

Anaphylaxis in children and adolescents: The European Anaphylaxis Registry

Linus B. Grabenhenrich, MD, MPH,^a Sabine Dölle, PhD,^b Anne Moneret-Vautrin, MD,^c Alice Köhli, MD,^d Lars Lange, MD,^e Thomas Spindler, MD,^f Franziska Ruëff, MD,^g Katja Nemat, MD,^h Ioana Maris, MD,ⁱ Eirini Roumpedaki, MD,^j Kathrin Scherer, MD,^k Hagen Ott, MD,^l Thomas Reese, MD,^m Tihomir Mustakov, MD,ⁿ Roland Lang, PhD,^o Montserrat Fernandez-Rivas, MD,^p Marek L. Kowalski, MD, PhD,^q Maria B. Bilò, MD,^r Jonathan O'B. Hourihane, MD,ⁱ Nikolaos G. Papadopoulos, MD,^j Kirsten Beyer, MD,^{s,t} Antonella Muraro, MD,^u and Margitta Worm, MD^b Berlin,
 Bonn, Wangen, Munich, Hannover, Rheine, and Dresden, Germany, Nancy, France, Zurich and Basel, Switzerland, Cork, Ireland, Athens, Greece, Sofia, Bulgaria, Salzburg, Austria, Madrid, Spain, Lodz, Poland, Ancona and Padua, Italy, and New York, NY

Background: Anaphylaxis in children and adolescents is a potentially life-threatening condition. Its heterogeneous clinical presentation and sudden occurrence in virtually any setting without warning have impeded a comprehensive description. **Objective:** We sought to characterize severe allergic reactions in terms of elicitors, symptoms, emergency treatment, and long-term management in European children and adolescents. **Methods:** The European Anaphylaxis Registry recorded details of anaphylaxis after referral for in-depth diagnosis and counseling to 1 of 90 tertiary allergy centers in 10 European countries, aiming to oversample the most severe reactions. Data were retrieved from medical records by using a multilanguage online form. **Results:** Between July 2007 and March 2015, anaphylaxis was identified in 1970 patients younger than 18 years. Most incidents occurred in private homes (46%) and outdoors (19%). One third of the patients had experienced anaphylaxis previously. Food items were the most frequent trigger (66%), followed by insect venom (19%). Cow's milk and hen's egg were prevalent elicitors in the first 2 years, hazelnut and cashew in preschool-

aged children, and peanut at all ages. There was a continuous shift from food- to insect venom- and drug-induced anaphylaxis up to age 10 years, and there were few changes thereafter. Vomiting and cough were prevalent symptoms in the first decade of life, and subjective symptoms (nausea, throat tightness, and dizziness) were prevalent later in life. Thirty percent of cases were lay treated, of which 10% were treated with an epinephrine autoinjector. The fraction of intramuscular epinephrine in professional emergency treatment increased from 12% in 2011 to 25% in 2014. Twenty-six (1.3%) patients were either admitted to the intensive care unit or had grade IV/fatal reactions.

Conclusions: The European Anaphylaxis Registry confirmed food as the major elicitor of anaphylaxis in children, specifically hen's egg, cow's milk, and nuts. Reactions to insect venom were seen more in young adulthood. Intensive care unit admissions and grade IV/fatal reactions were rare. The registry will serve as a systematic foundation for a continuous description of this multimorphic condition. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

From ^athe Institute for Social Medicine, Epidemiology and Health Economics, ^bthe Department of Dermatology and Allergy, and ^cthe Department of Pediatric Pneumology and Immunology, Charité - Universitätsmedizin Berlin; ^dthe Allergy Vigilance Network, University Hospital Nancy; ^ethe Division of Allergology, University Children's Hospital Zurich; ^fthe Department of Pediatrics, St Marien-Hospital, Bonn; ^gPediatric Pneumology and Allergology, Lungenzentrum Süd-West, Wangen; ^hthe Department of Dermatology and Allergology, Ludwig-Maximilians-Universität, Munich; ⁱPediatric Pneumology and Allergology, Kinderzentrum Dresden-Friedrichstadt, Dresden; ^jthe Department of Paediatrics and Child Health, University College Cork; ^kthe Allergy Department, University of Athens; ^lthe Department of Dermatology, University Hospital Basel; ^mPediatric Dermatology and Allergology, Children's Hospital Auf der Bult, Hannover; ⁿRheine Kinderklinik, Mathias-Spital, Rheine; ^othe Clinical Centre of Allergology, University Hospital Alexandrovskaya/Medical University Sofia; ^pthe Department of Dermatology, Paracelsus Medizinische Privatuniversität Salzburg; ^qthe Allergy Department, Hospital Clinico San Carlos IdISSC, Madrid; ^rthe Department of Immunology, Rheumatology and Allergy, Medical University of Lodz; ^sthe Department of Internal Medicine/Allergy Unit, University Hospital Ospedali Riuniti, Ancona; ^tthe Icahn School of Medicine at Mount Sinai, New York; and ^uthe Department of Mother and Child Health, Padua General University Hospital.

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Corresponding author: Margitta Worm, MD, Department of Dermatology and Allergy, Charité - Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany. E-mail: margitta.worm@charite.de.

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As the most severe course of an acute allergic reaction, anaphylaxis occurs in patients of all ages, but most research and guidelines are focused on adults.¹⁻³ Typical elicitors and the clinical presentation of anaphylaxis in children and adolescents were shown to be different from those in adults,⁴ calling for specific research and targeted guideline development for a pediatric population.^{5,6}

Increasing frequencies of allergic diseases have been observed over recent decades, but there is considerable uncertainty in whether this reflects true variations in disease frequency or differences in perception, labeling, and diagnostic habits.⁷ Little is known about the occurrence of severe allergic reactions and time trends on a population level,⁸⁻¹⁰ and even less is known for pediatric anaphylaxis.^{11,12}

Food items are the most common triggers of severe allergic reactions in childhood, with some allergens, such as cow's milk and hen's egg, specific to young ages. However, age-dependent distributions have not been published for adequately large populations to account for less frequent causes. The clinical picture of anaphylaxis in children, especially that in infants, is different from that in adults.^{4,13} This varied clinical picture reflects differences in allergen absorption, a developing immune system, and lack of preschoolers' ability to talk about subjective symptoms. Interpretation of diagnostic tests (eg, tryptase measurement) is valid only in light of age-dependent reference values and experience in pediatric allergology. Confirming the causal role of a suspected elicitor can become a tedious venture, even more so in children.

Emergency treatment, long-term management, and counseling are supported by current guidelines^{2,14} but are only partly adapted to pediatric settings.¹⁵ For example, there is a long-standing debate about the application and dose of epinephrine as the first-line treatment for anaphylaxis.¹⁶ Reactions initially treated by a layperson rely on epinephrine autoinjectors, which are also available for younger patients but not for infants.¹⁷ Implementation of treatment recommendations has been assessed in the general population,¹⁸ but data on emergency management in children and adolescents are lacking. Counseling to reduce the risk of recurrent reactions and emergency drug prescriptions could be tailored based on age-specific distributions of comorbidities and cofactors, such as asthma or physical exercise.

Based on data collected in the European Anaphylaxis Registry from 2007 to 2015,¹⁹ the aim of this analysis was to show data on the most severe allergic reactions occurring in children and adolescents. This large-scale survey comprises data on elicitors, symptoms, emergency treatment, and long-term management from 10 countries. The survey allows guideline adherence to be traced by comparing treatment habits over 8 consecutive years. The overall goal was to improve the timely recognition, emergency management, and prevention of recurrent reactions by disseminating knowledge of age-dependent distributions of pediatric anaphylaxis.

METHODS

Setting and design

The European Anaphylaxis Registry collected information on anaphylactic reactions through a Web-based data entry system. Data for the current analysis were provided by tertiary referral centers specialized in pediatric allergology,

dermatology, or both in Germany, France, Switzerland, Ireland, Greece, Austria, Spain, Bulgaria, Italy, and Poland. The study was approved by the Ethics Committee at Charité - Universitätsmedizin Berlin (the coordinating center) and by the local ethics committees in all participating countries.

Participants

Children who experienced anaphylaxis were referred to the participating specialized clinics for in-depth diagnosis, counseling, and, if possible, specific immunotherapy. On their first visit, parents were asked to provide written informed consent to allow registration of the child's medical history and reaction details in the database after completion of the diagnostic workup. The study centers were asked to enter their most severe cases, usually with circulatory or respiratory symptoms, but milder anaphylaxis could be recorded as well. Fatal anaphylaxis, known from either counseling of previous reactions in the referral center or from an emergency physician's notification, could be recorded with the parents' consent as well. Database entries were included if the sex of the child and the year of reaction were specified and the age at reaction was less than 18 years.

Data source and handling

The online data entry system comprised a German questionnaire for Germany, Austria, and Switzerland; a French version for centers in France; and an English version for all other participating countries. The questionnaire was initially developed and piloted in the German Anaphylaxis Registry^{20,21} and translated/back-translated for international use. The questionnaire was refined through yearly updates, with new items introduced based on expert judgment. Interrater reliability was assessed by using repeated data entry by 2 independent professionals. Data collected through questionnaire versions 2 to 6 ($n = 134, 219, 167, 689$, and 761) with entry dates from July 2007 to March 2015 were used. Trained professionals in each study center retrieved data retrospectively from the medical records, including laboratory measures and emergency protocols. Raw study data were stored with pseudonyms on a server at Charité - Universitätsmedizin Berlin.

Variables

Specific areas covered have been reported earlier,²² and the online version can be accessed through www.anaphylaxie.net. Age at reaction was categorized in 3 strata: preschoolers (0-5 years), schoolchildren (6-12 years), and adolescents (13-17 years). Assuming primary documentation habits to differ randomly, most variables were reported as a fraction of valid answers by item (comorbidities, cofactors, details of previous reactions, symptoms and severity, emergency treatment, and long-term management). Therefore the denominator used for calculating percentages might slightly vary from the column totals shown. The location of reaction was reported as a fraction of all cases, assuming missing answers to represent categories not presented as default. Elicitors were assessed by using a comprehensive list of typical foods, insect venoms, drugs, and other less frequently expected causes of allergic reaction, such as latex or allergen immunotherapy. Rare food items specified as free text entries were reported within the group of food elicitors. The diagnostic certainty of the causal agent was documented at the 2 levels *known* versus *suspected* based on the local allergy specialist's individual appraisal, without specifying reasons for their decision. Symptoms documented through free text were manually assigned to default answer categories, where reasonable. Severity was graded retrospectively based on the 4 levels of symptom profiles proposed by Ring and Messmer²³: grade II with involvement of at least 2 organ systems, grade III with signs of circulatory and/or respiratory failure/shock, and grade IV with circulatory or respiratory arrest. The criteria for selection of the most severe cases were (1) a known elicitor with grade III symptoms admitted to an intensive care unit, (2) grade IV symptoms, or (3) fatal reactions.

Statistics

Cleaning and analysis of data were carried out by using the SAS 9.4 system (SAS Institute, Cary, NC). Stratified analysis of frequencies was used to

TABLE I. Baseline data, reaction circumstances, and previous reactions by age group

	Preschoolers, <6 y		Children, 6-12 y		Adolescents, 13-17 y		All	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Total	861		655		454		1970	
Girls	291	33.8	204	31.1	197	43.4	692	35.1
Comorbidities (recent medical history)								
Allergic rhinitis	109	13.0	181	28.5	117	26.6	407	21.2
Asthma	150	17.8	190	29.9	98	22.3	438	22.9
Atopic dermatitis	348	41.4	110	17.3	45	10.2	503	26.3
Urticaria	10	1.2	7	1.1	4	0.9	21	1.1
Mastocytosis	1	0.1	1	0.2	1	0.2	3	0.2
Food hypersensitivity*	1	0.2	4	0.9	2	0.7	7	0.5
Cofactors (preceding the reaction)†								
Physical exercise	130	16.4	147	25.2	104	25.4	381	21.3
Psychological stress	14	1.6	16	2.4	17	3.7	47	2.4
Medication	27	3.2	37	5.6	40	9.0	104	5.3
Location (selected)								
At home (own or external)	526	61.1	252	38.5	129	28.4	907	46.0
Restaurant	30	3.5	28	4.3	34	7.5	92	4.7
Garden, park, countryside	37	4.3	149	22.7	77	17.0	263	13.4
Urban public place	27	3.1	31	4.7	48	10.6	106	5.4
School, work	82	9.5	59	9.0	45	9.9	186	9.4
Hospital, medical practice	71	8.2	66	10.1	38	8.4	175	8.9
Previous reaction(s), of these...	260	31.6	201	33.6	143	33.4	604	32.6
...milder and/or similar reaction(s)		10%		11%		10%		10%
...only similar reaction(s)		62%		47%		45%		53%
...more severe reaction(s)		28%		41%		45%		36%
...more than 1 previous reaction		36%		44%		54%		42%
...elicitor was diagnosed earlier		72%		75%		63%		71%

Cofactors reported only infrequently are not shown: menstruation (n = 10) and alcohol (n = 8).

*In addition to the food or foods incriminated to cause the anaphylaxis reported.

†As judged by the allergist counseling the family/child and not specified in detail by questionnaire items.

describe documented characteristics. Individual queries were performed in an attempt to complete missing data. All variables other than age at reaction, date of birth, and sex were allowed to remain missing by item because the registry aimed to cover only information documented in the underlying records.

RESULTS

Study centers and participants

The European Anaphylaxis Registry collected data on 1970 children from 90 study centers in 10 countries: Germany (n = 1040), France (n = 321), Switzerland (n = 297), Ireland (n = 95), Greece (n = 86), Austria (n = 59), Spain (n = 36), Bulgaria (n = 25), Italy (n = 6), and Poland (n = 5). Six hundred ninety-two (35%) were female, with a higher female proportion in adolescents (43%). All ages (in 1-year intervals) were represented similarly, except for infants (<1 year, n = 18) and 1-year-old children (n = 246). Of the 1970 children, 861 (44%) were preschoolers (<6 years), 655 (33%) were children between 6 and 12 years of age, and 454 (23%) were adolescents (13-17 years) with anaphylaxis.

In their recent medical history the following respiratory allergies were reported mainly for children between 6 and 12 years of age and for adolescents: asthma (30% and 22%, respectively) and allergic rhinitis (29% and 27%, respectively). Atopic dermatitis was predominant in preschoolers (41%). Other allergy-related conditions were not dependent on age: urticaria (1.1%), food hypersensitivity not related to the incriminated elicitor (0.5%), and mastocytosis (0.2%). Short-term factors (cofactors) potentially influencing allergenic disposition were physical exercise (21%) and medication other than that suspected

as the actual elicitor (5%), both of which were not specified in detail in the registry. Most reactions occurred in private homes (46%) and outdoor locations (countryside and urban, 19%), followed by school or working environments (9%).

Six hundred four (33%) children had allergic reactions before occurrence of the recorded incident. Of these, 10% reported at least 1 milder reaction, and 42% reported more than 1 previous event of any severity. The elicitor was already known and diagnosed before the recorded reaction in 71% of the recurrent cases. The characteristics of previous reactions were based on parent's report only and did not differ by age (Table I).

Elicitors

Severe allergic reactions were caused by food items in 1291 (66%) of 1970 of the patients, followed by 381 (19%) cases of insect venom and 101 (5%) cases of drug anaphylaxis. The cause was ascertained by a local allergy specialist in 1565 (79%) cases and was based on history, laboratory measures, and diagnostic procedures. Until school enrollment (<6 years), foods were the predominating elicitors reported (88%), and cow's milk (n = 120) and hen's egg (n = 115) were the predominating elicitors reported in the first 2 years. Most of the reactions to cashew (66 of all 87 reported) and hazelnut (57 of all 86 reported) occurred in the preschool-aged children. Peanut was an elicitor for anaphylaxis from infancy to young adulthood (overall n = 325). Insect venom-induced anaphylaxis appeared in early school age and continued until 17 years of age, with yellow jacket (overall n = 191) and bee stings (overall n = 161) responsible for the

TABLE II. Specific elicitors by age group, suspected in parentheses

	Preschoolers, <6 y	Children, 6-12 y	Adolescents, 13-17 y	All
Total	861	655	454	1970
Elicitor known (suspected) [†]	724 (110)	535 (94)	306 (100)	1565 (304)
Food	673 (88)	288 (57)	131 (54)	1092 (199)
Cashew	58 (8)	17	3 (1)	78 (9)
Hazelnut	52 (5)	21 (3)	3 (2)	76 (10)
Walnut	25 (4)	14 (3)	3	42 (7)
Pistachio	14 (1)	5 (1)	2	21 (2)
Pine nut	5	8	—	13
Other tree nuts*	6 (5)	9 (6)	11 (5)	26 (16)
Celery	—	3 (1)	5 (2)	8 (3)
Other vegetables*	1	6 (1)	4 (2)	11 (3)
Wheat	17	9 (1)	2 (2)	28 (3)
Other cereals*	7	4 (2)	6 (2)	17 (4)
Hen's egg	103 (12)	12 (2)	5	120 (14)
Cow's milk	114 (6)	10 (3)	4 (3)	128 (12)
Goat's milk	5 (1)	6	5 (1)	16 (2)
Shrimp	1 (1)	7 (2)	10 (4)	18 (7)
Codfish	12 (3)	4	1	17 (3)
Other animal products*	26 (3)	12 (1)	6 (5)	44 (9)
Peanut	176 (15)	92 (8)	29 (5)	297 (28)
Soy	4 (1)	7	6 (1)	17 (2)
Pea	6 (2)	3 (1)	—	9 (3)
Other legumes*	15 (1)	16 (1)	4	35 (2)
Sesame	8 (3)	3 (1)	4 (1)	15 (5)
Other spices*	5 (2)	3 (1)	4 (1)	12 (4)
Fruits*	8 (1)	15 (2)	13 (2)	36 (5)
Insects	31 (7)	194 (12)	121 (16)	346 (35)
Yellow jacket	12 (4)	98 (8)	61 (8)	171 (20)
Bee	17	84 (4)	51 (5)	152 (9)
Hornet	2	8	8	18
Drugs	13 (13)	15 (11)	27 (22)	55 (46)
Cephalosporins	3 (2)	6	(2)	9 (4)
Penicillin	2 (1)	2 (1)	3	7 (2)
Analgesics	5 (3)	5 (5)	12 (11)	22 (19)
Immunotherapy	—	32	18	50

Rare elicitors are not reported in detail: insects (mosquito, horsefly, and bumblebee), some drugs, and latex. Numbers of highly suspected elicitors are shown in parentheses.

*Other tree nuts include almond, brazil nut, macadamia, and pecan; other vegetables include carrot, lettuce, tomato, and cabbage; other cereals include buckwheat, barley, sweet corn, rye, rice, and spelt; other animal products include chicken, beef, pork, quail's egg, ewe's milk, tuna, mackerel, zander, swai (*Pangasius*), salmon, pollock, trout, calamari, mussels, snails, and crab; other legumes include bean, chickpea, lupine, and lentil; other spices include curry, poppy, pepper, mustard, sunflower seed, and pumpkin seed; and fruits include pineapple, apple, banana, pear, cherry, kiwi, lychee, tangerine, mango, melon, nectarine, peach, grape, fig, and other citrus fruits.

[†]The elicitor was not specified in 101 patients.

majority of cases. Drugs were elicitors primarily for adolescents, and analgesics ($n = 41$) and antibiotics ($n = 22$) were the most common causal agents. Fifty cases of anaphylaxis were attributed to specific immunotherapy (Table II). There was a continuous shift of elicitors from foods to insect venom and drugs from infancy until approximately 10 years of age, after which the pattern of elicitors remained relatively stable (Fig 1).

Symptoms

The skin was involved in almost all children (92%). The following specific skin symptoms occurred similarly across all ages (overall percentages): angioedema (53%), urticaria (62%), pruritus (37%), and erythema/flush (29%; details are provided in Table E1 in this article's Online Repository at www.jacionline.org). Gastrointestinal symptoms accompanied 45% of anaphylactic reactions, with vomiting (overall 27%) dominating in the preschool ages and nausea (overall 15%) increasing into

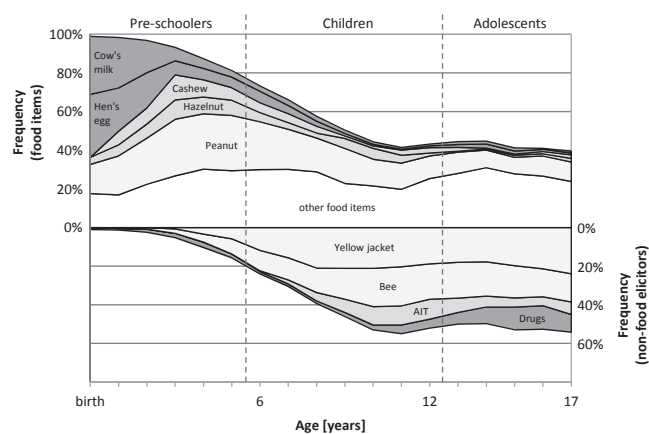


FIG 1. Elicitor of anaphylaxis by age only for known elicitors ($n = 1565$). Rare elicitors were omitted (eg, other insects and latex). AIT, Allergen immunotherapy.

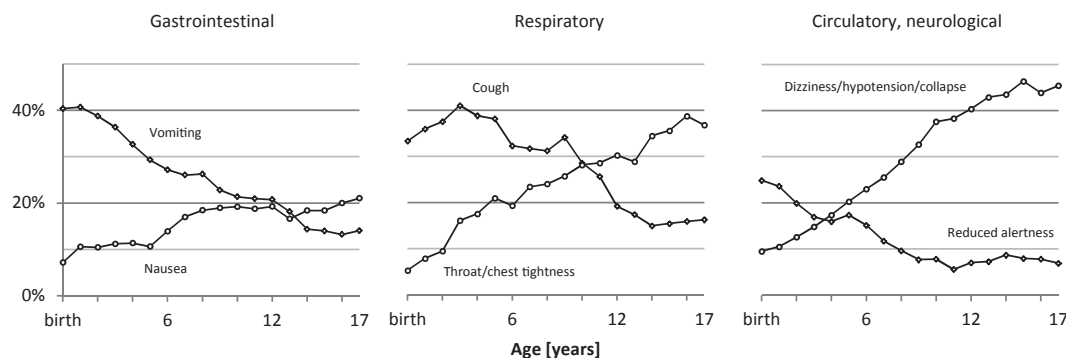


FIG 2. Frequency of symptoms by age, as documented by a local allergy specialist. Symptoms with similar frequencies across ages were omitted.

adolescence (Fig 2, left panel). The other gastrointestinal symptoms, such as abdominal pain (16%) and diarrhea (5%), occurred independently of age. The respiratory tract was affected in 80% of patients. Up to 55% of patients reported dyspnea, and 35% documented wheezing with similar frequencies from birth to adolescence. Life-threatening respiratory arrest occurred in all age groups (overall $n = 15$). Only throat and chest tightness increased with age, and cough was mainly reported before approximately 10 years of age (Fig 2, central panel). Cardiac and circulatory symptoms were less frequent (41%) and predominated by dizziness, hypotension, and collapse in adolescence (Fig 2, right panel). There were 7 cases of cardiac arrest. Other organ systems, mainly neurologic symptoms, were involved in 26% of the patients (eg, reduced alertness [13%]).

Most reactions were categorized as grade II (45%, ≥ 2 organ systems) or grade III (47%, 2 organ systems severely involved), with similar distributions in age strata. The time between exposure and onset of symptoms was usually less than 10 minutes (58%), but 8% of the patients reported a delayed reaction with an interval of more than 1 hour. Seventy-seven (5%) children experienced biphasic reactions. Of these, 42% had the second reaction more than 12 hours after the first reaction (see Table E1).

Emergency treatment

Five hundred sixty-two (30%) children were initially cared for by a layperson, of whom 5% were nursery or school teachers, and 10% of the children, mainly those older than 12 years (37%), administered emergency drugs themselves. The application of an epinephrine autoinjector increased with age from 10% (lay treated) in preschoolers to 19% in adolescents. An additional 14% of the patients had an autoinjector prescription but did not carry it or failed to apply it. Similar across all age groups, lay treatment included antihistamine (78%) and corticosteroid tablets (52%), as well as β_2 -agonist inhalers (28%).

Emergency treatment was administered by a health professional in 1363 (72%) of the children; of these, 38% were treated by an emergency physician. With few differences between age groups, professional treatment included epinephrine (28%), antihistamines (76%), corticosteroids (82%), or β_2 -agonists (23%). Second-line treatment (eg, additional doses or other drugs not used for initial management, usually on failure to improve after first-line treatment) was reported in 19% of professionally treated children, and 9% of the children received a second dose of epinephrine. Three hundred ninety-four children were

admitted to a hospital, of whom 6% (25) were treated in an intensive care unit (Table III). When treated by a health professional, epinephrine was mainly administered intramuscularly, with an increasing proportion from 12% in 2011-2012 to 25% in 2014-2015 (Fig 3).

Diagnosis and counseling

Similar in all age groups, the diagnostic workup included skin testing (72%, of which 85% of results were positive) and specific IgE (89%, of which 91% of results were positive) and tryptase (34%, of which 6% of results were ≥ 11.5 ng/mL) measurements. The current questionnaire did not collect laboratory test results. Allergen immunotherapy was started in 73% of cases of Hymenoptera-induced venom anaphylaxis. Almost all children received a prescription for emergency drugs (91%), mainly including an epinephrine autoinjector (90%), antihistamines (98%), and corticosteroids (91%, Table IV). Specifically, not receiving an epinephrine autoinjector prescription differed by elicitor (food, 10%; insects, 5%) and severity (grade I, 23%; grade II, 11%; grade III, 7%).

Life-threatening and fatal reactions

Twenty-six (1.3%) of the 1970 children experienced life-threatening or fatal reactions: 11 experienced grade III symptoms and intensive care unit admission, 10 experienced grade IV symptoms, and 5 of the patients died. The most severe anaphylactic reactions were seen in all age groups. The distribution of elicitors in the entire registry resembled that in the group of patients with the most severe reactions. In this group the most frequently reported causes of anaphylaxis, such as cow's milk, hazelnut, cashew, peanut, and insect venom (Table II), were also responsible for the most severe reactions; an exception was hen's egg allergy, which never led to life-threatening anaphylaxis despite being reported in 134 children. Eight children in this group were initially treated by a layperson in the family or a teacher, 4 of whom used an epinephrine autoinjector. Eight cases described previous reactions to the same allergen, usually with milder symptoms (Table V).²³

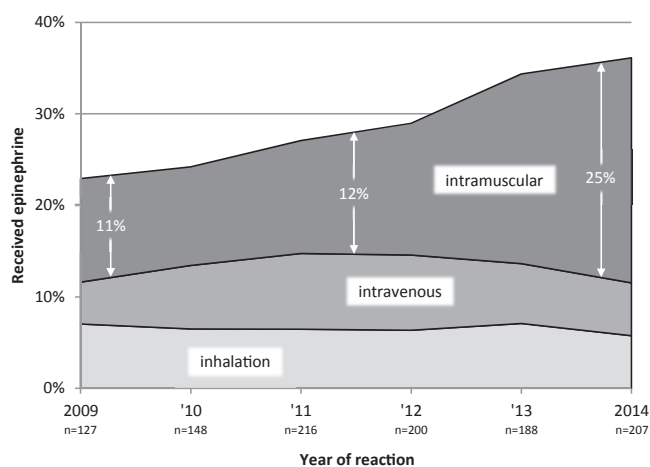
DISCUSSION

Key results

With 1970 patients, this is the first large-scale description of pediatric anaphylaxis. More data were collected on boys (about

TABLE III. Emergency treatment of anaphylaxis by age group

	Preschoolers, <6 y		Children, 6-12 y		Adolescents, 13-17 y		All	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Total	861		655		454		1970	
Lay treatment, of these...	271	32.7	193	30.5	98	22.6	562	29.6
...self-treated		3%		6%		37%		10%
...by nursery/schoolteacher		6%		5%		1%		5%
...epinephrine autoinjector		10%		13%		19%		12%
...autoinjector prescribed but NOT used		14%		17%		10%		14%
... β_2 -agonist inhaler		24%		36%		26%		28%
...antihistamine tablets		80%		80%		72%		78%
...corticosteroid tablets		56%		48%		49%		52%
Professional treatment, of these...	558	67.2	456	72.2	349	80.4	1363	71.9
...by emergency physician		39%		36%		42%		38%
...by allergy specialist		11%		12%		5%		10%
...epinephrine (intramuscular)		17%		16%		12%		15%
...epinephrine (intravenous)		5%		6%		11%		7%
...epinephrine (inhalation)		8%		8%		6%		7%
...epinephrine, second dose		10%		7%		10%		9%
... β_2 -agonist (inhalation)		20%		27%		23%		23%
...antihistamine (intravenous)		29%		55%		61%		45%
...antihistamine (oral)		42%		29%		20%		33%
...corticosteroid (intravenous)		37%		65%		71%		54%
...corticosteroid (oral)		24%		17%		14%		20%
...corticosteroid (rectal)		17%		7%		1%		10%
...O ₂		8%		10%		11%		10%
...fluids		16%		25%		25%		21%
Second-line treatment	111	17.1	90	20.3	67	22.0	268	19.2
Admitted to hospital, of these...	177	52.2	124	55.1	93	56.4	394	54.0
...treated in intensive care unit		5%		6%		11%		6%

**FIG 3.** Proportion of children receiving epinephrine and route of administration by year of reaction referring to those treated by a professional and with at least grade II reactions in 2009-2014 (n = 1086). If a child received epinephrine through more than 1 route, intramuscular is reported before the other 2, and intravenous is reported before inhalation.

two thirds) than on girls, but the European Anaphylaxis Registry covered all age groups, including a sparsely populated first year of life. Although sex differences have been described for several allergic diseases,²⁴ the sampling scheme used here does not support the interpretation of skewed distributions of age, sex, or other baseline information. One in 3 children experienced previous reactions and usually knew about the specific trigger.

In preschoolers, food was almost the only elicitor for anaphylaxis, dominated by cow's milk and hen's egg; peanut allergy was present in all ages. With the large data set of the current study, it was possible to describe a continuous shift from food-induced toward insect venom—and drug-induced anaphylaxis until 10 years of age, and few changes in trigger patterns were found thereafter. The predominance of food elicitors was in line with other data, such as from the United States.¹³ The signs and symptom patterns varied considerably by age, with vomiting and coughing limited to the first decade of life. In contrast, subjective symptoms, such as nausea, throat tightness, or dizziness, appeared more frequently into adolescence. Similar patterns have been described in a smaller sample of food-induced anaphylaxis treated in a US emergency department.²⁵

One in 3 anaphylactic reactions was initially treated by a layperson, including self-application of emergency drugs, which was rarely observed before adolescence. The use of epinephrine autoinjectors increased with age but reached only approximately 1 in 5 adolescents treated by a layperson. A similar proportion of children were already prescribed an autoinjector but either did not carry or apply the device. There is strong expert opinion toward including epinephrine as a first-line treatment of severe allergic reactions. This opinion is reflected in the current guidelines² but is not supported by clear evidence.¹⁶ In a community-based survey uncertainty about the severity of the reaction, fear of side effects, and difficulties deciding which drugs to use (eg, steroids) were identified as reasons for not applying autoinjectors, despite having them at hand.²⁶ From our data, 10% of children did not receive a prescription for an autoinjector. In addition to teaching

TABLE IV. Diagnosis and long-term management by age group

	Preschoolers, <6 y		Children, 6-12 y		Adolescents, 13-17 y		All	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Total	861		655		454		1970	
Elicitor confirmed by diagnostic test, of these...	611	92.2	396	87.4	263	84.6	1270	89.0
...already before the reported reaction		28%		35%		20%		29%
Skin test performed, of these...	559	70.3	418	71.7	291	74.2	1268	71.6
...positive		89%		87%		73%		85%
Intradermal test performed, of these...	16	2.6	58	14.6	54	20.5	128	10.1
...positive		63%		91%		83%		84%
Provocation performed, of these...	107	13.5	48	8.4	46	11.9	201	11.5
...positive		88%		83%		53%		80%
sIgE assessed, of these...	432	90.6	341	87.9	222	86.7	995	88.8
...positive		94%		93%		80%		91%
sIgE against recombinant allergen assessed, of these...	156	48.8	123	60.9	82	58.2	361	54.4
...positive		88%		92%		87%		89%
Tryptase assessed (baseline), of these...	179	21.8	246	38.4	226	51.6	651	34.3
...increased (≥ 11.5 ng/mL)		10%		6%		3%		6%
Allergen immunotherapy*	24	63.2	150	73.9	102	75.0	276	73.2
Counseling about avoidance	815	95.3	574	88.7	373	82.7	1762	90.2
Training (emergency plan/drug use)	798	93.3	585	90.4	365	80.9	1748	89.5
Prescription of emergency drugs, of these	804	94.0	595	92.0	374	82.9	1773	90.8
...epinephrine autoinjector		88%		93%		91%		90%
... β_2 -agonist inhaler		33%		40%		27%		34%
...antihistamine tablets		98%		98%		98%		98%
...corticosteroid tablets		91%		91%		93%		91%

sIgE, Specific IgE.

*Limited to cases of insect venom-induced anaphylaxis.

and training, availability of other noninvasive application routes might increase the application of epinephrine by laypersons. For example, sublingual epinephrine-containing microcrystals are currently being tested.²⁷

Professional first aid treatment was mainly administered by emergency physicians not specifically trained to tailor treatment options by age. Approximately one in 3 children received epinephrine, irrespective of age. A similar proportion was documented for adults in other populations.²⁶ The fraction of children who received epinephrine intramuscularly doubled during the observation period, which might reflect changes in professional education and the development of harmonized treatment guidelines.²

Despite the European Anaphylaxis Registry being targeted to collect information only on severe allergic reactions, only approximately 1% of cases were treated in the intensive care unit, had grade IV reactions, or led to the death of the child. Such reactions were seen in all age groups and caused by the same elicitors typically seen in the whole sample. There does not seem to be a specific age or a specific cause of life-threatening anaphylaxis, limiting the prediction of severe reactions.

Strength and limitations

The large number of participating countries, centers, and patients allowed a stratified report of reaction details by age, despite anaphylaxis being a relatively rare incident. The online assessment tool used in this Registry, which was developed in the German-speaking registry, iteratively refined and piloted,¹⁹ covered all major aspects of anaphylaxis, including elicitors, symptoms, emergency treatment, and long-term management. The study data were limited to what was initially documented in a nonstandardized way during the clinical visit because data

entry was based on medical records. Participating centers were asked to keep the registry's questionnaire items in mind while taking the medical history to improve the details of data recorded in the clinical routine. The parents' decision to seek further advice might be linked to symptom awareness or perceived severity, which could lead to a skewed distribution of the study population. Such self-referral might limit the study's external validity. On the other hand, collecting data in tertiary centers allowed identification of an adequately large number of cases to support the analysis of small subgroups of, for example, age or specific elicitors. Of note, the relative frequency of fatal reactions reported here is not a valid estimate of the fatality rate because most deaths attributed to an allergic cause are not expected to come to a tertiary center's attention. Therefore the actual occurrence of fatal anaphylaxis is probably more frequent. This registry collected 1-time data only. Measures of frequency cannot be estimated from this registry because it did not aim to represent the general population and did not clearly define the study base. Different participation of countries does not allow direct comparison of case numbers. However, this study excels in its comparison of patterns of elicitors or emergency treatment habits by age, year, or region. It applied harmonized methodology in all study centers, as necessary for sound comparisons.¹⁰

Conclusion

This is a large report of anaphylaxis in children and adolescents, including an age-dependent illustration of typical elicitors, symptoms, and emergency treatment. This study might serve as a robust knowledge base for how and where severe allergic reactions in the first years of life occur and how they are currently being treated. For example, analyzing time trends in epinephrine use, the registry was able to document a considerable

TABLE V. Most severe cases in order of increasing age

Age (y)	Sex	Elicitor	Interval	Grade	ICU	Symptoms	Treatment	Previous reactions	Diagnosis
0	M	Metamizole	<10 min	IV	*	Urticaria, cardiac arrest	Professional (epi. i.v. atropine)	No	Positive skin test response
0	M	Cow's milk formula (1 cup)	*	IV	No	Flush, respiratory arrest	Family member (antih.)	No	Positive provocation
1	F	Peanut	*	IV	*	Urticaria, vomiting, respiratory arrest, reduced alertness	Emergency doctor (oral antih., rectal steroids)	No	*
2	M	Cashew	*	IV	*	Urticaria, vomiting/nausea, respiratory arrest, collapse	Emergency doctor (epi. inhal., antih. i.v. and steroids, O ₂ and volume)	No	*
2	F	Cashew	<10 min (again after 4 h)	III	Yes	Angioedema, flush, respiratory symptoms, hypotension/tachycardia	Family member (antih.)	No	Positive sIgE level
3	M	Fish (fish sticks)	<10 min	III	Yes	Angioedema, vomiting, collapse	Family member (antih. and steroids), later both i.v.	Yes (milder, GI/skin)	Positive sIgE level
4	F	Hazelnut	<10 min	III	Yes	Urticaria, flush, dyspnea, wheezing, tachycardia	Professional (antih. i.v. and steroids, β_2 -agonist spray)	Yes (milder and more severe, all organ systems)	Positive skin test response and sIgE level
4	F	Cow's milk	>1 h	III	Yes	Urticaria, dyspnea, wheezing	Family member (AAI), steroids i.v. and i.m.	Yes (>2 times milder, skin)	Positive skin test response, sIgE level, and provocation
6	M	Goat's milk	<10 min	III	Yes	Urticaria, vomiting, wheezing, tachycardia	Emergency doctor (epi. i.v. and steroids, β_2 -agonist spray, O ₂ and volume)	No	Positive sIgE level
7	M	Peanut	* (again after 4 h)	IV	Yes	Angioedema, vomiting, respiratory arrest, collapse	Professional (epi. i.v., antih., and steroids)	No	Positive skin test response, sIgE level, and provocation
8	M	Cow's milk (1/2 cup)	*	IV	Yes	Angioedema, flush, respiratory arrest, collapse	Family member (AAI, antih., steroids, β_2 -agonist spray), later epi. i.v., O ₂ and volume	Yes (milder, circulatory/respiratory)	*
9	M	Snails	<10 min	Fatal	*	Angioedema, urticaria, cough, collapse	Emergency doctor (immediate resuscitation)	No	*
9	M	Cow's milk (suspected)	*	Fatal	No	Respiratory and cardiac arrest	Teacher (AAI, β_2 -agonist spray), emergency doctor (unknown)	Yes (once)	*
10	M	Hazelnut and kiwi (suspected)	*	Fatal	*	Vomiting, respiratory and cardiac arrest	Professional (epi. i.v. and steroids, O ₂ and volume)	No	*
11	M	Aspirin	>2 h (again after 4 h)	III	Yes	Pruritus, vomiting, throat tightness, loss of consciousness	Emergency doctor (epi. inhal., antih. i.v. and steroids, O ₂ and volume)	No	Negative skin test response and cellular stimulation
12	M	Bee	*	IV	*	Angioedema, flush, respiratory arrest, collapse	Emergency doctor (unknown)	No	*

(Continued)

TABLE V. (Continued)

Age (y)	Sex	Elicitor	Interval	Grade	ICU	Symptoms	Treatment	Previous reactions	Diagnosis
12	M	Bee	*	III	Yes	Urticaria, dyspnea, collapse	Professional (epi. i.v., antih. and steroids)	No	Positive skin test response and sIgE level
13	M	Brazil nut	<10 min	III	Yes	Angioedema, vomiting, dyspnea, reduced alertness	Emergency doctor (epi. inhal. and β_2 -agonist inhal., antih. i.v. and steroids, O ₂)	No	Positive sIgE level
13	M	Buckwheat (1 cup)	<10 min	III	Yes	Angioedema, flush, stridor, loss of consciousness	Family member (AAI, antih., steroids), later epi. i.m. and i.v., β_2 -agonist spray, steroids i.v. and O ₂	Yes (>2 times milder and more severe, skin/circulatory/respiratory)	Positive skin test response and sIgE level
14	M	General anesthetic	<10 min	IV	Yes	Urticaria, respiratory arrest, tachycardia	Professional (epi. i.v., antih. and steroids, β_2 -agonist spray, O ₂)	No	*
15	M	Volume expander (HES)	*	IV	*	Cardiac arrest	Professional (epi. i.v. and steroids, β_2 -agonist spray, O ₂)	No	*
15	F	Yellow jacket	<10 min (again after 4 h)	III	Yes	Angioedema, vomiting, dyspnea, collapse	Emergency doctor (antih. i.v. and steroids)	No	*
15	F	Narcotics	<10 min	IV	no	Angioedema, respiratory arrest, loss of consciousness	Emergency doctor (epi. i.v., antih. and steroids, O ₂ and volume)	No	Positive intradermal test response and sIgE level
16	M	Cow's milk (suspected)	<10 min	Fatal	*	Diarrhea, vomiting, respiratory and cardiac arrest	Family member (β_2 -agonist spray), later epi. i.v. and steroids	Yes (milder, GI)	*
17	F	Peanut and chicken (suspected)	<10 min	Fatal	*	Vomiting, respiratory and cardiac arrest	Emergency doctor (immediate resuscitation)	Yes (milder)	*
17	M	Tomato (1 plate)	>4 h (again after 12 h)	III	Yes	Angioedema, wheezing, collapse, tachycardia	Emergency doctor (steroids i.v.)	No	Positive skin test response

Selection criteria: known elicitor and grade III/ICU treatment or grade IV and fatal reactions. Grade: according to Ring and Messmer.²³

AAI, Epinephrine autoinjector; antih., antihistamine; epi., epinephrine; GI, gastrointestinal; ICU, intensive care unit; i.m., intramuscular; inhal., inhalation; i.v., intravenous; sIgE, Specific IgE.

*Not documented, no data available.

increase in intramuscular applications, probably because of improved training and harmonized guidelines. Further collection of case data in this registry will allow assessment of the adherence to new guidelines or recommended treatment modalities. Although only very few children with severe reactions are expected to experience a life-threatening course of anaphylaxis, this condition remains a real threat.

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Key messages

- Foods dominate as elicitors of anaphylaxis in the first decade of life and are then continuously replaced by insect venom and drugs.
- About one in 100 children reporting severe anaphylaxis experienced a life-threatening or fatal reaction.

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TABLE E1. Specific symptoms by age group

	Preschoolers, <6 y		Children, 6-12 y		Adolescents, 13-17 y		All	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Total	861		655		454		1970	
Skin	805	93.5	608	92.8	406	89.4	1819	92.3
Angioedema	473	54.9	336	51.3	238	52.4	1047	53.1
Urticaria	561	65.2	400	61.1	256	56.4	1217	61.8
Pruritus	270	31.4	263	40.2	198	43.6	731	37.1
Erythema/flush	253	29.4	191	29.2	130	28.6	574	29.1
Conjunctivitis*	80	12.0	49	10.6	33	10.3	162	11.2
Gastrointestinal	415	48.2	289	44.1	173	38.1	877	44.5
Nausea	94	10.9	113	17.3	86	18.9	293	14.9
Vomiting	315	36.6	154	23.5	63	13.9	532	27.0
Abdominal pain	120	13.9	107	16.3	78	17.2	305	15.5
Diarrhea	44	5.1	24	3.7	21	4.6	89	4.5
Dysphagia*	21	3.1	32	6.9	24	7.5	77	5.3
Incontinence	4	0.5	2	0.3	2	0.4	8	0.4
Respiratory	695	80.7	518	79.1	355	78.2	1568	79.6
Dyspnea	451	52.4	371	56.6	268	59.0	1090	55.3
Throat tightness*	57	8.5	85	18.4	77	24.0	219	15.1
Chest tightness*	32	4.8	42	9.1	54	16.8	128	8.8
Cough*	253	37.9	135	29.3	50	15.6	438	30.2
Wheezing, expiratory distress*	178	26.6	117	25.4	60	18.7	355	24.5
Change in voice*	89	13.3	47	10.2	23	7.2	159	11.0
Rhinitis*	90	13.5	55	11.9	31	9.7	176	12.1
Stridor, inspiratory	115	13.4	74	11.3	39	8.6	228	11.6
Respiratory arrest	5	0.6	5	0.8	5	1.1	15	0.8
Cardiac, circulatory	307	35.7	260	39.7	233	51.3	800	40.6
Dizziness	47	5.5	134	20.5	146	32.2	327	16.6
Hypotension, collapse	85	9.9	99	15.1	105	23.1	289	14.7
Loss of consciousness†	26	3.5	24	4.6	37	10.5	87	5.4
Tachycardia	87	10.1	57	8.7	52	11.5	196	9.9
Palpitations*	11	1.6	2	0.4	4	1.2	17	1.2
Cardiac arrest	1	0.1	3	0.5	3	0.7	7	0.4
Chest pain, angina*	0	0.0	4	0.9	4	1.2	8	0.6
Other	239	27.8	156	23.8	117	25.8	512	26.0
Reduced alertness	168	19.5	59	9.0	36	7.9	263	13.4
Sweating, tremble‡	21	5.9	29	12.4	47	26.9	97	12.7
Paresthesia‡	6	1.7	15	6.4	15	8.6	36	4.7
Cyanosis, pallor‡	54	15.3	37	15.9	21	12.0	112	14.7
Dysphonia‡	12	3.4	14	6.0	6	3.4	32	4.2
Agony‡	16	4.5	15	6.4	6	3.4	37	4.9
Sight disorder‡	1	0.3	2	0.9	6	3.4	9	1.2
Dysarthria‡	4	1.1	4	1.7	2	1.1	10	1.3
Severity grading (Ring)								
I (skin only)	73	8.5	39	6.0	20	4.4	132	6.7
II (2nd organ system mild)	316	36.8	315	48.2	260	57.5	891	45.3
III (2nd organ system severe)	464	54.0	294	45.0	166	36.7	924	47.0
IV (cardiac/respiratory arrest)	6	0.7	6	0.9	6	1.3	18	0.9
Biphasic, of these...	30	4.2	30	6.0	17	5.0	77	5.0
...after more than 12 h		23%		50%		63%		42%

*Only questionnaire versions 5 and 6 (n = 1450).

†Only questionnaire versions 4 to 6 (n = 1617).

‡Only questionnaire version 6 (n = 761).