

MANAGEMENT AND TREATMENT OF ANAPHYLAXIS IN CHILDREN: STILL TOO LOW THE RATE OF PRESCRIPTION AND ADMINISTRATION OF INTRAMUSCULAR EPINEPHRINE

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Despite it being well known that anaphylaxis is a severe life-threatening reaction requiring prompt management and treatment, this entity is still under-recognized and not correctly managed, above all in children. The aim of this study was to analyze the most frequent features of anaphylaxis in a pediatric population (n=65 patients) and to identify factors predicting more severe reactions. Among the 70 recorded episodes, food was the main culprit of anaphylaxis, and patients with a positive history for allergic asthma had more severe episodes ($P=0.008$). A self-injectable adrenaline was used only in 2 of the 70 episodes and none of the 50 episodes managed in the Emergency Department was treated with intramuscular adrenaline. Only 10/65 patients (15%) had a prescription for an auto-injector prior to the first episode of anaphylaxis. The retrospective analysis of the risk factors potentially requiring an epinephrine auto-injector prescription before the first anaphylactic episode, showed that of the 55 patients without prescription, at least 10 (18%) should have been provided with a device, according to the most recent guidelines. In conclusion, notwithstanding intramuscular adrenaline being the first-line treatment of anaphylaxis, many episodes are still undertreated and the risk of anaphylaxis is still underestimated. More efforts should be made to promote the correct management of anaphylaxis among both healthcare-providers and patients.

Anaphylaxis has been defined as “a severe, life-threatening generalized or systemic hypersensitivity reaction, characterized by being rapid in onset with life-threatening airway, breathing or circulatory problems; it is usually, but not always, associated with skin and mucosal changes” (1). In recent years, an increasing trend in hospitalization for anaphylaxis has been recorded in several countries, with the highest rates among children (1-5). Nowadays, its estimated prevalence is between 0.09 and 2.1%, (0.3% in Europe), whereas an incidence of 1.5-7.9 per 100,000 person-years was reported in the general

population and of 10.5 per 100,000 person-years in childhood (1-5). Foods are generally considered the most common elicitors of the anaphylactic episodes in children, while medications and hymenoptera venom play a more important role among adults (3, 6-8). Over the last decade, several guidelines have been published with the aim to provide evidence-based recommendations for the recognition, risk assessment and management of patients who have experienced or are at risk for anaphylaxis (1, 9, 10). Despite this, the persistence of under-recognition of clinical symptoms by patients or their

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caregivers and of under-diagnosis by healthcare-providers is still high (2). Furthermore, although has been ascertained worldwide that intramuscular epinephrine (adrenaline) is the treatment of choice for anaphylactic episodes, to date a low rate of prescription and administration is reported in the paediatric population (1-6, 9-17).

The aim of this study was to describe the clinical presentation, the eliciting factors and the management approach of the episodes of anaphylaxis in a population of children referred to the Paediatric Allergy Outpatient Unit of University of Bologna over the last decade, focusing on the possible risk factors which could be involved in the more severe reactions. Finally, we retrospectively analysed the prescribing practice of self-injectable adrenaline and the concordance with the most recent guidelines (1, 9).

MATERIALS AND METHODS

Study population and study design

This retrospective study analysed 65 children and adolescents, 46 males and 19 females (mean age 6 years old; range 3 months - 16 years) with a previous diagnosis of "anaphylaxis" referred to the Paediatric Allergy Outpatient Unit of University of Bologna from January 2000 to June 2013. The clinical features of each anaphylactic reaction were collected and reassessed, and the diagnosis of anaphylaxis was reconfirmed according to the criteria and the classification of severity of the European Academy of Allergy and Clinical Immunology (EAACI) position paper (1, 9). Data on the causative agents, timing of the reactions, setting of occurrence, managing and treatment of the anaphylactic episodes were collected. Personal and parental history of atopic diseases (atopic dermatitis, food allergy, allergic asthma/rhino-conjunctivitis, latex allergy) were investigated in all patients. The age at onset of the first episode of anaphylaxis and of the above-mentioned allergic diseases was recorded.

This research was carried out according to the principles of the Declaration of Helsinki; informed consent was obtained by the children's caregivers.

The need for an epinephrine auto-injector prescription was assessed according to the absolute and relative indications for prescribing self-injectable adrenaline in children recommended in the EAACI position paper (9). According to these recommendations, "absolute indications" are considered: i) previous cardiovascular or respiratory reaction to a food, insect sting or latex; ii) Exercise-induced anaphylaxis (EIA), iii) Idiopathic

anaphylaxis; and iv) food allergy and co-existent persistent asthma. Otherwise, "relative indications" include: i) any reaction to small amounts of a food; ii) history of only a previous mild reaction to peanuts and tree nuts; iii) remoteness of home from medical facilities; iv) food allergic reaction in a teenager.

Allergometric evaluation

For this study, we took into account the allergometric evaluations performed during the 4 months after the episode of anaphylaxis. Allergometric evaluation was carried out for all patients for a standard panel of inhalant allergens [timothy grass, birch, hazel-tree and pellitory, house dust mites (*D. pteronyssinus* and *D. farinae*), moulds (*Alternaria* and *Cladosporium*), pet dander (cat and dog)]. Foods and hymenoptera venoms were tested on the basis of each patients' clinical history.

Skin prick-tests (SPTs) were performed on all patients using commercial extracts (Lofarma, Milan, Italy). Histamine 0.1 mg/ml and physiological solution were used as a positive and negative control, respectively. Skin reaction was assessed 15 min after the prick-test; the average diameter of each wheal was established by measuring the longest diameter and the diameter perpendicular to it. An SPT result was considered positive when a wheal of at least 3 mm greater than the negative control was recorded.

Total and specific IgE (sIgE) against the above-mentioned allergens, were determined in all patients' sera by the means of ImmunoCAP 1000 (ImmunoCAP 1000 Thermo Fisher Scientific, Uppsala, Sweden). Specific IgE levels greater than 0.35 kU/L were considered positive.

Statistical analysis

Data were stored by means of customized databases. Categorical variables were summarized as numbers (n) and frequencies (%) and continuous data as means (geometric means in case of serum IgE levels). Patients were allocated into three groups according to the grade of severity of the anaphylactic reactions (9). The Kruskal-Wallis non-parametric test was used to compare the severity grade of the reactions among different age groups and the *Chi-squared* test (Armitage test) was used to evaluate the relationship between the potential triggering factors and severity of the episode of anaphylaxis. The univariate logistic regression was used to determine potential factors influencing the type of anaphylaxis (food-dependent or not food-dependent) among the following variables: symptoms during the episodes (cutaneous, gastrointestinal, respiratory or cardiovascular) and co-existent atopic diseases (allergic asthma, allergic rhino-conjunctivitis, atopic dermatitis). The odds ratio (OR) and 95% confidence intervals (95%

CI) were calculated. A *P* value <0.05 was considered statistically significant. Data were analysed with IBM-SPSS Statistic 20 for Mac-OS (IBM Corporation, North Castle Drive, Armonk, NY, U.S.A).

RESULTS

Demographic data of the study population

The demographic and clinical features of the study population are shown in Table I. Among the 65 children enrolled, 61 (94%) had a previous history of atopic diseases: 42 (65%) suffered from food allergy, 35 (54%) from allergic rhino-conjunctivitis, 28 (43%) atopic dermatitis and 22 (34%) from asthma. Of the 65 patients recruited, 44 (68%) had reported one episode of suspected anaphylaxis, 16 (25%) two, 5 (7%) three. Among the 91 recorded episodes, only 70 (77%) fulfilled the clinical criteria for the diagnosis of anaphylaxis (1, 9) and were included in this study.

The mean age of occurrence of the first episode of anaphylaxis was 6 years (range 3 months-16 years); 30 (43%) of the events happened in small children (0-5-year-old group), 29 (41%) among school-aged children (6-11-year-old group) and 11 (16%) in teenagers (12-16-year-old group). No relationship

was found between the different age groups and the severity score of the episodes.

Triggers

Of the 70 episodes, 57 (81%) were due to food ingestion, 5 (7%) to hymenoptera venom (3 to bee and 2 to wasp venom), 4 (6%) were exercise-induced [food-dependent EIA (FDEIA) or EIA], 1 (1%) to drugs (ketoprofen), 1 (1%) to allergen-specific immunotherapy and 1 (1%) to latex. In one episode (1%) it was not possible to identify the culprit; hence it was classified as "idiopathic anaphylaxis". Among food-induced anaphylaxis, cow's milk was implicated in 23 reactions (40%), tree nuts in 18 (32%; 8 cases due to hazelnut, 7 cases to peanuts, 3 to other nuts), hen's egg in 5 (7%), fish in 3 (5%), and kiwi in 2 (3%). Honey, wheat, peas, sesame seeds, potato and a candy with natural herb extracts were involved in one episode each one. The single fatal episode found in our series occurred in a teenage boy with multiple allergies after intake of wheat (Fig. 1).

Clinical presentation and characteristics of the episodes

The clinical presentation and the main features of

Table I. Demographic and main clinical data of the 65 children and adolescents (mean age 6 years; range 3 months-16 years) with a diagnosis of anaphylaxis referred to the Paediatric Allergy Unit of University of Bologna.

CLINICAL FEATURES		n (%)
Sex	Male	46 (71)
	Female	19 (29)
Confirmed episodes of anaphylaxis for each patient*	One	60 (92)
	Two	5 (8)
Previous history of atopic diseases	Food allergy	42 (65)
	Allergic	35 (54)
	Rhino-conjunctivitis	
	Atopic dermatitis	28 (43)
Age of the patient at the time of the anaphylactic episode (years)	Allergic asthma	22 (34)
	0 – 5 years	30 (43)
	6 – 11 years	29 (41)
	12 – 16 years	11 (16)

*According to the criteria from the EAACI Task Force on Anaphylaxis in Children (1, 9)

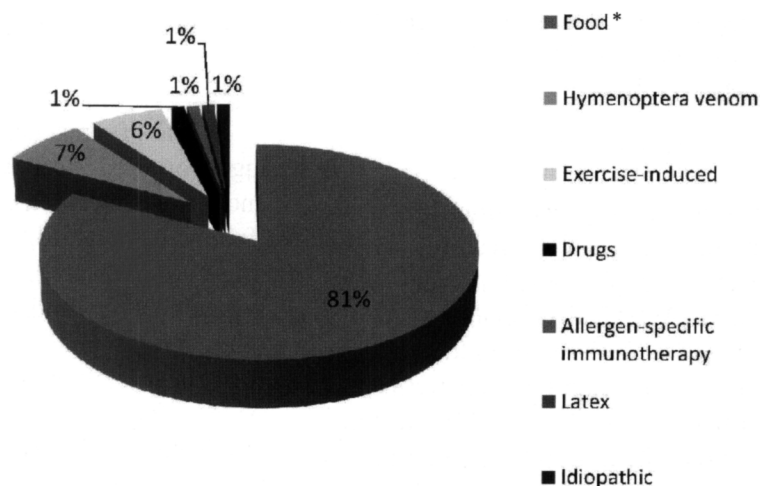


Fig. 1. Agents and specific allergens implicated in the 70 episodes of anaphylaxis which occurred in the 65 children and adolescents with a diagnosis of anaphylaxis included in the study. * This group includes one fatal episode of anaphylaxis.

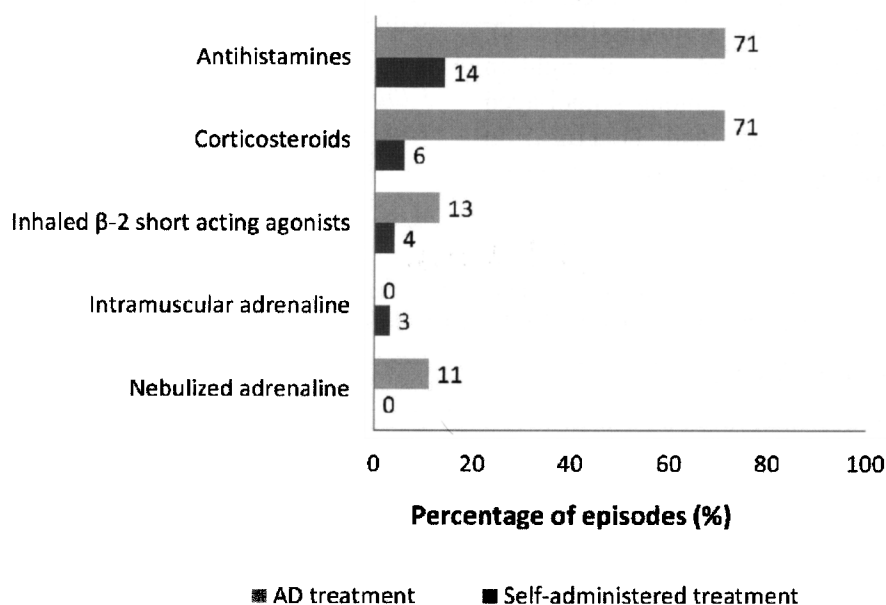


Fig. 2. Self-administered medications (by patients themselves or by their caregivers) and Emergency Department (ED)/physician management of the 70 episodes of anaphylaxis which occurred in the study population.

the episodes are summarized in Table II. According to the clinical presentation, 32 episodes (46%) were classified as mild, 34 (49%) were moderate and 4 (6%) severe. One episode led to the patient's death on the way to the hospital. Only in 13 episodes (18%)

patients had shown prodromal symptoms: in 12 cases (17%) oral itching and in one episode pruritus on upper and lower extremities. Most of the reactions were monophasic (65 episodes, 93%), while 5 episodes (7%) were biphasic. Skin (64 episodes,

Table II. Clinical presentation and characteristics of the 70 episodes of anaphylaxis which occurred in the 65 children and adolescents with a diagnosis of anaphylaxis included in the study.

CHARACTERISTICS	n (%)
Symptoms	
- Prodromal	13 (18)
- Cutaneous	64 (91)
- Gastrointestinal	36 (51)
- Respiratory	55 (79)
- Cardiovascular	7 (10)
Severity	
- Mild	32 (46)
- Moderate	34 (49)
- Severe	4 (6)*
Evolution	
- Monophasic	65 (93)
- Biphasic	5 (7)
Place	
- Patients' Home	39 (56)
- Relative's/friend's Home	4 (6)
- Restaurant	9 (13)
- School	3 (4)
- Streets/parks	11 (16)
Who first made the diagnosis	
- Emergency Department physician	46 (66)
- Child's parents	8 (11)
- Paediatric Allergist	6 (9)

*One fatal episode

91%) and respiratory symptoms (55 episodes, 79%) were the most common, followed by gastrointestinal (36 episodes, 51%) and cardiovascular (7 episodes, 10%) ones. The 57 patients (81%) with food-dependent anaphylaxis showed more frequent respiratory symptoms (OR=11.43; $P=0.0005$) during

the reaction and had previous diagnoses of asthma (OR=5.76; $P=0.03$) and atopic dermatitis (OR=5.76; $P=0.03$) than subjects with anaphylaxis elicited by other culprits. Most of the children (4 out of 5) with hymenoptera venom-induced anaphylaxis had a personal history negative for atopic diseases, whereas

Table III. Retrospective analysis of the prescribing practice of adrenaline autoinjector prior to the first episode of anaphylaxis episode in the 55 patients without adrenaline autoinjector prescription (85% of the enrolled population) according to the absolute and relative indications for prescribing self-injectable adrenaline recommended by EAACI position paper (1, 9).

Indications for prescribing self-injectable adrenaline*		Number of patients (n=55)	%
Absolute indications	Previous cardiovascular or respiratory reaction to a food, insect sting or latex.	0	0
	Exercise-induced anaphylaxis (EIA)	0	0
	Idiopathic anaphylaxis	0	0
Relative indications	Food allergy and co-existent persistent asthma	10	18
	Previous reaction to small amounts of a food	24	44
	History of only a previous mild reaction to peanut or a tree nut	13	24
	Food allergic reaction in a teenager	3	5
	> one relative indication	10	18
None of the above mentioned indications		15	27

*According to the criteria from the EAACI Task Force on Anaphylaxis in Children (1, 9)

the four patients with EIA had a previous histories of allergic asthma. Thirty-nine reactions (56%) had occurred at the patients' homes, whereas 4 (6%) at relatives'/friends' homes, 9 (13%) in a restaurant, 3 (4%) at school and 11 (16%) elsewhere (streets or parks). The diagnoses of anaphylaxis were first made by an Emergency Department (ED) physicians in 46 cases (66%), while in 8 episodes (11%) they were first suspected by the children's parents and in 6 cases by paediatric allergists (9%).

Management and treatment of the episodes

The management of the episodes is summarized in Fig. 2. Only in 10 episodes (14%) parents had self-injectable adrenaline and an action plan to manage and treat the anaphylactic reactions at the time of the first episode and self-injectable adrenaline was

used only in 2 episodes (3%); in one of these the administration was delayed and the patient died on the way to the hospital. Most of the reactions (50/70; 71%) were primarily treated in an ED setting (reports from EDs of different hospitals were collected). In all of the episodes treated in an ED a combination of antihistamines and steroids was used, inhaled β -2 short-acting agonists were administered in 9/50 cases (18%) and nebulized adrenaline in 8/50 (16%). None of the reactions managed in the ED setting was treated with intramuscular adrenaline. Thirteen episodes (19%) required hospitalization and 11 reactions (16%) completely resolved in more than 8 hours

Our retrospective analysis showed that only 2 (5%) of the 38 episodes classified as moderate and severe (based on the EAACI classification of severity

of anaphylaxis) had been treated with intramuscular adrenaline (1, 9).

Risk factors for severe reactions

Among the specific variables (triggers, personal history of atopic diseases) that might correlate with a higher grade of severity of the reactions, only a co-existent history of allergic asthma was associated with moderate and severe anaphylactic episodes ($P=0.008$).

Retrospective analysis of the prescribing practice of adrenaline auto-injector

Only 10/65 patients (15%) had a prescription for an auto-injector prior to the first episode of anaphylaxis. Thus, we retrospectively analysed whether any of the 55 patients without self-injector prescription had one or more risk factors potentially requiring an epinephrine auto-injector even before the first ascertained anaphylactic episode, according to the absolute and relative indications recommended in the EAACI position paper (1, 9). As shown Table III, we found that 10 (18%) of the 55 patients without auto-injector prescription had an absolute indication (previous diagnosis of food allergy and co-existent persistent asthma) for prescribing self-injectable adrenaline (1, 9). 32/55 subjects (58%) had at least one relative indication: 24 patients had a previous reaction to small amounts of a food, 13 had a history of a previous mild reaction to peanut or a tree nut, and 3 were teenagers with food allergy. Only 15 subjects (27%) did not have any of the suggested indications.

DISCUSSION

In this study we retrospectively investigated the main triggers and the management and treatment approach of anaphylaxis in a paediatric population. The strength of this study was the availability of the report of an ED physician in combination with the clinical data and the results of the allergometric tests performed by a pediatric allergist. Thus, the identification of the trigger(s) of the anaphylactic episodes was possible in almost all of the cases (99% of the episodes). This rate is significantly high if compared to epidemiological studies based only on the ED assessment, where in the 26% of the cases the identification of the specific eliciting factors was not possible. In line with Italian,

European and American studies, food was confirmed to be the main agent causing anaphylaxis in childhood (3, 5, 7, 18). Among food-induced anaphylaxis, cow's milk was most frequently involved, causing 40% of the food-dependent episodes: this rate, in line with a previous Italian study, differs from the American and British data, where peanuts and other tree nuts are reported to be the main elicitors among foods (18-20). This suggests how, in addition to the allergenic power of specific food, food habits and other environmental factors can also influence the allergic reactions. Even though an increasing trend is reported in the prevalence of peanut-dependent anaphylaxis in Italy [1.8% in 1998 (7), 3.1% in 2011(20), 10% in our study], among our patients hazelnut was the main agents within tree nuts. This finding is in line with another study carried out in Europe (21) but differs from studies from the United States (22) where, after peanuts, walnut and cashew are mainly responsible for tree nut-induced reactions. Anaphylaxis is characterized by a rapid onset with a short time of latency between the allergen exposure and the clinical manifestations (82% of the episodes had no prodromal symptoms) and our findings show that the majority of the episodes occurred outside the hospital setting and in the absence of physicians. These data underline the importance of training both high-risk children and their caregivers to manage and treat the episodes (23-25).

At the same time, few elements can help the clinicians to predict the severity of the episodes: our analysis showed that only a co-existent allergic asthma ($P=0.008$) and the involvement of the respiratory tract at the beginning of the episode [bronchospasm ($P=0.0001$) and dyspnoea ($P=0.0132$)] are related with a higher severity of the reaction.

Furthermore, notwithstanding the fact that intramuscular adrenaline is considered worldwide as the first-choice treatment in the management of anaphylaxis and its therapeutic efficacy and safety has been proved in the paediatric population (1, 6, 9, 10), our results confirm that anaphylaxis is still under-treated by physicians even in the ED setting, where intramuscular adrenaline had never been used, even if clinically indicated (16, 17, 26, 27). Moreover, in line with previous surveys, the association of steroids and antihistamines was the most common therapeutic approach among ED physicians (11, 26, 27). Even the most recent

guidelines placed intramuscular epinephrine as the first-line intervention for anaphylaxis treatment and its prompt administration in all patients experiencing anaphylaxis is strongly recommended, since a delayed or inadequate dose increases the risk of fatalities (1, 28, 29). Indeed the pharmacological effects of adrenaline on both α -1 and β 1 and 2 receptors have a faster onset than other second-line medications, causing peripheral vasoconstriction, increase in heart function and bronchodilation (1, 10, 30). The absence of absolute contraindications and the transient collateral effects reported (e.g. headache, pallor and palpitations) should be clearly illustrated to all patients and their caregivers to promote its administration in case of a reaction (1). Furthermore, our data confirmed the lack of a correct training among health-care givers, not only in treating but also in identifying patients at risk for experiencing anaphylaxis. The direct consequence of this is that most of the subjects enrolled had not been adequately prepared to manage a possible episode. Indeed, our retrospective analysis of the prescribing practice of adrenaline auto-injector showed that at the first episode of anaphylaxis only 10/65 children (14%) had a previous prescription of an epinephrine auto-injector and an action plan to manage the reaction. Moreover, among the 55 children without epinephrine prescription before the first anaphylactic episode, 10 (18%) had a previous diagnosis of food allergy and co-existent persistent asthma, which is an absolute indication for prescribing self-injectable adrenaline, and 32/55 subjects (58%) had at least one relative indication (1, 9). These data highlight that some risk factors (eg. the presence of co-existent persistent asthma) are still underestimated by clinicians as potential risk factors for anaphylaxis (16). On the other hand, a relevant number (15 subjects, 27%) of the 55 patients without epinephrine prescription before the first reaction did not have any of the suggested indications: this finding suggests that to date not all the risk factors have been clearly identified.

In conclusion, our study highlights that anaphylaxis is still under-recognized and undertreated even by physicians in the ED setting. Moreover, our research underlines the need to identify and to address correct preventive measurements (e.g. personalized management plans,

self-injector prescription and training) to those “high risk” patients even before the appearance of the first episode. On the other hand, since some reactions are so severe as to be refractory to all medications even if promptly recognized and treated, more efforts should be made to promote preventive strategies and correct management of anaphylactic episodes among both healthcare-providers and patients’ caregivers (29). Finally, further research should be addressed to better clarify all the mechanisms underlying this complex phenomenon.

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