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When is epinephrine prescribed for anaphylaxis?



Anaphylaxis represents a severe allergic reaction that is rapid in onset and can be fatal.¹ Epinephrine is the first-choice medication in the treatment of anaphylaxis in both the community and hospital settings.² Nonetheless, epinephrine is largely underused.³ The purpose of this study was to examine the reasons that currently motivate professionals to treat anaphylaxis with epinephrine in the emergency department (ED) and the prescription of an epinephrine autoinjector (EAI) for outpatient use after the allergy workup.

We performed a retrospective, observational study of patients seen at the pediatric and general ED and subsequently studied in the allergy department (AD) of Hospital General Universitario Gregorio Marañón, Madrid, Spain, with clinical symptoms of anaphylaxis. The clinical records were reviewed by allergy specialists. Data were collected and classified as previously described.^{4,5} Anaphylaxis was defined as fulfilment of the clinical criteria established by the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network.¹ Anaphylactic reactions were classified according to severity, following the criteria by Brown et al.⁶ Categorical variables were compared using the χ^2 test, and quantitative variables were compared using the Mann-Whitney test. Multivariate logistic regression was used to determine adjusted odds ratios (ORs). $P < .05$ was considered statistically significant. This study was approved by the Ethics Committee for Medical Research of Hospital General Universitario Gregorio Marañón.

The study included a cohort of 249 patients, 133 children and 116 adults; 52.6% were female and 47.4% were male. Median age was 11 years (interquartile range [IQR], 0–40 years), and 46.6% had a history of atopy. The pediatric group consisted of 59 boys and 74 girls, with median age of 4.3 years (IQR, 2.1–8.8 years). The ED pediatricians diagnosed anaphylaxis in 52.6% of the patients, and 9 (6.8%) presented with objective signs of severe anaphylaxis. The adult group was composed of 59 men and 57 women, with a median age of 42.7 years (IQR, 29.8–54.3 years). Diagnosis of anaphylaxis had been given to 44% by the ED physician, and 29 (25%) presented with objective signs of severe anaphylaxis. Only 41.8% of the patients (43.6% of children and 39.7% of adults) received epinephrine as treatment of anaphylaxis in the ED. In univariate analysis, epinephrine was more frequently administered to patients who had been diagnosed with anaphylaxis (Table 1).

After the acute reaction, 178 patients (88.7% of the children and 51.7% of the adults) were subsequently studied in the AD. The group included 99 females and 79 males, with a median age of 5 years (IQR, 0–33.7 years). No statistically significant differences were found between patients who came to the AD and those seen in the ED with respect to sex ($P = .54$), age ($P = .08$), atopy ($P = .13$), severity of anaphylaxis ($P = .89$), diagnosis of anaphylaxis in the ED ($P = .69$), or treatment with epinephrine of the acute episode ($P = .98$). The pediatric group studied in the AD consisted of 50 boys and 68 girls, with a median age of 4.1 years (IQR, 1.8–8.5 years). The adult group was composed of 29 men and 31 women, with a median age of 49.8 years (IQR, 31.4–65.2 years). The allergy workup confirmed the most frequent triggers of anaphylaxis were food allergy in children (89.8%) and drug allergy in adults (41.7%).

After the etiologic study, 82 patients (28.3% of the adults and 55.1% of the children) were prescribed self-injectable epinephrine. In univariate analysis, EAI were more commonly prescribed to children and patients with food allergy and less frequently to patients with drug allergy (Table 1). In multivariate analysis, epinephrine injection was strongly associated with having been correctly diagnosed with anaphylaxis by the ED physicians (OR, 32.9; 95% CI, 15.3–70.8), independent of age group, sex, history of atopy, the suspected trigger, or, more remarkably, the severity of anaphylaxis (Table 1).

Receiving an EAI device at the AD was mainly associated with having food-induced anaphylaxis (OR, 15.2; 95% CI, 2.5–91.1), independent of anaphylaxis, management at the ED, age group, sex, or history of atopy (Table 1).

Intramuscular epinephrine is the first-line treatment of anaphylaxis.⁷ Despite this, previous studies have demonstrated that epinephrine is systematically underused.³ In this study, we were able to gain insights into the reasons behind the use of epinephrine for the management of anaphylaxis. A large sample size, including patients of all ages, was reached following the most commonly accepted diagnostic criteria for anaphylaxis. A novel approach was focusing on not only the ED but also the use of EAI by allergists, which has been considered less frequently.

In our study, epinephrine was administered to 41.8% of the patients during their stay in the ED. Chances of receiving an epinephrine injection during the acute reaction increased when anaphylaxis was recognized by the ED physicians, independent of the severity. This finding reaffirms the importance of having physicians call anaphylaxis by its name.

The EAI is the preferred method to administer epinephrine in the extrahospital setting.⁸ It should be prescribed to those patients

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Table 1

Potential Risk Factors for Administration of Epinephrine in the ED and Prescription of EAI in the AD, Including Adjusted Effect Estimates for Associations With the Administration of Epinephrine in the ED and the Prescription of EAI in the AD

Risk factor	Epinephrine in the ED (n = 249)		EAI in the AD (n = 178)	
	Yes/no	aOR (95% CI)	Yes/no	aOR (95% CI)
Age group		1.3 (0.6–3.1)		1.2 (0.3–4.1)
Children	58/75		65/53 ^a	
Adults	46/70		17/39 ^a	
Sex		1.2 (0.6–2.4)		1.3 (0.6–2.7)
Male	49/69		32/45	
Female	55/76		50/47	
History of atopy	51/65	0.7 (0.3–1.6)	48/47	0.8 (0.4–1.9)
Diagnosis of	92/29 ^a	32.9 (15.3–70.9) ^a	47/42	1 (0.4–2.6)
anaphylaxis in the ED				
Severity of anaphylaxis	21/17	1 (0.4–2.7)	11/17	1.1 (0.3–3.7)
Trigger suspected in the		0.6 (0.3–1.2)	NA	NA
ED				
Food allergy	38/70			
Drug allergy	21/19			
Unknown	44/49			
Other	1/7			
Epinephrine in the ED	104/145	NA	40/33	1.7 (0.6–4.5)
Trigger of anaphylaxis	NA	NA		15.2 (2.5–91.1) ^a
Food allergy			68/52 ^a	
Drug allergy			2/22 ^a	
Idiopathic			6/10	
Other			6/12	

Abbreviations: AD, allergy department; aOR, adjusted odds ratio; EAI, epinephrine autoinjector; ED, emergency department; NA, not applicable.

^aP < .05.

with a history of anaphylaxis with a high probability of recurrence.⁷ In this study, EAI was prescribed to 47.1% of these same patients after the allergy workup. Previous studies reported prescription rates varying from 8.7%⁹ to 45%.¹⁰ Anaphylaxis elicited by food allergy increased the chances of having an EAI prescribed by 15 times. In contrast, the diagnosis of idiopathic anaphylaxis did not seem to affect the rate of prescription of EAI, despite being one of the most well-known indications of EAI.

The present study is subject to some limitations. First, data were collected in the ED and AD of a tertiary hospital, which could affect external validity. In addition, patients who did not arrive at the AD after the acute episode could not be studied, which could alter the conclusions of this study, although it seems unlikely, given the strength of the associations.

In conclusion, a correct diagnosis of anaphylaxis in the ED is a significant factor in the use of epinephrine, which surprisingly is not related to the severity of the anaphylaxis. Allergists, on the other hand, prescribe EAI more frequently when anaphylaxis is triggered by food allergy, whereas the diagnosis of idiopathic anaphylaxis did not affect the prescription of EAI.

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SERPING1 mutation in a rare hereditary angioedema with skin blisters



Hereditary angioedema (HAE) is a rare, autosomal dominant disease characterized clinically by recurrent episodes of edema that may affect the skin and internal organs. The pathophysiological background of HAE is primarily an increased vascular permeability reaction to a local overproduction of bradykinin.¹ The most frequent dermatological manifestation is angioedema, which may occur on any part of the body, and erythema marginatum is sometimes seen as symptomatic of the onset of an attack. The formation of blisters, described by some authors,^{2–5} is an

infrequent cutaneous manifestation of HAE. We report here the case of a patient with HAE with C1 inhibitor (C1-INH) deficiency that presented, from childhood, several episodes of blisters at the site of edema.

A 33-year-old woman of African descent presented with recurrent episodes of angioedema at the age of 6 months and was diagnosed with HAE with C1-INH deficiency at 31 years of age. She presented isolated edema affecting limbs, face, lips, eyelids, tongue, genitals, bowels, and upper airways. Since childhood, during some but not all crises, blisters had formed at the site of the edema when it occurred on the arms or legs (Fig 1). Two or three times per year, the blisters appeared at the same time as the edema, took more than 5 days to disappear, and sometimes left

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