

Insights from 275 cases of childhood anaphylaxis in the United States

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Clinical Implications

- Pediatric anaphylaxis occurs most often at home with low rates in school settings. Tree nuts appear to be the most frequent trigger. Infant anaphylaxis can be severe, requiring multiple doses of epinephrine in 20% of infants.

TO THE EDITOR:

The incidence of pediatric anaphylaxis is rising with a recorded increase in emergency department (ED) visits and hospitalizations.¹ Multiple published studies on anaphylaxis involve adults or mixed populations; however, data on childhood anaphylaxis are lacking. We sought to investigate the triggers and management of anaphylaxis in children of all ages presenting at Texas Children's Hospital over a 1-year period.

Medical records were searched for a single calendar year (2016) using all International Classification of Diseases 9 (ICD-9) codes related to anaphylaxis (995.XX, 909.XX, 988, 989.XX, 999.XX, 477.XX, 786.XX, 693.XX). Records were reviewed by 3 different allergists, and information was recorded on age, gender, race, ethnicity, allergic comorbidities, family history, presenting signs and symptoms, triggers, timing to onset of symptoms, treatment administered, biphasic reactions, hospitalizations, intensive care unit (ICU) admissions, follow-up, and fatalities. Descriptive statistics were used for analysis. A Fisher's exact test was performed using GraphPad Prism version 7.0 for Windows (GraphPad Software, La Jolla, Calif). *P* values of less than .05 were considered statistically significant. The study was approved by the Baylor College of Medicine institutional review board.

The majority of our patients were white (65%) and over a third Hispanic. Fifty-five percent were male. Median age was 7 years, with 5% less than 1 year (infants), 32% 1-4 years (preschool), 43% between 5 and 12 years (school-age), and 20% 13-17 years (adolescents). Despite fears that adolescents may be at higher risk of an ED visit as a result of anaphylaxis, especially food-induced, due to risk-taking behavior,² they were not the dominating group in our cohort. Anaphylaxis was more common in school-age children followed by preschoolers. As expected, the presence of atopy was a common finding in our cohort, but the number of children with a prior history of atopy in either a sibling (14%) or parent (23%) was low, as well as a prior history of anaphylaxis in either a sibling (1%) or parent (3%) (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

Most patients presented with cutaneous (89%) and respiratory (74%) symptoms, rather than gastrointestinal (43%), consistent with other studies.^{3,4} Cardiovascular symptoms were seen in only

8% (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). No deaths occurred.

More than 50% of anaphylactic episodes in our study occurred at home despite parents often expressing concerns about severe reactions occurring at school (Figure 1, A). We observed very low rates of anaphylaxis in school (6%) and day-care settings (1%), in line with published studies.^{3,4} Food was the most common trigger (48%) in all cases of anaphylaxis (Figure 1, B) and in all different age groups (Figure 1, C). Less common triggers included drugs in 12%, stinging insect venom in 11%, immunotherapy in 3%, vaccines in 1%, and skin prick testing in 0.4%. The reaction to skin prick testing involved an 8-year-old child with poorly controlled asthma, who developed cutaneous and severe respiratory symptoms shortly after skin testing to 34 allergens (food, aeroallergens). He required multiple epinephrine doses, continuous albuterol, intravenous fluids, and hospitalization in the ICU before recovery.

We observed that younger children (aged 1-4 years and 5-12 years) experienced stinging venom anaphylaxis more frequently than older children (aged 13-17 years). We hypothesize that younger children are spending time outdoors more; therefore, they may be more likely to be stung by insects, such as fire ants. Anaphylaxis due to immunotherapy was not observed in any patient below the age of 5 years, but was seen in 5% of 5- to 12-year-old patients and in 4% of 13- to 17-year-old patients. A likely explanation for this is that immunotherapy is generally not recommended in very young children (Figure 1, C).

Nuts represented the most frequent food trigger in 25% of our cohort (tree nuts: 12%, peanuts: 8%, unidentified nuts: 5%). Shellfish was found to be responsible in 5%, egg in 4%, and milk in 3% (Figure 1, D). An unexpected finding was that tree nut anaphylaxis occurred more frequently than peanut. We hypothesize that different dietary habits in different geographical areas may be responsible for this. Tree nut consumption is high in our area and is likely a reflection of the rich cultural diversity that exists in our region and influences our population's dietary habits. However, in 5% of cases, the type of nut (ie, peanut or tree nut) was unidentified; if these cases were all attributed to peanut, peanut would be the leading food allergen, albeit with a narrow margin. Of the tree nuts, cashew was identified as a trigger in 36% of tree nut-allergic patients, followed by walnut in 21%, pistachio in 12%, almond in 9%, and pine nut in 6% (Figure 1, E). It has been reported that cashew is a potent allergen resulting in severe reactions⁵ and our findings support this. Of drug-induced anaphylaxis, antibiotics were recorded as the most common trigger (Figure 1, F). Overall, in 72% of cases, the anaphylactic trigger was a newly identified allergen.

With regard to treatment, 88% of patients received epinephrine. Our rates are significantly higher than other published studies^{3,6} (Table I). Epinephrine was administered as first-line treatment in 50% of patients, suggesting that there is still room for improvement in the initial management of anaphylaxis. Reassuringly, the majority of patients receiving epinephrine (79%) required a single dose for symptom control. In 7%, 2 doses were required, whereas in 2%, multiple doses of epinephrine were administered. For most (60%) patients receiving multiple epinephrine doses, these were administered

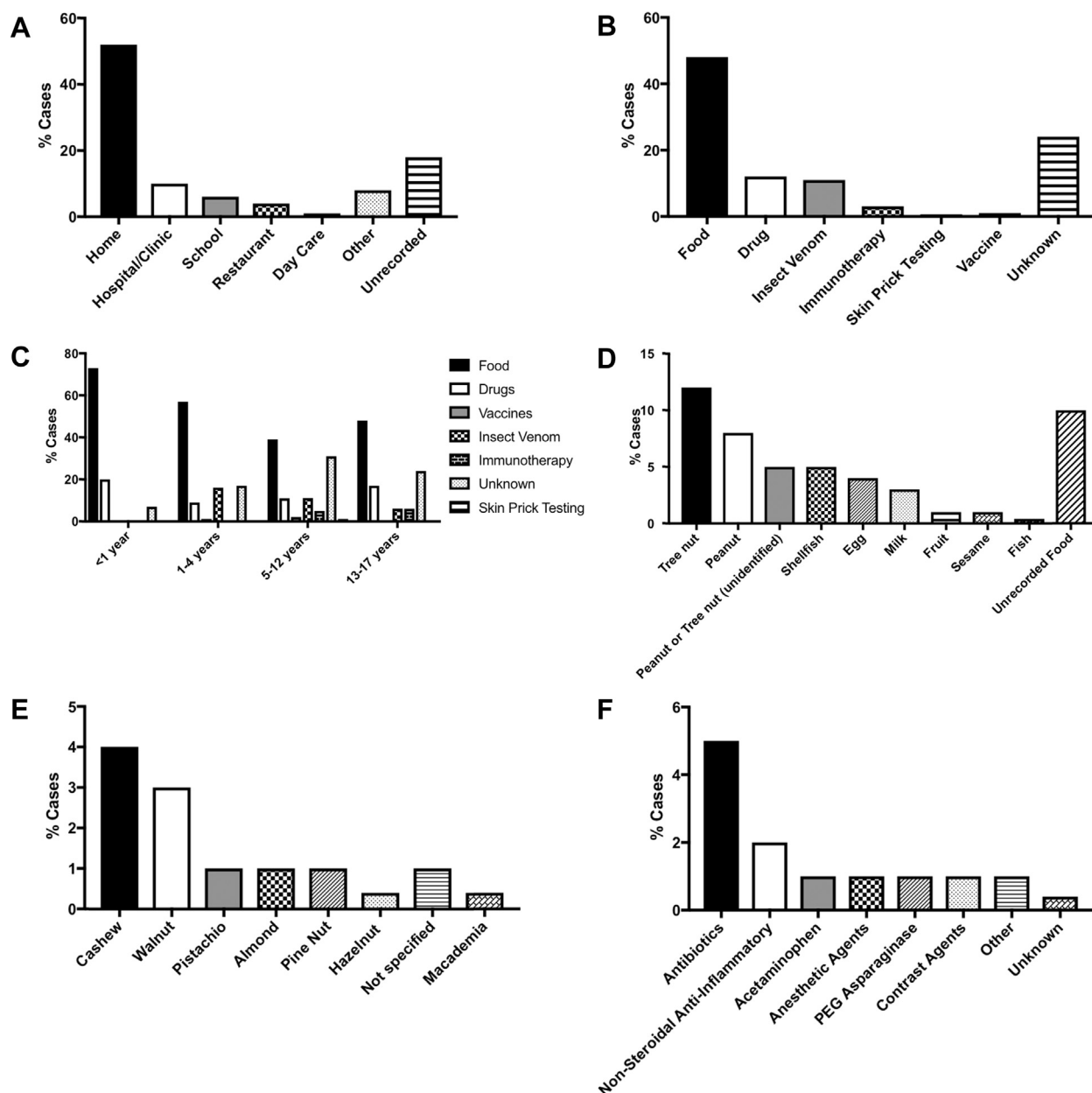


FIGURE 1. A, Percentage of anaphylaxis cases according to location. B, Percentage of cases of various anaphylactic triggers. C, Percentage of cases of different triggers of anaphylaxis based on age group. D, Percentage of cases of various food triggers causing anaphylaxis. E, Percentage of cases of the different tree nuts causing anaphylaxis. F, Percentage of cases of different classes of drugs triggering anaphylaxis. PEG, Polyethylene glycosylated.

because of incomplete response to initial treatment rather than a biphasic reaction. We noted that less than one-third of our patients had epinephrine available at the time of the reaction; this finding suggests that ED physicians administered most of epinephrine doses.

Biphasic reactions were defined as recurrence of symptoms within 72 hours without re-exposure to the trigger. These were uncommon (Table I) and occurred in 11%. Sixteen patients with biphasic reactions were hospitalized. There were no significant recorded differences in treatment between patients who suffered from biphasic versus uniphasic reactions (Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

Steroid use did not appear to prevent recurrence of symptoms compared with patients who did not receive steroids ($P = 1.0$). On 2 occasions, the patients were released home, but returned to the ED with recurrence of symptoms after 5 and 7 hours, respectively.

Patients requiring 2 or more doses of epinephrine were more likely to be hospitalized ($P = .0001$). There was also a strong association between asthma history and requiring 2 or more doses of epinephrine for symptom resolution ($P = .01$), supporting the notion that asthma is a risk factor for severe allergic reactions. In the majority of episodes, symptoms developed in less than 1 hour. We identified delayed reactions in 6% (Table I). Treatment was initiated within 15 minutes in the majority.

TABLE I. Management of anaphylaxis, including treatment, information on prior assessment and follow-up

Variable	N	Percentage
Treatment		
Treatment received		
Antihistamines	253	92%
Epinephrine (IM)	243	88%
Racemic epinephrine*	3	1%
Epinephrine infusion*	3	1%
Steroids	163	59%
Inhaled β_2 -agonist (albuterol)	69	25%
Inhaled ipratropium	3	1%
Unspecified inhalers or nebulizers	2	0.7%
Normal saline bolus	45	16%
Intubation	2	0.7%
None	2	0.7%
Unrecorded	5	2%
Used as first-line treatment		
Epinephrine (IM)	138	50%
Antihistamines	113	41%
Inhaled β_2 -agonist (albuterol)	8	3%
Steroids	2	0.7%
None	2	0.7%
Not documented	12	3%
Number of epinephrine doses administered		
1	218	79%
2	20	7%
>2	5	2%
No epinephrine	32	12%
Epinephrine available at the time of reaction		
No	189	69%
Yes	86	31%
Biphasic reaction		
No	227	82%
Yes	31	11%
Unrecorded	17	6%
Hospital admission		
No	228	83%
Yes	41	15%
Unrecorded	6	2%
Timing		
Time from exposure to symptoms developing		
<15 min	96	35%
15-60 min	44	16%
1-2 h	15	5%
>2 h	17	6%
Unrecorded	103	37%
Time to initiate treatment		
<15 min	118	43%
15-60 min	77	28%
1-2 h	25	9%
>2 h	30	11%
Unrecorded	24	9%
No treatment administered	1	0.4%
Time to symptom resolution		
<15 min	46	17%

(continued)

TABLE I. (Continued)

Variable	N	Percentage
15-60 min	55	20%
1-2 h	31	11%
>2 h	62	23%
Unrecorded	81	29%
Prior assessment and follow-up		
Previously seen by allergist		
Yes	72	26%
No	162	59%
Not recorded	41	15%
Referred to allergist		
Yes	259	94%
No	11	4%
Unrecorded	3	1%
Referred to other health professional		
Primary care physician	4	1.4%
Ear, nose, and throat	1	0.4%

IM, Intramuscular.

*Received in addition to IM epinephrine.

We identified 15 infants (5%) with anaphylaxis (Table E4, available in this article's Online Repository at www.jaci-inpractice.org). Of these, 53% were male. With regard to race, the majority were either white (47%) or Asian (47%) and only 1% were black. All presented with cutaneous symptoms (100%), followed by respiratory (60%) and gastrointestinal (53%), consistent with previous reports.⁷ Cardiovascular symptoms were not observed. Food, specifically egg (73%), was the most common suspected trigger of infant anaphylaxis, followed by drug (20%). Antibiotics (amoxicillin and ceftriaxone) were described as triggers in 2 infants and oral nystatin in a third. Epinephrine was administered in 87%, and 3 infants required more than 1 dose of epinephrine. No biphasic reactions were noted in infants who required multiple epinephrine doses. Of note, severe anaphylaxis can occur at any age group and awareness of presenting symptoms in very young children is crucial. With early food introduction now advised in the United States, infant anaphylaxis is an area of intense interest.

Almost all patients were referred to an allergist after anaphylaxis, in line with current recommendations; ours is a high referral rate compared with a recent study that only reported a referral rate of 30%³ (Table I).

Limitations of our study include retrospective collection of data, derived from a single institution, some missing data in patients' records, and some potential loss of diagnostic sensitivity and/or specificity if ED physicians use different ICD-9 codes than allergists. In addition, our findings involve a diverse population presenting in a tertiary pediatric hospital, and results may be different in community settings.

The strength of our study lies in the large number of cases, which provide an updated assessment of the presentation and management of pediatric anaphylaxis. New findings include a high proportion of anaphylactic episodes as a result of a new trigger, tree nuts surpassing peanuts as a recorded food for pediatric anaphylaxis, egg as the dominant trigger in infant anaphylaxis, multiple epinephrine doses administration in 20% of infants, a low rate of reported anaphylaxis in schools/daycare

settings, a high rate of epinephrine administration, and an appropriately high referral rate to an allergist after the episode.

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TABLE E1. Patient characteristics and demographics

Patient characteristics and demographics	N	Percentage
Age, y		
<1	15	5%
1-4	88	32%
5-12	118	43%
13-17	54	20%
Sex		
Male	151	55%
Female	124	45%
Race and ethnicity		
White (all)	177	64%
White, non-Hispanic	87	32%
White, Hispanic	90	33%
African American (all)	51	19%
African American, non-Hispanic	48	17%
African American, Hispanic	3	1%
Asian (all)	30	11%
Asian, non-Hispanic	29	11%
Asian, Hispanic	1	0.4%
Hispanic (all)	99	36%
American Indian, non-Hispanic	1	0.4%
Unknown, non-Hispanic	1	0.4%
Unknown	10	4%
Other allergic comorbidities		
Any atopy	188	68%
Asthma	94	34%
Allergic rhinitis	73	26%
Eczema	68	25%
Drug allergy	9	3%
No atopy	82	30%
Unrecorded	5	2%
Prior history of anaphylaxis		
No	211	77%
Yes	64	23%
Family history		
Sibling with prior anaphylaxis		
No	193	70%
Yes	3	1%
No siblings (only child)	1	0.4%
Unrecorded	78	28%
Sibling with atopic disease		
No	162	59%
Yes	38	14%
No siblings (only child)	1	0.4%
Unrecorded	74	27%
Parent with prior anaphylaxis		
No	187	68%
Yes	7	3%
Unrecorded	81	29%
Parent with atopic disease		
No	108	39%
Yes (1 parent)	62	23%
Yes (both parents)	26	9%

TABLE E2. Symptoms associated with anaphylactic episodes and common body systems involved

	N	Percentage
Symptoms and body systems involved		
Skin	246	89%
Respiratory (upper and lower)	204	74%
Gastrointestinal	118	43%
Cardiovascular	22	8%
Neurological	11	4%
Other*	9	3%
Body systems involved		
Skin and respiratory	102	37%
Skin and respiratory and gastrointestinal	64	23%
Skin and gastrointestinal	50	18%
Respiratory and gastrointestinal	9	3%
Skin and respiratory and gastrointestinal and cardiovascular	5	2%
Other	45	16%

*This includes the following symptoms: body aches, behavioral change, feeling of “impending doom,” and uterine cramping.

TABLE E3. Uniphasic and biphasic reactions and treatment

	Epinephrine (IM)	Epinephrine (IV)	Inhaled racemic epinephrine	Antihistamines	Steroids	Inhaled β_2 -agonists	IV fluid bolus	Intubation
Uniphasic N = 233	88% (206/233)	1% (2/233)	1% (2/233)	92% (215/233)	56% (131/233)	27% (63/233)	14% (33/233)	1% (2/233)
Biphasic N = 31	100% (31/31)	3% (1/31)	0% (0/31)	100% (31/31)	84% (26/31)	29% (9/31)	35% (11/31)	0% (0/31)

Percentages and numbers (N) of patients (in parentheses) are shown. Information was unrecorded in 11 cases.

IM, Intramuscular, IV, intravenous.

TABLE E4. Infant anaphylaxis: demographics, triggers, and management

	Age (mo)	Gender	Trigger	Body systems involved	Treatment
Patient 1	4	M	Drug (oral nystatin)	Skin, respiratory	Epinephrine ($\times 1$), racemic epinephrine ($\times 2$), diphenhydramine, ranitidine, dexamethasone
Patient 2	5	F	Unknown	Skin, respiratory	Diphenhydramine, prednisolone, albuterol, epinephrine
Patient 3	6	F	Food (egg)	Skin, respiratory, gastrointestinal	Diphenhydramine, epinephrine
Patient 4	6	M	Drug (ceftriaxone)	Skin, gastrointestinal	Albuterol, epinephrine
Patient 5	7	M	Food (banana)	Skin, gastrointestinal	Epinephrine, diphenhydramine, dexamethasone
Patient 6	7	F	Food (milk)	Skin, respiratory, gastrointestinal	Diphenhydramine, cetirizine
Patient 7	7	M	Food (egg)	Skin	Epinephrine, diphenhydramine, dexamethasone
Patient 8	9	M	Food (egg)	Skin, gastrointestinal	Diphenhydramine, epinephrine
Patient 9	10	M	Drug (amoxicillin)	Skin, respiratory	Epinephrine, albuterol, NS bolus, diphenhydramine, ranitidine, methylprednisolone
Patient 10	11	F	Food (peanut)	Skin, gastrointestinal	Epinephrine ($\times 2$), dexamethasone, ranitidine, diphenhydramine
Patient 11	11	M	Food (egg)	Skin, respiratory, gastrointestinal	Diphenhydramine, steroids (unspecified), epinephrine
Patient 12	11	F	Food (egg)	Skin, gastrointestinal	Diphenhydramine, epinephrine
Patient 13	11	M	Food (egg)	Skin, respiratory, gastrointestinal	Diphenhydramine, epinephrine, dexamethasone, ranitidine
Patient 14	11	F	Food (egg)	Skin, respiratory, gastrointestinal	None
Patient 15	11	F	Food (egg)	Skin, respiratory, gastrointestinal, neurological	Epinephrine ($\times 2$), diphenhydramine, methylprednisolone, pantoprazole

NS, Normal saline.

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