

Self-Management of Anaphylaxis Is Not Optimal

Música-García MV¹, Tejedor-Alonso MA¹, Moro-Moro M¹,
Esteban-Hernández J², Rojas-Perez-Ezquerro PE¹, Vila-Albelda C¹,
Rosado-Ingelmo A¹

¹Allergy Unit, Hospital Universitario Fundación Alcorcón, Alcorcón, Spain

²Preventive Medicine and Public Health Department, Universidad Rey Juan Carlos, Alcorcón, Spain

■ Abstract

Background: Our objective was to ascertain the degree of adherence to recommendations made to patients with anaphylaxis, most of whom were attended in our allergy outpatient clinic.

Methods: A questionnaire was sent to 1512 patients who had experienced anaphylaxis and completed by 887. The chosen definition of anaphylaxis was that of the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network Symposium. We evaluated the prescription, purchase, and use of epinephrine auto-injectors and oral drugs, as well as the avoidance of allergens involved in previous anaphylaxis episodes.

Results: Most patients (94.53%) reported that they had received advice on avoidance of responsible allergens after their allergy workup. Epinephrine auto-injectors and oral drugs were prescribed according to the subtype of anaphylaxis. Only 30.74% of patients used the epinephrine auto-injector; 54.26% took oral medication. Most patients (88.3%) avoided the allergen.

Conclusions: Despite general agreement that anaphylaxis occurring in the community should be treated with epinephrine auto-injectors, use of these devices to treat recurrences was low in our patients. Oral medication intake was more common than the epinephrine auto-injector in all subtypes. In order to increase adherence to epinephrine auto-injectors, it is necessary to think beyond the measures recommended during regular visits to allergy outpatient clinics.

Key words: Anaphylaxis recurrence. Self-management. Not optimal. Epinephrine. Auto-injectors.

■ Resumen

Antecedentes: Guías clínicas y documentos de posicionamiento recomiendan planes de acción urgentes personalizados para los pacientes que han tenido anafilaxia. El cumplimiento de estos planes es generalmente bajo.

Objetivo: Nuestro objetivo fue determinar el grado de adherencia a diferentes recomendaciones hechas a los pacientes con anafilaxia, que en la mayoría de los cuales fueron atendidos en la consulta externa de Alergia de nuestro hospital.

Métodos: Se envió un cuestionario a 1.512 pacientes que habían sufrido un episodio previo de anafilaxia y este fue completado por 887. La definición elegida de anafilaxia fue la del Instituto Nacional de Alergias y Enfermedades Infecciosas y el Simposio de la Food Allergy and Anaphylaxis Network (NIAID-FAAN). Se evaluó la prescripción, la compra y el uso de auto-inyectores de adrenalina y medicamentos orales, así como la evitación de alérgenos implicados en los episodios de anafilaxia anteriores.

Resultados: La mayoría de los pacientes (94,53%) informaron que habían sido aconsejados sobre la evitación de alérgenos responsables después de su evaluación alergológica. Los auto-inyectores de adrenalina y los medicamentos orales se prescribieron de forma diferente según el subtipo de anafilaxia. Sólo el 30.74% de los pacientes utilizaron el auto inyector de adrenalina y el 54,26% tomo la medicación oral. La mayoría de los pacientes (88,3%) evitaron el alérgeno.

Conclusiones: A pesar del acuerdo general que los episodios de anafilaxia que ocurren en la comunidad deben ser tratados con auto-inyectores de adrenalina, el uso de estos dispositivos para el tratamiento de las recurrencias fue baja en nuestros pacientes. La ingesta oral de medicamentos es más común que el auto inyector de adrenalina en todos los subtipos. Con el fin de aumentar la adherencia a autoinyectores de adrenalina, es necesario investigar más allá de las medidas recomendadas durante las visitas regulares a las consultas de Alergia.

Palabras clave: Recurrencia. Anafilaxia. Auto-manejo. No óptimo. Adrenalina. Auto-inyectores.

Introduction

Anaphylaxis is a recurrent condition; therefore, guidelines and position papers consider an individualized emergency action plan mandatory [1-8]. Such a plan would cover indications for self-injectable epinephrine, training in the use of auto-injectors, identification and avoidance of triggers, and medical identification of risks (eg, bracelet, wallet card).

Studies that analyze adherence to recommendations have focused mainly on those applying to epinephrine [9-17], probably because this drug remains the main treatment for anaphylaxis. The frequency of prescription in the allergy outpatient clinic ranges from 8.6% to 100% [4,10-14], availability of epinephrine for a new anaphylaxis episode ranges from 39% to 73% [9,10,12,14], and use ranges from 8% to 71% [10,12,15,16]. Therefore, epinephrine auto-injectors are not prescribed and used as often as they should be.

The objective of the present study was to know the degree of adherence to the recommendations made in our allergy outpatient clinic. These recommendations cover prescription, training, and indications for use of epinephrine auto-injectors and oral drugs (H₁ receptor antagonists, oral corticosteroids), as well as avoidance of the allergens involved in previous episodes.

Methods

Patients

Our cohort comprised 1512 patients with a mean (IQR) age of 34.9 (12-49) years (57.8% women) diagnosed with anaphylaxis between 1998 and 2005 in different clinical settings (see below) of the catchment area of Hospital Universitario Fundación Alcorcón (HUFA), Alcorcón, Spain. During the study period, our institution had a catchment population of about 500,000 people.

We retrieved all cases of anaphylaxis from the following computerized clinical records in our catchment area during the study period, as follows: (1) computerized records of hospitalized patients and patients attended at the Emergency Department of HUFA (Selene, Siemens); (2) the diagnosis database of the Allergy Unit of HUFA; and (3) clinical notes of primary care physicians recorded in the electronic clinical application used at this level (OMI, STACKS Group). Care in the allergy outpatient clinic, emergency department, and hospital is provided by the staff of HUFA, while primary health care is managed independently of HUFA.

Cases of anaphylaxis were retrieved from these databases by means of alphanumeric strings based on characters of words used in Spanish* to denominate acute allergic syndromes, as follows: *alergi** allergy, *anafila** anaphylaxis, *urtica** urticaria, *hipersensibili** hypersensitivity, *eritema** erythema, *picadu** bite, *advers** adverse, *edem** edema, *medica** drug, *reacc** reaction, *alimen** food, *abeja** honeybee, *avispa** wasp. The sensitivity of this strategy (91.7%-95% confidence interval [CI], 61.6%-99.8%) was published elsewhere [18].

Questionnaire

A questionnaire was designed to obtain information on possible recurrences of anaphylaxis and self-management

of recurrences. The comprehensibility of the questionnaire was tested twice among 6 experienced allergists, who recommended several changes. The questions included were designed to obtain information on subtype of recurrence, purchase of epinephrine auto-injectors and oral medication, use of both medications during the recurrence, and follow-up of avoidance measures.

The survey was sent by ordinary mail to all 1512 patients of the cohort from January to April 2008. We tried to contact the patients who did not respond (1082) by telephone (1 call in the morning and 2 calls in the afternoon) from September 2008 to January 2009. Replies were obtained from 887 people (58.7%): 430 by ordinary mail and 457 by telephone. Table 1 shows the demographic data, attendance level, severity, subtype, and causes of the first anaphylaxis episode in patients who completed the questionnaire. The responses for all patients aged <18 years were obtained from parents or guardians.

Only 7.2% of respondents had not undergone an allergy workup at our allergy outpatient clinic. Patients were attended for their anaphylaxis episodes in different care settings (Table 1). Patients attended in our allergy outpatient clinic after their clinical assessment received an integral plan for the self-management of recurrences. The plan included advice on avoiding known allergens, training in the use of epinephrine auto-injectors, and prescription of auto-injectors, H₁-receptor

Table 1. Summary of Data on the First Anaphylaxis Episode From Patients Who Returned a Completed Questionnaire

Care Level	Years Data Collected	No.	%
Primary care	2004-2005	105	11.8
Allergy outpatient clinic	1998-2005	823	92.8
Emergency department	2004-2005	151	17.0
Hospitalization	1999-2005	32	3.6
Severity of the First Episode of Anaphylaxis			
Moderate		717	80.9
Severe		169	19.1
Sex			
Female		507	57.4
Male		376	42.7
Previous Atopic Disease			
Allergic rhinitis		178	20.1
Allergic asthma		126	14.2
Previous food allergy without anaphylaxis		57	6.4
Atopic dermatitis		25	2.8
Subtype			
Drug		407	45.9
Food		228	25.7
<i>Anisakis simplex</i>		102	11.5
Idiopathic		71	8.0
Hymenoptera		30	3.4
Other causes		28	3.2
Exercise		12	1.4
Latex		8	0.9
<i>Echinococcus</i>		1	0.1

antagonists, and oral corticosteroids. The plan aimed to help patients to avoid recurrences and self-manage new episodes. Not all patients were counseled about all measures, which were established according to the evaluation of the risk of recurrence by allergists from the Allergy Unit of HUFA. For instance, patients with drug anaphylaxis were not prescribed an epinephrine auto-injector, because the risk of recurrence was considered low. We do not provide information on advice or prescriptions given to patients from the cohort outside our allergy outpatient clinic: however, since very few were evaluated elsewhere, it is very difficult or impossible to separate the effect of each clinical setting.

Definitions

We used the definition of anaphylaxis of the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network Symposium [19], which states that anaphylaxis is probable when several criteria are satisfied. These criteria are as follows: (1) presence of skin signs or symptoms, together with respiratory involvement or signs of organic dysfunction or hypotension; (2) involvement of at least 2 organs or systems after recent exposure to an allergen; or (3) signs of organ dysfunction or hypotension after exposure to a known allergen. Participants in this symposium believed that these criteria make it possible to accurately identify anaphylactic reactions in more than 95% of cases. This definition was used to select patients attended in our allergy outpatient clinic and patients retrieved from the databases of other clinical settings.

Patients identified their first episode of anaphylaxis in the questionnaire, explicitly rejecting the presence of previous episodes. Subsequent episodes were considered recurrences.

The first recurrence occurred after the first visit to our allergy outpatient clinic in 229 of 309 patients (74.1%). We classified the first anaphylaxis episode as severe or moderate according to the criteria of Brown [20], who recommended that only moderate generalized hypersensitivity reactions (suspected respiratory, cardiovascular, or gastrointestinal involvement) and severe generalized hypersensitivity reactions (hypoxia [$\text{SpO}_2 \leq 92\%$], hypotension [systolic blood pressure < 90 mmHg in adults], or neurologic involvement) should be considered anaphylaxis.

Design

The study was an observational retrospective cohort study and was approved by the Research Committee of our Institution (number 22/2005).

Statistical Analysis

We report percentages of events studied. Differences in the percentages were analyzed using the Pearson chi-square test. When the value for expected cases of the contingency tables was less than 5, the Fisher exact test was used. Correspondence analyses were made to detect correlations between purchase and use of epinephrine auto-injectors and oral drugs. *P* values lower than 0.05 were considered statistically significant. Unless indicated otherwise, data are from patients who answered the questionnaire and experienced a recurrence of anaphylaxis.

Results

Recommended Management in the Allergy Outpatient Clinic

Of the patients in the initial cohort (1512 patients), most (94.58%) were attended in the allergy outpatient clinic. Of those who completed the questionnaire (887), most (94.53%) received advice on avoidance measures after their allergy assessment, and no differences were detected in the incidence of recurrences between patients who were counseled on avoidance measures and patients who were not ($P=.2$; RR, 0.8; 95%CI, 0.5-1.1).

Auto-injectors were more frequently prescribed to patients whose anaphylaxis was induced by hymenoptera venom (72%) and exercise (60%), followed by patients whose anaphylaxis was induced by unknown triggers (34.48%), latex (25%), and food (21.53%). The lowest prescription rates were found in anaphylaxis caused by *Anisakis* (7.29%) and drugs (1.81%) ($P<.001$). Patients with severe anaphylaxis episodes had a higher probability of being prescribed an auto-injector ($P=.003$, RR 2; 95%CI, 1.3-3.0). Likewise, patients who had experienced recurrences were more likely to be prescribed auto-injectors ($P=.007$, RR, 1.5; 95%CI, 1.1-1.9). Data for this analysis were obtained from the clinical records of our hospital.

Purchase and Use of Epinephrine Auto-injectors and Oral Drugs

Table 1 shows the demographic data, care level, severity, and subtype of the first anaphylaxis episode in patients who completed the questionnaire. The patients in our series were generally attended in 2 or more care settings (76.78%), thus preventing the analysis of each group individually, since several groups shared patients. The incidence rate of anaphylaxis for the same subtype among respondents (first recurrence) was 3.2 episodes per 100 person-years (95%CI, 2.8-3.6). Twenty-eight per cent of patients reported having had at least 1 recurrence for the same subtype. The methodology for estimation of these rates and the factors involved in the risk of experiencing new anaphylaxis episodes have been published elsewhere [21].

Among respondents who experienced recurrences, 48.69% did not know they had to buy an epinephrine auto-injector, 34.46% purchased it, and 16.85% did not purchase it even though it had been prescribed. Drug purchases in Spain are covered by the National Health System according to patient income (from 100% to 40%). Among respondents who knew they had to buy an auto-injector, no significant differences were detected between the sexes (69.12% versus 64.18% [total, 67%]; $P=.54$), although significant differences were detected between the different anaphylaxis subtypes ($P<.001$) (Figure 1).

Among patients who had recurrences, 30.74% reported that they had used the auto-injector, 31.8% had not, and 37.46% reported that they had not received any prescription after their allergy assessment. As for subtype, use of the auto-injector was more frequent in patients with anaphylaxis caused by *Anisakis* (78.57%), drugs (59.57%), and hymenoptera (44.44%) ($P=.014$). In almost all subtypes, purchase of the auto-injector was more frequent than use ($P<.001$) (Figure 1). Finally, age

adjusted for subtype of anaphylaxis did not favor more frequent use of epinephrine (score test for trend of odds $P=.$ 44).

A small percentage of patients (19.4%) did not know they had to buy oral medication, 66.79% bought it, and 13.81% did not; 54.26% of patients took the oral medication prescribed. Significant differences were observed between subtypes of anaphylaxis in relation to purchase ($P=.$ 003) and use of oral medication ($P<.$ 001) (Figure 2). Likewise, more oral drugs were purchased than used in recurrences ($P<.$ 001).

In all cases, oral medication was purchased more frequently than the auto-injector ($P<.$ 001). For all subtypes of anaphylaxis, intake of oral medication was also more common than use of the auto-injector ($P<.$ 001). However, patients' behavior with regard to the purchase and use of auto-injectors and oral medication was similar: patients who used or did not use epinephrine in recurrences took or did not take oral

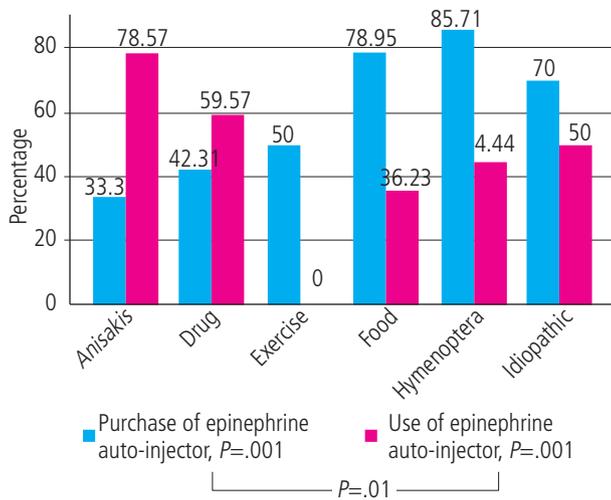


Figure 1. Comparison between purchase and use of epinephrine auto-injectors in relation to different subtypes of anaphylaxis. Cyan bars represent the purchase of epinephrine auto-injectors; magenta bars represent the use of epinephrine auto-injectors.

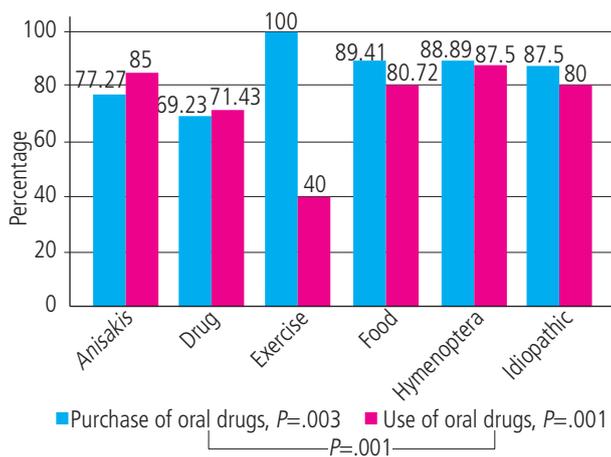


Figure 2. Comparison between purchase and use of oral medication in relation to different subtypes of anaphylaxis. Cyan bars represent the purchase of oral drugs; magenta bars represent the use of oral drugs.

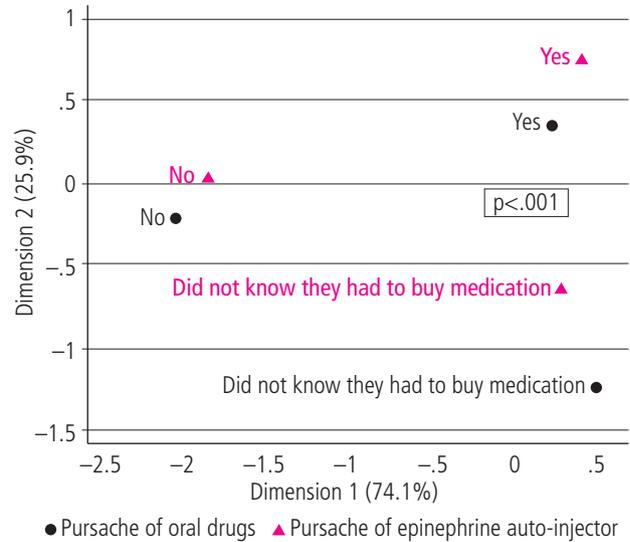


Figure 3. Correspondence analysis of the purchase of oral drugs and epinephrine auto-injectors. The triangles represent the purchase of epinephrine auto-injectors; the dots represent the purchase of oral drugs.

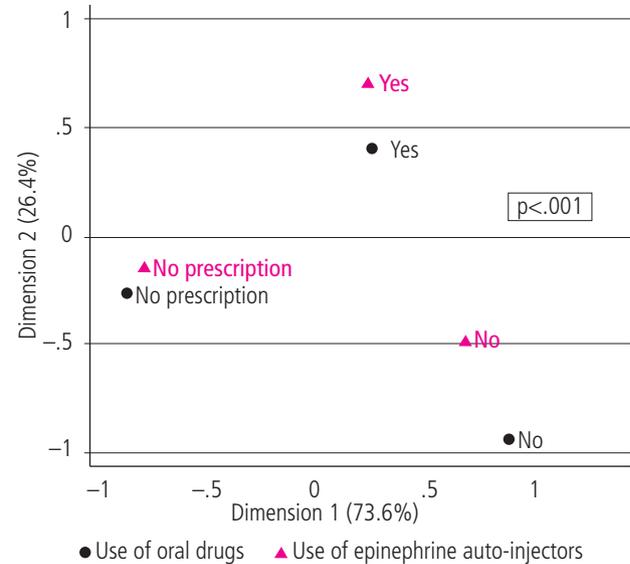
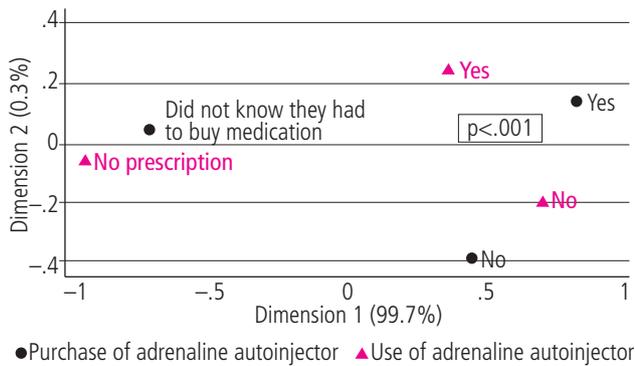


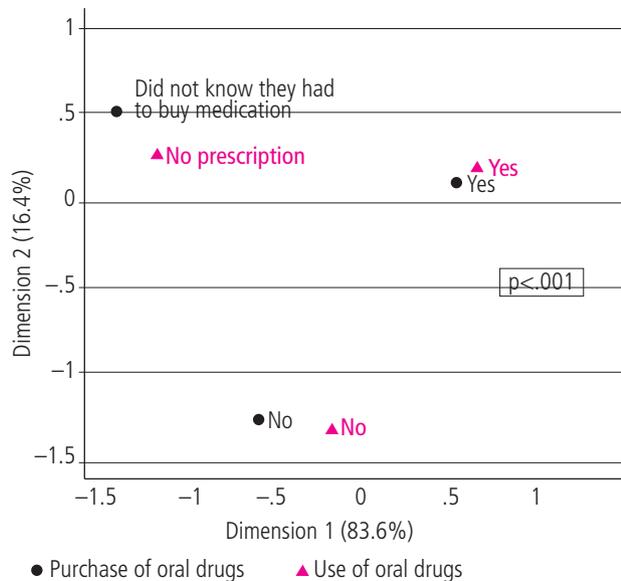
Figure 4. Correspondence analysis of use of oral drugs and epinephrine auto-injectors for recurrence of anaphylaxis. The triangles represent the use of epinephrine auto-injectors; the dots represent the use of oral drugs.

drugs ($P<.$ 001) (Figure 3), and patients who purchased or did not purchase epinephrine auto-injectors purchased or did not purchase oral drugs ($P<.$ 001) (Figure 4). In the corresponding analysis of the purchase and use of medication (epinephrine auto-injectors or oral medication), we observed a correlation ($P<.$ 001) between buying and self-administration, not buying and no self-administration, and not knowing whether the medications had to be purchased (Figures 5 and 6).



● Purchase of adrenaline autoinjector ▲ Use of adrenaline autoinjector

Figure 5. Correspondence analysis of the purchase and use of epinephrine for recurrence of anaphylaxis. The triangles represent the use of epinephrine auto-injectors; the dots represent the purchase of epinephrine auto-injectors.



● Purchase of oral drugs ▲ Use of oral drugs

Figure 6. Correspondence analysis of the purchase and use of oral drugs for recurrence of anaphylaxis. The triangles represent the use of oral drugs; the dots represent the purchase of oral drugs.

Avoidance of the Allergen

We observed significant differences according to subtype in avoidance of the cause ($P < .001$), with avoidance being more common in food anaphylaxis (93.5%) and less common in exercise anaphylaxis (20%). In most cases, avoidance was greater than 80% (Table 2).

Discussion

The most remarkable findings in our study were that the prescription of epinephrine auto-injectors varied considerably with subtype and never reached percentages close to 100%. Two-thirds of patients who knew that they had to buy the auto-injector did so (67%), although less than one-third used it in a new episode (30.74%).

While most studies agree that epinephrine auto-injectors are rarely prescribed in allergy outpatient clinics, 2 Australian studies [10,12] and 1 Italian study [14] found that auto-injectors were prescribed to 100% of patients attended or almost 100% (89%) [17]. Sicherer et al [13], on the other hand, observed that epinephrine auto-injectors were prescribed to 23% of adults and 46% of children after hypersensitivity reactions to peanut or walnut with respiratory or systemic involvement in their first episode and to only 8.6% of patients with allergy to fish and shellfish [11], despite the severity of the reaction. Our prescription frequency in food anaphylaxis was very close to that reported by Sicherer et al [11,13], but very different from that reported by other authors (100% or almost 100%) [10,12,14,17].

The studies discussed above reveal considerable variability in epinephrine prescription and low prescription percentages despite the existence of clinical guidelines published by international and national allergy associations [2,22,23]. These guidelines recommend auto-injectors to patients with a high risk of anaphylaxis, namely, those who had already experienced anaphylactic reactions and have comorbid persistent asthma or experience severe anaphylaxis episodes, those who have reacted to trace amounts of allergen, those who have experienced mild or severe reactions to peanut or tree nut, those with mastocytosis, and adolescents [24-25]. However, some authors [26] propose that after accurate identification of

Table 2. Avoidance of Allergen According to Subtype of Anaphylaxis (Pearson chi-square, $P < .001$)

Causes	Total Number of Patients Who Answered the Questionnaire	Number of Recurrences	Number of Patients Who Avoided the Cause of Anaphylaxis	Percentage of Patients Who Avoided the Cause of Anaphylaxis
Food	88	86	83	94.32
Drugs	80	85	71	88.75
Exercise	5	1	1	20
<i>Anisakis simplex</i>	26	20	22	84.62
Hymenoptera	9	8	8	88.89
Idiopathic	18	21	15	83.33
Total	225	238	200	83.81

the trigger, education on effective avoidance, and optimization of management of concomitant medical conditions that might make reactions more dangerous (asthma, hypertension, and other conditions), it would seem more appropriate to leave the choice of whether or not to carry an auto-injector to patients after they have been fully informed of the benefits and risks of all management options. In addition, the higher percentage of epinephrine prescriptions in series from other countries could be due to community concerns after several fatal cases involving food-allergic children, such as those reported with nuts in Australia in the early 2000s [27,28]. Likewise, local recommendations, such as those set out in national guidelines proposing adrenaline auto-injectors to patients who have already experienced at least 1 food-induced anaphylactic episode, are believed to account for the large numbers of prescriptions [17].

The controversial findings set out above explain why physicians in our study did not prescribe epinephrine auto-injectors to all their patients.

Nevertheless, prescription of epinephrine auto-injectors is not uniform in all subtypes. We found the highest percentages in patients with anaphylaxis caused by hymenoptera venom and exercise (>60% in both cases), while the lowest percentages were found in patients whose anaphylaxis was caused by drugs or *Anisakis simplex* (<7.5%) ($P<.001$). In their analysis of anaphylaxis episodes in an emergency department, Campbell et al [29] noted that epinephrine auto-injectors were prescribed more frequently to patients with hymenoptera anaphylaxis. Prescription of epinephrine auto-injectors to patients with generalized reactions after hymenoptera stings seems widely accepted by allergists, independently of the severity of previous reactions [30].

Although epinephrine auto-injectors are widely available, most studies show that few patients carry them [10,12,14-16]. We asked patients if they had actually bought an epinephrine auto-injector, the necessary previous step to carrying one. Only 67% of patients who knew that they had to buy the auto-injector had actually bought one. Mullins [12] found that 73% of patients carried their devices. In a survey of patients with anaphylaxis undertaken 7 years previously, Cianferoni et al [14] observed that only 39% of children had epinephrine auto-injectors at home. However, the other studies reported that 70%-92% carried them [9,10,15]. Therefore, percentages for purchasing and carrying auto-injectors are intermediate and high among patients who received prescriptions.

Even though patients have a prescription for an epinephrine auto-injector, purchase the device, and carry it, many do not use it when necessary [9,12,15]. We found that only 30.74% of patients who had a recurrence used auto-injectors. Mullins [12] reported an even lower percentage; only 8% of patients used their device during a recurrence. In the study by Webb and Lieberman [15], only 36.8% of patients used their auto-injector during a recurrence. Simons et al [16] carried out a mail survey of 1885 patients who had survived an anaphylaxis episode and noted that only 27% of those who answered had self-administered epinephrine or received it from another person. Only Gold and Sainsbury [10] reported significantly higher figures: 71% of children received epinephrine during a new episode. We found that age was not a predictor of the use of auto-injectors.

Several authors have reported differences in the use of auto-injectors according to the subtype of anaphylaxis [10,16]. We observed that the patients who most commonly self-administered epinephrine were those with anaphylaxis induced by *Anisakis simplex* (79%), drugs (60%), and hymenoptera (44%). Gold and Sainsbury [10] noted that patients with hymenoptera anaphylaxis used auto-injectors more often than patients with food or idiopathic anaphylaxis. In the study by Simons et al [16], patients with anaphylaxis due to peanuts, fish, and insect bites used their auto-injector more than other groups. These authors [7,16] did not explain the differences they found, and we have no solid evidence to account for them; therefore, any potential explanations would be speculative. Use of adrenaline auto-injectors to treat hymenoptera anaphylaxis could be related to the frequent contact between these patients and staff during immunotherapy sessions at the allergy outpatient clinic. However, while receiving hymenoptera immunotherapy, patients are not generally given specific information and have few opportunities to consult with an allergist. Furthermore, in the case of hymenoptera and drug anaphylaxis, severity has been attributed to cardiovascular involvement, while food allergy has been associated with lower and upper respiratory involvement [31,32]. The fact that the degree of concern a patient feels varies with the pathogenic mechanism involved could in some way explain differences in the use of auto-injectors. However, Simons et al reported that patients with food anaphylaxis caused by peanuts and fish used adrenaline auto-injectors more often than other patients.

In all subtypes of anaphylaxis, purchase and self-administration of oral medication was more common than the purchase and self-administration of epinephrine. Simons et al [16] found that medications other than epinephrine were used to treat anaphylaxis. This discrepancy between treatments recommended in guidelines and actual practice is common and could be due to medical culture, exaggeration of the effects of oral corticosteroids, lack of epinephrine, and fear of side effects. However, in the corresponding analysis of the 2 relevant questions (purchase and use of epinephrine auto-injectors and oral medication) in the whole group, we observed a correlation ($P<.001$) between buying and self-administration, not buying and no self-administration, and not knowing whether both medications had to be purchased. Consequently, patients who purchased and used medication tended to follow all recommended oral and parenteral medications prescribed by their allergists.

We also observed significant differences according to subtype in avoidance of the cause ($P<.001$), with avoidance being more common in food anaphylaxis (93.5%) and less common in exercise anaphylaxis (20%), although in the case of exercise anaphylaxis, the number of patients who responded to the questionnaire (5) and had recurrences (1) was very low. Consequently, the proportions could have changed significantly if more patients had returned the questionnaire. In most cases, avoidance was greater than 80%.

Our study could be subject to recall bias, because patients may have been unsure of the answers to some questions owing to the passage of time. Our results could also have been influenced by nonresponse bias. However, recall and nonresponse bias are a common feature of studies that analyze

self-treatment of anaphylaxis episodes [10,12,14,15]. The response rate in our study was 58.66%, which is considered an intermediate value compared with rates found in other studies that used mailed questionnaires and phone calls (33.5%-80%) [10,15]. If the responders were more motivated by their self-care, our real percentage of adherence to recommendations could be even lower.

In summary, the controversy surrounding use of epinephrine auto-injectors means that rates of prescription are low in our study. We can conclude that the recommendations for management of patients with anaphylaxis were not satisfactory. It is possible that more frequent visits to outpatient clinics, coordinated education programs in primary and specialized care, and training of educators to manage recurrences of anaphylaxis in schools and homes can improve management and avoidance of recurrences. Future research into the management of anaphylaxis recurrences should be performed along these lines.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentation

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■ **Miguel A Tejedor-Alonso**

Allergy Unit
Hospital Universitario Fundación Alcorcón
Avenida Budapest, 1
28922 Alcorcón (Madrid), Spain
E-mail: m914674227@telefonica.net