

RESEARCH LETTER

The time course of anaphylaxis manifestations in children is diverse and unpredictable

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To the Editor,

The most current clinical definition of anaphylaxis is that proposed by Sampson et al, and different scoring systems have been proposed to assess its severity.^{1,2} Anaphylaxis symptoms range from mild, self-limiting local reactions to life-threatening anaphylaxis.

All anaphylaxis guidelines emphasize early recognition and the need for prompt intramuscular adrenaline injection as the first-line treatment.³ However, adrenaline for anaphylaxis is underused by patients, families and even by health professionals. In the European anaphylaxis registry, 27% of patients treated by a health professional received adrenaline.⁴ Given this low rate, spontaneous resolution of anaphylaxis symptoms may occur without adrenaline injection. There are few data on the course of anaphylaxis manifestations in children treated with adrenaline or not.

This study aimed to describe the time course of clinical manifestations in children experiencing anaphylaxis.

All children (≤ 15 years) admitted for anaphylaxis to one of 18 paediatric emergency care units in the Nord-Pas-de-Calais region of France were prospectively included (2015-2017). A standardized questionnaire was filled out using data collected from the family and the medical records. Patients were diagnosed with anaphylaxis if they fulfilled the criteria reported by Sampson et al.¹ All medical records were analysed and reviewed by three independent physicians including one anaphylaxis expert to confirm the diagnosis. The

5-grade Astier score was used to analyse anaphylaxis severity.^{2,5} (Figure S1).

We assessed the effect of baseline characteristics on the risk of progression (improvement vs worsening) of anaphylaxis severity by using Chi-square and Student's *t* tests. Association of Astier score with adrenaline use was investigated by Mann-Whitney *U* test. Statistical testing was conducted at the two-tailed α -level of 0.05. This study was approved by the French Data Protection Authority and the Advisory Committee for Information Processing in Health Research.

A total of 152 cases of anaphylaxis were identified, but three families refused the inclusion. The final sample consisted of 149 cases; each child had been admitted only once. Mean age at inclusion was 7.4 (4.7) years, and 87 (58%) were boys. Thirty-five (23%) children had a known food allergy to the trigger involved in the study case, and 17 (20%) a history of past anaphylaxis. An emergency kit had been prescribed for 35 children, including an adrenaline autoinjector (AAI) in 31.

The main anaphylaxis triggers were foods ($n = 110$; 74%, including peanut, $n = 32$; 21%). The other triggers were medication ($n = 13$; 9%) and hymenoptera venom ($n = 1$). Twenty-five (17%) reactions were considered as idiopathic. Cofactors were involved in 35 (23%) cases including viral infection ($n = 23$; 15%) and physical exercise ($n = 11$; 7%).

The emergency medical services (EMS) were called by the family in 63 (43%) cases, and 95 (63%) patients went directly to the emergency care unit. In all, 55 (37%) children received prehospital care by

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Pediatric Emergency Medicine Group details see Appendix.

	Place of first signs N = 149	Prehospital care N = 55	Emergency care unit N = 149
Skin/mucosal symptoms	147 (99)	44 (80)	129 (87)
Rash	107 (72)	31 (63)	97 (66)
Pruritus	75 (50)	16 (33)	67 (45)
Angiooedema	49 (33)	21 (43)	63 (43)
Oral syndrome	39 (26)	10 (20)	17 (12)
Rhinitis	35 (24)	9 (18)	22 (15)
Conjunctivitis	28 (19)	7 (14)	20 (14)
Respiratory symptoms	95 (64)	34 (62)	51 (34)
Difficulty breathing	84 (56)	23 (47)	36 (24)
Bronchospasm	0 (0)	9 (18)	26 (18)
Stridor	28 (19)	6 (12)	9 (6)
Gastrointestinal symptoms	71 (48)	11 (20)	39 (26)
Abdominal pain	53 (36)	11 (23)	30 (20)
Vomiting	45 (31)	4 (8)	16 (11)
Neurological and cardiovascular symptoms	21 (14)	2 (4)	9 (6)
Dizziness/fainting	20 (13)	2 (4)	6 (4)
Hypotension	0 (0)	0 (0)	4 (3)
Altered mental status	4 (3)	1 (2)	0 (0)
Astier severity score			
0	0	1 (2)	13 (9)
1	3 (2)	4 (7)	22 (15)
2	10 (7)	9 (16)	36 (24)
3	71 (48)	22 (40)	29 (19)
4	65 (44)	19 (35)	49 (33)
5	0		

Note: Values are expressed as numbers (percentage).

an emergency medicine physician of the EMS. The clinical manifestations and Astier scores at the place of first signs, during prehospital emergency care, and in the emergency care unit, are shown in Table 1.

In the emergency care unit, of the 149 children, the severity of the anaphylaxis reaction was scored as follows: grade 1 (2%), 2 (7%), 3 (48%); 4 (43%) (Table 1). Regardless of adrenaline use, the Astier score between the prehospital assessment and the admission to the emergency care unit evolved favourably in 76 (51%) cases, unfavourably in 23 (15%) cases and was stable in 50 (34%) cases (Table 2a).

Of 116 children with a grade 3 ($n = 61$) or 4 ($n = 55$) anaphylaxis who did not receive adrenaline before admission to the emergency care unit, the symptoms at admission to the emergency department have progressed favourably in 60 (52%) cases, worsened in 13 (11%) cases and were stable in 43 (37%) cases (Table 2b). Thirty (55%) of the 55 children with a grade 4 anaphylaxis at the place of first signs improved without adrenaline injection (Table 2b). Thirteen (21%) of the 61 children with a grade 3 anaphylaxis at the place of the first signs who did not receive adrenaline worsened.

TABLE 1 Time course of clinical anaphylaxis manifestations and Astier severity grades at the place of first signs, during prehospital emergency care, and in the emergency care unit in 149 children

Of the 20 children who received adrenaline before admission to the emergency care unit, the Astier score at admission to the emergency care unit evolved favourably in 15 cases, worsened in one case and was stable in four cases (Table 2a/b).

The median time between the onset of the allergic reaction and the call was 10 minutes [4 to 37.5], and the median time between onset of the first signs and the first medical intervention by EMS or in the paediatric emergency care unit was 20 minutes [11 to 58].

Three patients had a biphasic reaction and were given a further dose of intramuscular adrenaline. No child had to be admitted to intensive care unit, and no deaths occurred.

In the 129 children who did not receive adrenaline before their hospital admission, neither gender, age (mean and age groups), history of asthma, triggers (food, peanut, tree nuts), idiopathic form nor treatment with antihistamines before admission has been associated with changes in the Astier score (Table S1, see online supplementary).

Fifteen of the 149 (10%) children were given adrenaline by a family member, 4 (3%) by EMS and 52 (35%) in the emergency care unit, for a total of 71 (48%) children treated with adrenaline. At the place

TABLE 2 Time course of anaphylaxis severity assessed by the Astier severity score in 149 children at the place of first signs to emergency care unit: 2a. In the whole population (n = 149); 2b. In children not having received adrenaline before hospital admission (n = 129)

Astier score at the place of first signs	Total	Astier severity score at the emergency care unit				
		0	1	2	3	4
2 (a)						
1	3 (2)	0	0	0	2 (67)	1 (33)
2	10 (7)	0	1 (10)	3 (30)	0	6 (60)
3	71 (48)	4 (6)	12 (17)	22 (31)	19 (27)	14 (19)
4	65 (43)	9 (14)	9 (14)	11 (17)	8 (12)	28 (43)
2 (b)						
1	3 (2)	0	0	0	2 (67)	1 (33)
2	10 (8)	0	1 (10)	3 (30)	0	6 (60)
3	61 (47)	3 (5)	10 (16)	17 (28)	18 (30)	13 (21)
4	55 (43)	5 (9)	8 (15)	11 (20)	6 (11)	25 (45)

Note: Values are expressed as numbers (percentage).

of the first signs, an AAI was used in 15 of 31 (48%) children who had an emergency kit containing an AAI. In the emergency care unit, patients receiving adrenaline had higher Astier scores (4 [3to4] vs 3 [3 to 4], $P = .019$).

In this prospective paediatric study, we confirm that anaphylaxis is a dynamic phenomenon. We highlight a spontaneous rapid resolution of anaphylaxis symptoms, especially respiratory and gastrointestinal symptoms, without adrenaline injection in nearly half of the patients, with moderate reactions but also with more severe reactions. In contrast, we report that anaphylaxis severity rapidly worsened in 17% of them.

Little is known regarding clinical course of anaphylaxis manifestations and severity, especially without adrenaline injection. Spontaneous resolution of anaphylaxis symptoms is reported in real life by family and physicians who cannot or fear to inject adrenaline. Our data suggest that around half of the reactions resolve spontaneously and rapidly (less than one hour). This fact is also supported by the apparent discrepancy between the low rate of adrenaline used to treat the anaphylaxis reactions, even severe, and the low rate of life-threatening or fatal anaphylaxis reactions.

Our data do not identify features or factors associated with the pattern of progression, regardless of adrenaline injection. Severity of the reactions may vary, both between episodes within the same individual and between different individuals. There may be temporal differences in severity from one allergen exposure event to another, possibly due to many factors (patient's clinical status, dose or type of allergen, cofactors, etc). In our study, around a quarter of anaphylaxis reactions had a cofactor which is quite similar to that previously reported.⁶

Because the clinical course of anaphylaxis is unpredictable, prompt and early intramuscular adrenaline injection remains the first-line treatment in all guidelines.³ The need for prompt adrenaline injection to prevent escalation of mediator release in anaphylaxis has been confirmed in vitro.⁷ Studies to better understand the molecular mechanisms underlying anaphylaxis and the role of amplifying cofactors are required. An important message to healthcare professionals, patients and caregivers is to recognize anaphylaxis promptly

and, as soon as it is recognized, inject intramuscular adrenaline in order to maximize the likelihood of survival and more severe or protracted reaction.

A major strength of this study is that the data collection was prospective which allowed a detailed description of the time course of anaphylaxis manifestations and treatment. However, our study has also limitations. It may be that some patients were not included in the survey so that our data may not represent a complete accounting of all cases resulting in a relatively small sample size. The description of anaphylaxis symptoms at onset of first signs is that reported by the patient, his family and/or caregivers. This may also constitute a potential reporting bias resulting in under- or overestimation of anaphylaxis diagnosis and its severity. We used the Astier score designed for food allergic children, but we are aware that there are many other severity scoring systems and a wide range in the interpretation of the same allergic reaction using one score as compared to another.²

Our data highlight that anaphylaxis is a dynamic reaction with a heterogeneous clinical time course that cannot be predicted at onset of first signs. Anaphylaxis may resolve spontaneously and rapidly but also can progress to a more severe reaction as fast. Adrenaline remains the first-line anaphylaxis treatment required at the onset of first signs. Further studies are required to determine which patients' profile is at higher risk of the most severe allergic reactions. The development of a harmonized scoring system for acute allergic reactions promoted by the European Academy of Allergy and Clinical Immunology will be an opportunity to address this issue.⁸

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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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.

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APPENDIX

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Table S1. Time course of anaphylaxis severity (Astier score) at the place of first signs to emergency care unit admission and comparisons with regards to gender, mean age, age groups, history of asthma and triggers in the 129 children who did not receive adrenaline before hospital (n=129).

		Time course of the Astier severity score at the place of first signs to emergency care unit			P value for comparison I vs W
Factors	Total	Improvement 61 (47)	Stability 46 (36)	Worsening 22 (17)	
Male	80 (62)	36 (59)	31 (67)	13 (59)	1.0
Age, years, mean (SD)	7.3 (4.8)	6.6 (4.9)	8.2 (4.4)	6.9 (4.7)	0.80
Age groups					0.97
Infants (< 2 y)	20 (15)	12 (20)	4 (9)	4 (18)	
Preschoolers (2-5y)	37 (29)	18 (30)	13 (28)	6 (27)	
School-age children (6-11y)	45 (35)	20 (33)	18 (39)	7 (32)	
Adolescents (12-18y)	27 (21)	11 (18)	11 (24)	5 (23)	
History of asthma	47 (36)	22 (36)	17 (37)	8 (36)	0.98
Allergen					
Food anaphylaxis	93 (72)	46 (75)	31 (67)	16 (73)	0.80
Peanut	26 (20)	12 (20)	8 (17)	6 (27)	0.55
Tree nuts	29 (22)	15 (25)	9 (20)	5 (23)	0.86
Idiopathic	19 (15)	8 (13)	9 (20)	2 (9)	1.0
Antihistamines before admission	49 (38)	29 (48)	14 (30)	6 (27)	0.10

Astier stage I: improved;W: worsened.

Values are expressed as numbers (percentage) unless otherwise as indicated.

Figure S1. Anaphylaxis scores according to Astier et al. [5]

Symptom score	Symptoms
0	No symptom
1	Abdominal pain that resolved without medical treatment, rhinoconjunctivitis or urticaria < 10 paplers, rash
2	One organ involved: abdominal pain requiring treatment, generalized urticaria, non laryngeal angioedema, mild asthma (cough, fall of peak expiratory < 20%)
3	Two organs involved (of symptoms mentioned under 2)
4	Three organs involved (of symptoms mentioned under 2) or asthma requiring treatment or laryngeal edema, or hypotension
5	Cardiac and respiratory symptoms requiring hospitalization in the intensive care unit