

Anaphylaxis in referred pediatric patients: demographic and clinical features, triggers, and therapeutic approach

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Abstract Anaphylaxis remains under-diagnosed and under-treated. A better knowledge of patterns and triggers of anaphylaxis might contribute to a better management. In this study we evaluated the demographic and clinical features of anaphylaxis in pediatric patients, as well as its triggers and therapeutic approach. From May 1st 2004 until April 30th 2006 we prospectively collected data on all patients referred for investigation of anaphylaxis to the pediatric department of the University Hospital Gasthuisberg Leuven and to two private pediatric practices. Data were stored in a MySQL database by use of an online encrypted web form. Sixty-four cases of anaphylaxis occurred in 48 children, aged 6 months to 14.8 years. Twenty-seven episodes (42.2%) occurred at home. The symptoms were dermatologic in 62 (96.9%) episodes, respiratory in 57 (89.1%), gastrointestinal in 19 (29.7%), cardiovascular in 14 (21.8%), and neurological or behav-

ioural in 19 (29.7%). Antihistamines were administered in 41/57 (71.9%) cases, corticosteroids in 26/57 (45.6%), beta-2-mimetics in 14/57 (24.6%), and adrenaline in 11/57 (19.3%). Out of nine cases where Epipen was available at the moment of anaphylaxis, it was administered in one case only. Food was the cause of anaphylaxis in 42/55 (76.4%) cases with identified trigger, while medication, insect stings, latex, and birch pollen triggered 5 (9.1%), 4 (7.3%), 3 (5.5%), and 1 (1.8%) case(s), respectively. Allergy to the trigger was known prior to anaphylaxis in 19/55 (34.5%) cases. In conclusion, anaphylaxis in pediatric patients generally presents with dermatologic and respiratory symptoms, while in 1/5 episodes cardiovascular symptoms occur. Food is by far the most frequent trigger. Allergy to the trigger is known in 1/3 cases only. Anaphylaxis is under-treated, even when appropriate medication is available.

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Abbreviations

SPT skin prick test

Introduction

Anaphylaxis is a “serious allergic reaction that is rapid in onset and may cause death” [27]. Although data on the incidence and prevalence of anaphylaxis are sparse and often imprecise, its frequency is estimated at a life-time prevalence of 0.05–0.2% [2, 10, 15]. The largest number of new cases occurs among children and adolescents [15]. Anaphylaxis often is under-diagnosed and under-treated

[12, 15, 17], which in some cases may result in a fatal course [1, 26]. Recognition of anaphylactic patterns and knowledge of possible anaphylactic triggers may contribute to a more accurate treatment of anaphylactic episodes [29].

In this study we sought to investigate the frequency of anaphylaxis in a pediatric population seen at a tertiary or a secondary referral level, the demographic characteristics of the patients, the clinical course and triggers of anaphylaxis, its therapeutic approach and the co-existence of allergic symptoms and asthma.

Materials and methods

Definition of anaphylaxis and severity grading

At the moment this study started there was no unique internationally accepted definition of anaphylaxis. We define anaphylaxis here as “a serious allergic reaction with rapid onset of symptoms occurring on a site that is remote from the contact site of the trigger and/or in at least two organ systems” [4]. Applying this definition, we meet the clinical criteria for the diagnosis of anaphylaxis as proposed in the position paper of the European Academy for Allergology and Clinical Immunology [19]. According to the guidelines presented in this paper, we discerned mild, moderate, and severe anaphylaxis.

Collecting of data

From May 1st 2004 until April 30th 2006 we prospectively collected data on all consecutive patients who were seen for investigation of anaphylaxis at the pediatric department's outpatient Allergy Clinic of the University Hospital Gasthuisberg Leuven, in a private practice for pediatric allergy situated in Mechelen, or in a private pediatric practice in Hasselt; these facilities will be henceforth referred to as PedAllUH, PedAllPM, and PedPH, respectively. All patients were seen by a pediatrician trained in pediatric allergy (LDS, DB, and MR at PedAllUH; LDS and AD at PedAllPM; MR at PedPH) who handled history taking, clinical examination, and planning of further examinations. Data were stored in a MYSQL database by use of an online encrypted web form written in PHP, which was filled in for each episode of anaphylaxis. The form asked for (1) demographic data; (2) detailed information on the symptoms of anaphylaxis, with separate questions for dermatologic, respiratory, gastrointestinal, cardiovascular, and behavioural or neurological symptoms; (3) the trigger of anaphylaxis, investigations used to confirm the implication of the trigger and previously known allergy to the trigger; (4) the course of anaphylaxis: time lapse between contact with the trigger and onset of subsequent symptoms,

total duration of symptoms, biphasic course or not; (5) the treatment of anaphylaxis and time lapse between onset of symptoms and administration of medication; (6) recurrence of anaphylaxis and presence of a management plan for it; and (7) coexistence of allergic and/or asthmatic symptoms.

Identification of the trigger

The trigger of anaphylaxis could be scored as “identified” or “unknown or unclear”. This scoring was left to the interpretation of the individual investigator as a result of careful history taking, with confirmation by skin prick testing (SPT), measurement of allergen-specific IgE serum levels, or by means of provocation testing when this was judged to be appropriate and ethically acceptable [29].

SPT, specific IgE, provocation

Depending on each individual case, SPTs were performed with one or more of the following: (1) a commercial extract of cow's milk, egg white, peanut, hazelnut, wheat, codfish, latex, and/or birch pollen (HAL, The Netherlands); (2) yellow jacket wasp or honey bee venom extract (ALK-Abellø, Hørsholm, Denmark) in a concentration up to 1.0 µg/ml; (3) self-prepared serial dilutions of methylprednisolone and amoxicillin; and (4) fresh food (apple, kiwi, scampi, lupine, walnut, pistachio, Brazil nut) by means of prick-to-prick testing [7]. SPTs were carried out on the back or on the volar side of the forearm by means of a microlance (HAL prick-lancette) and read after 15 min [22]. Histamine diphosphate 1 mg/ml (HAL) and Coca solution in 50% glycerol were used as positive and negative controls, respectively. Allergen-specific IgE levels were measured using the CAP-system (Phadia, Uppsala, Sweden).

In case food provocation testing was judged to be appropriate, open provocation testing was provided for children below the age of 3 and double-blind-placebo-controlled provocation for children 3 years and older [20].

Statistical analysis

Comparison between groups was done by chi-square, Fisher's exact, and Mann-Whitney U tests, with two-tailed significance testing.

Results

Demographic data and place of occurrence

We registered 64 cases of anaphylaxis which occurred in 48 children: 31 boys and 17 girls (Table 1). In 58 cases the patient was referred to us after anaphylaxis for further

Table 1 Demographic data, symptoms, time lapse to onset of symptoms, treatment, and trigger in 64 anaphylactic episodes

N	Age, months	Gender	Place	Symptoms						Time lapse Minutes	Treatment					Trigger	Allergy to trigger known
				D	UR	LR	GI	CV	N/B		AH	CS	β2	Adrenaline	Other		
1	53	M	F	X	Xs	X	X		X	<1	X					Hazelnut	No
2	136	M	H	X	Xs					60	X					Acetylsalicylic acid	No
3	117	M	H	X	Xs	X	X		X	10	X	X				Egg	Yes
4	127	M	H	X		X				15	X	X	X			Lupine	No
5	32	M	F	X	X					2	X					Peanut	No
6	6	M	H	X		X			X	5	X					Kiwi	No
7	64	F	R	X	Xs		X			?		No medication			Place left	?	na
8	143	M	O	X	Xs					<10	X	X				Food	na
9	146	M	O	X	Xs					<10	X	X				Food	na
10	83	F	H	X			X			1		No medication				Peanut	No
11	11	F	O	X		X				2	?	?	?	?		Cow's milk	No
12	18	F	H	X	X	X				<1	?	?	?	?		Peanut	Yes
13	49	M	O	X			X			15	X					Food additives	No
																+exercise	
14	90	M	H	X	Xs					<1	X					Apple	Yes
15	164	F	S	X	Xs	X				1	X	X				Apple	No
16	165	F	S		Xs	X				1			X	X		Kiwi	No
17	178	F	O	X	X	X	X	X		120	X	X				Egg	Yes
18	71	M	S	X	Xs					5	X					Brazil nut	No
19	95	F	R	X	Xs					10	X	X				Peanut	No
20	54	M	F	X				X	X	1	X	X				Wasp sting	No
21	55	M	F	X				X	X	1	X	X			Hospitalisation	Wasp sting	Yes
22	146	F	F	X	Xs	X	X			2		X				Walnut	No
23	91	M	O	X	X	X				10	X	X		X	Hospitalisation	Latex	No
24	132	F	F	X	X	X				<10		X			Hospitalisation	Food	na
25	17	M	H	X		X			X	15		X			Hospitalisation	Egg	Yes
26	38	M	H	X		X	X			15	X	X				Peanut	No
27	100	M	H	X			X	X	X	30				X		Acetylsalicylic acid	No
28	134	M	H	X		X				?	?	?	?	?		Latex	No
29	138	F	H	X	X	X				30	X	X				Food	na
30	30	M	H	X	Xs	X			X	1	X					Scampi	No
31	151	M	R		Xs		X			<1	X					Peanut	Yes
32	29	M	F	X		X			X	90	X	X				Cow's milk	Yes
33	152	F	R	X	X	X				30	X					Food additives	No
34	162	M	H	X	X					3	X					Egg	Yes
35	130	M	F	X			X			?	?	?	?	?		?	na
36	11	M	H	X		X				20		X	X			Egg	No
37	172	F	H	X	X	X				30	X		X			Food	na
38	167	F	O	X		X			X	30	X		X			Peanut+exercise	Yes
39	166	F	O	X	Xs	X		X	X	20	X		X			Food+exercise	na
40	172	F	O	X	X	X		X	X	60	X		X			Peanut+exercise	Yes
41	174	F	O	X	X	X		X	X	60	X		X			Peanut+exercise	Yes
42	104	M	S	X		X	X	X		15	X	X		X		Wasp sting	No
43	50	M	H	X	Xs	X				15		X				Egg	Yes
44	44	M	S	X		X				?	?	?	?	?		Hazelnut	No
45	45	M	H	X		X	X			15	?	?	?	?		Fish	No
46	42	M	O	X		X				?	X					?	na
47	42	M	O	X		X				?	X					Peanut	No
48	98	M	H	X		X				240	X		X			Benzoic acid	Yes
49	33	M	S	X	X					1		X				Egg	Yes
50	14	M	H	X			X	X		10	X			X		Wheat	Yes
51	14	M	Hosp	X		X	X	X	X	10				X		Food additives	No
52	11	M	Hosp	X		X		X		1			X	X		Methylprednisolon & amoxicillin-CA	No

Table 1 (continued)

N	Age, months	Gender	Place	Symptoms					Time lapse Minutes	Treatment					Trigger	Allergy to trigger known
				D	UR	LR	GI	CV	N/B	AH	CS	β 2	Adrenaline	Other		
53	17	M	H	X		X	X	X		40	X		X	X	Cow's milk	Yes
54	11	M	Hosp	X		X				25			X		Methylprednisolon	No
55	82	M	S	X	X	X				5		X			Brazil nut	No
56	35	F	H	X	Xs	X		X	X	1	?	?	?	?	Pistachio nut	No
57	94	F	H	X	Xs	X	X	X	X	<1			X	X	Intubation Paracetamol	No
58	20	F	F	X	X		X		X	1	X				Peanut	No
59	21	F	F	X	X		X			1		No medication			Kiwi	No
60	101	M	H	X	X	X			X	1	X	X	X		Bee sting	No
61	105	F	H	X	X	X				60	X	X		Place left	Latex	No
62	75	F	H	X		X				1	X	X			Peanut	Yes
63	62	M	S	X	X					30	X	X	X	X	Cow's milk	Yes
64	38	M	H	X		X			X	?	X	X			Tree pollen +exercise	No

D dermatological, UR upper respiratory tract, s swallowing difficulty, LR lower respiratory tract, GI gastrointestinal, CV cardiovascular, N/B neurological/behavioural, F family, friends, neighbours, H home, Hosp hospital, O outside, R restaurant, AH antihistamines, CS corticosteroids, β 2 beta-2-mimetics, na not applicable

investigation and management, while in only six cases we saw the patient at the moment of anaphylaxis. Twenty patients were seen at PedAllUH for a total of 25 episodes; 28 patients were seen in private practice, 25 of them at PedAllPM and 3 at PedPH, for a total of 36 and 3 episodes, respectively. These figures represent a frequency of 25:2000 ambulant visits at PedAllUH and of 36:2100 and 3:6000 at PedAllPM and at PEDPH, respectively. Age at anaphylaxis ranged from 6 months to 14.8 years, with a mean and median of 6.9 years (Fig. 1). Twenty-seven (42.2%) episodes of anaphylaxis occurred at home, ten episodes (15.6%) took place at the home of family, friends, or neighbours, while anaphylaxis occurring at school, outside, in a restaurant, or in a hospital accounted for 8 (12.5%), 12 (18.7%), 4 (6.2%), and 3 episodes (4.7%), respectively (Fig. 1). In children aged 0–11 years anaphy-

laxis occurred outside in 6 out of 51 episodes, compared to 6 out of 13 episodes in the adolescent group aged 12–14 years ($p < 0.01$).

Symptoms

The symptoms occurring during anaphylaxis were dermatologic in 62 episodes (96.9%), respiratory in 57 (89.1%), gastrointestinal in 19 (29.7%), and cardiovascular in 14 (21.8%), while neurological symptoms or changes in behaviour occurred in 19 (29.7%) cases (Table 2). Most patients showed a combination of symptoms. According to the above-mentioned severity grading, 9 (14.1%) of the anaphylactic episodes were classified as mild, 41 (64.1%) as moderate, and 14 (21.8%) as severe. In 57 cases the sequence of symptoms could be noticed, with dermatological and/or respiratory symptoms appearing first in 65% and 42% of cases, respectively.

Trigger

The anaphylactic trigger could be identified in 55 cases (86%), whereas it was unknown or unclear in 9 cases (14%) (Table 1). Out of the nine cases with an unidentified trigger, six had an onset of symptoms within minutes after the ingestion of food, but the ingredients of the ingested food could not be fully identified. Those six cases were considered to be caused by an unidentified food trigger. Taking together the 55 cases with an identified trigger and the six cases with an unidentified food trigger, food was the cause of anaphylaxis in 48 cases (75%), whereas medica-

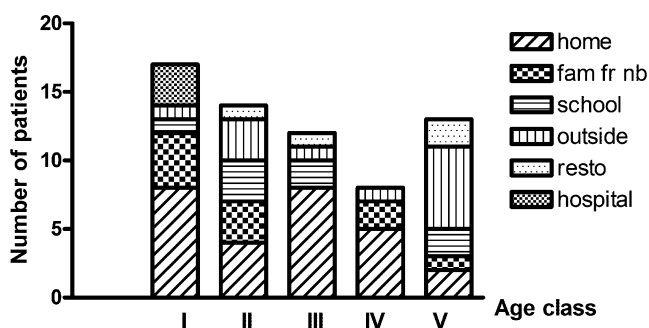


Fig. 1 Age distribution and place of occurrence of anaphylaxis. Age class I: 0–2 years, class II: 3–5 years, class III: 6–8 years, class IV: 9–11 years, and class V: 12–14 years. Fam fr nb family, friends, neighbours

Table 2 Frequency of specific symptoms in anaphylaxis

Symptoms		N=64		1st symptom N=57	
		n	%	n	%
Dermatological		62	96.7	37	64.9
	Urticaria	24	37.5		
	Angioedema	42	65.6		
	Oedema of the extremities	3	4.7		
	Erythema	27	42.2		
	Pruritus	22	34.4		
	Generalized pruritus	17	26.6		
Respiratory		57	89.1	24	42.1
Upper respiratory tract		36	56.2	16	28.1
	Rhinitis	13	20.3		
	Throat pruritus	11	17.2		
	Hoarseness	4	6.2		
	Swallowing difficulty	18	28.1		
	Saliva production	6	9.4		
Lower respiratory tract		43	67.2	6	10.5
	Dyspnoea	39	60.9		
	Wheezing	14	21.8		
Gastrointestinal		19	29.7	5	8.8
	Oral pruritus	3	4.7		
	Nausea	6	9.4		
	Vomiting	10	15.6		
	Diarrhoea	8	12.5		
	Abdominal pain	8	12.5		
Cardiovascular		14	21.8	1	1.8
	Hypotension	5	7.8		
	Collapse	3	4.7		
	Peripheral cyanosis	7	10.9		
Neurological/behavioural		19	29.7	4	7
	Irritability	9	14.1		
	Lethargy	8	12.5		
	Headache	1	1.6		
	Troubled vision	1	1.6		

tion, insect stings, latex, and birch pollen were responsible for 5 (9.1%), 4 (7.3%), 3 (5.5%), and 1 (1.8%) case(s), respectively (Fig. 2a). Out of a total of 48 food-induced cases, peanut was the trigger in 12, egg and nuts in seven cases each, cow's milk in four, kiwi in three, apple in two, and wheat, lupine, fish, and shellfish in one case each. Food additives triggered three cases, and in six cases the food trigger could not be identified (Fig. 2b).

In 5 out of 48 food-induced cases, exercise most likely contributed to the occurrence of anaphylaxis. This was the case in four episodes in the same patient, three of them being caused by peanut and one by an unidentified food trigger; the fifth case occurred in another patient after the ingestion of an additive containing sweets. Furthermore, exercise was a possible contribution to an episode of anaphylaxis caused by exposure to birch pollen.

Episodes of anaphylaxis triggered by medication were due to oral acetylsalicylic acid in two cases, methylprednisolone +

amoxicilline-clavulanic acid intravenously in one, methylprednisolone intravenously in one, and benzoic acid in a syrup in one case. The two cases of anaphylaxis due to methylprednisolone and to methylprednisolone + amoxicilline-clavulanic acid intravenously occurred in the same patient while hospitalized in a peripheral pediatric service (methylprednisolone was administered for the purpose of protecting against allergic reaction to antibiotics in this child known to have a complex food allergy and having already experienced two anaphylactic episodes due to food). Benzoic acid was identified as the anaphylactic trigger in a patient previously known to have urticaria due to benzoic acid, but not having previously experienced anaphylaxis to it.

Tests used to confirm the involvement of a specific trigger are shown in Table 3. In two cases a food provocation test was performed, because the food that triggered anaphylaxis contained two different allergens that both tested positive in SPT and CAP.

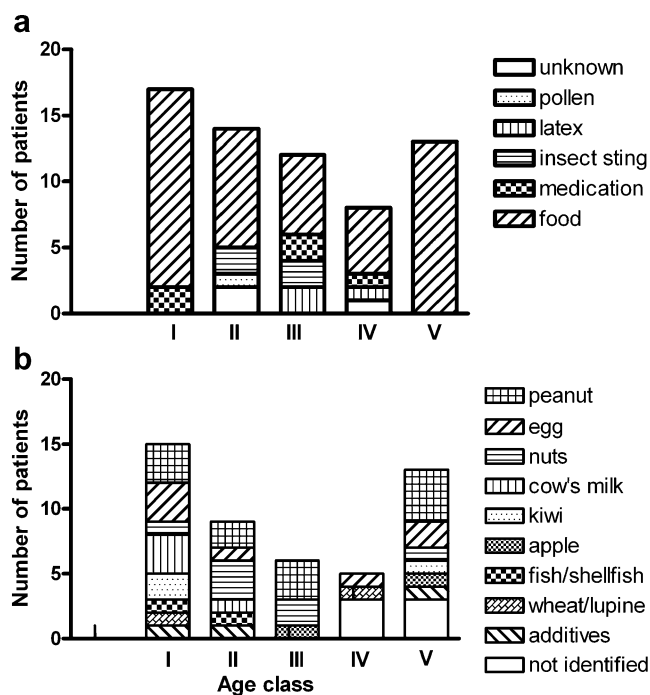


Fig. 2 **a** Trigger of anaphylaxis in different age groups. **b** Food trigger of anaphylaxis in different age groups

Previously known allergy to the trigger

Out of 55 cases with an identified trigger, allergy to the anaphylactic trigger had been documented prior to the moment of anaphylaxis in 19 (34.5%) cases (Table 4). This concerned a food allergen in 17 cases. In 14/17 (82%) food-induced cases, the subject and/or parents were unaware of

the presence of the causal allergen in the ingested food; the other three cases were triggered by ingestion of raw egg in a subject previously known with egg allergy but having become tolerant to cooked egg in the meantime in one case, by skin contact with raw egg in another case, while the third one was triggered by apple in a patient formerly known with oral allergy syndrome to apple, but not having experienced anaphylactic symptoms to apple before.

On the other hand, out of 36 cases caused by a previously unknown trigger, a food allergen was implicated in 25 (69%) cases: nuts and peanuts in seven and six cases, respectively, kiwi in three, additives in three, and egg, cow's milk, apple, lupine, fish, and scampi in one case each, respectively.

Course of anaphylaxis

The course of anaphylaxis could be seen in a detailed manner in 54 cases. Time lapse between contact with the trigger and onset of symptoms ranged from a few seconds to 240 min (median 10 min; mean 21 min) (Table 1). In case number 48, which occurred after 2 doses of a benzoic acid containing syrup, time lapse was 240 minutes from the first dose and 25 minutes from the second dose. In 17 children younger than 3 years, time lapse ranged from a few seconds to 90 min (median 2 min; mean 13.2 min), compared to a range from a few seconds to 240 min (median 15 min; mean 25) in 37 children older than 3 years (not significant). The total duration from onset of symptoms until complete recovery ranged from 20 min to 120 hours.

Table 3 Diagnostic tests used to confirm the implication of the trigger in 55 cases with an identified trigger

Trigger (number of cases)		SPT <i>n</i> positive / <i>n</i> performed	CAP	Provocation
Food (42)	Peanut (12)	10/10	12/12	-
	Nut (7)	3/3	7/7	-
		2/2*		-
	Egg (7)	7/7	7/7	1/1
	Cow's milk (4)	4/4	4/4	1/1
	Kiwi (3)	1/1*	3/3	-
	Apple (2)	2/2*	2/2	-
	Wheat (1)	1/1	1/1	-
	Lupine (1)	1/1*	1/1	-
	Fish (1)	1/1	1/1	-
	Scampi (1)	1/1*	-	-
	Additives (3)	-	-	-
	Medication (5)			
Insect venom (4)	Methylprednisolon (1)	1/1**	-	-
	Amoxicillin (1)	1/1**	-	-
	Acetylsalicylic acid (2)	-	-	-
	Benzoic acid (1)	-	-	-
	Wasp (3)	3/3	3/3	-
Latex (3)	Bee (1)	1/1	1/1	-
		3/3	3/3	-
Birch pollen (1)		1/1	1/1	-

SPT skin prick testing, CAP CAP-system testing

* SPT with fresh products

** SPT with self-prepared serial dilutions

Table 4 Episodes of anaphylaxis caused by a formerly known trigger

Case number	Trigger	Unknown, accidental contact	Management plan + Epipen	Adrenaline		Administered		Severity grading of anaphylactic episode
				Epipen available		On site	In hospital/ office	
12	Peanut	Yes	No	No		No	No	Moderate
31		Yes	Yes	No		No	No	Moderate
38		Yes	No	No		No	No	Moderate
41		Yes	No	No		No	No	Severe
42		Yes	No	No		No	No	Severe
62	Egg	Yes	Yes	Yes		No		Mild
3		Yes	Yes	Yes		No	No	Moderate
17		Yes	Yes	Yes		No	No	Severe
25		Yes	No	No		No	No	Moderate
34		No	Yes	Yes		No	No	Mild
43	Cow's milk	No	Yes	Yes		No	No	Moderate
49		Yes	No	No		No	No	Mild
32		Yes	Yes	No		No	No	Moderate
53		Yes	Yes	Yes		No	Yes	Severe
63		Yes	Yes	Yes	Yes	No	No	Moderate
14	Apple	No	Yes	Yes		No		Moderate
50	Wheat	Yes	Yes	Yes		No	Yes	Severe
48	Benzoic acid	Yes	Yes		No	No	No	Moderate
21	Wasp sting	Yes	No	No		No	No	Severe

A biphasic course was noticed in two cases, with a symptom-free interval of 4 h and 30 min, respectively.

Treatment

Medication

The medication used to treat anaphylaxis could be identified in 57/64 cases. It concerned antihistamines in 41 (72%), corticosteroids in 26 (46%), beta-2-mimetics in 14 (25%), adrenaline in 11 cases (19%), and paracetamol in one case, while in three cases no medication was used (Fig. 3a). In most cases several medications were used and in several cases one compound was administered in different ways (Fig. 3b). The first medication administered was an antihistamine in 27 (47.4%), cortisone in 14 (24.6%), beta-2-mimetics in 6 (10.5%), adrenaline in 6 (10.5%), and paracetamol in 1 case(s). Adrenaline was administered in 7 out of 14 (50%) severe cases of anaphylaxis and in 4 out of 41 (9.8%) moderately severe cases. In 4 of 11 cases where adrenaline was used, two or more doses were administered.

Other treatment

In 57 out of 64 (89%) episodes of anaphylaxis, the subject was treated in an ambulant way or kept under monitoring for less than 24 hours. In 4 of 64 (6.3%) cases the subject was hospitalised for treatment and monitoring for more than 24 hours; of these cases, one subject needed intubation and assisted ventilation for 4 days. Finally, three cases of anaphylaxis (4.7%) occurred in an already hospitalized subject.

Time lapse between onset of symptoms and administration of medication

Time lapse between onset of symptoms and first administration of medication was recorded in 38 out of 64 episodes, which ranged from 1 to 210 min (mean 30, median 7.5). In 13 of 14 cases with severe anaphylaxis this time lapse ranged from 1 to 30 min (mean 9.69, median 5), while in 24 of 41 cases with moderately severe anaphylaxis it ranged from 1 to 210 min (mean 52, median 30; $p < 0.05$).

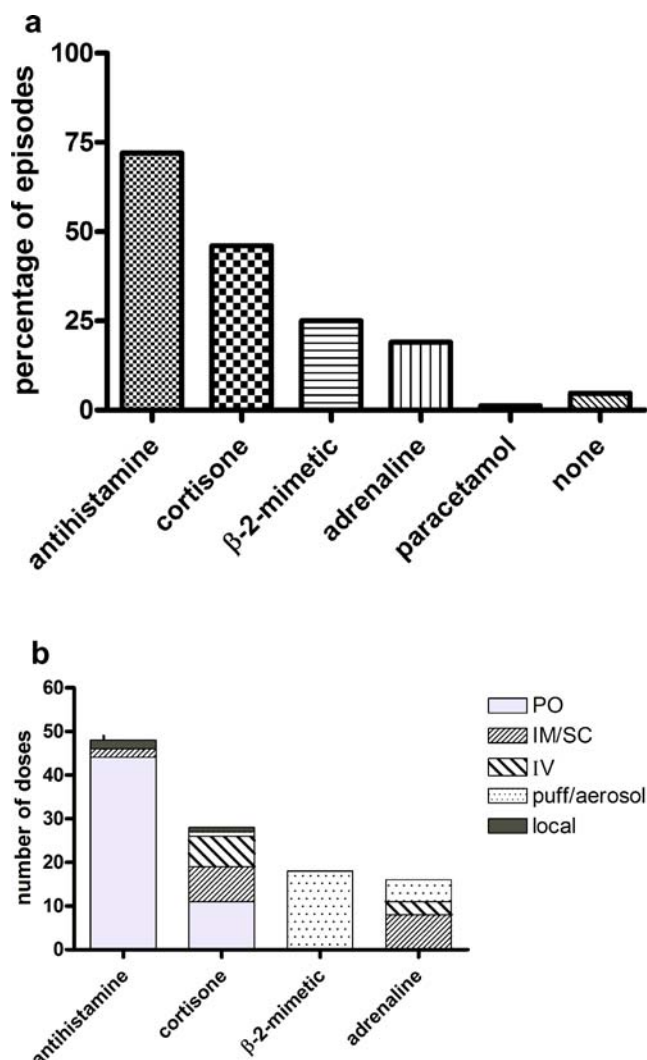


Fig. 3 **a** Medication used in 57 cases of anaphylaxis. **b** Method of administration of medication in 57 cases of anaphylaxis. *PO* oral, *IM* intramuscular, *SC* subcutaneous, *IV* intravenous

Recurrence of anaphylaxis and presence of a management plan

Eight out of 48 patients (16.6%) experienced two or more episodes of anaphylaxis for a total number of 24 episodes in those eight patients. The total number of episodes per patient and the anaphylactic triggers are given in Table 5. In those patients anaphylaxis was caused by a formerly unknown trigger in 12 cases, by accidental contact with a known trigger in seven cases, and by an unidentified trigger in five cases.

Out of 19 cases caused by a previously known trigger, a management plan for treatment of anaphylaxis—including Epipen—had been handed out prior to the actual episode in 12 cases (Table 4). In 9 of 12 cases Epipen was available at the moment of anaphylaxis, while it was used during the actual anaphylactic episode in one case only; in two other

cases Epipen was not administered at the location where anaphylaxis occurred, but the patient received adrenaline subsequently after arrival in the hospital.

Coexisting allergy and/or asthma

Out of 48 patients 32 (66.7%) had a history of atopic disease, 29 of whom having a previously documented sensitization to one or more allergens. The trigger of anaphylaxis in patients with known atopy as compared to patients not known with atopy is depicted in Table 6. Out of 48 patients, 22 (45.8%) were known to have asthma, in whom 33 episodes of anaphylaxis occurred, compared to 31 episodes in 26 patients without asthma. The frequency of moderate and severe anaphylaxis in subjects with asthma was 19/33 (57.6%) and 9/33 (27.3%), respectively, compared to 21/31 (67.7%) and 5/31 (16.1%) in subjects without asthma (not significant). At the moment of anaphylaxis the subjects' asthma was considered to be well controlled in 18/33 cases (54.5%) and as not controlled in 6/33 (18.2%), whereas the level of control of asthma was not clear in the remaining 9/33 (27.3%) cases.

Discussion

This is the first prospective study on anaphylaxis in children in Belgium. As far as we know, this is also the first survey on anaphylaxis that has been completed using an online database. Doing so allowed us to store detailed information on each individual episode of anaphylaxis at any moment and at any location where the patient was seen.

The number of anaphylactic episodes was highest in the age group 0–3 years, which is comparable with the findings of other authors [3, 6, 9]. This is also concordant with food allergy being the most prevalent in young children and food being the most frequent trigger of anaphylaxis in children [15, 17, 21, 31]. The latter might also explain the gradually lowering figures in subsequent age classes in our patient group. The relatively higher frequency of anaphylaxis in the age group 12–15 years is concordant with the findings of other authors [15] and might at least be partly explained by adolescents being less adherent to preventive measures [1].

Comparable with the findings of other authors, the children's home was the most frequent location of occurrence of anaphylaxis [17, 21]. However, in the age group 3–6 years a comparable number of episodes occurred at home, school, home of family, friends or neighbours, and outside. This probably reflects the daily schedule of children of this age in the population studied. Fifty percent of anaphylactic episodes in the adolescent group occurring outside compares to data from other authors [1] and can be partly explained by food associated exercise induced

Table 5 Trigger and number of anaphylactic episodes in patients with recurrent anaphylaxis

		Patient initials							
		BT	CaS	DY	HY	CS	VS	VL	VLu
Food	Number of anaphylactic episodes	2	2	2	2	5	4	5	2
	Peanut					[38, 40, 41]	[47]		[58]
	Egg	[3]							
	Nut						[44]		
	Cow's milk							[53]	
	Kiwi			[16]					[59]
	Apple			[15]					
	Wheat							[50]	
	Lupine	[4]							
	Fish						[45]		
	Additives							[51]	
	Unidentified		[8, 9]			[37, 39]	[46]		
Wasp venom					[20] [21]				
Medication	Amoxicillin + methylprednisolon							[52]	
	Methylprednisolon							[54]	

Numbers between brackets refer to the case numbers in Table 1.

anaphylaxis occurring more frequently in this age group. Indeed, out of five cases of food associated exercise induced anaphylaxis, four of them occurred at age 13–14 years, while the fifth occurred at age 4 years. This also stresses the importance of having the management plan and rescue medication available for anaphylaxis at any place and during any activity.

Frequencies of dermatologic, respiratory, gastrointestinal, and cardiovascular symptoms found in this study are comparable with the findings of another referral centre for pediatric allergy [21]. Similarly, we also found dermatologic and respiratory symptoms appearing most frequently as a first symptom. Twenty-two percent of anaphylactic reactions presenting with cardiovascular symptoms is comparable with the findings of a German questionnaire-based study [17]. The only near-fatal case in our survey was triggered by the ingestion of two hazelnuts. As our study concerned patients referred for investigation of anaphylaxis and as in only six cases the patient was seen at the moment of anaphylaxis, our survey clearly cannot be used for calculation of the frequency of fatal cases.

Food was by far the most frequent anaphylactic trigger in the total group, as was also true in all different age classes. In the age group 12–14 years food was even the only trigger. Peanut is the most important trigger, accounting for more than 20% of the cases with an identified trigger and for 25% of those triggered by food, followed by nuts and egg, each accounting for 12.5% of cases with identified triggers. This is in accordance with other investigations in children [17]. As in an earlier although retrospective study in our own pediatric population, cow's

milk was the cause of anaphylaxis in 11/39 cases compared to 6/39 for peanut, this might suggest that the relative importance of cow's milk and peanut as an anaphylactic trigger has changed in recent years [5]. In contrast to the findings of an Italian survey [21], in our survey only two cases were triggered by fish/shellfish. This distribution of food triggers might reflect different eating habits in different countries [25, 31]. In contrast to other surveys [17, 21], there

Table 6 Trigger of anaphylaxis in patients known or not known with atopy

		Atopic	Non-atopic
Number of episodes (number of patients)		47 (32)	17 (16)
Trigger			
Food	Food total	38	10
	Peanut	10	2
	Egg	6	1
	Nuts	3	4
	Cow's milk	4	0
	Kiwi	2	1
	Apple	2	0
	Fish/shellfish	1/1	0/0
	Wheat/lupine	1/1	0/0
	Additives	1	2
	Not identified	6	0
Medication		3	2
Insect sting		1	3
Latex		2	1
Pollen		1	0
Unknown		2	1

were no cases triggered by immunotherapy, although immunotherapy currently is prescribed at PedAllUH as well as at PedAllPM and PedPH. Anaphylaxis triggered by insect stings only appearing in the age groups 3–6 and 6–9 years and not in the older age groups probably reflects a local referral policy. Indeed, as in our university hospital rush immunotherapy for severe insect venom allergy is carried out at the department of internal medicine [11], older children and adolescents with insect venom anaphylaxis currently are directly referred to that department.

Anaphylaxis caused by a previously identified trigger occurred most frequently in connection with peanut and egg. In 14 out of 17 (82%) episodes caused by an already known food trigger, the patients/parents were unaware of its presence in the ingested food. This stresses the importance of clear food labelling and of extensive dietetic information [30]. On the other hand, for 6/12 patients with peanut anaphylaxis and for all seven patients with nut anaphylaxis, the actual episode was the first manifestation of peanut/nut allergy. Moreover, four of seven patients with nut anaphylaxis weren't even aware of any allergy at all. However, by means of careful history taking it was revealed that some of these patients had shown mild, but so far unnoticed signs that might have been preliminary symptoms of the actual food allergy (data not shown). The three episodes of anaphylaxis caused by ingestion of kiwi were also the first manifestation of kiwi allergy in the respective three patients. Thus, although features predictive of a serious allergic reaction to food have been identified, such features are lacking in a substantial proportion of cases [24, 29]. It will be a task for future studies and for pediatric allergists to further disclose the early signs of allergy that are predictive of a potentially serious reaction to the most frequent causal allergens of anaphylaxis.

As expected, an IgE-dependent mechanism could be confirmed in the majority of cases with identified trigger [28]. However, an IgE-independent, so-called pseudoallergic mechanism presumably was involved in two and one case(s) triggered by acetylsalicylic acid and by benzoic acid, respectively [23], while for three cases caused by food additives the underlying mechanism could not be documented.

Time lapse between contact with the trigger and onset of symptoms is comparable with other data on anaphylaxis in children and adolescents [2, 21]. In contrast to the findings of another referral centre for pediatric allergy [21], we found the latency period in children aged 0–3 years shorter than in older ones. The same applied to children aged 0–2 years as compared to older ones (data not shown). The only two biphasic reactions in our study were triggered by peanut and bee venom respectively. The low frequency of biphasic reactions we noticed is in contrast to the findings of other studies [8, 14], but comparable with the findings of one pediatric study [13]. As other surveys on anaphylaxis in

children currently do not mention biphasic anaphylaxis [6, 17, 21], this might suggest that biphasic anaphylaxis is less frequent in children than in adults. On the other hand, one can speculate that the administration of corticosteroids might have protected some patients from a biphasic course, although clear-cut documentation for such a protection is not available [14, 16].

The most frequently used medication to treat anaphylaxis was antihistamines, which is comparable with the findings of other surveys [15, 17]. As adrenaline was administered in only 50% of cases with cardiovascular symptoms and in only 10.5% of moderately severe cases, it must be stressed that anaphylaxis clearly was under-treated. This is concordant with previous appraisals on the management of anaphylaxis [12, 15, 17]. Moreover, although nine patients had Epipen available at the actual episode, this was used in only one case, while—according to the severity of the episode—its use was indicated in seven cases. Nevertheless, all parents had been extensively instructed on how to use Epipen. This suggests that parents and patients follow the instructions as to carry a management plan and Epipen with them, but are reluctant to use the pen when necessary. It also indicates that repeated training of parents and patients in the management of anaphylaxis is necessary.

The frequency of recurrence of anaphylaxis is in accordance with other investigations [18]. However, it must be stressed that two patients having experienced four and five cases of anaphylaxis, respectively, had not received preventive measures before, nor an adrenaline based management plan. Follow-up of our patients has to show if such measures are successful in decreasing the frequency of recurrence.

Although severe anaphylaxis was more frequent in patients with asthma as compared to patients without asthma, this difference was not statistically significant.

Conclusion

Anaphylaxis in children occurs most frequently at home, except in adolescents who experience 50% of their anaphylactic episodes outside. Food is the trigger of anaphylaxis in 75% of cases, with peanut counting for 25% of all food induced episodes and egg and nuts each for 12.5%. Most patients have dermatological and respiratory symptoms, while gastrointestinal and cardiovascular symptoms occur in 30% and 22%, respectively. Anaphylaxis clearly is under-treated, even when appropriate medication is available. In only one of three cases, allergy to the trigger is known prior to anaphylaxis.

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