



# Use of epinephrine in emergency department depends on anaphylaxis severity in children

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## Abstract

Despite multiple recommendations, intramuscular epinephrine is poorly prescribed in emergency department receiving pediatric anaphylaxis. To evaluate the role of severity symptoms on this use, we included all admissions for a diagnosis linked to possible allergy in the two pediatric emergency departments of our institution between January 2010 and December 2015. Selection and analysis were restricted to children under 18 years fulfilling Sampson's criteria for anaphylaxis. We retrospectively ranked these admissions with the Ring and Messmer anaphylaxis severity score and compared the use of epinephrine according to this classification. Among 422,483 admissions, 204 (0.05%) fulfilled the anaphylaxis criteria (170 (83.3%) grade II anaphylaxis, and 34 (16.7%) grade III; mean age 7.9 years). Previous allergy, anaphylaxis, and asthma were found in respectively 60.8%, 36.8%, and 35.1%. Food allergy was the main suspected causal trigger. Epinephrine was used in 32.7% ( $n = 65/199$ ), before admission (11.4% ( $n = 23/201$ )) or in the emergency department (22.2% ( $n = 45/202$ )). Epinephrine was more frequently prescribed in grade III than in grade II anaphylaxis (84.8% vs 22.3%,  $p < 0.001$ ; OR = 19.05 [7.05–54.10]). Upon discharge, epinephrine auto-injectors prescription and allergy referral were rare (31.7% and 44.2%).

**Conclusion:** Pediatricians intuitively adapt their epinephrine use to the severity of the anaphylaxis and contribute to epinephrine underuse in pediatric anaphylaxis.

## What is known:

- Intramuscular epinephrine is the recommended treatment for pediatric anaphylaxis. However, most of the European and North-American studies show a low prescription rate of epinephrine in both prehospital and pediatric emergency department management.
- Reasons for such a low prescription rate are unknown.

## What is new:

- This study confirms that intramuscular epinephrine is poorly prescribed in pediatric anaphylaxis (about one case among 10 before admission and one among 5 in pediatric emergency departments).
- Despite recommendations, pediatricians intuitively adapt their prescription to the clinical severity of anaphylaxis, with a fourfold increase prescription in grade III compared to grade II anaphylaxis. This medical behavior ascertainment may be in part explained by the delay between the ED admission/management and the anaphylactic episode onset.

**Keywords** Allergy · Food allergy · Management · Hospital treatment · Prehospital treatment

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## Introduction

Anaphylaxis is the most severe manifestation of immediate hypersensitivity with an incidence of 0.05 to 2% in general population [25]. Anaphylaxis concerns 4.5 to 18 admissions on 10,000 in pediatric emergency departments (EDs), with a trend to increase during the last years [14, 15]. In France, the anaphylaxis-related mortality rate in children is 0.83 per million per year [19]. A rapid clinical diagnosis, based on Sampson's criteria [23], is required for administering epinephrine as quickly as possible in accordance with the different recommendations [16, 26]. However, many studies underline constant under-use of epinephrine in children with anaphylaxis not only in pre-hospital but also in ED management [6, 11, 21, 24, 30]. One possible explanation for this gap between recommendations and practice could be a kind of "intuitive" adaptation of epinephrine delivery according to the severity of symptoms. This study aimed to analyze pediatricians' epinephrine prescription as a function of clinical severity during a 6-year period in children admitted for anaphylaxis in the two pediatric EDs of the University Hospitals of Marseille, France.

## Methods

### Patients

#### Design and setting

This was a retrospective study performed in the two pediatric EDs of the Assistance Publique-Hôpitaux de Marseille, France, between January 2010 and December 2015. These EDs received patients up to 18 years.

#### Data source and inclusion criteria

In France, for each patient admitted to an ED, an Electronic Emergency Department Abstract (EEDA), directly available from the patients' computerized medical files, is anonymously transmitted to the French Institute of Public Health Surveillance. EEDAs report on date and hour of ED admission, age, sex, disposition after ED visit (home discharge, hospitalization, death), and final diagnosis according to the national standardized thesaurus based on the International Classification of Diseases, Tenth Revision (ICD-10), codes were collected. We also analyzed the clinical severity appreciated by the triage nurse scale upon admission (high levels of severity were levels 1–2), which was therefore not specific for anaphylaxis.

Visits related to "anaphylaxis" ("anaphylactic shock" or "Quincke edema"), "urticaria," and "other allergic reaction" were defined using grouping of ICD-10 codes. The medical files of all patients with an ICD-code related to anaphylaxis

were reviewed. Patients who met Sampson's criteria were considered to have confirmed anaphylaxis. Patients were excluded if Sampson's criteria were not fulfilled. The anaphylaxis severity was defined by the Ring and Messmer classification (grade I: mucocutaneous symptoms; grade II: moderate multivisceral failure; grade III: severe mono/multivisceral failure; grade IV: cardiac arrest) [20]. Medical history, anaphylaxis features, and management (biological tests, treatments, planned allergist visit, and auto-injectable epinephrine prescription) were noted for each patient.

### Statistical analysis

Visits related to anaphylaxis, urticaria, and other allergic reaction were compared for age, sex, severity, and hospitalization rate. A descriptive analysis of the admissions for anaphylaxis according to Sampson's criteria was performed. Comparison of the data according to anaphylaxis severity rank was realized. Variables were described as percent, and mean (standard deviation). Associations were tested with simple logistic regression for qualitative variables and quantified by unadjusted odd ratio (OR) and their confidence interval. Quantitative variables were compared with a Student or Fisher test depending on the number of data. Analysis was performed with SPSS version 20.0® (SPSS Inc., Chicago, IL, USA). A *p* value of 0.05 or less was considered as statistically significant.

### Ethical considerations

This study was approved by the Ethics Committee of the French Society of Pediatrics (Société Française de Pédiatrie, No. 2016\_018\_2) and the National Commission of Informatics and Liberty (Commission Nationale Informatique et Libertés, No. 2016-16).

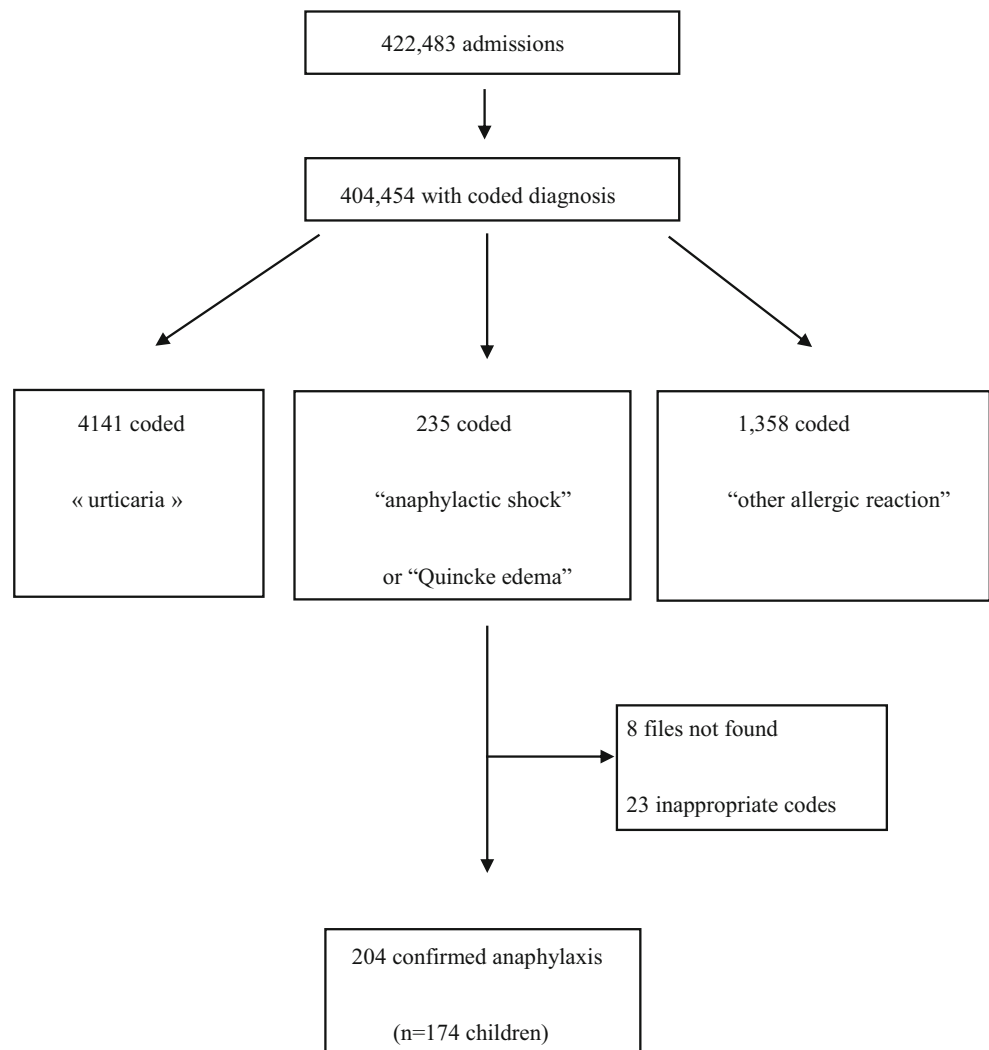
## Results

### Admissions with a diagnosis related to allergy

During the study period, 422,483 admissions took place (Fig. 1). The diagnosis discharge was missing for 18,029 (4.2%). Overall, 4141 visits were coded urticaria (102.13/10,000 admissions), 1358 other allergic reaction (33.49/10,000), and 235 anaphylaxis (5.76/10,000).

Compared with visits coded urticaria and to other allergic reaction, visits coded anaphylaxis concerned older children, more severe patients (according to the triage scale), and had a higher hospitalization rate (Table 1). Under 12 years, the rate of admissions for anaphylaxis was higher in boys than in girls (5.27/10,000 vs 3.25/10,000, *p* = 0.006). Conversely, above 12 years old, this rate was higher in girls (16.25/10,000 vs 9.25/10,000, *p* = 0.011).

**Fig. 1** Flowchart of the study evaluating anaphylaxis episodes in two French pediatric emergency departments during the 2010–2015 period



## Admissions with confirmed anaphylaxis

### History and clinical presentation

Among visits related to anaphylaxis, 204 (86.8%) fulfilled Sampson's criteria (Fig. 1 and Table 2), underlying a high predictive value of our coding for correct diagnosis. The mean age was 7.9 years (2 months to 17.7 years) with a sex ratio of 1.27 ( $n = 114$  boys, 55.9%). A history of allergy was reported in 124 files (60.8%). When a previous episode of anaphylaxis was reported ( $n = 75$ ; 36.8%), an epinephrine auto-injector was available at home. Asthma was reported in 61 files (35.1%), with a prophylactic daily treatment in 24 (39.3%). A total of 174 different children were concerned.

The current anaphylactic episode mainly occurred in private homes ( $n = 63/111$ , 56.7%) or schools ( $n = 32/111$ , 28.8%), during or after food intake ( $n = 122/155$ , 78.8%). Initial symptoms were mucocutaneous ( $n = 200/204$ , 98.5%), respiratory ( $n = 154/204$ , 75.7%), gastrointestinal ( $n = 47/204$ ,

23%), cardiovascular ( $n = 23/204$ , 11.3%), or neurological ( $n = 21/204$ , 10.3%). No cardiac arrest or death was noted.

In 67.2% of admissions, patients self-presented to the ED. At ED admission, 170 cases (83.3%) were classified grade II according to the Ring and Messmer classification and 34 grade III (16.7%). A causal allergen was suspected in 129 cases (63.2%): food allergen ( $n = 101$ , 78.3%, with nuts  $n = 42$ , 32.5%; fruits  $n = 17$ , 16.8%; milk  $n = 15$ , 14.9%; egg  $n = 6$ , 5.9%; others  $n = 21$ , 16.3%), drugs ( $n = 11$ , 8.5%), insect venom ( $n = 6$ , 4.7%), and other allergens ( $n = 11$ , 8.5%). Specific IgEs were measured in 28 cases (13.7%) and tryptase in 42 cases (20.6%).

### Treatment

Data concerning treatments administered before arrival at the EDs were available for 201 episodes. Intramuscular epinephrine was administered in 23 cases (11.4%). Admissions with recurrent anaphylaxis received epinephrine fourfold more

**Table 1** Comparison of the coded admissions characteristics for anaphylaxis, urticaria, other allergic reactions, and other diagnosis in two French pediatric emergency departments during the 2010–2015 period

	Anaphylaxis, <i>n</i> = 235	Urticaria, <i>n</i> = 4141	Other allergic reactions, <i>n</i> = 1358	Other diagnosis, <i>n</i> = 398,720
Mean age (year)	7.96 ± 4.77	5.08 ± 4.02	5.16 ± 4.68	5.05 ± 4.67
Boys (%)	57.0 ( <i>n</i> = 134)	54.5 ( <i>n</i> = 2,214)	56.5 ( <i>n</i> = 754)	56.2 ( <i>n</i> = 224,878)
Triage scale high severity levels (%)	63.4 ( <i>n</i> = 149)	13.7 ( <i>n</i> = 566)	3.4 ( <i>n</i> = 149)	5.6 ( <i>n</i> = 22,328)
Mean emergency department stay (h)	235.6 ± 170.1	120.2 ± 139.5	134.6 ± 122.1	162.2 ± 157.7
Hospitalization rate (%)	46.2 ( <i>n</i> = 108)	2.3 ( <i>n</i> = 94)	4.9 ( <i>n</i> = 66)	11.4 ( <i>n</i> = 45,454)

often than others (16/75 vs 7/126, 21.3% vs 5.6%). Epinephrine was mainly injected by family or school staff (14/23, 60.9%). Other treatments included antihistamines (*n* = 93/201, 46.3%), steroids (*n* = 83/201, 41.3%), inhaled beta-2 agonists (*n* = 26/201, 12.9%), or inhaled epinephrine (*n* = 5/201, 2.5%).

Data on ED treatments were available for 202 episodes. Intramuscular epinephrine was administered in 45 cases (22.3%). Overall, 65/199 (32.7%) children received epinephrine before arrival or in the ED. The epinephrine injection rate was higher for grade III than for grade II anaphylaxis (84.8% vs 22.3%, *p* < 0.001; OR = 19.05 [7.05–54.10]). Epinephrine was also more often prescribed when the patients were classified as urgent by triage nurses (level 1 and 2), but in a less important proportion (47.8% vs 24.6%; *p* < 0.001; OR = 2.81 [1.51–5.21]). Other treatments included antihistamines (*n* = 156/202, 90.7%), steroids (*n* = 126/202, 73.3%), inhaled beta-2 agonists (*n* = 25/202, 14.5%), inhaled epinephrine (*n* = 10/202, 5.8%), oxygen (*n* = 9/202, 5.2%), and vascular filling (*n* = 8/202, 4.7%). The length of stay in the ED was longer (378 min versus 197 min; *p* < 0.001), and the hospitalization rate higher (76.2% versus 34.1%, *p* < 0.001) in case of epinephrine administration. To note, all hospitalized children did not received epinephrine (rate of administration 52.7%;

*n* = 48/91). When the child was discharged at home (*n* = 104/204), an epinephrine auto-injector was prescribed in 33 (31.7%) cases, and an allergist visit planned in 46 (44.2%) cases, solely (Table 2).

## Discussion

To our knowledge, this is the first study reporting the link between epinephrine administration and the severity of pediatric anaphylaxis. Our study also shows that epinephrine is underused during pediatric anaphylaxis management. Among the ED admissions that met Sampson's anaphylaxis criteria, only one third received epinephrine before or during ED management.

Our study has several limitations due to its retrospective design. First, inclusion criteria (Sampson's criteria) and Ring and Messmer classification are not, in daily practice, pre-registered in the medical record, but they have been deducted by investigators from the medical data. However, in our institution, Sampson's criteria and Ring and Messmer classification are specified in the institutional protocol for anaphylaxis management, are well-known to pediatricians, and are well reported by physicians in the medical files. Also because of

**Table 2** Main characteristics of 204 pediatric admissions to two French emergency departments (EDs) for confirmed anaphylaxis (clinical severity was classified according to the Ring and Messmer criteria)

	Anaphylaxis grade II ( <i>n</i> = 170 admissions)	Anaphylaxis grade III ( <i>n</i> = 34 admissions)	<i>p</i> value
Mean age (year)	7.69 ± 4.86	9.03 ± 4.93	0.12
Boys (%)	57.6 ( <i>n</i> = 98/170)	47.8 ( <i>n</i> = 16/34)	0.25
Previous allergy (%)	55.9 ( <i>n</i> = 95/170)	85.3 ( <i>n</i> = 29/34)	0.001
Previous asthma (%)	25.9 ( <i>n</i> = 44/170)	50.0 ( <i>n</i> = 17/34)	0.005
Triage scale high severity levels (%)	27.6 ( <i>n</i> = 47/170)	67.6 ( <i>n</i> = 23/34)	< 0.001
Mean tryptase dosage (µg/L)	7.32 ± 8.59 ( <i>n</i> = 24)	9.91 ± 4.81 ( <i>n</i> = 18)	0.014
Hospitalization rate (%)	40.7 ( <i>n</i> = 68/170)	84.8 ( <i>n</i> = 28/34)	< 0.001
Prehospital epinephrine (%)	10.2 ( <i>n</i> = 17/167)	17.6 ( <i>n</i> = 6/34)	0.21
Epinephrine in EDs (%)	12.4 ( <i>n</i> = 21/169)	72.7 ( <i>n</i> = 24/33)	< 0.001
Discharge from EDs (%)			
Epinephrine autoinjector	31.3 ( <i>n</i> = 31/99)	40.0 ( <i>n</i> = 2/5)	0.68
Referral to an allergist	43.4 ( <i>n</i> = 43/99)	60.0 ( <i>n</i> = 3/5)	0.49

the retrospective design of the study, many data that would have been relevant to explain the underutilization of epinephrine, such as the specific delay between the onset of symptoms and ED visit, are not available. From this point of view, a qualitative approach exploring the reasons given by pediatricians to justify the absence of adrenaline prescription would also be relevant.

To minimize some bias, and in accordance with other studies [7, 12, 13, 22], we have carefully selected our cases of anaphylaxis following Sampson's criteria. First, we have compared the visits for possible allergic reactions (urticaria and "nonspecific allergy") to those for anaphylaxis, and we have shown that visits for anaphylaxis clearly concerned more severe patients as assessed by the clinical score value and the hospitalization rate. Second, when analyzing all the files coded as anaphylaxis, we have observed that anaphylaxis was correctly coded in 86.8% of the cases, better than the 63.1% figure reported by Walsh in the same context [29]. In another study in Australian children, ED diagnosis of anaphylaxis had a sensitivity of 43.2% and specificity of 97.9% [27].

Admissions with confirmed anaphylaxis had the same clinical characteristics as these described in the most recently published studies [10, 21, 24, 30]: age around 6–7 years, boys, mainly mucocutaneous symptoms, and food trigger. Our results also confirm the female predominance of anaphylaxis in children older than 12 years [1]. In keeping with the European Anaphylaxis Registry [11], a previous anaphylactic episode was found in about one third of current admissions for anaphylaxis. The utility of assessing tryptase and specific IgE is still a matter of debate [8], and these laboratory tests were seldom prescribed during the ED stay. Our rate of hospitalization was in agreement with the literature, between 36 and 54% [9, 15].

We have retrospectively classified anaphylaxis episodes according to the Ring and Messmer severity classification. Grade III cases (16.7% of our patients) presented well-known risk factors of severe anaphylaxis, such as asthma or allergy [3], more frequently than grade II cases. They also had higher blood tryptase levels and rate of hospitalization. Others have defined the anaphylaxis severity on the basis of anaphylaxis outcome [10, 14], estimating at 13% to 34.3% the part of severe anaphylaxis. Using this definition, severe anaphylaxis has been linked to drug allergy [10], or fewer administrations of epinephrine [14].

Current treatment recommendations for anaphylaxis highlight a prompt intramuscular epinephrine injection as the gold standard allowing to reduce morbidity, mortality, and hospitalization [16, 26]. However, the use of epinephrine is still insufficient in almost all pediatric studies. Prehospital administration of epinephrine varies in the literature from 36 to 62% [2, 6, 21, 28]. Anaphylaxis occurring at school and a one-organ system involvement would be favoring factors for use [21]. Our rate of ED administration of epinephrine is similar to

that described in other European pediatric EDs that has nevertheless doubled between 2011 and 2014 [11]. In USA, EDs' epinephrine prescription concerns about one admission among three for the first episode [24, 30], increasing to two admissions among three in case of recurrence [17]. In Asia, epinephrine is given in about 90% of the admissions for anaphylaxis [10, 14]. Such gaps between medical epinephrine prescriptions in EDs may reflect inclusion of different phenotypes of anaphylaxis and/or different prehospital management attitudes among countries.

Our results suggest that pediatricians had an intuitive approach of severity and reserved epinephrine for the most severe admitted children (grade III). This medical behavior ascertainment may be explained by the delay between the ED admission/management and the episode onset, and maybe also by a relative fear of the epinephrine side effects, even if its safety has been clearly demonstrated (21.6% of usually mild and transient side effects, such as tremors, palpitations, anxiety, more frequent among adults) [5]. Indeed, if anaphylaxis signs lowered or disappeared before ED admission, practitioners might have considered that the epinephrine administration was useless. The absence of hemodynamic or respiratory dysfunctions might also contribute to under-prescription as it has been previously shown on the management of a 2-year-old child with peanut-induced anaphylaxis where one in five interviewed pediatricians reported not using epinephrine because of this reason [18]. It also could explain why 15% of grade III anaphylaxis episodes had not received epinephrine in our study. Our data do not allow us to determine whether the behavior of our pediatricians induces more hospitalization, but a lack of epinephrine prescription in nearly half of the hospitalized patients is clearly amazing and questioning. Currently, to improve epinephrine prescription in EDs, the use of auto-injectors should be encouraged. Easy to use, they could also favor family education and encourage a too low medical prescription upon home discharge, as also found in other studies [24, 30]. However, auto-injectors have therefore some limitations such as a too high dose (0.15 mg) for the lightest children, especially < 7.5 kg [26]. In addition, auto-injectors with self-retracted needle should be clearly preferred in order to reduce the risk of lacerations and embedded needles [4]. Finally, better medical education on allergy is clearly required. Indeed, recent attendance of continuing medical education on food allergy induces significantly more epinephrine prescription [18].

## Conclusion

This study shows that epinephrine was underused in EDs face to children with anaphylaxis, but that its prescription was intuitively adapted to the clinical severity. Auto-injector devices



may enhance the epinephrine use in EDs, as well as family education.

**Author contributions** JCD, MSL, and GN conceived the study and designed the trial. JCD, JV, MSL, PM, AB, AC, and GV supervised data collection. GN provided statistical advice on study design and analyzed the data. JCD, MSL, and JV drafted the manuscript, and all authors contributed substantially to its revision. JCD takes responsibility for the paper as a whole.

### Compliance with ethical standards

This study was approved by the Ethics Committee of the French Society of Pediatrics (Société Française de Pédiatrie, No. 2016\_018\_2) and the National Commission of Informatics and Liberty (Commission Nationale Informatique et Libertés, No. 2016-16).

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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