Anaphylaxis in Children: Clinical and Allergologic Features

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ABSTRACT. *Background.* **Despite the importance of anaphylaxis, little information is available on its clinical features.**

Objective. **To evaluate the clinical and allergologic features of anaphylaxis in children referred to the allergology and immunology unit of A. Meyer Children's Hospital (Florence, Italy) from 1994 to 1996.**

Results. **Ninety-five episodes of anaphylaxis occurred in 76 children (50 boys and 26 girls). Sixty-six children (87%) had only one episode of anaphylaxis, while 10 (13%) had two or more episodes. Sixty-two (82%) of the 76 patients had a personal history of atopic symptoms, although 14 (18%) did not.**

Sixty (79%) of the 76 children studied had at least one positive skin prick test to one or more of the common inhalant and/or food allergens. Children with venom-induced anaphylaxis usually had negative skin tests to the allergens tested. A younger age and eczema were more frequent among children with food-dependent anaphylaxis, whereas an older age together with urticaria-angioedema were common among those with exercise-induced anaphylaxis. The mean latent period (±SD) of the anaphylaxis episodes was 15.4 ± 27.5 minutes. Skin and respiratory manifestations had an earlier onset and were more common than the gastrointestinal and cardiovascular ones. The most frequent clinical manifestation in children with food anaphylaxis was gastrointestinal symptoms, whereas cardiovascular symptoms were rare. The most probable causative agents in the 95 episodes described were foods (57%), drugs (11%), hymenoptera venom (12%), exercise (9%), additives (1%), specific immunotherapy (1%), latex (1%), and vaccines (2%), but in 6 cases (6%) the agent was never determined. Among the foods, seafood and milk were the most frequently involved. As for location, 57% of the anaphylactic events occurred in the home (54/95), 12% outdoors (11/95); 5% in restaurants (5/95); 3% in the doctor's office (3/95); 3% in hospitals (3/95); 3% on football fields (3/95); 2% on the beach (2/95); 1% in the gym (1/95); 1% at school (1/95); and 1% in the operating room (1/95). In the remaining 12% of cases (11/95) the site remained unknown. Sixty-two percent of the patients (59/95) were treated in an emergency room or hospital, while 32% (30/95) were not (this information is lacking in 6% of the cases [6/95]). Patients were treated with corticosteroids in 72% of the cases (68/95), with antihistamines in 20% (19/95), with epinephrine in 18% (17/95), with β_2-agonists in 5% (5/95), and with oxygen in 4% (4/95).

Conclusions. **In our area, foods, particularly seafood and milk, seem to be the most important etiologic factors triggering anaphylaxis. Food-induced anaphylaxis often occurs in younger children with a severe food allergy, whereas exercise-induced anaphylaxis occurs more often in older children with a history of urticaria-angioedema. The venom-induced variant usually presents itself in nonatopic subjects. Given the fact that most of the children had only one anaphylactic reaction, prevention is almost impossible. Epinephrine, although it is the first-choice treatment of anaphylaxis, often goes unused, even in hospitals and doctors' offices.** *Pediatrics* **1998;101(4). URL: http://www.pediatrics.org/cgi/content/full/101/4/e8;** ***anaphylaxis, child, clinical features, allergologic features.***

ABBREVIATIONS. IgE, immunoglobulin E; EAACI, European Academy of Allergology and Clinical Immunology; ELISA, enzyme-linked immunosorbent assay.

Anaphylaxis is usually considered an acute, severe reaction, often with dyspnea, angioedema, and hypotension, resulting from the release of preformed, newly sensitized bioactive mediators from mast cells and basophils.[1] Food, venom, and drugs are the most common exogenous antigens that can cause an immunoglobulin E (IgE)-mediated reaction, while exercise, radiocontrast media, and some nonsteroidal antiinflammatory drugs may induce the clinical symptoms with a mechanism that is not yet completely understood. When no etiologic agent has been found despite repeated evaluations, the term idiopathic anaphylaxis is used.[2]

Even if anaphylaxis is considered a life-threatening event, there is a lack of information on its prevalence and characteristics, particularly in children. In this study we describe the clinical features of 95 episodes of anaphylaxis occurring in 76 children.

MATERIALS AND METHODS

Selection of Patients

Patients referred to the clinical allergology and immunology unit of A. Meyer Children's Hospital (Florence, Italy) suffering from anaphylaxis between 1994 and 1996 were considered. A questionnaire was compiled so as to provide complete information including demographic data, both personal and family atopy history, with the symptoms, treatment, and allergologic evaluation of each child. Those who presented at least two of the main anaphylactic reaction indicators (hypotension, inspiratory dyspnea, and urticaria/angioedema) within 2 hours after exposure to one of the most probable causative agents were included.

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Allergologic Evaluation

Every child was tested with glycerinated extracts (1/20 w/v) from a panel of food (milk, egg white, tomato, peanut, codfish, wheat, soy) and the most common inhalant substances (*Dermatophagoides pteronissimus, Dermatophagoides farinae,* horse, cat dander, dog dander, *Alternaria alternata, Cladosporium herbarum,* grass pollen, *Parietaria officinalis, Artemisia vulgaris,* plane tree, cypress, olive tree) (Bayropharm, Milan, Italy). Skin prick tests were performed on the volar side of the forearm with a lancet (Dome-Hollister Stier, Slough, United Kingdom), pricking through a drop of extract, which was immediately removed.

When necessary, additional skin tests with other commercial extracts (specific food, latex) or with fresh vegetables and fruit were carried out using the Dreborg & Foucard prick+prick technique.[3]

The reactions were assessed according to the recommendations of the European Academy of Allergology and Clinical Immunology (EAACI).[3] The average diameter of each wheal was established by measuring the longest diameter and the diameter perpendicular to it. Positivity was rated 4+ in the presence of a wheal double the size of the wheal induced by histamine 10 mg/mL; 3+ in the presence of a wheal induced by histamine; and 2+ if the average diameter was half that of the wheal induced by histamine. Only wheals 2+ or more were considered positive.

A double-blind challenge for a food additive (sodium glutamate) and for acetaminophen was performed on two occasions when the etiologic factor was misleading.

For children with a hymenoptera venom-induced anaphylaxis, skin tests with honey bee, yellow jacket, and polistes wasp (Alk-Abellò) venom extract in concentration up to 1.0 μg/mL were performed.[4,5]

The allergen-specific IgE was measured using the Cap System (Pharmacia, Uppsala, Sweden) and the total IgE by an enzyme-linked immunosorbent assay (ELISA) (Kallestad-Chaska-MN).

Statistical Analysis

The data were analyzed with the statistical programs STATA 4.0 for Windows (College Station, TX) and EPI INFO version 5.0 (Centers for Disease Control and Prevention, Atlanta, GA). The children were categorized (positive or negative) on the basis of the principal anaphylaxis triggering agent (venom, food, exercise, drugs, other). The relationships between the different types of anaphylaxis and other characteristics regarding both the children and the anaphylaxis episodes were analyzed by calculating the odds ratio and confidence intervals using a univariate logistic regression or by Spearman's correlation coefficient. A P value of less than .05 was considered significant.

RESULTS

Ninety-five episodes of anaphylaxis occurring in 76 (50 boys, 26 girls) children, ranging in age from 1 month to 16 years (mean age ± SD = 6.1 ± 4.6 years), were analyzed. Sixty-six children (87%) had only one episode of anaphylaxis, while 10 (13%) had two or more episodes (4 had two episodes, 4 had three episodes, 2 had 4 and 5 episodes, respectively).

Sixty-two of the 76 patients studied (82%) had a personal history of atopic symptoms, while 14 (18%) did not. Sixty (79%) of the 76 children investigated were positive to at least one of the inhalant or food allergens tested, whereas 16 children (21%) were negative. Seventeen (21%) had more than eight reactions. Forty-three children (57%) were sensitized to at least one inhalant allergen and 48 (63%) to at least one food allergen (18 [24%] to more than six food allergens).

The most probable causative agents of the 95 episodes described are foods (57%), drugs (11%), hymenoptera venoms (12%), exercise (9%), additives (1%), specific immunotherapy (1%), latex (1%), and vaccines (2%), but in 6 cases (6%) the causative agent was never determined (Table 1). Anaphylaxis was predominant especially in boys due to hymenoptera venom and exercise (odds ratio 9, 72 [95% confidence limits 1.29, 427.21]: $P < .03$).

The mean latent period (±SD) of the 95 episodes of anaphylaxis was 15.4 ± 27.5 minutes. The age of the patients is inversely related to latency, ie, to the length of time between the initial contact with the triggering agent, when known, and the onset of anaphylaxis (Fig 1). Skin and respiratory symptoms are more frequent than gastrointestinal and cardiovascular ones (78% and 79% vs 24% and 25%, respectively). Moreover, skin and respiratory manifestations have an earlier onset than gastrointestinal and cardiovascular ones (mean latent period of 11.08 and 10.64 minutes vs 34.04 and 33.08 minutes, respectively [p = .01; p = .005; p = .002; p = .004]). As for the site of anaphylactic events, 57% of cases occurred in the home (54/95), 12% outdoors (11/95), 5% in restaurants (5/95), 3% in a doctor's office (3/95), 3% in a hospital (3/95), 3% on a football field (3/95), 2% on the beach (2/95), 1% in the gym (1/95), 1% at school (1/95), and 1% in the operating room (1/95). The site of remaining 12% (11/95) of the cases was unknown.

Sixty-two percent of the patients (59/95) were treated in an emergency room or hospital, while 32% (30/95) were not (this information is lacking in 6% [6/95] of the cases). Seventy-two percent of the anaphylactic episodes were treated with corticosteroids (68/95), 20% (19/95) with antihistamines, 18% (17/95) with epinephrine, 5% (5/95) with β_2-agonists, and 4% (4/95) with oxygen.

Some points may be made regarding the following etiologic agents of anaphylaxis:

1. Food-dependent IgE-mediated anaphylaxis
   - Forty-four children had a food-dependent anaphylaxis in 54 different episodes.
   - The anaphylaxis was attributed to food when a

TABLE 1. Specific Causative Agent With Frequency of Occurrence in 95 Episodes of Anaphylaxis

Causative Agent	N° (%/95)	Specific Agent	N° (%)
Food	54 (57%)	Fish	16/54 (30%)
		Cow milk	12/54 (22%)
		Nuts	7/54 (13%)
		Egg	6/54 (11%)
		Fruit	6/54 (11%)
		Cereals	3/54 (5%)
		Vegetables	2/54 (4%)
		Goat milk	2/54 (4%)
Drugs	10 (11%)	NSAID	5/10 (50%)
		Antibiotics	4/10 (40%)
		Muscle relaxant	1/10 (10%)
Venom	11 (12%)	Polistes	3/11 (27,2%)
		Bee	4/11 (36.4%)
		Wasp	4/11 (36.4%)
Exercise-related	9 (9%)	Specific	2/9 (22%)
		Nonspecific	7/9 (78%)
Vaccine	2 (2%)		
Additive	1 (1%)	Glutamate	
Specific Immunotherapy	1 (1%)	Grass mix	
Latex	1 (1%)		
Idiopathic	6 (6%)		

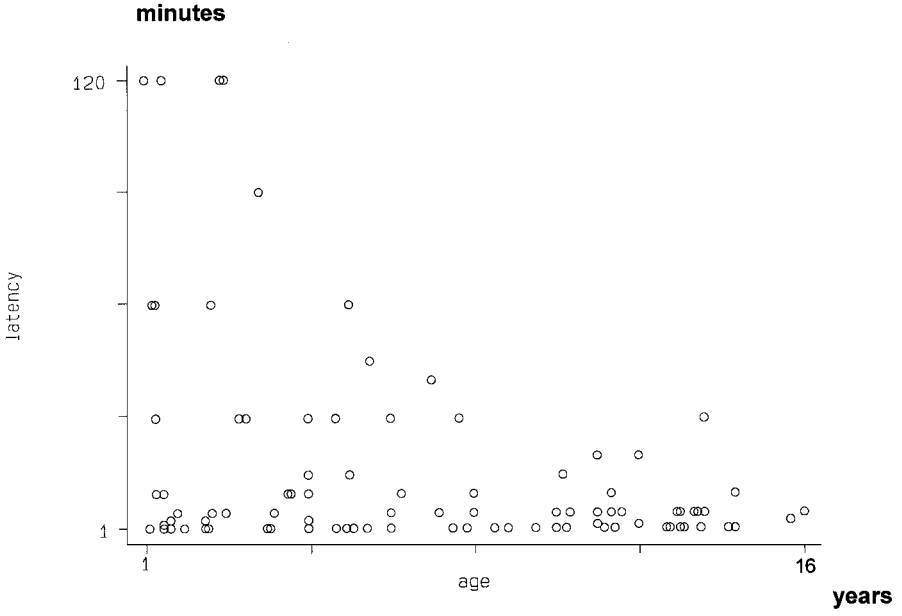

Fig 1. Correlation between latency and age at time of episode (Spearman's correlation coefficient: −0.23 $P = .0217$).

strongly suggestive history was corroborated by an allergologic evaluation (skin tests and/or serum-specific IgE and/or prick by prick).
- Fish caused anaphylaxis in 16 cases (shellfish in 4 episodes, mussels in 2, various kinds of fish in 10 cases); cow's milk in 12; nuts in 7 (Brazil nuts in 3 episodes, hazelnuts in 1, peanuts in 1, pinefruit in 1, and chestnuts in 1); egg in 6; fruit (1 watermelon, 3 kiwi, 1 dates, 1 pomegranate) in 6; cereals (barley, oat, and wheat in 1 episode each) in 3; vegetable (French beans, celery) in 2; and goat's milk in 2.
- The female:male ratio was 16:28.
- The patients with food-dependent anaphylaxis more often have a personal history of eczema ($P = .005$) (Table 2).
- The initial symptoms of the 54 episodes involved ($P = .001$) the gastrointestinal system more often than the cardiovascular system (<0.05) (Table 3).
- The 54 episodes occurred in a younger age (mean age ± SD = 5.1 ± 4.8) (Fig 2).

2. Drug-dependent anaphylaxis
   - Drugs caused anaphylaxis in 10 cases: antibiotics in 5 episodes (ceftriaxone in 3, cefaclor in 1 episode, and penicillin in 1), nonsteroidal antiinflammatory drugs in 4, and a muscle relaxant in 1.
   - The mean age ± SD was 6.5 ± 3.3 (range, 2.5–12) years.
   - The female:male ratio was 5:5.
   - Specific IgE were demonstrated in 3 cases (cefaclor, ceftriaxone, and penicillin).
   - In 1 case, with an unconvincing history of anaphylaxis after acetaminophen ingestion, a double-blind challenge was performed resulting in a generalized urticaria that occurred 30 minutes after a 100-mg dose of the active substance.
3. Hymenoptera venom-dependent anaphylaxis
   - Hymenoptera venom caused 11 episodes of anaphylaxis in 10 subjects; specific IgE against polistes were detected in 3 cases, against wasps in 4, and against bees in 3.
   - The mean age ± SD was 7.6 ± 3.5 (range, 3–13) years.
   - The female:male ratio was 1:9.
   - Children with hymenoptera venom anaphylaxis more frequently have a negative personal atopic history ($P < .0001$) together with negative skin prick tests to inhalant and food allergens ($P < .0001$) (Table 2).
4. Exercise-induced food-dependent anaphylaxis
   - Anaphylaxis has been related to exercise in 9 cases (5 patients); in 2 cases it was specifically food-dependent (pear, chick pea), ie, a strongly suggestive history was corroborated by an allergic evaluation (skin tests, serum-specific IgE, prick by prick). In the other cases there was a strong connection with the meal; ie, the onset of symptoms occurred a few hours after the ingestion of food, but without any specific food being clearly responsible for the symptoms.
   - They were all atopic subjects, with inhalant sensitivities in 4 subjects (3 had a history of asthma and oculorhinitis) while all had food sensitivities to vegetables and/or cereals and/or fruit (all of them had a history of urticaria-angioedema and 2 had also a history of diarrhea and eczema).
   - The female:male ratio was 0:5.
   - These patients often had a history of urticaria-angioedema ($P < .01$) (Table 2).
   - The episodes occurred in older children (mean age ± SD = 12 ± 3.4) (Figure 2).
5. Vaccine-dependent anaphylaxis
   - In 1 case anaphylaxis occurred in a 4½-year-old boy who was polysensitized (*dermatophagoides*, milk, egg, fish, rabbit meat, and wheat) and had a previous history of urticaria-angioedema. He had immediate cardiorespiratory arrest after the administration of a measles vaccine grown on human diploid cells while still in the doc-

TABLE 2. Clinical and Allergologic Features in Different Types of Anaphylaxis in 76 Subjects

	Food Anaphylaxis				Exercise Anaphylaxis				Drug Anaphylaxis				Venom Anaphylaxis			
	Food Dep	Food Indep	OR (95% CL)	*P*	Exercise Dep	Exercise Indep	OR (95% CL)	*P*	Drug Dep	Drug Indep	OR (95% CL)	*P*	Venom Dep	Venom Indep	OR (95% CL)	*P*
Personal history negative for atopy	7/44 (16%)	7/32 (22%)		NS	0/5 (0%)	14/71 (20%)		NS	0/10 (0%)	14/66 (22%)		NS	7/10 (70%)	7/66 (11%)	19.66 (4.39, 87.25)	$<10^{-4}$
Personal history of eczema	22/44 (50%)	6/32 (18%)	4.33 (1.52, 12.24)	.005	2/5 (40%)	26/71 (37%)		NS	1/10 (10%)	27/66 (41%)		NS	0/10 (0%)	28/66 (11%)	U	.009
Personal history of urticaria- angioedema	19/44 (43%)	15/32 (47%)		NS	5/5 (100%)	29/71 (40%)	U	<.01	6/10 (60%)	28/66 (42%)		NS	1/10 (10%)	33/66 (50%)	0.11 (0–0.73)	.018
Personal history positive for asthma	17/44 (39%)	14/32 (44%)		NS	3/5 (60%)	28/71 (34%)		NS	5/10 (50%)	26/66 (39%)		NS	0/10 (0%)	31/66 (47%)	U	<.005
Skin tests positive for at least 1 common inhalant or food allergen	41/44 (93%)	19/32 (59%)	9.53 (2.51, 34.10)	<.0004	5/5 (100%)	55/71 (77%)		NS	7/10 (70%)	53/66 (80%)		NS	1/10 (10%)	59/66 (89%)	0.013 (0–0.097)	$<10^{-4}$
Male sex	28/44 (64%)	22/32 (69%)		NS	5/5 (100%)	45/71 (63%)		NS	5/10 (50%)	45/66 (68%)		NS	9/10 (90%)	41/66 (62%)		NS

Abbreviations: Dep, dependent; Indep, independent; OR, odds ratio; CL, confidence limit; NS, not significant; U, the odds ratio is undefined.

TABLE 3. Characteristics of Clinical Presentation of Different Types of Anaphylaxis in 95 Episodes

Presenting Symptoms	Food Anaphylaxis				Exercise Anaphylaxis				Drug Anaphylaxis				Venom Anaphylaxis			
	Food Dep	Food Indep	OR (95% CL)	*P*	Exercise Dep	Exercise Indep	OR (95% CL)	*P*	Drug Dep	Drug Indep	OR (95% CL)	*P*	Venom Dep	Venom Indep	OR (95% CL)	*P*
Gastrointestinal	22/54 (41%)	2/41 (4.8%)	13.41 (2.72, 123.27)	.001	1/9 (11%)	23/86 (27%)		NS	1/10 (10%)	23/85 (27%)		NS	0/11 (0%)	24/84 (29%)	U	.04
Skin	41/54 (76%)	33/41 (80%)		NS	9/9 (100%)	65/86 (76%)		NS	8/10 (80%)	66/85 (78%)		NS	10/11 (91%)	64/84 (76%)		NS
Respiratory	43/54 (80%)	32/41 (78%)		NS	9/9 (100%)	66/86 (77%)		NS	9/10 (90%)	66/85 (78%)		NS	9/11 (82%)	66/84 (79%)		NS
Cardiovascular	9/54 (17%)	14/41 (34%)	0.39 (0.15, 0.95)	<.05	2/9 (22%)	21/86 (24%)		NS	5/10 (50%)	18/85 (21%)		NS	4/11 (36%)	19/84 (23%)		NS

Abbreviations: Dep, dependent; Indep, independent; OR, odds ratio; CL, confidence limit; NS, not significant; U, the odds ratio is undefined.

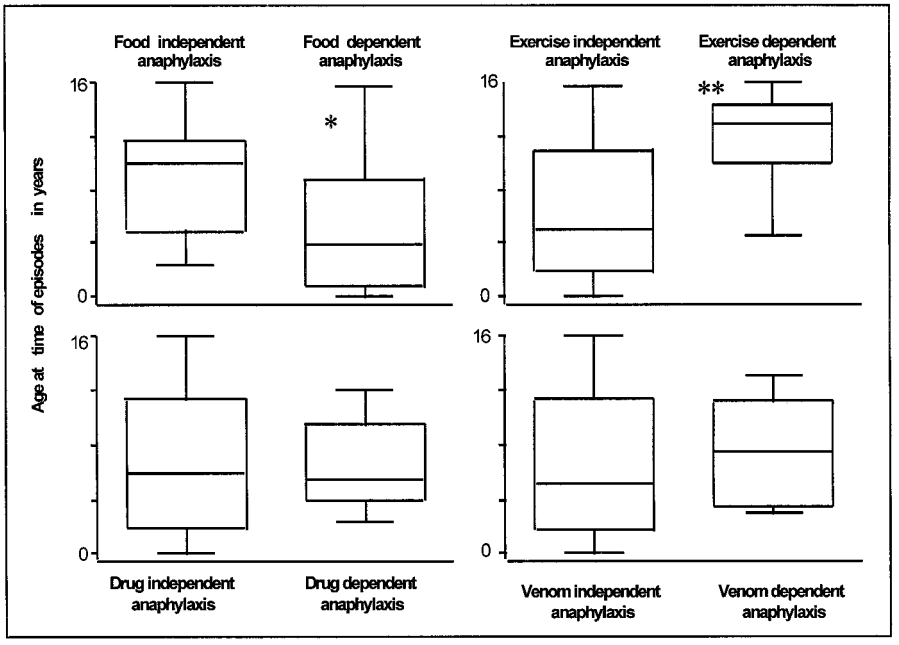

Fig 2. Age distribution in different kinds of anaphylaxis (statistical analysis with logistic regression).

tor's office, but quickly recovered after an ABC (airways, breathing, circulation) resuscitation and a prompt administration of epinephrine and corticosteroids.

- The other case involved a 4-year-old girl who was sensitized to dermatophagoides, cat dander, and *Parietaria officinalis*, with a previous history of respiratory allergy (asthma, rhinitis). She experienced inspiratory dyspnea, angioedema, and glottis edema 10 minutes after the administration of a measles-mumps-rubella vaccine grown in cultures of chicken embryo fibroblasts. She was treated with parenteral corticosteroids and recovered within 30 minutes.

6. Latex anaphylaxis occurred in a 13½-year-old boy who was polysensitized to inhalant and food (meat, vegetables, fruit) allergens and also had a previous history of asthma, urticaria-angioedema, and atopic dermatitis. He developed urticaria oculorhinitis, asthma, and angioedema after 30 minutes and hypotension 120 minutes after undergoing appendectomy surgery. Epinephrine, corticosteroids, and antihistamines were continuously administered intravenously in an intensive care unit. An allergic evaluation disclosed a positive cutaneous response to latex.
7. Immunotherapy anaphylaxis occurred in a 13-year-old girl with a previous history of rhinitis and asthma, monosensitized to grass. One minute after the administration of ITS to grass she developed inspiratory dyspnea, urticaria, and angioedema.
8. Additive anaphylaxis with a severe reaction (pruritus, urticaria-angioedema, glottis edema) occurred in a 11-year-old girl a few minutes after eating a slice of mortadella (a typical Tuscan cold-cut). The girl was polysensitized to inhalant allergen and had suffered from rhinitis previously, but had neither sensitivities to food nor any personal history of food allergy. A double-blind challenge with 100 mg of sodium glutamate was performed in order to better understand the cause of this anaphylaxis. A positive response (urticaria, angioedema) occurred after 5 minutes. Oral corticosteroids and epinephrine were administered and all symptoms disappeared in 1 hour.
9. "Idiopathic" anaphylaxis.
   - Six episodes occurred in 3 patients, for which no specific etiologic factor could be discovered.
   - The mean age ± SD was 10.3 ± 4 (range, 3–13.3) years.
   - The female:male ratio was 1:2.

DISCUSSION

Anaphylaxis is widely understood to be an immediate life-threatening condition that can occur at all ages and frequently in subjects with a history of atopy.

Data about the prevalence of the various causes of anaphylaxis is scarce, especially in children. In adults some reasonable estimates report that hymenoptera sting anaphylaxis occurs in 0.4% of the population[6] and penicillin-induced anaphylaxis occurs every 10–50 cases/100 000 injections.[7] In a review of patients admitted to a university hospital during 1 year there were 9 cases of anaphylaxis out of 20 000 admissions.[8]

In a retrospective study carried out among adult subjects, Sorensen et al[9] have reported an incidence of 3.4 cases/100 000 inhabitants of anaphylactic shock per year that occurred in a hospital catchment area over a 13-year period. The precipitating agents were penicillin in 7 cases, aspirin in 3 cases, food in 2 cases, and bee or wasp stings in 8 cases. In one study of 172 anaphylactic reactions, foods, especially nuts, were the major causative agent, predominantly in children and adolescents. Therefore, foodstuffs appear to be the most important etiologic factor, as

far as children are concerned, while hymenoptera venom, drugs, and idiopathic forms are more likely to occur in adults.[10] In our study we have collected details of 95 reactions in 76 children providing information on the clinical features of anaphylaxis in this age group, until now insufficiently reported.

As in other allergic diseases[11] there is a predominance of the male gender (2:1); the reason for this phenomenon is probably due to the high degree of the male/female ratio in hymenoptera and exercise anaphylaxis (Table 2). Insect sting anaphylaxis has been reported to be more frequent in adult male subjects.[12] This phenomenon may be explained on the basis of exposure in adults, but in children this phenomenon cannot be so easily explained away, as the time spent by both male and female subjects outside is almost the same.

The reports on exercise-induced anaphylaxis describe just a few cases each, so the relevance of the gender of the subjects is not clear. However, it has recently been pointed out that there is indeed a male predominance within a group of subjects with exercise-induced anaphylaxis (female:male = 4:10).[13]

Sixty-four percent of our patients had a personal history of atopic disease (atopic eczema, asthma, and allergic rhinitis unrelated to anaphylactic reactions). However, this was less frequent among children with hymenoptera-induced anaphylaxis (Table 2).

A previous allergic eczema is more frequent among patients with food-induced anaphylaxis. Children with food anaphylaxis are highly atopic, with a severe allergy to food; indeed, the association between atopy and food anaphylaxis has been previously reported.[10]

A positive history for urticaria-angioedema (Table 2) is more prevalent among patients with exercise-induced anaphylaxis. This is not surprising because exercise-induced anaphylaxis is a dramatic manifestation of mast cell activation pathophysiology, a phenomenon not yet fully understood.[14] Moreover, urticaria-angioedema is a characteristic initial symptom of this clinical type of anaphylaxis for which other cofactors are often needed.[15]

The mean latency period in the 95 episodes of anaphylaxis was 15.45 ± 27.53 minutes. No difference was found in the latency of anaphylaxis on the basis of a difference in agents. On the other hand, the age at which the 95 episodes occurred, was inversely related to latency (Fig 1). This is probably attributable to the fact that the most important cause of anaphylaxis in the younger child is food and the anaphylaxis caused by ingested agents is often not so severe and slower to begin. Skin and respiratory symptoms are more common and earlier in onset than cardiovascular ones.

In our study food was the most important cause of anaphylactic reactions, especially in children of a younger age (Fig 2). Seafood and milk were the foodstuffs most often incriminated, while nuts, eggs, fresh fruit, cereals, and vegetables as well as goat milk were cited in relatively few cases. It is of particular interest to note that in our study nuts were not the main food responsible for anaphylaxis, as was reported in another paper[10] in which the majority of subjects with food anaphylaxis were younger than 18 years of age. In particular, peanuts were responsible for only one episode of anaphylaxis. In other countries (United States, England) peanuts are the most common cause of life-threatening reactions both in children and adults.[16] Increased exposure early in life and a greater consumption of peanuts in these countries (in the United States peanut consumption is 3.5 kg per person/year,[16] while in Italy it is only 0.68 kg per person/year[17]), as well other factors, may explain these different data.[18]

Drugs accounted for 11% of the episodes reported in our study with nonsteroidal antiinflammatory drugs and antibiotics as the substances most frequently involved. Only a small number of epidemiologic studies have been carried out on the role of drugs as an etiologic factor of anaphylaxis. Pumphrey and Stanworth[10] failed to find any drug-related anaphylaxis in children and adolescents. On the other hand among adults, anaphylaxis caused by a number of different drug substances (muscle relaxant, haemeccel, penicillin, and naproxin)[10] was not a rare adverse event.

Exercise, which was not cited as a cause of anaphylaxis in the previous reports, is quite a frequent trigger among adolescents and young adults.[13] In our study this factor is related to 9% of the total episodes and in 20% of the cases occurring in patients more than 8 years old. It is often food-dependent, but it is difficult to identify the specific foodstuff involved. Usually these patients are polysensitized to either vegetable protein or inhalant antigens and the anaphylaxis occurs only if more than one of the allergenic foods are ingested before exercise is performed outdoors in the presence of a high concentration of inhalant allergens. Furthermore, other cofactors are often needed, such as drugs, high humidity, etc, and for this reason it is not always a reproducible syndrome. Avoiding the consumption of solid foods 4 hours before any physical exercise is the best means to prevent relapses, at least in atopic subjects with a very suggestive history.[13]

Systemic reactions to hymenoptera stings are commonly present in 6/1000 of the general population,[19] but the prevalence in the pediatric population is unknown, especially as far as the anaphylactic reaction is concerned. In our study 11/95 (12%) of episodes were attributable to hymenoptera stings. Wasp, bee, and polistes were equally responsible for anaphylactic reactions. As previously reported, atopy was not necessarily a risk factor, as the majority of children have negative skin tests to common inhalant and food allergens. Two episodes of vaccine-dependent anaphylaxis occurred. The etiologic factors in these cases are unknown, but according to a recent paper, the gelatin could be suspected in at least in one case (the child was polysensitized to food).[20] These data confirm recent evidence[21] that the vaccine-induced anaphylaxis occurred, whether or not there was an egg allergy, and independently of whether the vaccine was grown in a fibroblast embryo chicken culture or on human diploid cells. However, in the case of an adverse reaction after the administration of a vaccine, the patient should be

investigated carefully, with close attention to all components of the vaccine.

Latex, additive, and immunotherapy anaphylaxis are rare events, but may also sometimes occur in children.[22–24]

Anaphylaxis with an unknown etiology, not triggered by any exogenous stimulus, occurred in 3/76 patients (3.8%). All had infrequent idiopathic anaphylaxis, according to the definition of Ditto et al.[2] An impressive increase of idiopathic anaphylaxis in the pediatric population has been reported by the same authors[2] in an extensive report of 335 cases of idiopathic anaphylaxis, 32 (9.5%) of which occurred in children and adolescents under the age of 20. At present there is no explanation for this increase.

The place where the anaphylactic reactions occur is very important in terms of providing adequate therapy.[25] We found that in 57% of cases (54/95) the anaphylactic event occurs at home; 12% outdoors (11/95); 5% in restaurants (5/95); 3% in the doctor's office (3/95); 3% in hospitals (3/95); 3% on football fields (3/95); 2% on the beach (2/95); 1% in the gym (1/95); 1% at school (1/95); and 1% in the operating room (1/95) and in the other 12% of cases (11/95), the place was never determined. Sampson et al[26] reported that all the near-fatal reactions described took place in private homes, whereas 5 out of the 6 fatal ones occurred in a public setting, while children were outdoors.

In our series the most frequent initial symptoms involved the skin and respiratory system (Table 3). We had no fatal reactions. It is interesting to note that in yet another report[26] there was no correlation between cutaneous symptoms and fatal reaction.

As the home is the most frequent place in which an anaphylactic event can occur, all family members, especially parents, should be adequately informed on medical treatment. In particular, the home administration of epinephrine should be encouraged.[23] Unfortunately, as 62/76 children (87%) had only one anaphylactic attack, babysitters were unprepared to deal with this situation. However, epinephrine use in the treatment of anaphylaxis should be promoted, because in only 17 out of the 95 episodes of anaphylaxis was epinephrine actually administered. In fact, even among those patients who were hospitalized the first drug used in the emergency room was corticosteroids although it is well-known that epinephrine is the first choice of treatment during anaphylaxis.

Finally, on the basis of what has been said, we can draw the following conclusions:

- The anaphylactic reactions in our study appeared to be dangerous, but not usually a life-threatening event.
- Food, and in particular seafood and milk, at least in our area, seems to be the most important etiologic factor.
- There are some particular features related to the different types of anaphylactic reactions.
- Food-related anaphylaxis is more frequent in younger children with a previous history of eczema. The symptoms usually affect the gastrointestinal system and rarely the cardiovascular one.
- Exercise-induced anaphylaxis occurs more often in older children with a previous history of urticaria-angioedema.
- Venom-induced anaphylaxis occurs to subjects with negative skin prick tests to common inhalant and food allergens.

Almost all children who experienced an anaphylactic reaction were suffering from it for the first time; hence, prevention was almost impossible. It would, however, probably be good practice to give specific counseling on the treatment of anaphylaxis at least to those patients with severe food allergies, as it is usually these children who have food-related anaphylaxis.

Epinephrine, although the absolute first-choice treatment in anaphylaxis, appears to be insufficiently used even in a medical setting. Therefore, a more adequate use of this drug, especially in children where its great effectiveness is associated with minimal cardiovascular side effects, should be promoted among both general and hospital physicians.

REFERENCES

1. Bochner BS, Lichtestein LM. Anaphylaxis. *N Engl J Med.* 1992;324:1785–1790
2. Ditto AM, Harris KE, Krasnick J, Miller MA, Patterson R. Idiopathic anaphylaxis: a series of 335 cases. *Ann Allergy.* 1996;77:285–291
3. Dreborg S, Backman A, Basomba A, et al. Skin tests used in type I allergy testing. Position paper prepared by the subcommittee on Skin Tests of the EAACI. *Allergy.* 1989;44(suppl10):1–59
4. Hunt KJ, Valentine MD, Kagey-Sobotka A, Lichtestein LM. Diagnosis of allergy to stinging insects by skin testing with hymenoptera venoms. *Ann Intern Med.* 1976;85:56–59
5. Valentine MD, Schuberth KC, Sobotka AK, et al. The value of immunotherapy with venom in children with allergy to insect sting. *N Engl J Med.* 1990;323:1601–1603
6. Settipane GA, Boyd GK. Prevalence of bee sting allergy in 4,982 boy scouts. *Acta Allergologica.* 1970;25:286–291
7. Rudolph AH, Price EV. Penicillin reactions among patients in venereal disease clinics: a national survey. *JAMA.* 1973;223:499–501
8. Amormarn L, Bernard L, Kumar N, Bielory L. Anaphylaxis admissions to university hospital. *J Allergy Clin Immunol.* 1992;89(suppl):349
9. Soresen HT, Nielsen B, Ostergaard M, Nielsen J. Anaphylactic shock occurring outside hospital. *Allergy.* 1989;44:288–290
10. Pumphrey RSH, Stanworth SJ. The clinical spectrum of anaphylaxis in northwest England. *Clin Exp Allergy.* 1996;26:1364–1370
11. Skobeloff EM, Spivey WH, St Clair SS, Shoffstall MJ. The influence of age and sex on asthma admissions. *JAMA.* 1992;268:3437–3440
12. Reisman RE. Insect allergy. In: Middelton E Jr, Reed CE, Ellis EF, eds. *Allergy Principles and Practice.* St Louis, MO: Mosby-Year Book; 1978:1100
13. Romano A, Di Fonso M, Giuffreda F, et al. Diagnostic work-up for food-dependent, exercise-induced anaphylaxis. *Allergy.* 1995;50:817–824
14. Lin RY, Barnard M. Skin testing with food, codeine, and histamine in exercise induced anaphylaxis. *Ann Allergy.* 1993;70:474–478
15. Wade JP, Liang MH, Sheffer AL. Exercise-induced anaphylaxis: epidemiological observations. *Biochemistry of the Acute Allergic Reactions: Fifth International Symposium.* 1989:175–182
16. Ewan PW. Clinical study of peanuts and nuts allergy in 62 consecutive patients. *BMJ.* 1996;312:1074–1078
17. Perelli M, Faella P, Maggiolo R. Peanut: a new old crop for European agriculture. From: Proceedings of the Third Congress of the European Society of Agronomy; Abano-Padova. 1994:732–733
18. Hourihane J O'B, Dean TP, Warner JO. Peanut allergy in relation to heredity, maternal diet and other atopic diseases: results of a questionnaire survey, skin prick testing and food challenges. *BMJ.* 1996;313:518–521
19. Charpin D, Birnbaum J, Lanteaume A, Vervloet D. Prevalence of allergy to hymenoptera stings in different samples of the general population. *J Allergy Clin Immunol.* 1992;90:331–334

20. Kelso J, Jones RT, Yunginger JW. Anaphylaxis to measles, mumps, rubella vaccine mediated by IgE to gelatin. *J Allergy Clin Immunol.* 1993;91:867–872
21. James JM, Burks W, Roberson PK, Samson HA. Safe administration of the measles vaccine to children allergic to eggs. *N Engl J Med.* 1995;332: 1262–1266
22. Reid MJ, Lockey RF, Turkeltaubt PC, Platts-Mills TAE. Survey of fatalities from immunotherapy and skin testing 1985–1989. *J Allergy Clin Immunol.* 1993;92:6–15
23. Wuntrich B. Adverse reaction to food additives. *Ann Allergy.* 1993;71: 379–384
24. Kelly KJ, Pearson ML, Kurup VP, et al. A cluster of anaphylactic reactions in children with spina bifida during general anesthesia: epidemiological features, risk factor, and latex hypersensitivity. *J Allergy Clin Immunol.* 1994;94:53–61
25. Patel I, Radiven FS, David TJ. Management of anaphylactic reaction to food. *Arch Dis Child.* 1994;71:370–375
26. Sampson HA, Mendelson L, Rosen JP. Fatal or near fatal reaction to food in children and adolescents. *N Engl J Med.* 1992;327:380–384

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