

Anaphylaxis in the community: Learning from the survivors

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Background: Most studies of anaphylaxis in the community focus on persons at risk who might, or might not, have experienced anaphylaxis.

Objective: We sought to focus on survivors of anaphylaxis in the community and their experiences in using, or not using, an epinephrine autoinjector for first-aid treatment.

Methods: An e-mail survey was conducted. Responses were anonymous and could not be traced to any person or location. Anaphylaxis was defined as the most severe sudden-onset allergic reaction ever experienced by the participants or a person for whom they were responsible (eg, a child). There were 17 core questions for all participants, with 16 additional questions for users who injected epinephrine either into themselves or someone else, and 1 additional question for nonusers.

Results: Of the 1885 participants, 500 (27%) were epinephrine users, and 1385 (73%) were nonusers. The groups were similar with regard to multisystem organ involvement (82% vs 78%, $P = .07$) and many other aspects of anaphylaxis; however, epinephrine users were more likely (all $P < .05$) to report respiratory or shock symptoms; to report peanut, fish, or insect sting triggers; to be asthmatic; and to have taken or been given asthma medication on the day of the episode. Epinephrine users reported problems in deciding whether to give the injection, repeat the dose, and/or go to an emergency department. Nonusers reported not injecting epinephrine for various reasons, including use of an H₁-antihistamine (38%), no prescription for epinephrine (28%), and/or a mild anaphylaxis episode (13%).

Conclusions: In a unique population composed of 1885 survivors of anaphylaxis in the community, users of epinephrine autoinjectors for first-aid treatment were outnumbered by nonusers. The insights reported by epinephrine users and the

reasons why nonusers did not inject epinephrine are documented. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Epinephrine, adrenaline, autoinjector, anaphylaxis, acute allergic reaction, food allergy, insect sting allergy

Epinephrine injection is the cornerstone of emergency treatment for anaphylaxis.¹⁻⁵ Failure to inject it in a timely manner is reported to contribute to fatality.⁶⁻⁸ In most persons dying of anaphylaxis, it has either not been injected at all or has been injected late in the course of clinical events.⁶⁻⁸ Failure to inject an adequate dose is reported to increase the risk of a biphasic reaction, in which anaphylaxis symptoms recur 1 to 72 hours after the initial symptoms have abated, despite no additional exposure to the trigger.⁹

For all of these reasons, epinephrine autoinjectors are recommended for the first-aid treatment of anaphylaxis in community settings.¹⁻⁵ To date, studies of these devices have focused on the clinical pharmacology of epinephrine injected through them,¹⁰ prescribing^{11,12} or dispensing^{13,14} them, demonstrating how to use them correctly,^{15,16} or carrying them in the community and having them available at all times.¹⁶⁻¹⁸ Most studies have focused on persons at risk for anaphylaxis who might, or might not, have actually experienced anaphylaxis. To date, no studies have focused specifically on persons who have survived anaphylaxis in the community.

We hypothesized that clinically relevant information could be obtained from persons who used an epinephrine autoinjector to treat themselves or someone else with anaphylaxis and from those who did not use an epinephrine autoinjector to treat anaphylaxis.

METHODS

We collected information from persons who had survived anaphylaxis or been responsible for someone who survived anaphylaxis in the community, by using a survey consisting of multiple-choice questions that was e-mailed to visitors to the Center for Anaphylactic Support (www.epipen.com). This Web site provides information about anaphylaxis and epinephrine and has links to other relevant online resources. Participants could opt out at any time. Their responses were anonymous and could not be traced to any person or location.

Anaphylaxis was defined as a severe, sudden-onset allergic reaction. When answering the survey questions, participants were asked to focus on the most severe sudden-onset allergic reaction they or a person for whom they were responsible (eg, a child) had ever experienced. Users were defined as those who had injected epinephrine through an autoinjector, either into themselves or into someone else for first-aid treatment of anaphylaxis. Nonusers were defined as those who did not inject epinephrine through an autoinjector either into themselves or into someone else for first-aid treatment of anaphylaxis.

All participants were asked 17 core multiple-choice questions about the anaphylaxis episode, including when and where it occurred; the trigger; the symptoms; the medications taken in addition to epinephrine; whether the

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Disclosure of potential conflict of interest: F. E. R. Simons has received research grants from the Canadian Institutes of Health Research and is on advisory boards for Dey, Intelliject, ALK-Abelló, and Sciele. S. Clark has received consulting fees from Dey Pharmaceuticals and Partners Healthcare/Massachusetts General Hospital. C. A. Camargo, Jr has served as a consultant for and received research support from Dey Pharmaceuticals.

Received for publication December 19, 2008; revised March 25, 2009; accepted for publication March 31, 2009.

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0091-6749/\$36.00

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doi:10.1016/j.jaci.2009.03.050

person with anaphylaxis was asthmatic and, if so, whether asthma medications were taken or given on the day of the episode; and questions about other medications and preparedness to cope with anaphylaxis in the community.

Epinephrine users were asked 16 additional multiple-choice questions, for a total of 33 questions, about rate and sequence of symptom improvement, body position at the time of the epinephrine injection, total number of injections given during the anaphylaxis episode, and any problems encountered in using the autoinjector. Nonusers were asked 1 additional multiple-choice question, for a total of 18 questions, about why the epinephrine autoinjector was not used during the anaphylaxis episode.

All analyses were performed with STATA 10.0 software (StataCorp, College Station, Tex). Data are presented as proportions (with 95% CIs) or medians (with interquartile ranges). Associations were examined by using χ^2 tests and Kruskal-Wallis rank tests, as appropriate. All *P* values were 2-tailed, with a *P* value of less than .05 considered statistically significant.

RESULTS

In total, 1885 persons participated in the survey. Of these, 500 (27%) were epinephrine users, meaning they had injected epinephrine into themselves or into someone else for whom they were responsible during the anaphylaxis episode. Of the 1885 participants, 1385 (73%) were nonusers, meaning they had not injected epinephrine either into themselves or into a person for whom they were responsible.

Of the 500 epinephrine users, 428 (86%) completed their 33-question survey in its entirety, and 72 (14%) skipped at least 1 question. Of the 1385 nonusers, 1388 (99%) completed the 18-question survey in its entirety, and 8 (1%) skipped at least 1 question. The nonusers' survey was 46% shorter than the users' survey. Within the epinephrine user group and within the nonuser group, there were no significant differences between the participants who completed the entire survey and those who did not (data not shown); therefore the results are presented for all participants in each group.

The epinephrine users (whether they self-injected or were injected by someone else) and the nonusers were similar in many respects; for example, in both groups 60% were female, and the median number of symptoms was 3, with 82% of epinephrine users and 78% of nonusers having involvement of 2 or more organ systems (*P* = .07). Among epinephrine users, 18% had involvement of 1 organ system, 42% had involvement of 2 organ systems, 30% had involvement of 3 organ systems, and 10% had involvement of 4 organ systems. Among nonusers, 22% had involvement of 1 organ system, 40% had involvement of 2 organ systems, 28% had involvement of 3 organ systems, and 10% had involvement of 4 organ systems. Across all categories of organ system involvement, there was no significant difference between epinephrine users and nonusers (*P* = .30).

Similar numbers of users and nonusers experienced mouth symptoms (49% vs 52%), gastrointestinal symptoms (29% vs 33%), or behavioral symptoms (infants/children only, 11% vs 15%). Similar numbers of users and nonusers had anaphylaxis triggered by tree nut (14% vs 11%), milk (5% vs 5%), shellfish (3% vs 5%), egg (2% vs 3%), wheat (0.4% vs 1%), soy (1% vs 0.5%), and other foods (5% vs 4%), and by latex (2% vs 1%) or medications (7% vs 8%).

In both groups about 47% of the anaphylaxis episodes occurred in the home, 11% during outdoor activities, 10% in a health care facility, 10% in a restaurant, and 6% in a school or childcare facility; 15% of participants did not provide an answer to this question.

TABLE I. Epinephrine users versus nonusers: Differences

	Epinephrine users*	Nonusers†	<i>P</i> value
In which year did anaphylaxis occur?			
<1 y before	35%	20%	<.001
Age of person with anaphylaxis‡			<.001
<2 y	7%	18%	
3-18 y	28%	29%	
19-65 y	62%	50%	
>65 y	3%	3%	
Symptoms§	73%	79%	.02
Breathing (eg, cough, wheeze, "hard to breathe")	70%	53%	<.001
Throat (eg, itch, throat closing, hoarseness)	59%	49%	<.001
Nose (eg, itch, sneezing, discharge, congestion)	17%	22%	.03
Shock (eg, dizzy, faint, passing out, loss of bladder control)	25%	20%	.04
Triggers of the episode§			
Peanut	13%	19%	.001
Fish	0.4%	2%	.01
Insect sting or bite	24%	17%	<.001
Taken to emergency department by ambulance	28%	15%	<.001

*Self-injected epinephrine or injected it into a person for whom they were responsible (eg, a child).

†Did not self-inject epinephrine or inject it into a person for whom they were responsible (eg, a child).

‡This *P* value represents a Pearson χ^2 test comparing users and nonusers across all age categories.

§The groups did not differ with regard to all other symptoms or triggers (see text for details).

Differences between the 2 groups are summarized in Table I. Epinephrine users were more likely to report anaphylaxis in the previous year; to be 19 to 65 years of age; to report respiratory or shock symptoms; to report peanut, fish, or insect sting triggers; to go to an emergency department; and to be taken there by ambulance, but were less likely to be under 2 years of age or to report skin or nasal symptoms.

Medication use on the day of the anaphylaxis episode is described in Table II. Epinephrine users were more likely to be asthmatic (214/428 [50%]) than nonusers (560/1377 [41%]; *P* = .001) and to have taken or been given 1 or more asthma medications on the day of the episode (all *P* < .001). Among all participants, epinephrine users were more likely than nonusers to have taken a prescription medication for a disease other than asthma (*P* < .001); however, there were no differences between the groups for those taking a nonprescription drug (*P* = .46) or an herbal or alternative medicine (*P* = .36).

With regard to preparedness for first-aid treatment of anaphylaxis (Table III), 62% of epinephrine users and 64% of nonusers had no written anaphylaxis emergency action plan.

Responses from epinephrine users

Among the 500 users, 59% injected themselves with epinephrine. Of the 41% who injected epinephrine into someone else, many (63%) were parents or other relatives; 7% injected an infant, 23% injected a child age 3 to 12 years, 3% injected a teenager,

TABLE II. Medications taken on the day of the anaphylaxis episode

	Epinephrine users* (n = 500)	Nonusers† (n = 1385)	P value
Asthma medications‡			
Median no. of asthma medications (IQR)	1 (0-1)	0 (0-0)	<.001
Any inhaled corticosteroid	12%	6%	<.001
Montelukast	11%	6%	<.001
Any inhaled bronchodilator	21%	14%	<.001
Any oral corticosteroid	14%	6%	<.001
Other medications§			
Prescription medications for diseases other than asthma (eg, hypertension)	35%	25%	<.001
Nonprescription medications (eg, cough medicine or aspirin)	10%	8%	.46
Herbal or alternative medicines	1%	2%	.36

IQR, Interquartile range.

*Self-injected epinephrine or injected it into a person for whom they were responsible (eg, a child).

†Did not self-inject epinephrine or inject it into a person for whom they were responsible (eg, a child).

‡The multiple-choice question about medications for asthma was answered only by participants who were asthmatic or reporting on behalf of an asthmatic person (ie, 214 epinephrine users with asthma and 560 nonusers with asthma). Participants could select 1 or more of 21 asthma medications from the list provided.

§The questions about other (nonasthma) medications were answered by all 1885 participants.

7% injected an adult age 19 to 65 years, and 0.2% injected an adult older than 65 years.

Additional responses from epinephrine users, 93% of whom used an EpiPen or EpiPen Jr (Dey Pharmaceuticals, Napa, Calif), are summarized in Table IV. Epinephrine was injected within 30 minutes of the onset of the first symptom by 78%, and symptom relief generally occurred promptly, with 25% reporting it in less than 5 minutes and 23% reporting it in 5 to 10 minutes. A total of 18% reported giving more than 1 epinephrine injection, and among this group, 29% reported giving a second injection within 15 minutes of the first. Among users, 53% had previously injected epinephrine from an autoinjector during an anaphylaxis episode. Many users (40%) reported taking or giving an H₁-antihistamine or an asthma puffer before the epinephrine injection.

Approximately half (55%) of the epinephrine users reported 1 or more problems (Table V), most commonly deciding whether to use the autoinjector, repeat the injection, and/or go to an emergency department.

Responses from nonusers

Nonusers' reasons for not injecting epinephrine are summarized in Table VI and included prescription for an epinephrine autoinjector not received (28%), a mild episode (13%), or another medication being taken or given (antihistamine, 38%; asthma puffer, 8%).

DISCUSSION

Most studies of anaphylaxis in the community focus on persons at risk, many of whom have never experienced an anaphylaxis

TABLE III. Preparedness for first-aid treatment of anaphylaxis

	Epinephrine users* (n = 500)	Nonusers† (n = 1385)	P value
Training in autoinjector use‡			<.001
Never trained	10%	15%	
Self-trained	38%	26%	
Physician-trained	26%	32%	
Nurse, pharmacist, EMT trained	23%	22%	
Other	4%	4%	
Personal professional medical training			
Yes	24%	20%	.06
Anaphylaxis emergency action plan available§			.66
Yes, self-written	17%	15%	
Yes, written by physician	21%	21%	
No plan	62%	64%	

EMT, Emergency medical technician.

*Self-injected epinephrine or injected it into a person for whom they were responsible (eg, a child).

†Did not self-inject epinephrine or inject it into a person for whom they were responsible (eg, a child).

‡This P value represents a Pearson χ^2 test comparing users and nonusers across categories of training in autoinjector use.§This P value represents a Pearson χ^2 test comparing users and nonusers across categories of anaphylaxis emergency action plan availability.

episode. In contrast, this study focuses on the experiences of more than 1800 self-selected participants who reported that they or someone for whom they were responsible had survived anaphylaxis in a community setting. The study design does not provide a true denominator to assess the potential magnitude of the selection bias¹⁹; however, we know that participants had access to a computer, were motivated to seek information about anaphylaxis online, were interested enough to spend up to 15 to 25 minutes completing the survey, and were literate enough to comprehend the multiple-choice questions. They were likely in reasonably good economic circumstances or had reasonably adequate health insurance because few nonusers reported difficulty in affording an epinephrine autoinjector. Taking all of these factors into consideration, we believe that participants represent a best-case scenario and that there would likely be a higher proportion of nonusers of epinephrine in a more generalizable population experiencing anaphylaxis.

Nonusers predominated: Underuse of epinephrine

Among the survey participants, 27% were epinephrine users, and 73% were nonusers. Although the study design precludes any definitive statement of the precise ratio of users to nonusers, these data support previous studies using a variety of other methods in other populations, concluding that epinephrine autoinjectors are underused in the treatment of anaphylaxis episodes in community settings.^{1,6,7,17,18} It also confirms the clinical impression that spontaneous resolution of anaphylaxis sometimes occurs.²⁰ Epinephrine users (whether they self-injected or were injected by someone else) and nonusers did not differ significantly with respect to involvement of 2 or more organ systems, suggesting that both groups experienced reactions that warranted epinephrine use.

TABLE IV. Experiences of epinephrine auto-injector users*

Time from first symptom to epinephrine injection	<30 min, 78%; 30-60 min, 18%; 1-3 h, 3%; >4 h, 0.5%; don't know, 9%
Time from injection to start of symptom relief	<5 min, 25%; 5-10 min, 23%; 11-30 min, 26%; 31-60 min, 7%; >60 min, 4%; don't know, 9%; no improvement, 6%
First symptom to improve	Breathing, 40%; throat, 18%; skin, 16%; shock, 8%; mouth, 6%
More than 1 injection given	Yes, 18%; no, 82%
If >1 injection was given, time interval between injections	0-15 min, 29%; 15-30 min, 35%; 30-45 min, 15%; 45-60 min, 11%; >1 hr, 6%
Previous use of autoinjector in anaphylaxis	Yes, 53%; no, 47%
In addition to epinephrine injection, an H ₁ -antihistamine or asthma puffer was used on the day of the episode	Yes, 80%; of these, before epinephrine injection, 40%; after epinephrine injection, 34%; not sure if before or after, 6%
Type of autoinjector used	EpiPen or EpiPen Jr, 93%; Twinject 0.3 mg or 0.15 mg (Sciele Pharma, Inc, Atlanta, Ga), 4%; other, 3%
Epinephrine within expiry date	Yes, 88%; no, 5%; not sure or don't know, 7%
If past expiry date	1-6 mo, 60%; 6-12 mo, 30%; 1-2 y, 5%; >2 y, 5%
Body position of person getting epinephrine injection	Sitting, 51%; standing, 28%; lying down, 16%; don't remember, 5%

*Self-injected epinephrine or injected it into a person for whom they were responsible (eg, a child).

Differences between epinephrine users and nonusers

Although there were more similarities than differences between users and nonusers, some of the differences deserve comment. Infants with anaphylaxis were less likely to receive an epinephrine injection compared with people in all other age groups. This might reflect either a lower rate of occurrence of anaphylaxis in infancy, difficulty in recognizing anaphylaxis in this age group, or reluctance to inject epinephrine because of awareness that the lowest dose available in an autoinjector (0.15 mg) is too high for many infants.²¹

This study extends current knowledge of the relationship between anaphylaxis and asthma. Epinephrine users were significantly more likely to have asthma and to have taken 1 or more asthma medications on the day of their anaphylaxis episode. Previous studies have found that asthma, especially if poorly controlled, increases the risk of fatal anaphylaxis.⁶⁻⁸

On the day of the episode, among all participants, epinephrine users were also more likely to have used or been given other prescription medications; however, few of them reported having taken or been given an herbal or alternative medication, which is in contrast to a recent study in patients with food allergy.²²

Comments from epinephrine users

Most users reported injecting epinephrine within 30 minutes of noticing the first anaphylaxis symptom; however, many (40%) of them also reported that they took or gave an H₁-antihistamine, an asthma puffer, or both before injecting the epinephrine. This is a

TABLE V. Problems encountered with epinephrine autoinjector use*

Deciding whether to use it	32%†
Deciding whether to go to emergency department	16%†
Holding the autoinjector in place for 10 seconds	11%
Disposing of the autoinjector	9%
Choosing exact place on the thigh for the injection	8%
Deciding whether to repeat the dose	8%†
Deciding whether to inject through clothes	6%
Remembering which end to put against thigh	3%
Following the instructions	2%
Remembering to pull off the safety release	2%

*One or more of the problems listed above were encountered by 275 (55%) of 500 epinephrine users. Users were defined as having self-injected epinephrine or injected it into a person for whom they were responsible (eg, a child).

†Some of the commonly encountered problems involved judgment about the severity of the reaction.

concern, because delay in injecting epinephrine appears to increase the likelihood of fatality.⁶⁻⁸

Although relief of anaphylaxis symptoms generally occurred promptly after epinephrine injection, a minority (6%) of epinephrine users reported no relief. This response is difficult to interpret without additional data that are not available because of study design. Lack of improvement of symptoms has been attributed previously to factors such as rapid anaphylaxis progression, concurrent use of a medication (eg, a β -adrenergic blocker), delay in epinephrine injection, subtherapeutic epinephrine dose, suboptimal autoinjector needle length, suboptimal route of injection, or suboptimal injection site.¹⁰

The proportion of users who reported more than 1 epinephrine injection (18%) is consistent with the 16% to 19% reported for food-triggered anaphylaxis in the community, as ascertained by review of emergency department records²³ and a questionnaire.²⁴ In two thirds of the users, the second injection was given more than 15 minutes after the first, and in some of them, it was given considerably later. Although intervals of 5 to 15 minutes between injections are often recommended,^{1,2,4} the optimal interval has not yet been established in prospective studies.

At the time of epinephrine injection, most (79%) of the users were sitting or standing. It is likely difficult to self-inject epinephrine into the anterolateral aspect of the mid-thigh while lying supine; however, it has been observed that suddenly sitting up, standing, or being placed in the vertical position during an anaphylaxis episode might lead to the empty ventricle syndrome and to fatality.²⁵

Most participants, whether epinephrine users or nonusers, did not have an anaphylaxis emergency action plan available. Although randomized controlled trials of the effectiveness of such plans are needed, there is evidence from nonrandomized studies, supported by expert opinion, that action plans have the potential to improve outcomes in persons with anaphylaxis.²⁶

Problems encountered by epinephrine users

Approximately half (55%) of the users reported 1 or more problems, most commonly deciding whether to use the autoinjector, go to an emergency department, or repeat the epinephrine dose. Health care professionals, too, sometimes have

TABLE VI. Why epinephrine autoinjectors were not used*

An antihistamine was used	38%
Did not receive a prescription for epinephrine autoinjector	28%
The allergic reaction was mild	13%
An asthma puffer was used	8%
Did not have epinephrine autoinjector available	8%
Unsure when to give the epinephrine injection	8%
In previous reaction no treatment was needed	8%
Afraid to inject epinephrine	6%
Quick recovery time (reaction went away fast)	4%
Concern about possible side effects of epinephrine	4%
Did not think autoinjector was needed because trigger was being avoided	3%
Epinephrine autoinjector was past expiry date	2%
Could not afford to purchase epinephrine autoinjector	1%
Was given prescription for autoinjector but did not purchase it	0.1%

*All 1385 nonusers responded to this multiple-choice question. Of these, 997 (72%) had received a prescription for an epinephrine autoinjector. When an additional analysis was performed, restricting the denominator to those nonusers who had access to an epinephrine autoinjector, the results did not materially change (data not shown). Nonusers could select 1 or more of 14 optional answers from the list provided. Nonusers were defined as having not self-injected epinephrine or injected it into a person for whom they were responsible (eg, a child).

difficulty making clinical decisions about the severity of the episode and the need for interventions. Users also reported problems that related to the epinephrine autoinjector itself, such as holding it in place for the appropriate length of time, choosing the injection site on the thigh, deciding whether to inject through clothes, and remembering which end to put against the thigh. For the first time, we have documented users' concerns about disposal of autoinjectors, which might represent concern about the possibility of needle-stick injuries,²⁷ medical waste in the environment, or other issues.

Why nonusers did not use

Approximately 28% of nonusers reported that the person at risk for anaphylaxis had not received a prescription for an epinephrine autoinjector. This is consistent with published literature documenting that only 16% and 27% of persons treated in emergency departments for food- or insect sting-triggered anaphylaxis, respectively, receive a prescription for epinephrine at discharge.^{11,12} Almost half of nonusers reported taking or giving another medication, most commonly an antihistamine. This, too, reflects the published literature documenting that whether anaphylaxis is self-treated in the community or treated by health care professionals in a hospital emergency department, H₁-antihistamines are more commonly used than epinephrine,²⁸ although antihistamines do not prevent or reverse life-threatening upper and lower respiratory tract obstruction or shock.

Other reasons for not injecting epinephrine included mild symptoms, rapid disappearance of symptoms, lack of severity of previous episodes, or spontaneous recovery from previous episodes. It is sometimes assumed that a mild or moderate previous anaphylaxis episode predicts mild future episodes; however, in the same person and among different persons, anaphylaxis severity remains unpredictable from one episode to another because of variable target organ involvement and the influence of comorbid illness and concurrently used medications.^{5,17,28,29} Even health care professionals trained and experienced in anaphylaxis

assessment are unable to predict consistently and accurately those who will have a benign course, and those who will die.^{2,8,30}

Only 2% of nonusers did not inject epinephrine because the autoinjector was past the expiry date. Although such autoinjectors still contain epinephrine, the dose might be lower than that stated on the label and inversely proportional to the length of time past the expiry date. Despite this, use of such autoinjectors is preferable to not injecting epinephrine at all.¹⁰

Lessons learned

By focusing on this unique population of anaphylaxis survivors, we have confirmed and extended the findings of previous studies in which information about anaphylaxis was collected using diverse methods and in which participants were at risk for anaphylaxis but had not necessarily experienced it. We have documented the problems of survivors who actually injected epinephrine in anaphylaxis and nonusers' reasons for not injecting epinephrine in this medical emergency. We think these insights based on the real-life experiences of persons who survived an anaphylaxis episode in the community will be useful to health care professionals in the management and education of persons at risk for anaphylaxis in this setting. For example, it might be important to increase the emphasis on prescription of epinephrine autoinjectors for those at risk, key symptoms and signs that should lead to epinephrine injection, the importance of going to a hospital emergency department after epinephrine injection, limitations of H₁-antihistamines in the first-aid treatment of anaphylaxis, and the variable severity of anaphylaxis from one episode to another in the same person and among different persons.

We thank all the survey participants, as well as Peter Bawin (Dey LP) and Melanie Stewart (Cegedim Dendrite) for their assistance.

Clinical implications: Among survivors of anaphylaxis in the community, epinephrine autoinjector users were outnumbered by nonusers. The participants' concerns regarding epinephrine use and nonuse have important implications for anaphylaxis education.

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