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Article type : Research Letter

Factors associated with the underuse of adrenaline in children with anaphylaxis.

Running title : Adrenaline underuse in children with anaphylaxis

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Word count: 1368

Tables: 2

Abbreviations

ECU: emergency care unit

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/CEA.13821](https://doi.org/10.1111/CEA.13821)

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AAI: adrenaline auto-injector
EMS: emergency medical service

Declarations

Conflict of interest:

Guillaume Pouessel received Bausch+Lomb, Meda/Mylan, Stallergenes Greer, ALK-Abello AImmune grants for consultant and speaker's participations, financial grants for research. Antoine Deschildre reports personal fees and other from Novartis, personal fees and other from ALK, personal fees from TEVA, personal fees and other from GSK, grants and personal fees from Stallergenes Greer, personal fees from AImmune, personal fees from Zambon, personal fees and other from CHIESI, personal fees and other from Astra Zeneca, personal fees and other from DBV technologies, personal fees from Boehringer Ingelheim, outside the submitted work. The other authors declare no conflict interest.

Funding:

This study received financial support from ALK-Abello.

Ethics:

This study was approved by the French Data Protection Authority (No. 915264) and received a favorable opinion from the Advisory Committee for Information Processing in Health Research (No. 14.490bis). Families were given a written information document on study modalities and written consent for study participation was obtained.

Acknowledgements:

Collaborators and members of the Pediatric Emergency Medicine Group: Sylvie Akitani (Seclin), Mohamed Amani (Boulogne), Hélène Audry-Degardin, (Valenciennes), Cécile Bonnel (Béthune), Mohamed Boulyana (Saint-Omer), Michel Chenaud (Tourcoing), Emmanuel Cixous (Roubaix, Seclin), Flore Chagnon (Valenciennes), Sarah Combes (Roubaix), Florence Delepoule (Dunkerque), Céline Delvart (Arras), Tahar Dhaoui (Cambrai), Martine Glowacki (Armentières), Magloire Gnansounou (Maubeuge), Olivier Guilluy (Saint-Omer), Thérèse Heuclin (Douai), Nicolas Kalach (Lille Saint Vincent), Armelle Le Mée (Tourcoing), Sylvie Louf (Montreuil sur Mer), Alain Martinot (Lille), Anne Martinet (Béthune), Sarah Mitha (Lens), Delphine Penel (Lens), Manuela Scalbert

(Dunkerque), Caroline Thumerelle (Lille), Capucine Trochu (Roubaix).

Authors' contributions:

GP and MA analyzed and interpreted the data and wrote the draft. AP performed the statistical analysis and contributed in writing the manuscript. SL, AD, and FD were major contributors in reviewing the draft and improving the paper with critical analysis. All authors read and approved the final manuscript.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Keywords: adrenaline, anaphylaxis, child, emergency care unit, food allergy

To The Editor,

Intramuscular adrenaline injection is the first-line treatment of anaphylaxis [1]. More serious and even fatal or biphasic reactions may occur if there is a delay in administering it [1]. Adrenaline injection for anaphylaxis that occurs outside of a healthcare setting should be immediately followed by a call to emergency medical services (EMS) (“911” in North America, “112” in Europe) [1]. Before discharge from the emergency care unit (ECU), an adrenaline auto-injector (AAI) should be prescribed with clearly written instructions for its use and safety recommendations [1].

Despite international guidelines and education about the treatment of anaphylaxis, adrenaline is underused by caregivers and healthcare professionals. This study aimed to understand the factors associated with the underuse of adrenaline in children experiencing anaphylaxis. Preliminary results of this study focusing on the clinical outcome of the anaphylaxis manifestations have been previously reported [2].

All children (≤ 15 years) admitted for anaphylaxis (2015-2017) to one of 18 pediatric ECUs in the Nord-Pas-de-Calais region of France, were prospectively included. Diagnosis of anaphylaxis was based on the criteria proposed by the National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis Network symposium [3]. All medical records were reviewed by an emergency medicine pediatrician and two allergists. All families received a phone call three months after the emergency admission in order to confirm anaphylaxis diagnosis. The 5-grade Astier score designed for food-induced anaphylaxis in children was used to analyze severity [4].

Factors associated with the use of adrenaline were identified using a χ^2 or Fisher exact test for qualitative variables and a Mann-Whitney U test for continuous variables. Tests were two-sided with significance set at $p < 5\%$.

A total of 152 cases of anaphylaxis were identified and three families refused inclusion. Therefore the final sample consisted of 149 cases of anaphylaxis. Patient characteristics are detailed in Table 1. Eighty-seven (58.4%) were boys. Mean age at inclusion was 7.4 years ($SD=4.7$ years) and age groups were as follows: infants (< 2 years), $n=21$ (14%); preschoolers (2-5 years), $n=42$ (28%); school-age children (6-11 years), $n=54$ (36%); adolescents (12-18 years), $n=32$ (22%). Thirty-five children (23%) had known food allergy to the same trigger and 17 (11%) had previously experienced anaphylaxis. An

emergency kit had been prescribed for 35 children, including 31 (89%) of which contained an AAI.

The anaphylaxis cases mainly involved food triggers (n=110; 74%), mainly peanut (n=32, 21%), cashew (n=20, 13%), hazelnut (n=5, 3%), and pistachio (n=5, 3%) (Table 1). EMS were called in 63 (43%) cases, and 55 children (37%) received prehospital care by EMS. In 18 cases (27%), the EMS did not intervene outside a hospital setting despite being called by caregivers. Before EMS arrival or hospital admission, 15 of the 31 (48%) children with an AAI available received adrenaline. Adrenaline was administered by EMS in 4 of the 55 (7%) cases. In the ECU, 52 of 149 (35%) children received adrenaline.

In all, 71 of 149 (48%) children were treated with adrenaline. An AAI was prescribed or renewed in 103 (69%) cases before discharge from ECU.

Three patients (2%) had a biphasic reaction and were given a further dose of adrenaline. No child was transferred to intensive care unit and no deaths occurred.

Table 1 details the characteristics of children who did and did not receive adrenaline. Adrenaline was more often used in younger children (mean age: 6.5 versus 8.3; $p < 10^{-3}$) but we did not identify any other factor associated with a more frequent use of adrenaline.

The two main reasons why the adrenaline was not used before EMS arrival, by EMS or in the ECU were the following: underestimation of the potential severity of the reaction and spontaneous clinical improvement since the first signs (table 2). Fear of adrenaline side effects and fear of injection were not frequent reasons for this underuse.

In this study, we have confirmed that, despite clear guidelines, adrenaline is underused by caregivers (48%) and even by emergency medicine physicians, both in prehospital care (7%) and ECU (35%). The main reasons for this underuse were the lack of recognition of anaphylaxis severity and spontaneous rapid improvement of symptoms.

According to data from the Anaphylaxis European registry, the overall rate of adrenaline use by caregivers is 27% and, in France, 47% which is similar to that reported in our study [5]. However, in our study, the use of adrenaline in prehospital care was low (7%), as compared with most studies according to the organization of EMS (31% in Canada) [6]. Although all international guidelines endorse adrenaline as the first-line treatment for anaphylaxis, no randomized controlled trials of any therapeutic intervention in anaphylaxis have been performed due to ethical concerns and only expert opinion supports the use of intramuscular adrenaline as the first-line drug [1].

In the present study, we did not find any factor, except the young age, associated with a more frequent use of adrenaline.

Behind adrenaline underuse, we found that the lack of recognition of the potential severity of anaphylaxis and rapid improvement of symptoms were the most common reasons not to administer adrenaline. Regarding caregivers' attitudes, these findings have been reported before. When describing gaps in the anaphylaxis management by patients and caregivers, Kastner et al. reported that the underestimation of the seriousness of anaphylaxis symptoms was the main reason for not using AAI [7]. The other reasons were here the use of other medication and fear of using AAI. There are few prospective studies reporting the reasons for not administering adrenaline by emergency medicine physicians. We previously reported the results of a questionnaire (sent electronically to the 2,100 members of the French Emergency Medicine Society) based on a clinical scenario of a child experiencing moderate anaphylaxis related to peanut [8]. We found a high rate (98%) of accurate anaphylaxis diagnosis but intramuscular adrenaline injection was considered as the first-line treatment in only 24% of cases. The main reason for not administering adrenaline was that symptoms were not considered to be severe enough, i.e. without any compromise in breathing and/or circulation. A close collaboration between Allergy and Emergency Medicine Physicians academics is required to implement anaphylaxis guidelines and improve patients' prevention and care.

We found that rapid improvement of anaphylaxis symptoms was a major reason for not administering adrenaline. In our study, half of the reactions resolved spontaneously and rapidly even without adrenaline injection [2]. Therefore, the majority of anaphylaxis reactions cannot be described as life-threatening. This fact is also supported by the apparent discrepancy between the low rate of adrenaline use in anaphylaxis, and the low rate of life-threatening or fatal anaphylaxis reactions. Consequently, the World Allergy Organization (WAO) anaphylaxis committee proposed to revisit the anaphylaxis criteria and to define anaphylaxis as "a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death" whereas "severe" anaphylaxis is characterized by "potentially life-threatening compromise in breathing and/or the circulation, and may occur without typical skin features or circulatory shock being present" [9]. However, given our inability to predict severe reactions at the onset of the first symptoms and evidence that early adrenaline may help reduce risk of rapid worsening, all anaphylaxis reactions require prompt intramuscular adrenaline.

Beside adrenaline underuse, the lack of recognition of the potential severity contributed to gaps in the management of anaphylaxis: failure to call EMS since the onset of anaphylaxis signs (57%), failure to send emergency medical assistance after the call for help

to EMS (27%), failure to prescribe AAI before discharge from ECU (31%). Most guidelines recommend “immediately calling 911/112” after adrenaline injection. However, given that biphasic reactions are rare (0.6%-14.7%), that reactions requiring a second dose of adrenaline are infrequent (12%-19%) [10], and the results of a cost-effective analysis, new United-States recommendations during the COVID-19 pandemic suggest that patients experiencing anaphylaxis should watch and observe for the response to adrenaline [11]. If symptoms do not promptly resolve after adrenaline, EMS should be activated. This “wait-and-see” approach should arguably endure once the pandemic risk passes but clinical trials are lacking to confirm its safety and utility through an individual risk/benefit in other countries.

Educational programs to allergic patients and caregivers and guidelines to healthcare professionals should emphasize the potential severity of anaphylaxis and the risk of unpredictable rapid more severe reaction. Therefore, intramuscular adrenaline should be promptly injected as soon as anaphylaxis is recognized. The updated WAO definitions for anaphylaxis may help clinicians to be aware of the large spectrum of anaphylaxis severity.

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243 **Table 1. Characteristics of 149 children admitted to pediatric emergency care units for**

	Total n=149 (100%)	Adrenaline used n=71 (48%)	Adrenaline NOT used n=78 (52%)	p
Male, n (%)	87 (58)	42 (59)	45 (58)	0.65
Mean age, years (SD)	7.4 (4.7)	6.5 (4.7)	8.3 (4.5)	< 10 ⁻³
History of asthma, n (%)	58 (39)	26 (38)	32 (41)	0.63
History of allergic rhinitis, n (%)	31 (21)	17 (24)	14 (18)	0.34
History of atopic dermatitis, n (%)	30 (20)	16 (23)	14 (18)	0.48
Allergen				
Food	110 (74)	54 (76)	56 (72)	0.55
Peanut	32 (21)	17 (24)	15 (19)	0.48
Tree nuts	34 (23)	17 (24)	17 (22)	0.75
Cashew	20 (13)	9 (13)	11 (14)	0.80
Hen's egg	13 (9)	7 (10)	6 (8)	0.64
Medication	13 (9)	4 (6)	9 (12)	0.20
Idiopathic	25 (17)	13 (18)	12 (15)	0.16
Astier severity score				0.14
Grade 2	12 (8)	8 (11)	4 (5)	
Grade 3	70 (47)	28 (39)	42 (54)	
Grade 4	67 (45)	35 (49)	32 (41)	

244 **anaphylaxis and comparison with adrenaline use or not.**

245 **AAI: adrenaline autoinjector**

Table 2. Reasons why the adrenaline autoinjector was not used before EMS arrival, by the emergency medical services and in the emergency care unit (several reasons for the same patient).

Before EMS arrival (AAI available in 17 cases)	By the EMS (adrenaline not used in 51 cases)	In the ECU (adrenaline not used in 97 cases)
Family considered reaction not severe enough (3)	Reaction not considered severe enough (18; 35%)	Clinical improvement since first signs (68; 70%)
AAI not available (3)	Patient improved since first signs (13; 25%)	Reaction not considered severe enough (40; 41%)
Family afraid to use the AAI (3)	Unsure of diagnosis (3; 6%)	Adrenaline already administered (1)
Family did not think of adrenaline (1)	Fear of adrenaline side effects (1)	Duration in two injections too short (1)
AAI had expired (1)	Adrenaline already administered by family (1)	No reason specified (2)
AAI not used based on advice of phone call to EMS (1)	No reason specified (15; 29%)	
Possible to see a doctor quickly because reaction occurred close to the hospital (1)		
No reason specified (4)		

AAI: adrenaline autoinjector

EMS: emergency medical services

ECU: emergency care unit