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Adherence to the guidelines for adrenaline auto-injector prescription should be improved.

Short title: Prescription practices of adrenaline auto-injector

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To the Editor,

Patients at risk of anaphylaxis or who have experienced anaphylaxis should have an adrenaline auto-injector (AAI) and should be educated when and how to use it. In 2003, French recommendations were designed for the personalized care project of food allergic children at school. Five absolute and some various relative indications for prescription of AAI were proposed (Table I) [1]. Recently, EAACI taskforce on anaphylaxis provided recommendations for prescription of AAI: six absolute indications and four relative indications were retained (Table I) [2]. The aim of our study was to assess prescription practices of AAI by the French allergists, all members of the Allergy Vigilance Network (AVN) (www.allergyvigilance.com) and to confront the EAACI anaphylaxis guidelines and the French guidelines.

In January 2015, an electronic questionnaire was sent to the 299 members of the AVN. The aim of the questionnaire was to assess the prescription practices of AAI in children. This assessment was based on multiple-choice, true-false and open questions. The main collected data were: indications for prescription of an AAI, for the prescription of a second AAI, weight determining the dose of adrenaline (0.15 versus 0.3 mg) and criteria associated with the choice of the device. Statistical data have been validated and analyzed by the Biostatistics Unit of the Lille University Hospital. The analysis was descriptive and used Wilcoxon and Chi-square tests for comparisons of categoric data. A p-value <0.05 was considered significant.

The response rate was of 40% (n=121). Among these 121 physicians, 100 of them were used to prescribe AAI for children. They were exclusive allergist (64%), pediatrician-allergist (23%), pulmonologist allergist (7%) and others (6%). Their practice was exclusive private (45%), exclusive hospital (29%) or mixed (26%). The answers regarding the prescription in children are summarized in table I. According to the French guidelines, 81%

of the allergists adhered to at least 4 or 5 absolute indications in children. Only 33% of the surveyed allergists adhered to all 5 absolute indications in children. According to the European guidelines, 77% of the allergists adhered to at least 5 or 6 absolute indications in children and about 50% adhered to all 6 absolute indications in children. Isolated generalized hives included in the French recommendations was not considered as an indication by two third of the allergists. Unstable or moderate-to-severe asthma was a criterion of prescription for 77% of the allergists in children. Medical specialties of the allergists did not influence their adherence to European or French guidelines (Wilcoxon test).

A second AAI was always prescribed in 34% of the surveyed allergists. Half of them were used to prescribe a second AAI for at least one of the six suggested indications of the European guidelines (Table II). Eighty-eight percent of the allergists had a trainer available for demonstration during the medical visit; 55% of them provided written instructions in case of accidental allergic reaction and 13% provided a multimedia training. Twenty-eight percent of the allergists recommended the 0.3 mg dosage for children who weighed ≥ 20 kg and 53% for those who weighed ≥ 25 kg. The main criteria for selecting the device were: availability (56%), ergonomics (38%), trainer's availability (33%), needle's length (22%), patient's overweight (8%), age (8%), device's cost (4%).

In the present study, overall prescription practices for AAI of the AVN allergists were in accordance with the European guidelines and have evolved regarding the French guidelines published in 2003. The relatively low response rate of 40% is clearly a limitation of our study because these results may not be representative of general practices and overestimate the relatively acceptable adherence to the guidelines. The definition of anaphylaxis is that proposed by Sampson et al. [3], emphasizing the rapid onset of multiple symptoms and signs with most of times cutaneous manifestations. A history of isolated generalized hives or angioedema was included in the indication for AAI in the French guidelines but not in the

updated European guidelines. Two third of allergists considered that it was not an indication in accordance with these guidelines. Unstable moderate-to-severe persistent asthma, induced anaphylaxis exercise and venom allergy with previous systemic reactions are absolute indications of the EAACI guidelines but were not included in the French guidelines designed for food allergic children at school. These are shared by more than 2/3 of allergists in the present study.

Asthma is known to be a high-risk factor of severe anaphylaxis and fatalities, in particular for food allergic patients [4, 5]. Asthmatic patients are known to overestimate their control and are often poorly controlled, undertreated and insufficiently educated [6]. History of asthma in food allergic children is associated with a greater risk of severe anaphylaxis, wheezing and respiratory arrest [4]. Children requiring multiple doses of adrenaline for treating a food-induced anaphylaxis have more often a history of asthma than those receiving a single dose [7]. Seventy-eight percent of the patients who died from food anaphylaxis in England and Wales from 1992 to 2012, had asthma [8]. However, asthma is a frequent comorbidity in children with food allergy. There is still a lack of clear recommendations for AAI prescription in patients with mild asthma and/or with asthma controlled with medication.

Surprisingly, only 16% of the allergists were used to prescribe AAI for adolescents or young adults with food allergy although it is considered as a relative indication of the European guidelines. Hospital admissions fatalities caused by food anaphylaxis are significantly overrepresented in this age group [8]. There might be age-physiologic factors that account for the vulnerability of this age group.

The European guidelines highlight the significant risk of anaphylaxis associated to peanut and tree nuts, which accounted for 73% of food allergic fatalities in United-Kingdom from 1992 to 2012 and for more than 90% in the USA [8, 12]. However, fatal cases can potentially occur with any food allergens. Other food allergens than peanuts or tree nuts

responsible for mild-to-moderate reactions are not yet considered as relative indications for adrenaline prescription.

There is no high quality data on the number of AAI that should be available per patient. The percentage of patients requiring a further dose of intramuscular adrenaline after the first injection varies from 0 to 32% [2]. European guidelines suggest various indications for prescribing an additional adrenaline device (Table II) [2]. AAAACI/ACAAI guidelines recommend this prescription in all the allergic patients requiring an AAI [13]. In our study, a second AAI was always prescribed in about a third of the surveyed allergists and was prescribed only for various indications in half of these allergists.

In 2015, in France, three AAI were available with two doses for each (0.15 and 0.30 mg): Anapen®, EpiPen® and Jext®. The 0.15 mg dose is recommended by the manufacturer for children weighing < 30 kg and 0.30 mg for those weighing ≥ 30 kg. The allergists were used to prescribe the dose 0.30 mg before 30 kg in about half and from 20 kg in a quarter of the patients. EAACI guidelines rightly recommend a dose of 0.15 mg for patients weighing 7.5 to 25 kg and 0.30 mg for patients weighing ≥ 25 kg [2]. There are some concerns for children weighing < 7.5-10 kg and uncertainties about AAI efficacy due to needle length in obese patients. Needle's length was rightly considered as a selection criterion for AAI in 22% of AVN allergists.

In conclusion, our findings may be useful to improve knowledge and adherence to the new European guidelines and to update French guidelines for prescribing AAI. Nevertheless, there is still a lack of high-quality evidences to provide firm recommendations for some relative indications of AAI, in particular for asthmatic patient (severity level and asthma phenotype), regarding the other allergic comorbidities (atopic dermatitis, allergic rhinitis) also associated to a risk of anaphylaxis and for the optimal number of AAI the patient should

have access to. This should be clarified through further large prospective studies involving well-phenotyped participants with clear criteria of anaphylaxis.

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Table I. Indications for prescription of adrenaline auto-injector (French 2003 recommendations, EAACI anaphylaxis Taskforce 2014 recommendations) and rate of prescription by 100 Allergy Vigilance Network allergists in children.

French recommendations for food allergic children at school (2003)	EAACI anaphylaxis recommendations (2014) (evidence level, grade)	Prescription in children (n=100) N
Absolute indications		
Food anaphylaxis	Previous anaphylaxis triggered by food, latex or aeroallergens (IV, C)	90
	Previous exercise-induced anaphylaxis (IV, C)	77
	Idiopathic anaphylaxis (IV, C)	84
Acute severe bronchospasm due to food allergy		98
	Co-existing unstable or moderate to severe, persistent asthma and a food allergy (IV, C)	77
Laryngoedema due to food allergy		98
Generalized hives due to food allergy		37
	Venom allergy in adults with previous systemic reactions (not receiving maintenance VIT) and children with more than cutaneous/mucosal systemic reactions (IV, C)	96
	Underlying mast cell disorders or elevated baseline serum tryptase concentrations together with any previous systemic allergic reaction to insect stings, even in VIT treated patients (IV, C)	83
Relative indications		
Food allergy to specific allergens (peanut, tree nut...)	Previous mild-to-moderate allergic reaction to peanut and/or tree nut* (IV, C)	70
Food allergy to other specific allergens (fish, crustaceans...)		75
Food allergy to traces of food*	Previous mild-to-moderate allergic reaction to traces of food* (V, D)	78

Multiple food allergy syndrome		57
Asthma with a food allergy		40
Mastocytosis due to food allergy		83
	Teenager or young adult with a food allergy* (IV, C)	16
	Remote from medical help and previous mild-to-moderate allergic reaction to a food , venom, latex or aeroallergens (V, D)	62

* excluding pollen food syndrome (oral allergy syndrome)

Table II. Suggested indications for prescription of a second adrenaline auto-injector and rate of prescription by the 100 Allergy Vigilance Network allergists (EAACI anaphylaxis recommendations 2014).

Indications (evidence level, grade)	Rate of prescription (%)
Co-existing unstable or moderate to severe, persistent asthma and a food allergy* (IV, C)	43
Co-existing mast cell diseases and/or elevated baseline tryptase concentration (IV, C)	47
Lack of rapid access to medical assistance to manage an episode of anaphylaxis due to geographical or language barriers (V, D)	Not evaluated
Previous requirement for more than one dose of adrenaline prior to reaching hospital (V, D)	61
Previous near fatal anaphylaxis (V, D)	57
If available auto-injector dose is much too low for body weight (V, D)	50

* excluding pollen food syndrome (oral allergy syndrome)