Risk Factors for Severe Anaphylaxis in Children

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Objective To identify risk factors associated with severe anaphylaxis in children.

Study design We carried out a multicenter prospective observational study including children less than 18 years old diagnosed with anaphylaxis in 7 Spanish pediatric emergency departments (EDs) between May 2016 and April 2018. Children were considered to have severe anaphylaxis if they met one or more of the following criteria: requirement for 2 or more doses of epinephrine, clinically important biphasic reaction, endotracheal intubation, intensive care unit admission, and/or death.

Results We included 453 episodes of anaphylaxis. Of these, 61 were classified as severe anaphylaxis (13.5%, 95% CI [10.6-16.9]): 53 (11.7%) required more than 1 dose of epinephrine, and there were 14 (3.1%) cases of clinically important biphasic reactions, 2 (0.4%) intubations in the ED, and 6 (1.3%) admissions to the intensive care unit. No patients died. In the multivariable regression, we identified 5 independent risk factors for severe anaphylaxis: history of asthma (P = .002; OR 2.705, 95% CI [1.431-5.113]), onset of the symptoms less than 5 minutes after the allergen exposure (P = .002; OR 2.619, 95% CI [1.410-4.866]), non-well appearance (P = .005; OR 2.973, 95% CI [1.380-6.405]), tachycardia (P = .014; OR 2.339, 95% CI [1.191-4.959]), and hypotension (P = .036; OR 3.725, 95% CI [1.087-12.762]).

Conclusions Childhood anaphylaxis is usually well controlled in the ED. Children with a history of asthma, rapid onset of the symptoms, who are non-well appearing, or have tachycardia or hypotension upon arrival to the ED are more likely to have severe episodes. *(J Pediatr 2020;225:193-7)*.

Anaphylaxis is an acute, potentially life-threatening syndrome and may involve airway, breathing, or circulation problems.[1,2] Nevertheless, anaphylaxis in children is not usually fatal and some cases resolve spontaneously because of the endogenous production of vasoconstrictors.[3] Clinical biomarkers are needed to recognize patients at risk of more severe outcomes and even death and to distinguish them from the majority of patients with mild-to-moderate reactions who can safely be discharged home.[4] Asthma has been related to fatal anaphylaxis, especially in adults,[5] although this is controversial.[6] As many as one-half of food-allergic children have asthma, but only a few will have a fatal food-induced anaphylactic reaction.[7,8] Cardiovascular involvement has also been associated with worse outcome and admission to an intensive care unit (ICU) in children.[9-11]

Nevertheless, most of the research carried out on pediatric anaphylaxis, and specifically severe anaphylaxis, is based on retrospective series or cases recruited during follow-up with an allergist. Many children attended to in the emergency department (ED) for anaphylaxis will not have adequate follow-up.[12] Therefore, studies including patients recruited during follow-up may not be fully representative of all the patients seen in the ED.

Our hypothesis was that certain factors identified upon arrival to the ED would be related to severe anaphylaxis in children. Therefore, we aimed to identify risk factors associated with children presenting to the ED with severe anaphylaxis.

Methods

We conducted a prospective multicenter study in 7 Spanish pediatric EDs between May 2016 and April 2018 endorsed by the Spanish Society of Pediatric Emergencies. We included all children diagnosed with anaphylaxis at the ED. Depending on the local policy at each hospital, 3 EDs included children up to age 14 years old and 4 up to 18 years old.

ED	Emergency department
ICU	Intensive care unit
PAT	Pediatric Assessment Triangle

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Definitions

Anaphylaxis. Children were diagnosed with anaphylaxis according to National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network Criteria for Emergency Department Diagnosis of Anaphylaxis[1] or based on an atypical presentation of anaphylaxis at the discretion of the physician.

Clinically Important Biphasic Reaction. We included children with recurrent or new signs or symptoms occurring after an initial allergy-related presentation, which satisfied the definition for anaphylaxis, with no obvious further exposure to an offending allergen.[13] Time delay between the initial reaction and onset of symptoms was identified and less than 5 minutes was considered by researchers' consensus as rapid onset of symptoms.

Severe Anaphylaxis. Anaphylaxis was considered to be severe when children met 1 or more of the following criteria: required 2 or more doses of epinephrine, clinically important biphasic reaction, endotracheal intubation, admission to ICU, and/or death.

Abnormal Appearance. We evaluated appearance within the Pediatric Assessment Triangle (PAT). The PAT is an assessment tool that facilitates immediate physiologic evaluation using only visual and auditory clues.[14] According to the PAT, the physical characteristics to be considered when evaluating the appearance of a child are tone, interactiveness, consolability, gaze, and speech/cry.

Altered Vital Signs. We used the age-specific cut points presented in **Table I** (available at www.jpeds.com).[15]

Exclusion Criteria

An exclusion criterion was the lack of informed consent.

Data Collection

All patients diagnosed with anaphylaxis had specific electronic questionnaires completed via Google Drive by the physicians in charge of their care (**Table II**; available at www.jpeds.com). Questionnaires were initially distributed to all participating EDs seeking to ensure the clarity of the methods and to enhance the quality of the data collected. The questionnaires were then completed by the physician after ED discharge for patients discharged home and after hospital discharge for patients admitted to the hospital. The completed questionnaires were then sent to the principal investigator. Patients were identified by ED physicians with the following data collected via interviews of patients and caregivers: patient age, sex, medical history, time of ED presentation, triggers, clinical symptoms and signs, pre-hospital management (and, specifically, epinephrine administration), ED management, disposition on discharge, and outcome.

Statistical Analyses

Descriptive statistics were reported as absolute frequencies or percentages for categorical variables and as medians and IQR for continuous variables. Multivariable logistic regression analysis was performed to identify the independent risk factors for severe anaphylaxis. A univariate logistic regression analysis was carried out initially, including demographic data, medical history, suspected allergen, clinical presentation, and condition on arrival to the ED. All variables with P value of $<.1$ were subsequently included in a nonautomatic multivariable logistic regression stepwise model. The results of the model are presented as OR and 95% CI. The area under the receiver operating characteristic curve was calculated for the final model. All statistical analyses were carried out using the IBM SPSS Statistics for Windows, version 23.0 (IBM, Armonk, New York).

Ethical Considerations

The Clinical Research Ethics Committee of the Basque Country, and the institutional review boards of each participating institution, approved the study. Written patient informed consent was obtained from parents or guardians, and informed assent was obtained from children age 7 years or older.

Results

During the study period, we registered 707 431 pediatric ED presentations to the 7 EDs, of which 565 were for children diagnosed with anaphylaxis (0.79 cases/1000 ED visits) and 453 (80.2%) were included in the study (**Figure**; available at http://www.jpeds.com). Distribution of the recruitment in the participating centers is shown in **Table III** (available at http://www.jpeds.com).

The characteristics of patients diagnosed with anaphylaxis are shown in **Table IV**. Nine patients (2%) were included based on an atypical presentation of anaphylaxis at the discretion of the physician.

Overall 428 (94.5%; 95% CI 91.6-96.3) children received epinephrine. Of those, 87 (19.2%; 95% CI 15.8-23.1) received epinephrine in a prehospital setting, 315 (69.5%; 95% CI 65.2-73.6) upon the arrival to the ED, and 26 (5.7%; 95% CI 3.9-8.3) in both prehospital setting and ED.

Sixty-one patients had severe anaphylaxis (13.5%; 95% CI 10.6-16.9) (**Table V**). All the children with a clinically important biphasic reaction required at least 1 additional dose of epinephrine. History of asthma, onset of symptoms in the first 5 minutes after exposure, and abnormal appearance, hypotension, or tachycardia upon arrival were independent risk factors for greater severity (**Table VI**). This model showed an area under the receiver operating characteristics curve of 0.73; 95% CI 0.66-0.80. Patients requiring more than 1 dose of epinephrine were more likely to receive intravenous fluids (OR 6.20; 95% CI 3.31-11.61). Of this cohort, 143 patients (31.6%) had none of these risk factors, 178 (39.3%) had 1 risk factor, 105

Table IV. Characteristics of patients diagnosed with anaphylaxis

Variables	n	% (95% CI)
Sex (male)	288	63.6 (59.1-67.9)
Median age (IQR), y	5 (2-9)	
Previous episode of anaphylaxis	143	31.6 (27.5-36)
Known allergies	200	44.2 (39.7-48.8)
History of asthma	173	38.2% (33.8-42.8)
Triggers		
Food	396	87.4 (84 -90.2)
Milk	124	27.4 (23.5-31.7)
Nuts	119	26.3 (22.4-30.5)
Egg	63	13.9 (11-17.4)
Fruit	41	9.1 (6.7-12.1)
Fish	39	8.6 (6.3-12.7)
Other food	48	10.6 (8.1-13.8)
Drugs	24	5.3 (3.6-7-8)
Insect sting	1	0.2 (0-1.4)
Others	7	1.5 (0.7 -3.2)
No trigger identified	25	5.5 (3.7-8.1)
Median time elapsed between contact with the trigger and onset of symptoms (IQR), min	15 (5-45)	
Onset of symptoms less than 5 min after the allergen exposure	143	31.2 (27.4-36)
Abnormal appearance upon arrival to the ED	56	12.4 (9.6-15-7)
Hypotension	17	3.8 (2.3-6)
Tachycardia	86	19 (15.6-22.9)

More than 1 trigger per patient can be identified. Data are expressed as n (%) and 95% CI except for age (median) and time elapsed between contact with the trigger and onset of symptoms (median). More than 1 trigger was suspected in 1 patient.

(23.2%) had 2, 22 (4.9%) had 3, 4 (0.9%) had 4, and 1 (0.2%) had 5 risk factors. The risk for severe anaphylaxis increased with the number of risk factors (Table VII).

Discussion

The risk for having a severe episode may be related to certain clinical factors. Specifically, children with a history of asthma, with a rapid onset of symptoms, and who were non-well appearing or had tachycardia or hypotension upon arrival to the ED were found to be more likely to have severe episodes. In addition, the risk is higher in children with more than 1 risk factor.

In previous studies, the rate of severe anaphylaxis showed great variability, ranging from 1% to 31%,[2,4,16] related to the way episodes were classified as severe. We decided to use broad criteria including the requirement of more than 1 dose of epinephrine and clinically important biphasic reaction. When managing a child with anaphylaxis, it is desirable to identify children not only with fatal or near fatal reactions but also those requiring interventions in the following hours

Table V. Criteria defined as severe anaphylaxis

Criteria for severe anaphylaxis	n	% (95% CI)
Required more than dose of epinephrine	53	11.7 (9-15)
Clinically important biphasic reaction	14	3.1 (1.8-5.2)
Endotracheal intubation at the ED	2	0.4 (0-1.7)
Admitted to the ICU	6	1.3 (0.5-2.9)
Death	0	

One patient may meet more than 1 criterion.

Table VI. Univariate and multivariate analyses to identify the risk factors for severity in children diagnosed with anaphylaxis

	Univariate analysis		Multivariate analysis	
Variables	*P* value	OR (95% CI)	*P* value	OR (95% CI)
History of anaphylaxis	.096	1.60 (0.92-2.78)		
History of biphasic reactions	.001	17.59 (3.33-92.88)		
Suspected allergen: Milk	.026	1.89 (1.08-3.32)		
History of asthma	.003	2.28 (1.32-3.94)	**.002**	**2.70 (1.43-5.11)**
Onset of symptoms less than <5 min after exposure	.001	2.67 (1.52-4.69)	**.002**	**2.61 (1.41-4.86)**
PAT: abnormal appearance	.003	2.79 (1.43-5.43)	**.005**	**2.97 (1.38-6.40)**
PAT: abnormal circulation	.009	2.87 (1.30-6.34)		
Hypotension	.010	3.88 (1.37-10.96)	**.036**	**3.72 (1.08-12.76)**
Tachycardia	.006	2.33 (1.28-4.24)	**.014**	**2.33 (1.19-4.95)**
Flushing	.040	1.76 (1.02-3.04)		
Dizziness	<.001	5.76 (2.17-15.25)		

Independent risk factors for greater severity appear in bold.

and not suitable for outpatient management. In our sample, patients requiring more than 1 dose of epinephrine were more likely to receive intravenous fluids. In addition, all the children with a clinically important biphasic reaction required at least another dose of epinephrine. The reported incidence of biphasic reactions varies from 0.18% to 23%,[13,17-22] attributable to a wide variety of definitions used for anaphylaxis and biphasic reactions. Nevertheless, the majority of studies have found that recurrent symptoms are usually less severe than the initial symptoms,[18-21] urticaria often being the only finding.[22]

A history of asthma has been strongly associated with fatal anaphylaxis, especially in food anaphylaxis.[5,23] Nonetheless, some authors have suggested that the utility of asthma as a predictor for fatal reactions is poor[24] based on the high prevalence of childhood asthma and that the vast majority of children with asthma will never have a fatal reaction (probably not even one anaphylaxis). Although controversial, our study underscores the importance of managing children with anaphylaxis and a concurrent diagnosis of asthma more cautiously. In addition, it seems reasonable to encourage

Table VII. Number of risk factors and rate of severe anaphylaxis

Variables	n	Severe anaphylaxis	% (95% CI)
Risk factors			
0	143	7	4.9 (2.2-9.9)
1	178	21	11.8 (7.8-17.4)
2	105	20	19.1 (12.6-27.7)
3	22	8	36.4 (19.6-57.1)
4	4	4	100
5	1	1	100
Total	453	61	13.5 (10.6-16.9)

Risk factors: history of asthma, onset of symptoms in the first 5 minutes after exposure, and abnormal appearance, hypotension, or tachycardia upon arrival.

strategies for controlling asthma, even if there is no evidence of the reduction of the risk of fatal anaphylaxis when symptoms are well controlled.[25]

In our study, severe anaphylaxis was also related to a rapid onset of symptoms after exposure. This may be at least partially explained by early mast cell degranulation and higher peak concentrations of inflammatory-response mediators being associated with the severity of the allergic reaction.[16]

An abnormal ("non-well") appearance upon arrival to the ED was also an independent risk factor for severe anaphylaxis. This highlights the importance of the initial evaluation when the child arrives to the ED. Both hypotension and tachycardia upon arrival were also independent risk factors for severe anaphylaxis. Cardiovascular system involvement has been related to an elevated risk of hospital admission, including ICU admission and death.[10,26] Although isolated hypotension is a rare presentation for anaphylaxis,[10] we recommend that blood pressure be measured in every child with suspected anaphylaxis.

The triggering allergen was not related to higher or lower risk for severe anaphylaxis. We did not find any relationship between the severity of the anaphylaxis and the triggering allergen, not even in the case of peanuts, cows' milk, or seafood. Cardiac disease, classically associated with severe anaphylaxis in adults,[4] was not related to severe anaphylaxis. This may be explained by the fact that cardiac diseases in childhood are substantially different from those in adults.

Our study has certain limitations. The definition of severe anaphylaxis is controversial. Some authors have focused on the outcome of the children (hospitalization, ICU admission, death, etc).[4] We decided to also include patients requiring more than 1 dose of epinephrine, regardless of whether they were admitted to hospital. Nevertheless, we believe that this increases the chances of including all children with severe anaphylaxis and does not bias the main results obtained. On the other hand, we are not able to analyze the time elapsed until epinephrine administration, as the time when prehospital epinephrine was administered was not recorded. Similarly, we did not collect data on the control of symptoms in patients with a history of asthma, and hence, we are unable to analyze the influence of asthma control on the severity of anaphylaxis. Further, although this was a multicenter study, it is possible that there are different food triggers in other environments that might alter the results of the analysis. Nevertheless, we have not identified any food triggers omitted in our study related to severe anaphylaxis. Thus, we believe that our results should be similar to those that would be obtained in other Western countries. However, the lower rate of pre-hospital epinephrine of our study[11] may affect the extrapolation of our results to other populations. Finally, we failed to recruit approximately 20% of cases because of the attending physician failing to invite patients and their families/guardians to participate in the study. We sought to include patients 24 hours a day, but we were not able to ensure the continuous presence of a research coordinator to remind physicians about the study.

This large multicenter prospective study on childhood ED anaphylaxis presentation may be helpful in identifying children upon the arrival to the ED more likely to have severe episodes. This may include children with a history of asthma, with a rapid onset of symptoms, and who are non-well appearing or have tachycardia or hypotension upon arrival to the ED. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *The Journal of Pediatrics*

Suicide among Adolescents with Chronic Illness: A Path Forward

Weinberg S. Suicidal Intent in Adolescence: A Hypothesis about the Role of Physical Illness. J Pediatr 1970:77:579-86.

Similar to 1970, suicides continue to be a major cause of death among adolescents with chronic illness. Weinberg describes 12 adolescents who had expressed suicide intent while hospitalized for a medical condition or were admitted after attempting suicide. Chronic illness was a significant contributing factor, and the authors felt that the suicide intent was due to concerns about impact of illness on their lives. These included factors such as the inability to obtain a job in the future and the pain of separation from an important person. Some adolescents viewed illness as an obstacle to success, blaming themselves for difficulty in underachieving, whereas in others, suicidal intent was linked to family discord. Weinberg described sex-related differences in these concerns.

Fifty years later, suicide continues to be a leading cause of death in adolescents, with significant sex differences. Although adolescent suicide attempts are twice as high in females, completed suicides are 3 times higher in males than in females.[1] Suicide intent and attempts continue to be common among adolescents with chronic illness. However, depression and mood disorders are now known to be significant and modifiable risk factors for all sexes.[2] Given the path from chronic illness to depression and mood disorders to suicide, pediatricians and pediatric subspecialists have instituted screening for depression, anxiety, and suicidal risk with tools such as the Patient Health Questionnaire-9 for depression and the Global Assessment of Disability-7 for anxiety. Unfortunately, connection to mental health services remains a challenge for all adolescents.[1] Many pediatric subspecialty groups now employ social workers and counselors in their subspecialty clinics to immediately connect adolescents with chronic illness with suspected co-occurring depression and mood disorders to needed assessments and services. Appropriate screening and provision of mental health resources to adolescents with chronic illness provide a much needed mechanism to reduce the number of attempted and completed suicides.

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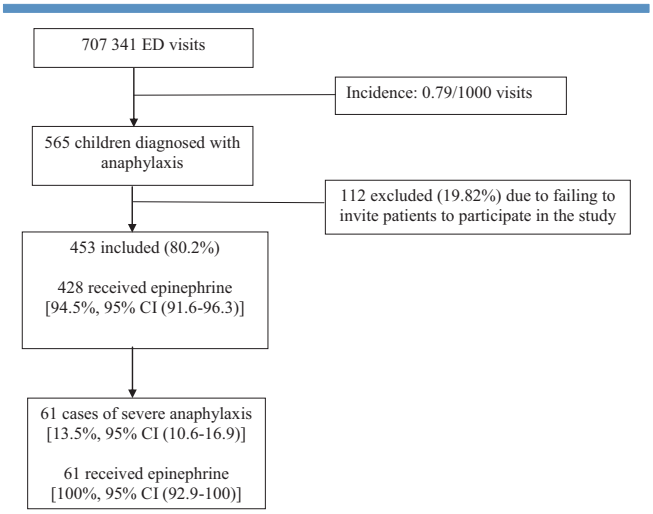

Figure. Flow of the patients through the study.

Table I. Age specific vital signs

Age	Heart rate (bpm)	Respiratory rate (bpm)	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)
0-7 d	100-160	<60	>60	>30
8-30 d	100-160	<60	>65	>30
31 d -<2 y	90-160	<50	>70	>35
2-<6 y	<140	<30	>75	>40
6-<13 y	<130	<24	>85	>45
>13 y	<110	<20	>90	>50

From Balamuth F, Fitzgerald J, Weiss SL. Shock. In Sahw KN, Bachur RG. Fleisher & Ludwig's Textbook of Pediatric Emergency Medicine. 7th edition. Philadelphia Lippincott Williams & Wilkins; 2016. p. 55-67.

Table II. Specific electronic questionnaire for patients diagnosed with anaphylaxis

1

Where multiple options are given, tick the corresponding box (circle) and, if asked, also tick a more specific response (square)

DEMOGRAPHIC DATA

1. Initials: ___ / ___ / ___

2. Sex: O F O M **3.** Date of birth: _ _ / _ _ / _ _ _ _

MEDICAL HISTORY

5. Asthma
- O Yes
- O No

6. History of anaphylaxis:
- O Yes
- O No

Number of episodes: _____

7. Heart disease
- O Yes
- O No

Specify: _____

8. History of biphasic reactions (recurrence of anaphylactic symptoms after initial remission):
- O Yes
- O No

Number of episodes:_____

9. Previous delayed use of epinephrine autoinjector:
- O Yes
- O No

EVENT FEATURES

10. Place of event onset:
- O School
- O Home
- O Street
- O Hospital
- O Other

11. Date/time of contact with allergen:
_ _ /_ _ /_ _ _ _ _ _ _ _

12. Date/time of event onset:
_ _ / _ _ / _ _ _ _ _ _ _ _

13. Allergy is previously known:
- O Yes
- O No

14. Previous prescription of epinephrine autoinjectors:
- O Yes
- O No

15. If there is a known allergen, did caregivers at the time know of the allergy?
- O Yes
- O No
- O Not known

16. Suspected allergen:

- O Aeroallergen:
  - ☐ House dust mite
  - ☐ Pollen
  - ☐ Other: _____
- O Animals:
  - ☐ Dog
  - ☐ Cat
  - ☐ Rodent
  - ☐ Others: _____
- O Food:
  - ☐ Nuts
  - ☐ Milk
  - ☐ Egg
  - ☐ Legumes
  - ☐ Fish
  - ☐ Meat
  - ☐ Fruit
  - ☐ Other: _____
- O Drugs:
  - ☐ Antibiotics
  - ☐ Analgesics
  - ☐ Immunotherapy
  - ☐ Other: _____
- O Insects:
  - ☐ Hymenoptera
  - ☐ Diptera
  - ☐ Arachnids
  - ☐ Other: _____

(continued)

PREHOSPITAL MANAGEMENT

17. Medication before transfer to hospital:
- ○ Epinephrine
- ○ Corticosteroids
- ○ Antihistamines
- ○ Bronchodilators
- ○ Other: _____

18. Person who administered epinephrine (only whenadministered before transfer):
- ○ Patient
- ○ Parents
- ○ Other relatives
- ○ Teachers
- ○ Doctor
- ○ Other: _____

19. Epinephrine autoinjector was available at the onset of the event:
- ○ Yes
- ○ No
- ○ Unknown

20. Place where the transfer to the hospital begins:
- ○ Home
- ○ School
- ○ Street
- ○ Primary care center
- ○ Other hospital
- ○ Not known

21. Mode of transportation:
- ○ On foot
- ○ Family vehicle
- ○ Public transport
- ○ BLS ambulance
- ○ ALS ambulance
- ○ Other: _____

22. If medical transport, which interventions were performed:
- ○ Epinephrine
- ○ Corticosteroids
- ○ Antihistamines
- ○ Bronchodilators
- ○ Supplementary oxygen
- ○ Intubation
- ○ IV access
- ○ IV fluids
- ○ Other:_____

HOSPITAL MANAGEMENT

23. Arrival time: _ _ _ _

24. Vital signs on arrival:
- ○ HR (bpm):
- ○ BP (mmHg):
- ○ RR(bpm):
- ○ SpO2:

25. PATon arrival (indicate the affected side):
- ○ Normal
- ○ Appearance
- ○ Circulation
- ○ Breathing

26. Initial stabilization:
- ○ Monitoring
- ○ Supplementary oxygen
- ○ Orotracheal intubation
- ○ IV access

Position of the patient:
- ○ Supine
- ○ Prone
- ○ Lateral
- ○ Trendelenburg

27. Diagnosis: Indicate the diagnostic criterion which established the diagnosis of anaphylaxis:
- ○ CRITERION 1: sudden onset of skin + respiratory symptoms or skin symptoms + hypotension
- ○ CRITERION 2: rapid onset of at least two of the following after exposure to a potential allergen: skin and/or mucous membrane involvement, respiratory compromise, decreased BP or associated symptoms, persistent gastrointestinal symptoms (abdominal pain, colic, vomiting)
- ○ CRITERION 3: decreased BP after exposure to a known allergen
- ○ ATYPICAL PRESENTATION (justify): _____

28. Measurement of tryptase: ○Yes ○No

29. Symptoms (in all cases):

○ Skin:
- ☐ Angioedema
- ☐ Urticaria
- ☐ Pruritus
- ☐ Erythema
- ☐ Other:_____

○ Breathing:
- ☐ Dyspnea
- ☐ Wheezing
- ☐ Cough
- ☐ Dysphonia
- ☐ Chest tightness
- ☐ Respiratory arrest
- ☐ Other:_____

○ GI:
- ☐ Vomiting
- ☐ Nausea
- ☐ Abdominal pain
- ☐ Diarrhea
- ☐ Other:_____

○ Cardiovascular
- ☐ Recorded hypotension
- ☐ Dizziness
- ☐ Syncope
- ☐ Decreased level of consciousness
- ☐ Cardiac arrest
- ☐ Other:_____

(continued)

3

Epinephrine administration in the ED:

30. Time of administration:
_ _ _ _
31. Dose (mg/kg):_____
32. Route of administration:
- ○ IM
- ○ IV
- ○ SC
- ○ IO
- ○ Nebulized
- ○ Other:_____

33. Site of administration:
- ○ Anterolateral thigh
- ○ Other site on the thigh
- ○ Upper arm
- ○ Abdomen
- ○ Chest
- ○ Other:_____

34. Number of doses required:_____
35. Side effects:_____

36. If a second dose is required, route of administration:
- ○ IM
- ○ IV
- ○ SC
- ○ IO
- ○ Other:_____

37. Anaphylaxis is controlled:
- ○ Yes
- ○ No

38. Other actions:
- ○ Corticosteroids
- ○ Antihistamines
- ○ Bronchodilators
- ○ IV fluids
- ○ Other:_____

Stay in the ED:

39. Observation time (hours):_____
40. Biphasic reaction that meets anaphylaxis criteria:
- ○ Yes
- ○ No

41. Number of required epinephrine dosesfor biphasic reaction control:
_____

42. Route of administration:
- ○ IM
- ○ IV
- ○ SC
- ○ IO
- ○ Other

43. Other interventions for biphasic reaction control:
- ○ Corticosteroids
- ○ Antihistamines
- ○ Bronchodilators
- ○ IV fluids

44. Period of time from primary anaphylaxis control to the onset of the biphasic reaction (hours):
_____

45. The biphasic reaction is controlled:
- ○ Yes
- ○ No

46. Disposition:
- ○ ICU
- ○ Hospital ward
- ○ Outpatient
- ○ Dead

Home discharge from ED:

47. Epinephrine autoinjectors are prescribed:
- ○ Yes
- ○ No

48. Number of autoinjectors prescribed: _____

49. Instructions on the use of autoinjectors are given:
- ○ Yes
- ○ No

50. The patient demonstrates how to use the autoinjector:
- ○ Yes
- ○ No

51. The patient is referred to an allergy specialist:
- ○ Yes
- ○ No

4

NOTES (Write down everything that is considered relevant and is not reflected in the questionnaire):

Table III. Distribution of the recruitment across the participating centers

Centers	ED episodes	Number of anaphylaxis	Number of anaphylaxis recruited	Incidence /1.000	Recruitment rate
1	111 175	115	88	1.03	76.5%
2	80 915	61	57	0.75	93.4%
3	188 585	79	62	0.41	78.5%
4	111 362	104	71	0.93	68.3%
5	115 078	120	101	1.04	84.2%
6	45 466	44	43	0.96	97.7%
7	54 760	42	31	0.76	73.8%