ORIGINAL ARTICLE

Adherence to Anaphylaxis Guidelines: Real-World Data From the Emergency Department of a Tertiary Hospital

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Abstract

Background: Few studies have evaluated adherence to anaphylaxis guidelines in emergency departments (EDs).
Objective: The objective of this study was to evaluate adherence to anaphylaxis guidelines in the ED of a tertiary hospital.
Methods: Medical records of patients attended in the ED of University Hospital of Salamanca, Spain were reviewed. Those patients fulfilling the anaphylaxis criteria proposed by the NIAID/FAAN were selected.
Results: During a 1-year period, we identified 89 patients (74 adults and 15 children). The anaphylactic reaction was moderate in 65% of adults, severe in 34%, and very severe in 1%. In children, all reactions were moderate. Fewer than half of the patients (42%) received adrenaline in the ED; this was administered intramuscularly in only 19% of cases. As for the severity of the reaction, 65% of patients with moderate reactions and 42% with severe reactions were not treated with adrenaline. At discharge from the ED, an adrenaline auto-injector was recommended to only 5.6% of patients. Fifty-two percent of patients received a documented allergy referral (57% adults vs 27% children, *P*=.047), 29% instructions about avoidance of triggers (31% adults vs 20% children, NS), and 51% written instructions for recognition of anaphylaxis warning signs (41% adults vs 100% children, *P*<.001).
Conclusion: The results of the study show a large discrepancy between recommendations in guidelines and management of anaphylaxis in the ED. Additional training efforts are needed to improve the treatment of patients with anaphylactic reactions.

Key words: Anaphylaxis. Guidelines. Adrenaline.

Resumen

Antecedentes: Pocos estudios han evaluado el cumplimiento de las recomendaciones de las guías clínicas de anafilaxia en los servicios de urgencias.
Objetivo: El objetivo de este estudio fue conocer el cumplimiento de las guías de anafilaxia en el servicio de urgencias (SU) de un hospital terciario.
Métodos: Se revisaron los informes de los pacientes atendidos en el SU del Hospital Universitario de Salamanca durante un año y se seleccionaron los que cumplían los criterios de anafilaxia propuestos por el NIAID/FAAN.
Resultados: Se identificaron 89 pacientes, 74 adultos y 15 niños. El 65% de los adultos presentó una reacción moderada, el 34% grave y el 1% muy grave; en todos los niños la gravedad fue moderada. Menos de la mitad de los pacientes (42%) fueron tratados con adrenalina, solo el 19% por vía intramuscular. El 65% de las reacciones moderadas y el 42% de las graves no recibieron adrenalina. Al alta, se recomendó un auto-inyector de adrenalina al 5,6% de los pacientes, se remitió al Servicio de Alergia al 52% (57% adultos frente a 27% niños, p=0,047), se dieron indicaciones para evitar posibles desencadenantes al 29% (31% adultos frente a 20% niños, p=.5) e instrucciones para reconocer los signos de alarma de una reacción anafiláctica al 51% (41% adultos frente a 100% niños, P<0,001).
Conclusión: Los resultados del estudio muestran importantes discrepancias entre las recomendaciones de las guías clínicas y el manejo de la anafilaxia en un SU hospitalario. Es necesario un mayor esfuerzo en educación para mejorar el tratamiento de los pacientes con anafilaxia.

Palabras clave: Anafilaxia. Guías clínicas. Adrenalina.

1. Introduction

Anaphylaxis is defined as a serious, potentially fatal allergic reaction of sudden onset [1-3]. Diagnosis of anaphylaxis can be difficult because the reaction can mimic other, more common diseases. In addition, rapid recognition of anaphylaxis is essential for prompt and adequate treatment. This is particularly important for physicians working in emergency services. Anaphylaxis guidelines recommend intramuscular adrenaline as first-line treatment [1-3]. The guidelines also recommend self-treatment measures, such as adrenaline auto-injectors and written instructions to patients and caregivers for the early recognition of symptoms and avoidance of possible triggers. In addition, follow-up by a specialist is essential to investigate possible triggers, perform a comprehensive risk assessment, and prevent future episodes. To date, few studies have evaluated adherence to anaphylaxis guidelines in the emergency department (ED). These studies have confirmed major discrepancies with the recommendations on treatment and follow-up [4-7]. The objective of this study was to evaluate management of anaphylaxis and adherence of clinicians to recommendations on anaphylaxis in guidelines. We conducted a 1-year study in children and adults who presented at the ED of a tertiary hospital and were diagnosed with anaphylaxis.

2. Methods

2.1. Patients

Ours was a single-center study. The medical records of patients attended in the ED of University Hospital of Salamanca, Spain, from September 1, 2011 to August 31, 2012 were reviewed the following working day. Anaphylactic reactions were identified by reviewing the medical records of patients who were discharged with any of the following diagnostic codes of the *International Classification of Disease, Ninth Revision*: anaphylactic shock caused by food (995.60-995.69); other anaphylactic shock (995.0); angioneurotic edema (995.1); urticaria (708); allergic urticaria (708.0); idiopathic urticaria (708.1); an unspecified adverse effect caused by the correct administration of a drug, medicinal, or biologic substance (995.2); an unspecified allergic reaction (995.3); other specified urticaria (708.8); unspecified urticaria (708.9); edema of larynx (478.6); edema of pharynx or nasopharynx (478.25); and the toxic effect of venom (989.5).

Those patients fulfilling the anaphylaxis criteria proposed by the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) were selected [8]. In addition, we telephoned all of the patients, who agreed to participate. Data were confirmed and missing data completed when possible. The study was authorized by the local ethics committee (PI4505/2011). We considered pediatric age to be between 0 and 14 years.

We recorded demographic data, symptoms, physical examination findings, suspected triggers, and ED management. In addition, at discharge, we recorded prescription of self-injectable adrenaline, other prescriptions, provision of an action plan (or not), and referral to the allergy department.

2.2. Definition and Severity of Anaphylaxis

Patients were considered to have anaphylaxis when their condition met the clinical criteria established by the NIAID/FAAN [8], as follows: (*i*) Involvement of skin and/or mucosal tissue and with respiratory compromise or signs of cardiovascular dysfunction or hypotension; (*ii*) Involvement of 2 or more systems (skin and/or mucosal tissue, respiratory, cardiovascular, and gastrointestinal) after recent exposure to a likely allergen; or (*iii*) Signs of cardiovascular dysfunction after exposure to a known allergen.

Anaphylaxis was classified into 5 grades according to severity following the classification of Ring and Behrendt [9]. An episode was defined as severe if the patient presented arterial oxygen saturation ≤92%, arterial hypotension (systolic arterial tension <90 mmHg), and/or neurologic involvement.

2.3. Data Analysis

Data were collected and analyzed using SPSS 19.0 (IBM Corp). Continuous parametric data are presented as mean (SD), and the exact 95% confidence interval (CI) is indicated. Nonparametric continuous data are represented as median (IQR). ANOVA or ANOVA on ranks was used to determine statistical significance between continuous variables; dichotomous variables were analyzed using the χ^2 and Fisher exact test. Statistical significance was set at $P<.05$.

3. Results

3.1. Patient Characteristics

A total of 148 712 patients were attended in the ED during the observation period. The initial screen identified 1575 records of potential anaphylaxis. A meticulous review of these medical records identified 89 patients fulfilling the NIAID/FAAN criteria for the diagnosis of anaphylaxis, with an

Table 1. Demographic Characteristics

	No.	%
Global sample	89	100
Sex		
Male	45	50.60
Female	44	49.40
Age		
<14 y (mean age 5.4 [3.13] y)	15	16.85
Males	11	73.33
Females	4	26.66
>14 y (mean age 47.85 [17.67] y)	74	83.14
Males	34	45.94
Females	40	54.05
Personal history of allergy	36	40.44
Adults	26	35.13
Children	10	66.66
Previous episodes of anaphylaxis	10	11.23
Adults	8	10.81
Children	2	13.33

incidence of 0.06% in relation to the total number of patients attended in the ED. Data for the anaphylactic reaction were recorded from all patients. In addition, we telephoned all patients to collect further data. Overall, 74 patients (83%) were adults and 15 patients (17%) were children, with a slight predominance of males (51%) in the overall sample, a predominance of females in the adults (54%), and a predominance of males in children (73%). These differences did not reach statistical significance. Mean age for the whole sample was 41 (22.7) years (range, 1 to 86 years). Mean age was 5.4 (3.1) years in children (Table 1).

Thirty-six (40%) patients had a personal history of allergic diseases, distributed as follows: food allergy, 50%; asthma, 16.7%; drug allergy, 16.7%; rhinoconjunctivitis, 2.8%; *Anisakis simplex* allergy, 2.8%; latex allergy, 2.8%; urticaria, 2.8%; and atopic dermatitis, 2.8%. The percentage of patients reporting a history of allergic diseases was significantly higher in children than adults (67% vs 35%, respectively, *P*=.023). Of the 89 patients, 10 (11%) reported a previous anaphylactic event.

According to the ED medical report, most reactions were triggered by food, both in adults and children (43%), followed by drugs (34%), and unknown causes (13.5%). One reaction was associated with the administration of specific subcutaneous immunotherapy, and 8 reactions were due to hymenoptera sting.

3.2. Clinical Manifestations

All patients had cutaneous symptoms during the anaphylactic episode. Seventy-two patients (81%) presented respiratory symptoms, and 28 patients (31.5%) complained of gastrointestinal symptoms. Twenty-six patients (29%) experienced hypotension in the ED. All patients who had hypotension were adults (*P*=.006) (Table 2).

The mean duration of symptoms was 103 minutes (10-480 minutes). Only 2 adult patients (2.2%) experienced a biphasic reaction.

Sixty-three (71%) had a moderate anaphylactic reaction, 25 (28%) had a severe reaction, and 1 (1%) had a very severe reaction. In the case of pediatric patients, the reactions were moderate in 100%. In comparison, 48 adult patients (65%) had moderate anaphylaxis (*P*=.024).

Table 2. Presentation of Symptoms During the Anaphylactic Episode

Symptoms	Adults No. (%)	Children (%)	*P* Value	Total No. (%)
Skin	74 (100)	15 (100)	–	89 (100)
Gastrointestinal	24 (32.43)	4 (26.66)	NS	28 (31.46)
Respiratory	58 (78.37)	14 (93.33)	NS	72 (80.89)
Cardiovascular	26 (35.13)	0	.006	26 (29.21)

Only 6 patients (7%) underwent determination of tryptase during the episode; all 6 were adults.

3.3. Pharmacological Treatment Received in the Emergency Department

3.3.1. Frequency of administration of adrenaline

Of the 89 patients, only 37 (42%) were treated with adrenaline; of these, 31 were adults (42%) and 6 (40%) children (Table 3).

In relation to the severity of the reaction, adrenaline was administered in 35% of moderate anaphylactic reactions and in 58% of severe and very severe reactions. Although this difference was not statistically significant (*P*=.07), there was a trend toward using adrenaline in the more severe cases.

In the group of adult patients who received adrenaline, 68% presented respiratory symptoms, 32% gastrointestinal symptoms, and 48% hypotension. Therefore, respiratory symptoms were the clinical manifestation that most frequently led to administration of adrenaline in both children and adults. Although hypotension was not the most frequent cause for administration of adrenaline, a higher percentage of patients with hypotension received adrenaline (58%) than patients with respiratory manifestations (37.5%) or digestive manifestations (39%). All the children who received adrenaline experienced respiratory symptoms. None of them presented hypotension.

Table 3. Treatment Administered in the Emergency Department During the Anaphylactic Episode

	Adults n=74 (%)	Children n=15 (%)	*P* Value	Total N=89 (5%)
Adrenaline	31 (41.89)	6 (40)	NS	37 (41.57)
Intramuscular[a]	4 (12.90)	3 (50)	.068	7 (18.91)
Subcutaneous[a]	26 (83.87)	3 (50)	.10	29 (78.37)
Intravenous[a]	1 (3.22)	0	–	1 (2.7)
Administration of adrenaline according to symptoms				
Respiratory[a]	21 (67.74)	6 (100)	NS	27 (72.97)
Gastrointestinal[a]	10 (32.25)	1 (16.66)	NS	11 (29.72)
Hypotension[a]	15 (48.38)	0	–	15 (40.54)
Corticosteroids	64 (86.48)	12 (80)	NS	76 (85.39)
H_1-antihistamines	65 (87.83)	13 (86.66)	NS	78 (87.64)

[a]Percentage refers only to patients treated with adrenaline.

3.3.2. Dose and route of administration of adrenaline

Thirty of 37 patients (81%) received a single dose of adrenaline. Of these, 21 (70%) had a moderate reaction, 8 (27%) a severe reaction, and only 1 (3%) a very severe anaphylactic reaction (this patient was subsequently transferred to the intensive care unit, where he received intravenous adrenaline). Seven patients (19%) received more than 1 dose of adrenaline: 6 (86%) had severe reactions and 1 (14%) had a moderate reaction. Thus, patients with severe anaphylaxis received a significantly higher number of doses of adrenaline than patients with moderate anaphylaxis (27% vs 86%, *P*=.01).

Adrenaline was administered subcutaneously in 78% of patients and intramuscularly in 19%. Only 1 patient received a single dose of intravenous adrenaline (3%). Half of the pediatric patients received subcutaneous adrenaline and the other half intramuscular adrenaline (Table 3).

3.3.3. H_1 antihistamines and corticosteroids

Most patients were treated with H_1 antihistamines (88%) and corticosteroids (85%) regardless of the severity of the reaction. No significant differences were observed in relation to age.

3.3.4. Other treatments

Despite the high frequency of respiratory symptoms, only 21% of patients were treated with supplemental oxygen. Other treatments administered included $ß_2$-agonist nebulization (14%), intravenous fluids (45%), and ranitidine (32%).

3.3.5. Management at discharge

Nearly all patients (99%) with anaphylactic reactions were discharged home. Only 1 patient was hospitalized in the intensive care unit. The minimum stay in the ED was 30 minutes, and the maximum was 900 minutes, with an average of 180 minutes. A pharmacological treatment was prescribed at discharge in 86 patients (97%) (Table 4).

3.3.6. Prescription for adrenaline auto-injector

In the adult population, an adrenaline auto-injector was recommended at discharge to only 5 patients (5.6%). No pediatric patients were prescribed adrenaline at discharge.

3.3.7. H_1-antihistamines and corticosteroids

A combination of antihistamines and corticosteroids was prescribed for most children (60%). For adults, the most common prescription was H_1-antihistamines (49%).

3.3.8. Referral to an allergist

At discharge from the ED, 52% of patients were referred to an allergist. Of these, 42 were adults (57%) and 4 were children (27%) (*P*=.047) (Table 4).

3.3.9. Written instructions for avoidance of triggers and identifying symptoms of a new reaction

Only 48 patients (54%) received written instructions for avoidance of suspected triggers or recognition of anaphylaxis symptoms. No differences were found between children and adults with respect to recommendations for trigger avoidance, although 100% of children were instructed to recognize the warning symptoms of anaphylaxis compared with 41% of adults (*P*<.001) (Table 4).

4. Discussion

We analyzed the management of anaphylaxis in 89 patients treated for an episode of anaphylaxis in the ED of a tertiary hospital. The World Health Organization classifies adrenaline as an essential medication for the treatment of anaphylaxis [1] because it has life-saving vasoconstrictor effects in most organ systems (except skeletal muscle). Adrenaline also prevents and alleviates airway obstruction caused by mucosal edema and relieves hypotension and shock [10-11]. However, there is a clear discrepancy between the information provided by guidelines on the management of anaphylaxis and the actual use of adrenaline as a first-line drug. In our study, adrenaline

Table 4. Management at Discharge

	Adults n=74, No. (%)	Children n=15, No. (%)	*P* Value	Total N=89, No. (%)
Adrenaline auto-injector + H_1-antihistamines + corticosteroids	4 (5.40)	0	–	4 (4.49)
Adrenaline auto-injector	1 (1.35)	0	–	1 (1.12)
H_1-antihistamines	36 (48.64)	5 (33.30)	NS	41 (46.06)
Corticosteroids	3 (4.05)	0	–	3 (3.37)
H_1-antihistamines + corticosteroids	28 (37.83)	9 (60)	.066	37 (41.57)
No medication	2 (2.70)	1 (6.66)	NS	3 (3.37)
Referral to allergist	42 (56.75)	4 (26.66)	.047	46 (51.68)
Avoidance of suggested triggers	23 (31.08)	3 (20.00)	NS	26 (29.21)
Recognition of alarm symptoms	30 (40.54)	15 (100)	<.001	45 (50.56)

was administered to only 42% of the population, clearly indicating that there is a deficit in the treatment of this disease, as described in several studies [4-6,12-14]. Huang et al [15] included only patients younger than 18 years and found that 79% had received adrenaline in the ED. The authors reported that this high percentage could be due to the fact that the pediatric emergency department was affiliated to an allergy service. However, in other studies, adrenaline was much less frequently used. Helbing et al [16] reported that adrenaline was administered to 47.9% of patients. Orhan et al [17] found that only 32.2% of their patients received adrenaline as treatment for anaphylaxis. Beyer et al [18] also found a low percentage of use of adrenaline in the ED in Berlin, Germany, where it was used in only 22.7% of cases. In an observational study of patients aged more than 15 years attended at the ED of a tertiary hospital in Spain, Alvarez-Perea et al [19] found that only 40% of patients received adrenaline, which was administered more frequently when the ED physician diagnosed anaphylaxis, regardless of severity.

Conversely, Baalmann et al [20] conducted an observational study of patients treated in ED for anaphylaxis. Questionnaires and electronic health records were retrospectively reviewed by 2 board-certified allergists-immunologists, who considered that the treatment of the reaction had been appropriate in 98% of cases, although more than 60% of anaphylaxis patients did not receive adrenaline [20]. In our study, 58% of the patients did not receive adrenaline; however, when only severe reactions were considered, this percentage fell to 42%. It is our understanding that all of these patients should have received adrenaline as a part of their treatment. Moreover, although the need for adrenaline in patients presenting moderate reactions is open to debate, it should be taken into account that it is not possible to predict the clinical picture of a patient who goes to the emergency department with an anaphylactic reaction and that these reactions progress rapidly and are potentially life-threatening.

Simons et al [21,22] clearly demonstrated the superiority of the absorption of adrenaline injected intramuscularly into the thigh. In our study, 78% of adrenaline administered in the ED was by the subcutaneous route, with only in 19% of cases administered intramuscularly. On the contrary, Alvarez-Perea et al [23] found that the intramuscular route was used in 96% of children with anaphylaxis who received adrenaline [23].

Taken together, these data mean that clinicians require further training on administration of adrenaline in anaphylaxis.

Guidelines also recommend administration of high-flow oxygen by facemask to all patients with anaphylaxis. In our study, only 21% of patients received oxygen, despite the fact that 81% presented respiratory manifestations. However, we found that H_1-antihistamines and corticosteroids were the most frequently used drugs in the treatment of anaphylaxis in the ED (88% and 85.4%, respectively). These results are similar to those found in other studies [4-6,12,15,18,24]. In most medical centers, the main drugs used to treat anaphylaxis regardless of the severity of the reaction are antihistamines and corticosteroids, although there are no placebo-controlled trials that support their effectiveness [1].

The WAO Anaphylaxis Guidelines state that patients must remain under observation in a medically supervised setting after improvement. The duration of monitoring should be individualized: at least 4 hours for patients with moderate anaphylaxis, and up to 8-10 hours or longer for patients with severe or protracted anaphylaxis. The average stay in the ED for the patients of our study was 3 hours (30-900 minutes). This figure refers to the total duration of emergency care, and not only the observation time after improvement, thus implying a much shorter observation time than recommended.

In addition, the guidelines emphasize the prevention and treatment of new anaphylactic episodes at discharge from hospital, with particular emphasis on prescription of adrenaline auto-injectors [1-3]. In our study, an adrenaline auto-injector was prescribed in the ED to only 6% of patients, all of whom were adults. Prescription of an adrenaline auto-injector and the number prescribed to an individual patient are controversial issues [25]. In our opinion, an adrenaline auto-injector should be prescribed in the ED at least to patients with a history of previous anaphylactic reactions and to all patients with severe reactions. In other studies, the rates of prescription of adrenaline varied between 8% and 63% [12,15,24,26-28].

Guidelines also recommend that an emergency action plan should be drawn up and personalized with recommendations for avoiding suggested triggers and how to recognize the warning signs. In our series, 54% of patients received these recommendations. All children and 41% of adults were instructed how to recognize warning signs, but only 29% of all patients were advised to avoid the suspected triggers.

In addition, guidelines recommend referring patients with anaphylaxis treated in the ED to an allergist for follow-up. In our study, 52% of patients were referred to the allergy department. Interestingly, only 27% of children were referred. This is in agreement with other authors, such as Rudders et al [27] and Banerji et al [24], who reported that only 18% of adults and 22% of children were referred from the ED for specialized assessment. Taken together, these data show the need to train and update emergency physicians in the importance of the prevention and treatment of a new episode, as anaphylaxis is a potentially deadly disease.

Consistent with other studies in this area [19,29], our study is limited by the fact that it was conducted in a single center and with a short observation period. Furthermore, since the incidence of anaphylaxis is low, the number of patients included, especially children, is small. In addition, some cases of anaphylaxis may not have been included owing to the identification method used. The lack of appropriate codes in the *International Classification of Diseases, Ninth Revision* makes this classification insufficient for identification of all anaphylactic reactions, particularly when only codes specifically indicating anaphylaxis are used [30-31]. The combination of several codes and the subsequent evaluation by an allergy specialist provides better results [15,32,33]. Finally, the lack of agreement in the main anaphylaxis guidelines (Galaxia, EAACI, WAO, AAAAI/ACAAI) regarding specific aspects of the management of patients with anaphylaxis could hamper studies that evaluate adherence of clinicians to recommendations.

In summary, we analyzed management of patients and adherence to anaphylaxis guidelines in the ED of a tertiary hospital. Adherence to recommendations was poor, with less than half of the patients treated with adrenaline. Furthermore, adrenaline was subcutaneously administered in most cases. In

addition, about 50% of patients were referred to the allergist and were given a written action plan, although only 6% received a prescription for adrenaline auto-injectors. Taken together, these data reveal the need for a further and continuous effort for the implementation of guidelines for the management of anaphylaxis.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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