances of FIA occurred during the first year of life, usually during initial exposure to the food, and most occurred at home. In the infant group, the symptom distribution of anaphylaxis was different than the other age-groups and anaphylaxis mostly affected skin, gastrointestinal, and neurologic systems, which resulted in less severe forms of anaphylaxis. Although infants were brought to ED more frequently for FIA, effective treatments, namely adrenaline, were used less frequently.

The spectrum of food allergies varies according to geography, lifestyle, and dietary habits. The most common classic food allergies in East Mediterranean children aged <2 years are unique to the region and include egg white, cow's milk, tree nuts, and sesame.¹² The European Anaphylaxis Registry recorded a cohort of pediatric anaphylaxis reactions, and cow's milk and hen's egg were common etiologies in those aged 0-2 years, hazelnut and cashew were common etiologies in preschool-aged children, and peanut was a common trigger in all age-groups.¹³ Pouessel et al.¹⁴ compared infants and preschool children in France, reporting that the primary food allergens were cow's milk, hen's egg, wheat, and peanut in infants, versus peanut and cashew in preschool children; however, a more recent study by Anvari et al.¹⁵ observed that tree nuts were responsible for most of the FIA and more frequently than peanut in the United States. In the present study, cow's milk, tree nuts, and hen's egg were the most common triggers in the infant group, whereas tree nuts, cow's milk, and hen's egg were the most common triggers in the toddler and preschool children groups.

According to the literature, the characteristics of allergy to tree nut species are extremely variable, and allergy to tree nuts is uncommon during the first year of life due to limited tree nut consumption.¹⁶

Turkey is a distinguished producer of tree nuts worldwide and cultivates particularly hazelnut, which accounts for 70% of world production. Tree nuts, such as pistachio, hazelnut, and walnut, are widely used in many Turkish recipes, including those for desserts and meats.¹⁷ Additionally, the consumption of tree nuts in Turkey usually begins during infancy. The high rate of allergy to tree nuts in Turkey is consistent with the country's consumption patterns.¹⁸ A study previously conducted in Turkey reported that the most frequent tree nut allergies were hazelnut, pistachio, and cashew,¹⁹ which is consistent with the present study's findings that pistachio was the most frequent trigger of FIA in the infant group and hazelnut was the most common trigger in the toddler and preschool children groups.

Evaluation of some symptoms of anaphylaxis in infants might be challenging, including behavioral changes such as irritability, clinging to a caregiver, and inconsolable crying, as well as somnolence and flushing, which can also be observed in healthy infants. Moreover, infants do not have the ability to describe symptoms, included pruritus, throat tightness, and a feeling of impending doom.^{20,21} Consequently, these issues make it difficult to diagnose anaphylaxis in infants. The initial presentation of anaphylaxis in infants typically involves organ systems in the following order of frequency: mucocutaneous, the respiratory system, and the gastrointestinal system.²² In a US cohort of 191 children aged <2 years with food allergy reactions, hives and vomiting were commonly documented in infants, and certain respiratory findings were frequently observed in preschool children (2-5 years).²² Samady et al.²³ showed that infants more frequently presented with skin and gastrointestinal involvement than school-aged children, whereas respiratory symptoms were more common in school-aged children. Recently, it was reported that hives, hypotension, and neurologic symptoms were more common in infants than in preschool children.¹⁴ We also demonstrated that skin (especially redness and pruritus), nausea-vomiting, and neurologic symptoms were noted more frequently in the infant group, whereas respiratory symptoms were noted more frequently in the groups of toddlers and preschool children.

Symptom, n (%)	All n = 451	Infants n = 175	Toddlers n = 151	Preschoolers n = 125	P
Skin	376 (83.4)	159 (90.9)	119 (78.8)	98 (78.4)	.003
Hives	295 (65.4)	119 (68)	98 (64.9)	78 (62.4)	.31
Redness and pruritus	105 (23.3)	53 (30.3)	32 (21.2)	20 (16)	.003
Flushing	64 (14.2)	32 (18.3)	16 (10.6)	16 (12.8)	.137
Mucosal					
Angioedema	218 (48.3)	79 (45.1)	77 (51)	62 (49.6)	.404
Respiratory	322 (71.4)	103 (58.9)	115 (76.2)	104 (83.2)	<.001
Cough	204 (45.2)	55 (31.4)	76 (50.3)	73 (58.4)	<.001
Wheezing	135 (29.9)	43 (24.6)	44 (29.1)	48 (38.4)	.011
Dyspnoea	134 (29.7)	41 (23.4)	50 (33.1)	43 (34.4)	.032
Stridor	13 (2.9)	5 (2.9)	4 (2.6)	4 (3.2)	.878
Cyanosis	8 (1.8)	5 (2.9)	3 (2)	-	.072
Gastrointestinal	220 (48.8)	98 (56)	67 (44.4)	55 (44)	.03
Nausea and vomiting	207 (45.9)	98 (56)	63 (41.7)	48 (38.4)	.003
Abdominal pain	15 (3.3)	-	4 (2.6)	11 (8.8)	NA
Cardiovascular					
Hypotension	6 (1.3)	-	2 (1.3)	4 (3.2)	.725
Neurologic	37 (8.2)	26 (14.9)	7 (4.6)	4 (3.2)	<.001
Hypotonia	22 (4.9)	16 (9.1)	4 (2.6)	2 (1.6)	.002
Persistent crying and restlessness	20 (4.4)	13 (7.4)	5 (3.3)	1 (0.8)	.004
Confusion	3 (0.7)	-	3 (2)	-	-
Eosinophil count, /mm ³ *	400 (200-700)	400 (200-625)	400 (200-700)	400 (225-700)	.706
Eosinophil, %*	4.8 (2.7-7)	4.6 (2.7-6.9)	4.6 (2.7-6.9)	4.9 (2.1-7.1)	.329
Total IgE, kU/L*	153 (72.9-421.5)	113.5 (43.1-268)	113.5 (43.1-268)	168 (73.7-456)	<.001
Positive SPT with culprit food, n (%)	404 (89.6)	146 (83.4)	141 (93.4)	117 (93.6)	.001
Positive sIgE with culprit food, n (%)	423 (93.8)	165 (94.3)	140 (92.7)	118 (94.4)	.732
Severity, n (%)					
Mild	137 (30.4)	65 (37.1)	44 (29.1)	28 (22.4)	
Moderate	285 (63.2)	92 (52.6)	100 (66.2)	93 (74.4)	.25
Severe	29 (6.4)	18 (10.3)	7 (4.6)	4 (3.2)	

*Median, IQR, inter-quartile range; NA, not applicable.

TABLE 2 Symptoms, laboratory findings, and the severity of FIA in the three study groups

Adrenaline is the mainstay of treatment for anaphylaxis, regardless of age, and fatal anaphylaxis is associated with delayed administration of adrenaline. According to the European Anaphylaxis Registry,²⁴ 861 preschool children (43.7%) were affected with anaphylaxis, of whom 271 (32.7%) were lay-treated (10% were treated with an epinephrine auto-injector, and 15% received intramuscular adrenaline administered by a health professional), and 12% of cases in 2011 received intramuscular epinephrine from professional emergency service, increasing to 25% in 2014. Pouessel et al.¹⁴ reported that 25% (n = 15) of infants received adrenaline (intramuscular,

n = 10; nebulization, n = 3; subcutaneous, n = 2), and no AAI was used. Another study including 48 infants reported that 43 (68.3%) received H1 antihistamines, 31 (49.2%) corticosteroids, and 23 (36.5%) adrenaline.²⁵ A more recent study that included 275 cases of childhood anaphylaxis in the United States reported that 88% of the patients received epinephrine—a significantly higher percentage than that reported in other studies.¹⁵ In the current study, 71 (40.6%) of the infants received adrenaline; only one infant received ≥2 doses of intramuscular adrenaline, and none of the infants needed intravenous infusion. Additionally, adrenaline use was most common

TABLE 3 Risk factors for moderate-to-severe versus mild anaphylactic reactions in infants

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Gender	0.838 (0.435-1.614)	.597		
Atopic dermatitis	1.388 (0.746-2.583)	.301		
History of recurrent wheezing	5.464 (1.571-19.002)	.008	6.837 (1.940-24.097)	.003
Presence of main food allergy (cow' milk or hen's egg or wheat)	0.700 (0.345-1.419)	.322		
Presence of tree nut allergy	2.744 (1.057-7.124)	.038	2.849 (1.056-7.688)	.039
Eosinophil count, /mm3	1.001 (1.000-1.002)	.060	1.001 (1.000-1.002)	.044
Total IgE, kU/L	1.000 (1.000-1.001)	.621		

Note: The bold data indicate statistically significant P value ($P < .05$).

TABLE 4 Treatment and follow-up of FIA according to the groups

	All n = 451	Infants n = 175	Toddlers n = 151	Preschoolers n = 125	P
Treatment					
Adrenaline auto-injector available at the time of the reaction	156 (32.4)	18 (10.3)	58 (38.4)	80 (64)	<.001
Auto-injector used	13 (2.7)	-	7 (4.6)	6 (4.8)	.761
Adrenaline use by medical personnel	219 (45.5)	71 (40.6)	75 (49.7)	72 (57.6)	.005
Corticosteroids	342 (71.1)	124 (70.9)	111 (73.5)	107 (85.6)	.012
Antihistamines	379 (78.8)	150 (85.7)	122 (80.8)	107 (85.6)	.230
Inhaled bronchodilators	93 (19.3)	25 (14.3)	32 (21.2)	36 (28.8)	.003
O2	91 (18.9)	27 (15.4)	31 (20.5)	33 (26.4)	.082
IV fluids	36 (7.5)	12 (6.9)	14 (9.3)	10 (8)	.718
Emergency department visit	353 (78.2)	153 (87.4)	112 (74.1)	88 (70.4)	<.001
Hospitalization	75 (15.6)	36 (16)	22 (14.5)	17 (13.6)	.088
Admission in intensive care unit	5 (1)	2 (1.1)	2 (1.3)	1 (0.8)	

in patients with tree nut allergy. Furthermore, the adrenaline utilization rate was significantly lower in the infant group than in the groups of toddler and preschool children; we think that infants may be at greater risk of delayed adrenaline injection because of the difficulty in the identification of symptoms during infancy. We noted that an AAI was prescribed to 18 (10.3%) of the infants because of the anaphylaxis history; however, none used it. Similar to our findings, a previous study from the same region²⁶ has shown that only 29.5% of the children used an AAI (correctly in only 75% of these cases). In the present study, only 13 (2.7%) of all patients used an AAI. In addition, the use of adrenaline was lowest in the infant group, as compared to the toddler and preschool children groups ($P = .005$).

Biphasic reactions have been reported in 3%-5% of children aged <2 years with anaphylaxis, but they are unusual in infants and the frequency in infants is not clearly known.^{25,27} Similarly, in the present study, only one biphasic reaction was noted in the infant group. Additionally, severe anaphylaxis was less common in the infant group than in children, as reported earlier.²⁸ We determined

that moderate-to-severe anaphylaxis was least common in the infant group and a history of recurrent wheezing, tree nut allergy, and an elevated eosinophil count were observed to be risk factors for moderate-to-severe versus mild anaphylactic reactions in the infant group; nevertheless, some studies have shown that there were no differences between age-groups.¹⁴

In conclusion, FIA is a potentially life-threatening condition that frequently affects children of all ages. The strengths of the present study are a large patient population, real-life practice, and its age-dependent description of typical triggers, symptoms, and emergency treatment. We are confident that this study can serve as a robust knowledge based on the nature of anaphylactic reactions than can occur in infants, toddlers, and preschool children. Pediatricians should be aware of the distinct features of infant anaphylaxis, mainly neurologic and gastrointestinal symptoms to provide effective treatment as soon as possible.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

AUTHOR CONTRIBUTION

Melike Kahveci: Data curation (lead); Formal analysis (lead); Resources (equal); Writing-original draft (lead); Writing-review & editing (equal). Aysegül Akarsu: Data curation (supporting); Investigation (equal); Writing-review & editing (equal). Gizem Koken: Data curation (supporting); Investigation (equal); Writing-review & editing (supporting). Umit M Sahiner: Formal analysis (equal); Methodology (supporting); Software (equal); Writing-review & editing (equal). Ozge Soyer: Conceptualization (supporting); Methodology (supporting); Writing-review & editing (equal). Bulent Enis Sekerel: Conceptualization (lead); Methodology (lead); Writing-original draft (supporting); Writing-review & editing (equal).

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/pai.13320>.

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REFERENCES

- Rudders SA, Arias SA, Camargo CA Jr. Trends in hospitalizations for food-induced anaphylaxis in US children, 2000–2009. *J Allergy Clin Immunol*. 2014;134(4):960–962.e963.
- Vetander M, Helander D, Flodstrom C et al. Anaphylaxis and reactions to foods in children—a population-based case study of emergency department visits. *Clin Exp Allergy*. 2012;42(4):568–577.
- Jacobs TS, Greenhawt MJ, Hauswirth D, Mitchell L, Green TD. A survey study of index food-related allergic reactions and anaphylaxis management. *Pediatr Allergy Immunol*. 2012;23(6):582–589.
- Lieberman P, Camargo CA Jr, Bohlke K et al. Epidemiology of anaphylaxis: Findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. *Ann Allergy, Asthma Immunol*. 2006;97(5):596–602.
- Simons FE, Arduzzo LR, Bilo MB et al. International consensus on (ICON) anaphylaxis. *World Allergy Org J*. 2014;7(1):9.
- Greenhawt M, Gupta RS, Meadows JA 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):1148–1156.e1145.
- Dyer AA, Lau CH, Smith TL, Smith BM, Gupta RS. Pediatric emergency department visits and hospitalizations due to food-induced anaphylaxis in Illinois. *Ann Allergy Asthma Immunol*. 2015;115(1):56–62.
- Parlaman JP, Oron AP, Uspal NG, DeJong KN, Tieder JS. Emergency and hospital care for food-related anaphylaxis in children. *Hosp Pediatr*. 2016;6(5):269–274.
- Muraro A, Roberts G, Worm M et al. Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy*. 2014;69(8):1026–1045.
- Simons FE, Sampson HA. Anaphylaxis: Unique aspects of clinical diagnosis and management in infants (birth to age 2 years). *J Allergy Clin Immunol*. 2015;135(5):1125–1131.
- Muraro A, Roberts G, Clark A et al. The management of anaphylaxis in childhood: Position paper of the European academy of allergology and clinical immunology. *Allergy*. 2007;62(8):857–871.
- Kahveci M, Koken G, Sahiner UM, Soyer O, Sekerel BE. Immunoglobulin E-mediated food allergies differ in east mediterranean children aged 0–2 years. *Int Arch Allergy Immunol*. 2020;181(5):365–374.
- Anagnostou K. Anaphylaxis in children: Epidemiology, risk factors and management. *Curr Pediatr Rev*. 2018;14(3):180–186.
- Pouessel G, Jean-Bart C, Deschildre A et al. Food-induced anaphylaxis in infancy compared to preschool age: A retrospective analysis. *Clin Exp Allergy*. 2020;50(1):74–81.
- 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):1696–1699. e1692.
- McWilliam V, Peters R, Tang MLK et al. Patterns of tree nut sensitization and allergy in the first 6 years of life in a population-based cohort. *J Allergy Clin Immunol*. 2019;143(2):644–650.e645.
- https://apps.fas.usda.gov/newgainapi/api/Report/DownloadReportByFileName?fileName=Tree%20Nuts%20Annual_Ankara_Turkey_09-15-2019
- Cetinkaya PG, Buyuktiryaki B, Soyer O, Sahiner UM, Sackesen C, Sekerel BE. Phenotypical characterization of tree nuts and peanut allergies in east Mediterranean children. *Allergologia et Immunopathologia*. 2020;48(4):316–322.
- Cetinkaya PG, Buyuktiryaki B, Soyer O, Sahiner UM, Sekerel BE. Factors predicting anaphylaxis in children with tree nut allergies. *Allergy Asthma Proc*. 2019;40(3):180–186.
- Simons FE, Arduzzo LR, Bilo MB et al. 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis. *Curr Opin Allergy Clin Immunol*. 2012;12(4):389–399.
- Simons FE. Anaphylaxis in infants: Can recognition and management be improved? *J Allergy Clin Immunol*. 2007;120(3):537–540.
- Rudders SA, Banerji A, Clark S, Camargo CA Jr. Age-related differences in the clinical presentation of food-induced anaphylaxis. *J Pediatr*. 2011;158(2):326–328.
- Samady W, Trainor J, Smith B, Gupta R. Food-induced anaphylaxis in infants and children. *Ann Allergy Asthma Immunol*. 2018;121(3):360–365.
- Grabenherrich LB, Dolle S, Moneret-Vautrin A et al. Anaphylaxis in children and adolescents: The European Anaphylaxis Registry. *J Allergy Clin Immunol*. 2016;137(4):1128–1137. e1121.
- Dibek Misirlioglu E, Vezir E, Toyran M et al. Clinical diagnosis and management of anaphylaxis in infancy. *Allergy Asthma Proc*. 2017;38(1):38–43.
- Esenboga S, Kahveci M, Cetinkaya PG et al. Physicians prescribe adrenaline autoinjectors, do parents use them when needed? *Allergologia et immunopathologia*. 2020;48(1):3–7.
- Mehr S, Liew WK, Tey D, Tang ML. Clinical predictors for biphasic reactions in children presenting with anaphylaxis. *Clin Exp Allergy*. 2009;39(9):1390–1396.
- Topal E, Bakirtas A, Yilmaz O et al. Anaphylaxis in infancy compared with older children. *Allergy Asthma Proc*. 2013;34(3):233–238.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: 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;00:1–8. <https://doi.org/10.1111/pai.13320>

Supplementary Table 1: Comparison of the reaction characteristics of non-OFC and OFC groups

	Infants			Toddlers			Preschoolers		
	OFC (n=6)	Non-OFC (n=169)	p	OFC (n=27)	Non-OFC (n=124)	p	OFC (n=30)	Non-OFC (n=95)	p
Skin, n (%)	6 (100)	153 (90.5)	0.429	24	95 (76.6)	0.15	24 (80)	74 (77.9)	0.807
<i>Hives</i>	5 (83.3)	114 (67.5)	0.414	(88.	78 (62.9)	7	20 (66.7)	58 (61.1)	0.580
<i>Redness and pruritis</i>	1 (16.7)	52 (30.8)	0.461	9)	29 (23.4)	0.27	-	20 (21.1)	0.006
<i>Flushing</i>	1 (16.7)	31 (18.3)	0.917	20	9 (7.3)	0	7 (23.3)	9 (9.5)	0.048
				(74.		0.15			
				1)		9			
				3		0.00			
				(11.1		4			
				)					
				7					
				(25.					
				9)					
Mucosal, n (%)									
<i>Angioedema</i>	3 (50)	76 (45)	0.808	5	72 (58.1)	<0.001	6 (20)	56 (58.9)	<0.001
				(18.					
				5)					
Respiratory, n (%)	5 (83.3)	98 (58)	0.216	18	97 (78.2)	0.20	24 (80)	80 (84.2)	0.591
<i>Cough</i>	3 (50)	52 (30.8)	0.320	(66.	63 (50.8)	1	17 (56.7)	56 (58.9)	0.825
<i>Wheezing</i>	3 (50)	40 (23.7)	0.142	7)	33 (26.6)	0.80	12 (40)	36 (37.9)	0.836
<i>Dyspnoea</i>	-	41 (24.3)	0.169	13	42 (33.9)	2	4 (13.3)	39 (41.1)	0.005
<i>Stridor</i>	-	5 (3)	0.670	(48.	4 (3.2)	0.14	2 (6.7)	2 (2.1)	0.216
<i>Cyanosis</i>	-	5 (3)	0.639	1)	3 (2.4)	3	-	-	-
				11		0.67			
				(40.		1			
				7)		0.34			
				8		4			
				(29.		0.41			
				6)		5			
				-					
				-					
Gastrointestinal, n (%)	4 (66.7)	96 (56.8)	0.256	14	53 (42.7)	0.38	17 (56.7)	38 (40)	0.109
<i>Nausea and vomiting</i>	2 (33.3)	94 (55.6)	0.282	(51.	52 (41.9)	8	13 (43.3)	35 (36.8)	0.524

<i>Abdominal pain</i>	-	-	-	9) 11 (40. 7) 2 (7.4)	2 (1.6)	0.90 9 0.08 9	4 (13.3)	7 (7.4)	0.315
Cardiovascular, n (%)									
<i>Hypotension</i>	-	-	-	-	4 (3.2)	-	1 (3.3)	1 (1.1)	-
Neurologic, n (%)	2 (33.3)	26 (15.4)	0.240	2	6 (4.8)	0.59	-	4 (4.2)	0.253
<i>Hypotonia</i>	-	16 (9.5)	0.430	(7.4)	3 (2.4)	0	-	2 (2.1)	0.423
<i>Persistent crying, restlessness</i>	2 (33.3)	11 (6.5)	0.014	1	4 (3.2)	0.70	-	1 (1.1)	0.573
<i>Confusion</i>	-	-	-	(3.7) 1 (3.7) -	3 (2.4)	7 0.90 0 0.41 6	-	-	-
Severity, n (%)			0.364			0.37 8			0.433
<i>Mild</i>	3 (50)	62 (36.7)		7	37 (29.8)		5 (16.7)	23 (24.2)	
<i>Moderate</i>	3 (50)	89 (52.7)		(25. 9)	80 (64.5)		24 (80)	69 (72.6)	
<i>Severe</i>	-	18 (10.7)		20 (74. 1) -	7 (5.6)		1 (3.3)	3 (3.2)	

**OFC; oral food challenge