

Anaphylaxis in infancy compared with older children

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ABSTRACT

Although there has been increasing data on pediatric anaphylaxis, information about anaphylaxis in the 1st year of life is scarce. This study provides detailed information on clinical signs and symptoms of anaphylaxis in the 1st year of life. A retrospective review was performed of our pediatric allergy database between 2007 and 2011. Children who met the diagnostic criteria of anaphylaxis were included. They were categorized as "infant" if they were ≤ 12 months of age at the time of anaphylactic reaction and "children" if > 12 months. There were 104 patients (60 male and 44 female subjects) who met the diagnosis criteria of anaphylaxis. From the 104 cases of anaphylaxis, 23 (22.1%) were infants. Boys ($p = 0.043$), atopic eczema ($p = 0.049$), and history of food allergy ($p < 0.001$) were significantly higher in infants than in children with anaphylaxis. Severe anaphylaxis was less frequent in infants than in children ($p = 0.04$). There was no significant difference between infants and children considering cutaneous and respiratory symptoms ($p > 0.05$ for both) but persistent vomiting was ($p = 0.023$). Irritability, persistent crying, and somnolence are the signs which are difficult to interpret in infants with anaphylaxis. Within these signs, irritability, persistent crying, and somnolence were present in 69.6, 43.5, and 26.1% of infants, respectively. Blood pressure was measured in 5 infants (21.7%) compared with 44 children (54.3%; $p = 0.005$). Four children (4.9%) required more than one epinephrine treatment, but no infant did. Median observation periods were 4 hours in both groups ($p = 0.087$) and no biphasic reactions occurred in either. Food ($p < 0.001$) was significantly more and drugs ($p = 0.015$) were a less frequent cause of anaphylaxis in infants than in children. Anaphylaxis in infants is not rare but many signs of anaphylaxis are overlooked and still undertreated.

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There has been increasing epidemiological and clinical data on anaphylaxis since the term was first used in 1902.¹ However, there has been more data from adults than from children. In the last 10 years, pediatric publications on anaphylaxis have increased. Most of these published articles provided descriptive data about all pediatric anaphylaxis cases from single or multiple centers from different countries.^{2–4} The data may differ when specific groups are evaluated. Among these specific groups, food-related allergy and anaphylaxis receive more attention because food is the most common cause of anaphylaxis in children.^{2–6} Age is another important parameter. Age-related differences in hypersensitivity patterns do exist between children and adults⁷ but also within the pediatric age groups.⁸ The 1st year of life has been the least investigated period considering anaphylaxis.^{9,10} Only six infants < 1 year of age with anaphylaxis were reported over a 5-year period from a single pediatric emergency department.¹¹ Infants with food-related anaphylaxis were

included in an extended period from newborn to 2 years of age along with other age groups.⁸ An infant in the 1st year of life is different from children because they generally can not speak and therefore can not express most of the anaphylaxis symptoms. Also, the interpretation of some signs (irritability, persistent crying, and somnolence) in anaphylaxis by the physicians may be difficult and nonspecific.¹⁰ Therefore, our primary aim is to provide detailed information on clinical signs and symptoms of anaphylaxis in the 1st year of life. The second aim is to determine similarities and differences of anaphylaxis in infants and children.

METHODS

We made a retrospective medical chart review for a 5-year period between January 2007 and December 2011. Patients referred from the pediatric emergency department or the inpatient and ambulatory pediatric clinics of our hospital for allergic reaction, anaphylaxis, or shock were seen within 72 hours at our pediatric allergy department. Patients who were seen at the allergy department earlier on were given a call after 72 hours to be questioned about any biphasic reactions. The patients' files were retrospectively and independently reviewed by two pediatric allergy specialists. Children with a confirmed diagnosis based on the criteria of the Second Symposium on the Definition and Management of Anaphylaxis were included in the final analysis.¹² The severity of anaphylaxis episode

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Table 1 Grading the severity of anaphylactic reactions

Grade	Skin	Gastrointestinal Tract	Respiratory	Cardiovascular	Neurological
Mild	Sudden itching of eyes and nose, generalized pruritus, flushing, urticaria, and angioedema,	Oral pruritus, oral tingling, mild lip swelling, nausea or emesis, and mild abdominal pain	Nasal congestion and/or sneezing, rhinorrhea, throat pruritus, throat tightness, and mild wheezing	Tachycardia (increase >15 beats/min)	Change in activity level plus anxiety
Moderate	Any of the above	Any of the above, crampy abdominal pain, diarrhea, and recurrent vomiting	Any of above, hoarseness, barky cough, difficulty swallowing, stridor, and dyspnea, moderate wheezing	As above	Light headedness, feeling of pending doom
Severe	Any of the above	Any of the above, loss of bowel control	Any of the above, cyanosis, or saturation <92%, respiratory arrest	Hypotension* and/or collapse, dysrhythmia, severe bradycardia, and/or cardiac arrest	Confusion and loss of consciousness

Source: Ref. 13.

*Hypotension defined as systolic blood pressure: 1 mo to 1 yr, <70 mmHg; 1–10 yr, <70 mmHg + (2 × age); 11–17 yr, <90 mmHg.¹²

was determined according to the position paper of the European Academy of Allergy and Clinical Immunology on the management of anaphylaxis in childhood¹³ (Table 1). A biphasic reaction is defined as a recrudescence of symptoms within several hours (as late as 72 hours) after resolution of anaphylaxis.¹⁴ The patients were categorized as “infant” if they were ≤12 months old at the time of anaphylactic reaction and “children” if they were >12 months of age. The patients with recurrent episodes of wheezing of three or more per year were regarded as asthma. Demographics, family characteristics, triggers, symptoms and signs before and at the index event, the interval between exposure and the onset of anaphylaxis, the location of reaction, treatment of the acute episode, diagnostic evaluations, comorbid diseases and long-term management were recorded. Triggers were investigated by means of the patient’s history, measurements of serum levels of allergen-specific IgE, and skin-prick and/or intradermal tests. Each patient with a diagnosis of anaphylaxis was scheduled with an allergy department follow-up visit within 6 months of the initial episode. The patients who enrolled into the study gave informed consent. The study was approved by the Ethics Committee of Gazi University (approval number 153/11.05.2011). All authors significantly contributed the work, have approved the final article and take full responsibility for the study.

Statistical Analysis

Statistical analysis was performed by Statistical Package for Social Sciences (SPSS) 11.5 software (SPSS, Inc., Chicago, IL). A descriptive analysis was used for the characterization of patients. Qualitative variables are described in frequency and percent. Quantitative variables are expressed with medians. Comparison between groups was performed by Pearson chi-square test (Fisher’s exact test when needed) and by Mann-Whitney *U* test. A two-sided value of $p < 0.05$ was considered statistically significant.

RESULTS

Similarities and Differences between Infants and Children

There were 104 patients (60 male and 44 female subjects) who met the criteria for the diagnosis of anaphylaxis. Distribution of patients who met the three criteria of anaphylaxis was shown in Table 2. At the time of the reaction, 23 patients (22.1%) were infants. Male gender ($p = 0.043$), atopic eczema ($p = 0.049$), and history of food allergy ($p < 0.001$) were significantly more common in infants than in children with anaphylaxis (Table 3). Infants were not different from children considering the time lapse between exposure and the onset of the symptoms and frequency of first time of anaphylactic reaction ($p > 0.05$ for both). Severe

Table 2 Distribution of patients who met the three criteria of anaphylaxis

Criteria of anaphylaxis*	Infant (aged ≤1 yr) n = 23 (%)	Children (aged >1 yr) n = 81 (%)
The first criteria (skin plus respiratory or cardiovascular symptoms)		
SMT + respiratory	18 (78.3)	67 (82.7)
SMT + cardiovascular	0	16 (19.8)
The second criteria (involvement of at least two systems after exposure to a likely allergen)		
SMT + respiratory	18 (78.3)	67 (82.7)
SMT + reduced BP or associated symptoms	0	16 (19.8)
SMT + persistent gastrointestinal symptoms	6 (26.1)	7 (8.6)
SMT + respiratory + reduced BP or associated symptoms	0	1 (1.2)
SMT + respiratory + persistent gastrointestinal symptoms	1 (4.3)	5 (6.2)
The third criteria (reduced BP after exposure to a known allergen)	0	18 (22.2)

*Patient who met the one of these criteria were diagnosed as anaphylaxis.
SMT = skin mucosal tissue; BP = blood pressure.

anaphylaxis was less frequent in infants than children ($p = 0.04$; Table 3).

There was no significant difference between infants and children with anaphylaxis considering cutaneous and respiratory signs; however, persistent vomiting was more frequent in infants ($p = 0.023$; Table 2 and Table 4). Blood pressure had been measured only in 5 infants (21.7%) compared to 44 children (54.3%; $p = 0.005$). Both age groups were treated similarly in the emergency department ($p > 0.05$ for all; Table 3). No infant required more than one epinephrine treatment but four children (4.9%) were given two doses of epinephrine injections and were admitted to an intensive care unit during the anaphylaxis episode. Median observation period was 4 hours both in infants (minimum–maximum, 1–24 hours) and children (minimum–maximum, 1–48 hours; $p = 0.087$). No biphasic reactions were reported either in infants or in children. Two infants had an anaphylactic reaction caused by drugs. Food ($p < 0.001$) was significantly more and drugs ($p = 0.015$) were less frequent causes of anaphylaxis in infants compared with children (Table 5). There were no fatalities either in infants or in children.

Anaphylaxis Signs That Are Potentially Difficult to Interpret or Nonspecific in Infants

Anaphylaxis signs that are potentially difficult to interpret such as irritability, persistent crying, and somnolence were present in 69.6, 43.5, and 26.1% of infants, respectively. No parents described rapid onset of sweating, pallor, unresponsiveness, lethargy, hypotonia, or seizures in their babies during anaphylaxis.

Epinephrine Autoinjector in Infants

An individualized anaphylaxis emergency action plan was provided to each family. An autoinjector contain-

ing 0.15 mg of epinephrine was prescribed to 18 infants with food-related anaphylaxis except for three infants who weighed <7.5 kg and were prescribed an ampule of epinephrine and a syringe.¹³

Social Issues in Infants with Anaphylaxis

Caregivers were mothers in 15 cases (65.2%), babysitter in 7 cases (30.4%), and grandmother in 1 case (4.3%). One of the 8 working mothers (34.7%) quit her job after the baby had suffered from an anaphylaxis. One mother was taking an antipsychotic drug at the time of the reaction (4.3%). All mothers and babysitters, 18 fathers (75%), and 3 grandparents were given an interactive education on prevention, recognition, and treatment of anaphylaxis individually.

Follow-Up

The median follow-up of infants with anaphylaxis was 18 months (4–51 months). Anaphylaxis recurred in two infants within 1 year (8.7%). One of them was allergic to milk and had been looked after by a babysitter. Although the babysitter did recognize anaphylaxis, she did not use the epinephrine autoinjector. The other was an infant with Pompe disease who developed anaphylaxis to α -glucosidase and was taken to a desensitization program. Moderate anaphylaxis recurred in the first session of desensitization in the hospital. Eight infants (34.7%) developed tolerance to the specific food and six (26.0%) developed recurrent wheezy lower respiratory tract infections.

DISCUSSION

This study documents the largest case series of anaphylaxis in infants in the medical literature. We examined the overlooked signs of anaphylaxis in infants as

Table 3 Demographics of children with anaphylaxis at the time of diagnosis

	Infant (aged ≤1 yr) n = 23 (%)	Children (aged >1 yr) n = 81 (%)
Male*	18 (78.3)	42 (51.9)
Median age (minimum–maximum), mo	9 (3–12)	100 (13–204)
First time anaphylactic reaction	20 (86.9)	66 (81.4)
Referred from		
Pediatric Emergency Department	18 (78.3)	62 (76.6)
Inpatient	2 (8.7)	16 (19.8)
Ambulatory care	3 (13)	3 (3.7)
History of atopic disease		
Food allergy*	10 (43.5)	11 (13.6)
Drug allergy	—	6 (7.4)
Atopic eczema*	6 (26.1)	1 (1.2)
Asthma	1 (4.3)	18 (22.2)
Allergic rhinitis	—	11 (13.6)
Location of reaction		
Home#	21 (91.3)	34 (42)
Hospital	2 (8.7)	23 (28.4)
Outdoors	—	24 (29.6)
Time lapse between exposure and symptoms		
0–5 min	8 (34.8)	32 (39.5)
5–30 min	14 (60.9)	33 (40.7)
30 min–2 hr	1 (4.3)	9 (11.1)
Unknown (idiopathic)	—	7 (8.6)
Severity of reaction		
Mild	11 (47.8)	24 (29.6)
Moderate	10 (43.5)	31 (38.3)
Severe*	2 (8.7)	26 (32.1)
Treatment		
Epinephrine	6/20 (30)	31/78 (39.7)
Antihistamine	20/20 (100)	75/78 (96.1)
Corticosteroids	19/20 (95)	72/78 (92.3)
Salbutamol	4/20 (20)	15/78 (19.2)
Unknown	3/23 (13)	3/81 (3.7)

* $p < 0.05$; # $p < 0.001$.

well as difficulties and defects in its treatment. This article also provided follow-up data about the recurrent anaphylaxis episodes, development of tolerance and other allergic diseases, and social impacts after the anaphylaxis event. Finally, comparison data displayed similarities and differences of infants with anaphylaxis from children.

There is limited data about the prevalence of anaphylaxis in infants.^{11,15} Previously, Huang *et al.*¹¹ reported 6 of 192 children (3.1%), and de Silva *et al.*¹⁵ reported 22 of 123 children (18%) in their case series of anaphylaxis were infants. Infants made up over one-fifth of all anaphylaxis patients in our study group, which designates the importance of this age group.

All infants with anaphylaxis had at least one cutaneous sign in our group. In fact, all six infants reported by

Huang *et al.*¹¹ and 98% of children <2 years old with food-related anaphylaxis reported by Rudders *et al.*⁸ presented with cutaneous signs. Interestingly, pruritus was not uncommon (39%) in infants in our analysis although it was the least observed among other cutaneous signs.

Respiratory system involvement in infants was as frequent as in children with anaphylaxis; however, the same was not true for the gastrointestinal system. Persistent vomiting stood out as the major gastrointestinal sign of anaphylaxis in infants and was significantly more frequent than in children. Therefore, vomiting, which is an obvious sign but may be nonspecific in infants, should draw the attention of physicians when it is acute, repetitive, and associated with urticaria, angioedema, or flushing as an alarm signal for anaphylaxis.

Table 4 Anaphylaxis symptoms/signs in children

	Infant (aged ≤1 yr) n = 23 (%)	Children (aged >1 yr) n = 81 (%)
Cutaneous	23 (100)	72 (88.9)
Urticaria	17 (73.9)	47 (58)
Angioedema	11 (47.8)	51 (63)
Flushing	12 (52.2)	23 (28.4)
Pruritus	9 (39.1)	19 (23.5)
Respiratory	18 (78.3)	73 (90.1)
Dyspnea	NA	35 (43.2)
Stridor	11 (47.8)	30 (37)
Cough	7 (30.4)	15 (18.5)
Wheezing	4 (17.4)	9 (11.1)
Cyanosis	2 (8.7)	14 (17.3)
Rhinitis	4 (17.4)	4 (4.9)
Hoarseness	1 (4.3)	8 (9.9)
Cardiovascular	—	23 (28.4)
Hypotension	0/5 (0)	18/44 (54.4)
Arrest	—	3 (3.7)#
Syncope	—	12 (14.8)
Gastrointestinal	6 (26.1)	8 (9.9)
Persistent vomiting*	6 (26.1)	6 (7.4)
Abdominal pain	NA	2 (2.5)
Diarrhea	—	—

* $p < 0.05$.

#Etiological; agents: General anesthetic in one case and cephalosporins in two cases.

NA = not available.

Cardiovascular signs were not present in any infants whereas they were present in almost one-fourth of children in our study. Similarly, Huang *et al.*¹¹ and Rudders *et al.*⁸ reported no cardiovascular signs in infants in their studies. Perhaps, some of the nonspecific signs such as irritability may be an indirect finding of cardiovascular system involvement in infants with anaphylaxis.

Blood pressure measurement seems to be the most neglected examination in infants with anaphylaxis.^{8,9,12} In our patients, blood pressure measurement was performed in only one-fifth of infants and was significantly less than in children. Also, in the study by Huang *et al.*¹¹ only one of six infants had blood pressure measured. Neglecting blood pressure measurement may lead to misclassification of an episode as allergic reaction instead of anaphylaxis.¹⁶ Blood pressure measurement in anaphylaxis was reported to show a significant rise from 60% <2 years old to 99% >12 years old children in a large food-related anaphylaxis report.⁸ This may be related to the difficulty of blood pressure measurement in a crying and irritable

Table 5 Etiology of anaphylaxis

	Infant (aged ≤1 yr) n = 23 (%)	Children (aged >1 yr) n = 81 (%)
Food†	21 (91.3)	14 (17.3)
Milk	14 (60.9)	2 (2.5)
Heng's egg	5 (21.8)	3 (3.7)
Fish	—	3 (3.7)
Walnut	2 (8.7)	—
Peanut	—	1 (1.2)
Apple	—	1 (1.2)
Lentil	—	1 (1.2)
Pea	—	1 (1.2)
Peach	—	1 (1.2)
Pomegranate	—	1 (1.2)
Drugs*	2 (8.7)	31 (38.3)
Antibiotics	1 (4.3)	12 (14.7)
General anesthesia	—	4 (4.9)
Paracetamol	—	4 (4.9)
NSAIDs	—	4 (4.9)
ERT	1 (4.3)	3 (3.7)
Chemotherapeutic agent	—	2 (2.5)
Vitamin B complex	—	1 (1.2)
Regular insulin	—	1 (1.2)
Venom	—	25 (30.9)
Vespid	—	20 (24.7)
Apids	—	5 (6.2)
Idiopathic	—	7 (8.6)
Other#	—	3 (3.6)

* $p < 0.05$; † $p < 0.001$.

#Other: Exercise induced, latex, and transfusion-related anaphylaxis.

NSAIDs = Nonsteroidal anti-inflammatory drugs; ERT = enzyme replacement therapy.

infant or may be a general issue with triage/medical assessment. Factors such as availability of appropriate size sphygmomanometer cuffs for the infants may be another factor although there is no scientific evidence supporting this issue.

We saw that general anaphylaxis signs such as irritability, persistent crying, and somnolence that are potentially difficult to interpret in this age group were not rare. However, these signs were less questioned and underreported because they were probably thought to be among the normal behaviors of this age group.

In the present study, mistakes and defects in management of anaphylaxis in pediatric emergency departments were similar in infants and children. Treatment of acute episode with epinephrine in infants (30%) was as low as in children (39%). No infant had been given i.v. epinephrine infusion in our study. In contrast, all

except one had received both antihistamine and corticosteroid injections similar to children. This was not surprising because epinephrine was reported to be underused by physicians in most anaphylaxis studies in children.^{2,3,5,17,18} Besides our analysis, there is only one report giving details of acute anaphylaxis treatment in six infants.¹¹ In this report, also, two infants were treated with antihistamines and salbutamol rather than epinephrine.

Food is the most important trigger in infants in our study. However, the rates of drug- and venom-related anaphylaxis in children were higher in our study than previously reported ones.^{4,5,11} Venom-related anaphylaxis is encountered more in Turkey³ than other countries.^{4,5,11} This may be caused by a longer warm climate that prolongs the time that bees fly around. In addition, i.v. and i.m. treatment units in outpatient clinics might have increased the probability to experience anaphylactic cases related with medications at our hospital.

There is no doubt that anaphylaxis influences the social life of the family. However, our data provide limited information about this issue, which needs larger number of patients to be generalized. Also, retrospective nature of our study limits the data attainable and means that some biases are inevitable.

In conclusion, this report provided detailed clinical information on difficulties and gaps in diagnosis and treatment of anaphylaxis in infants and its similarities/differences from children. We think that it may help to add some cautions such as "Be aware of anaphylaxis in an infant with cutaneous signs associated with persistent vomiting, persistent crying, irritability or somnolence and do not forget to measure blood pressure!" to the present available reports and task forces for diagnosis of anaphylaxis in infants.^{12,13}

REFERENCES

- Portier P, and Richet C. De l'action anaphylactique de certains venins. *C R Soc Biol Paris* 54:170–172, 1902.
- Silva R, Gomes E, Cunha L, et al. Anaphylaxis in children: A nine years retrospective study (2001–2009). *Allergol Immunopathol (Madr)* 40:31–36, 2012.
- Orhan F, Canitez Y, Bakirtas A, et al. Anaphylaxis in Turkish children: A multi-centre, retrospective, case study. *Clin Exp Allergy* 41:1767–1776, 2011.
- Hoffer V, Scheuerman O, Marcus N, et al. Anaphylaxis in Israel: Experience with 92 hospitalized children. *Pediatr Allergy Immunol* 22:172–177, 2011.
- De Swert LF, Bullens D, Raes M, and Dermaux AM. Anaphylaxis in referred pediatric patients: Demographic and clinical features, triggers, and therapeutic approach. *Eur J Pediatr* 167:1251–1261, 2008.
- Amin AJ, and Davis CM. Changes in prevalence and characteristics of IgE-mediated food allergies in children referred to a tertiary care center in 2003 and 2008. *Allergy Asthma Proc* 33:95–101, 2012.
- Braganza SC, Acworth JP, Mckinnon DR, et al. Paediatric emergency department anaphylaxis: Different patterns from adults. *Arch Dis Child* 91:159–163, 2006.
- Rudders SA, Banerji A, Clark S, and Camargo CA Jr. Age-related differences in the clinical presentation of food-induced anaphylaxis. *J Pediatr* 158:326–328, 2011.
- Kimata H. Latex allergy in infants younger than one year. *Clin Exp Allergy* 34:1910–1915, 2004.
- Simons FE. Anaphylaxis in infants: Can recognition and management be improved? *J Allergy Clin Immunol* 120:537–540, 2007.
- Huang F, Chawla K, Järvinen KM, and Nowak-Węgrzyn A. Anaphylaxis in a New York City pediatric emergency department: Triggers, treatments, and outcomes. *J Allergy Clin Immunol* 129:162–168, 2012.
- Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 117:391–397, 2006.
- Muraro A, Roberts G, Clark A, et al. EAACI Task Force on Anaphylaxis in Children. The management of anaphylaxis in childhood: Position paper of the European academy of allergology and clinical immunology. *Allergy* 62:857–871, 2007.
- Lieberman PL. Anaphylaxis. In Middleton's Allergy: Principles and Practice, 7th ed. Adkinson NF Jr, Bochner BS, and Busse WW (Eds). Mosby: Philadelphia, PA, 1027–1049, 2009.
- de Silva IL, Mehr SS, Tey D, and Tang ML. Paediatric anaphylaxis: A 5 year retrospective review. *Allergy* 63:1071–1076, 2008.
- Caffarelli C, Rico S, Rinaldi L, et al. Blood pressure monitoring in children undergoing food challenge: Association with anaphylaxis. *Ann Allergy Asthma Immunol* 108:285–286, 2012.
- Novembre E, Cianferoni A, Bernardini R, et al. Anaphylaxis in children: Clinical and allergologic features. *Pediatrics* 101:8, 1998.
- Greenberger PA, and Ditto AM. Chapter 24: Anaphylaxis. *Allergy Asthma Proc* 33(Suppl 1):S80–S83, 2012. □

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