Real life evaluation of the degree of compliance to recommendations of anaphylaxis guidelines in an emergency department of a tertiary hospital

Short title: Compliance to anaphylaxis guidelines

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CONFLICTS OF INTEREST

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ABSTRACT

Background: To date, few studies have evaluated the degree of compliance with recommendations of anaphylaxis guidelines in emergency departments (EDs). **Objective**: The objective of this study was to evaluate adherence to anaphylaxis guidelines recommendations in an ED of a tertiary hospital. **Methods**: Medical records of patients that were assisted in the ED of the University Hospital of Salamanca (Spain) were reviewed. Those patients fulfilling anaphylaxis criteria proposed by the NIAID/FAAN were selected. **Results**: During one year period, we identified 89 patients, 74 adults and 15 children. In the 65% of adults the anaphylactic reaction was moderate, in 34% severe and in 1% very severe. In children, all reactions were moderate. Less than half (42%) of patients received adrenaline at ED, which was administered intramuscularly only in 19% of the cases. Regarding the severity of the reaction, 65% of patients with moderate reactions and 42% with severe reactions were no treated with adrenaline. At discharge from ED, an adrenaline auto-injector was recommended only to 5.6% of patients. Fifty-two percent of patients received a documented allergy referral (57% adults vs. 27% children, p=0.047), 29% instructions about avoidance of triggers (31% adults vs. 20% children, n.s.), and 51% written instructions for recognition of anaphylaxis warning signs (41% adults vs. 100% children, p<0.001). **Conclusion**: The results of the study show a large discrepancy between guidelines recommendations and anaphylaxis management in ED. Additional efforts in education to improve the treatment of patients with anaphylactic reactions are needed.

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=0.5) 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.

INTRODUCTION

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

METHODS

1. PATIENTS

This is a single center study. Medical records of patients that were assisted in the ED of the University Hospital of Salamanca (Spain), from September 1st of 2011 to August 31st of 2012 were reviewed the following labor day. Anaphylactic reactions were identified reviewing the medical records of patients that were discharged with any of the following ICD-9 diagnostic codes (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, and biologic substance (995.2) or 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 telephonically contacted with all and patients assented 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 between 0 and 14 years.

Demographics, symptoms, physical examination findings, suspected triggers and ED management were recorded. In addition self-injectable adrenaline prescription, other prescriptions, whether a plan of action was provided, and whether allergy referral was indicated were evaluated at discharge.

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]: 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 five 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 O2 ≤92%, arterial hypotension (systolic arterial tension <90 mmHg), and/or neurologic involvement.

3. DATA ANALYSIS

Data were collected and analyzed using SPSS 19.0 software (Armonk, NY: IBM). Continuous parametric data are presented as means ± SDs, and exact 95% confidence interval (CI) is indicated. Nonparametric continuous data are represented as medians and interquartile ranges. ANOVA or ANOVA by ranks tests were used for determining statistical significance between continuous variables; dichotomous variables were analyzed with the $\chi 2$ and Fisher's exact test. Statistical significance was set at a P value less than 0.05.

RESULTS

1. PATIENT CHARACTERISTICS

A total of 148,712 patients were attended in the ED during the observation period. The initial screen identified 1,575 records of potential anaphylaxis. After meticulous review of these medical records, we identified 89 patients fulfilling the NIAID/FAAN criteria for the diagnosis of anaphylaxis, giving an incidence of 0.06% in relation to the total number of patients attended the ED. Data for the anaphylactic reaction were recorded from all the patients. In addition, we telephonically contacted with all of them to collect further data. Overall, 74 patients (83%) were adults and 15 patients (17%) were children. Sex distribution showed a slight predominance of males (51%) in the global sample. Nevertheless, in adults there was a female predominance (54%) whereas in children there was a male predominance (73%). These differences did not reach statistical significance. Median age for global sample was 41 years (SD 22.7) (range, 1 to 86 years). Median age was 5.4 years (SD 3.1) in children. (Table I)

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 = 0.023). Of the 89 patients, 10 (11%) reported a previous anaphylactic event.

According to the emergency medical report, most reactions were triggered by food, both in adults and children (43%), followed by drugs (34%), and unknown etiology (13.5%). There was also one reaction related to the administration of specific subcutaneous immunotherapy and 8 reactions were due to hymenoptera sting.

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%) had hypotension during their visit to ED. All patients that had hypotension were adults (p = 0.006) (Table II).

The mean duration for symptoms was 103 minutes (10- 480 minutes). Only two adult patients (2.2%) exhibited a biphasic reaction.

Among all patients, 63 (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, 100% of them showed moderate anaphylactic reactions. In comparison, 48 adult patients (65%) had a moderated anaphylaxis (p = 0.024).

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

3. PHARMACOLOGICAL TREATMENT RECEIVED IN THE EMERGENCY DEPARTMENT

3.1. Frequency of administration of adrenaline

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

In relation to the severity of the reaction, epinephrine 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=0.07) there was a trend to use adrenaline in the more severe cases.

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

3.2. Dose and route of administration of adrenaline

Thirty out of 37 patients (81%) received a single dose of adrenaline. Of them, 21 (70%) had a moderate reaction, 8 (27%) had a severe reaction and only 1 patient (3%) had 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 one 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 that patients with moderated anaphylaxis (27% vs. 86%, p = 0.01).

Adrenaline was administered subcutaneously (SC) in 78% of patients and intramuscularly (IM) in 19% of them. Only one patient received a single dose of intravenous (IV) adrenaline (3%). Half of pediatric patients received SC adrenaline and the other half, IM (Table III).

3.3. H1 antihistamines and corticosteroids

Most patients were treated with antihistamines H1 (88%), and corticosteroids (85%), regardless of the severity of the reaction. No significant differences were observed in relation to age.

3.4. Other treatments

Despite the high frequency of respiratory symptoms, only 21% of patients were treated with supplemental oxygen. Other administered treatments drugs were: beta-2 agonist nebulization (14%), intravenous fluids (45%), and ranitidine (32%).

4. 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. In 86 patients (97%) a pharmacological treatment was prescribed at discharge (Table IV)

4.1. Prescription for epinephrine auto-injector

In the adult population an auto-injector of adrenaline was recommended at discharge only to 5 patients (5.6%). No pediatric patients received a prescription of adrenaline at discharge.

4.2. H1 Antihistamines and corticosteroids

For the majority of children, a combination of antihistamines and corticosteroids was prescribed (60 %). For adults, the most common prescription was H1 antihistamines (49%).

4.3. Referral to allergist

At ED discharge, 52% of patients received a documented allergy referral. From them, 42 were adults (57%) and 4 were children (27%) (p=0.047) (Table IV).

4.4. 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 how to recognize anaphylaxis symptoms. No differences were found between children and adults in trigger avoidance recommendations, but 100% of children were instructed to recognize the warning symptoms of anaphylaxis compared with 41% of adults ($p<0.001$) (Table IV).

DISCUSSION

In this study we have analyzed the management of anaphylaxis in 89 patients treated in the ED of a tertiary hospital for an episode of anaphylaxis. 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 body organ systems (except skeletal muscle). Additionally, adrenaline prevents and alleviates airway obstruction caused by mucosal edema, as well as prevents 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 was administered only to 42% of the population, clearly indicating that there is a deficit in the treatment of this disease, which has also been described in several studies [4-6, 12-14]. Huang et al, which included only patients younger than 18 years, found that 79% of their patients had received epinephrine in the ED [15]. The authors reported that this high percentage could be due to the fact that the Pediatric Emergency Department was affiliated to an Allergy Service and this could have been reflected in the treatment of anaphylaxis. However, in other studies, the use of epinephrine was much lower. Helbing et al reported that epinephrine was administered to 47.9% of patients [16]. Orhan et al found that only 32.2% of their patients received epinephrine as treatment for anaphylaxis [17]. Beyer et al also found a low percentage of use of epinephrine in the ED in Berlin, where it was used in only 22.7% of cases [18]. Alvarez Perea et al, in an observational study of patients aged more than 15 years

attended at the ED of a tertiary-level hospital in Spain, found that only 40% of patients received epinephrine, which was administered more frequently when the ED physician diagnosed anaphylaxis, regardless of severity [19].

Conversely, Baalman et al conducted an observational study of patients treated in ED for anaphylaxis. Questionnaires and electronic health records were retrospectively reviewed by two board-certified allergists-immunologists, who considered that the treatment of the reaction had been appropriate in 98% of the cases, although more than 60% of anaphylaxis patients did not receive adrenaline [20]. In our study, 58% of the patients did not receive adrenaline, while the percentage was of 42% considering severe reactions alone. 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 administration in patients presenting moderate reactions might be debatable, it should be taken into account the fact that it is not possible to predict the evolution of the clinical picture of a patient who goes to the emergency department with an anaphylactic reaction and that these reactions are rapidly progressing and potentially lethal.

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

All together, these data mean that a great educational effort has still to be made regarding the use and the route of administration of adrenaline in anaphylaxis.

Also, guidelines recommend administration of high-flow oxygen should by face mask to all patients with anaphylaxis. In our study, only 21% of patients received oxygen, despite the fact that 81% presented respiratory manifestations. However, in our study, H1 antihistamines

(88%) and corticosteroids (85.4%) were the most frequently used drugs in the treatment of anaphylaxis in ED. These results are similar to those found in other studies [4-6,12,15,18,24]. As it can be seen, in most medical centers the drugs mainly used as a treatment for anaphylaxis regardless of the severity of the reaction are antihistamines and corticosteroids, although there are no placebo-controlled studies 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 time of stay in the ED for the patients of our study was 3 hours (30-900 minutes). It should be taken into account that this is the total duration of emergency care, and not only the observation time after the improvement, which implies a much shorter observation time than the recommended one.

In addition, the guidelines emphasize the prevention and treatment of new anaphylactic episodes at time of discharge from hospital, recommending the adrenaline auto-injectors prescription [1-3]. In our study, an adrenaline auto-injector was prescribed in ED only to 6% of patients, which were all of them adults. There are some controversies concerning which patients should be prescribed with an adrenaline auto-injector and how many auto-injectors should be prescribed to each patient [25]. In our opinion, an adrenaline auto-injector should be prescribed in EDs 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 an emergency action plan that should be written and personalized with recommendation 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 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 EDs to an allergist for further follow up. In our study, 52% of patients were referred to allergy service (AD). Interestingly, only 27% of children were referred. This is in agreement with other authors, like Rudders [27] and Banerji [24], who described that only 18% of adult and 22% of children were referred for specialized assessment from the ED. All together, these data show the need to educate and update emergency physicians about the importance of the prevention and treatment of a new episode, as anaphylaxis is a potentially deadly disease.

Like previously published studies in this area [19,29], our study may be limited because it was conducted in a single center and with a short observation time. Furthermore, since anaphylaxis is a disease with a low incidence, the number of included patients, especially children, may be small. In addition, it is possible that some cases of anaphylaxis may not have been included due to the method of identification used. The lack of appropriate codes in the International Classification of Diseases, ICD-9, makes this classification insufficient to identify 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 certain aspects of the management of patients with anaphylaxis, might be an inconvenient for studies that evaluate the adherence of clinicians to their recommendations.

In summary, in this study we analyzed the management of patients and the adherence to anaphylaxis guideline recommendations in the emergency department of a tertiary hospital. The degree of compliance with recommendations was low with less than half of patients being treated with epinephrine. Furthermore, epinephrine was subcutaneously administered in most cases. In addition, only about 50% of patients were referred to the allergist and were given a written action plan, but only 6% were received a prescription of epinephrine auto-injectors. All

together, these data reveal the need of a further and continuous effort for the implementation of guidelines for the management of anaphylaxis.

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Table I. Patients' demographic characteristics

	n	%
Global sample	89	100
Sex		
Male	45	50.60
Female	44	49.40
Age		
< 14 years (median age 5.4; SD=3,13)	15	16.85
Males	11	73.33
Females	4	26.66
>14 years (median age 47,85 SD=17,67)	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

Table II. Presentation symptoms during the anaphylactic episode.

Symptoms	Adults n=74 (%)	Children n= 15 (%)	P Value	Total n= 89 (%)
Skin	74 (100)	15 (100)	_	89 (100)
Gastrointestinal	24 (32.43)	4 (26.66)	n.s	28 (31.46)
Respiratory	58 (78.37)	14 (93.33)	n.s	72 (80.89)
Cardiovascular	26 (35.13)	0	**0.006**	26 (29.21)

Table III. Treatment administered in the ED during the anaphylactic episode. *Percentage refers only to patients treated with adrenaline. IM, intramuscular; SC, subcutaneous; IV, intravenous.

	Adults n=74 (%)	Children n=15 (%)	P value	Total n=89 (5%)
Epinephrine	31 (41.89)	6 (40)	n. s	37 (41,57)
IM*	4 (12.90)	3 (50)	0.068	7 (18.91)
SC*	26 (83.87)	3 (50)	0.10	29 (78.37)
IV*	1 (3.22)	0	n. d.	1 (2.7)
Administration of epinephrine according to symptomatology				
Respiratory*	21 (67.74)	6 (100)	n. s	27 (72.97)
Gastrointestinal*	10 (32.25)	1 (16.66)	n .s	11 (29.72)
Hypotension *	15 (48.38)	0	n. d.	15 (40.54)
Corticosteroids	64 (86.48)	12 (80)	n. s.	76 (85.39)
Antihistamines H1	65 (87.83)	13 (86.66)	n. s.	78 (87.64)

Table IV. Management at discharge

	Adults n=74 (%)	**Children n=15 (%)**	**P value**	**Total n=89 (%)**
Adrenaline auto-inyector + H1-antihistamines+ corticosteroids	4 (5.40)	0	n. d.	4 (4.49)
Adrenaline auto-injector	1 (1.35)	0	n. d.	1 (1.12)
H1-antihistamines	36 (48.64)	5 (33.30)	n. s.	41 (46.06)
Corticosteroids	3 (4.05)	0	n. d.	3 (3.37)
H1-antihistamines + corticosteroids	28 (37.83)	9 (60)	0.066	37 (41.57)
No medication	2 (2.70)	1 (6.66)	n. s.	3 (3.37)
Referral to allergist	42 (56.75)	4 (26.66)	**0.047**	46 (51.68)
Avoidance of suggested triggers	23 (31.08)	3 (20.00)	n. s	26 (29.21)
Recognition of alarm symptoms	30 (40.54)	15 (100)	**<0.001**	45 (50.56)