

# Something is still wrong: Epinephrine use in venom immunotherapy patients

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## Abstract

**Backgrounds:** Anaphylaxis is hard to recognize and, therefore, a poorly treated systemic allergic reaction. The aim of the treatment in anaphylaxis is to prevent the progression of the clinical picture to life-threatening respiratory and/or cardiovascular symptoms and signs through early diagnosis of anaphylaxis and administration of adrenaline.

**Methods:** Seventy-eight patients [(Female (F): 22 (28.2%), Male (M): 56 (71.8%)] who received venom immunotherapy were included in this study. A mini questionnaire was applied to these patients about in which situation they should use the adrenaline auto-injector (AAI), what to do after using AAI, and how to use it.

**Results:** Thirty-four patients (43.6%) were stung by a bee after initiation of immunotherapy while 16 patients (47.1%) developed urticaria/angioedema. Ten patients (29.4%) used AAI following a bee sting, whereas 24 patients (70.6%) didn't use AAI. Fifty-two (66.7%) patients correctly answered the four questions regarding what to do following administering AAI, in what cases and frequency they should have AAI prescribed, storage and transportation conditions of AAI, and how to administer AAI. Among the patients who were stung by a bee during immunotherapy, the rate of answering all questions correctly of the patients who administered AAI during anaphylaxis was determined to be significantly higher ( $p=0.001$ ).

**Conclusions:** Although adrenaline treatment is the most vital method of treatment in anaphylaxis, patients still do not have a sufficient level of awareness on the importance and vitalness of adrenaline treatment. It is very important to train patients at risk and patient relatives primarily by physicians at appropriate intervals.

**Keywords:** Anaphylaxis, Venom Allergy, Adrenaline auto Injector.

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## INTRODUCTION

Unfortunately, anaphylaxis is hard to recognize. Thus, a poorly treated systemic allergic reaction is partly related to failure to understand that anaphylaxis is a more extensive syndrome than “anaphylactic shock”. The aim of the treatment in anaphylaxis is to prevent the progression of the clinical symptoms to life-threatening respiratory and/or cardiovascular symptoms and signs through early diagnosis and administration of adrenaline. As respiratory or cardiac arrest may develop within minutes of anaphylaxis, rapid evaluation and treatment are vital (1–3). The treatment is most effective in anaphylaxis in this early period, and delayed adrenaline administration is associated with mortality (4–7).

Anaphylaxis to bee stings ranges from 0.3% to 3% (8, 9). Moreover, it was reported to affect 8% of the population in some parts of the world (10, 11). Treatment of venom-related anaphylaxis is similar to the treatment of anaphylaxis due to other causes, which is an intramuscular injection of adrenaline from the anterolateral area of the thighs. Although adrenaline administration is the only effective treatment, studies have reported its limited use to treat anaphylaxis (12, 13). The most important mistakes made in the treatment of anaphylaxis are delaying administration of adrenaline via relying on treatments with drugs such as antihistamines, steroids, and albuterol; not carrying an adrenaline auto-injector (AAI); insufficient training of the patients; not knowing how and when to use the AAI, and the wish to avoid potential side effects of adrenaline (13). Thus, it is important to increase awareness, particularly in patients at risk, and corroborate the educational level of these patients for the rapid and effective administration of adrenaline treatment.

This study aimed to evaluate attitudes and knowledge levels regarding AAI use and approaches to AAI use in case of anaphylaxis to bee stings during venom-specific immunotherapy in patients due to venom-related anaphylaxis and prescribed AAI.

## MATERIAL AND METHODS

All patients with a history of venom-related anaphylaxis followed up in our clinic (Necmettin Erbakan University Department of Clinical Immunology and Allergy)

were prescribed AAI following recommendations of international guidelines (14–16). At the same time, these patients were referred for venom immunotherapy. Prior to each venom immunotherapy shot, the patients were asked about whether a local and/or systemic reaction occurred; if yes, what interventions were made; whether they have had bee sting; and if yes, whether they used adrenaline. Following a bee sting, a dose adjustment was made under international guidelines. Furthermore, when the patient’s required adrenaline, where and how the anaphylaxis occurs, by whom adrenaline is administered, adrenaline side effects, difficulties in administration, and the mistakes made were investigated. Knowledge levels of the patients regarding the use of AAIs were evaluated, and, if needed, training on the use of adrenaline auto-injectors was repeated. Seventy-eight patients [(Female (F): 22 (28.2%), Male (M): 56 (71.8%)] who were followed-up in the Necmettin Erbakan University Department of Adult Allergy Clinic between 2014 and 2019, who participated and received venom immunotherapy, were included in the study. The patients who participated in the study were asked to complete a mini-survey. Whether they had anaphylaxis after prescription of AAI; if yes, where it was; what was used for treatment; the number of AAIs used; by whom AAI shot was administered; whether a side effect occurred following the shot and; if not used, why they did not use the AAI were investigated. Furthermore, independent of the history of anaphylaxis, following the AAI training, the patients were asked about how they were feeling, from where and how the AAI should be administered, how frequently they should have it prescribed, and what they should do after administration.

Venom (*Apis mellifera* and *Vespula vulgaris*) specific IgE antibody levels and baseline tryptase levels were measured using the CAP fluoroenzyme method (ImmunoCAP Tryptase, Unicap 100; Phadia, Uppsala, Sweden).

The whole blood count was measured by Sheath reagent with Abbott Cell Dyn 3700 series (Chicago, USA). Quantitative determination of serum immunoglobulin IgE was made using particle-enhanced immunonephelometry by the Siemens BN II/BN ProSpec system (Erlangen, Germany).

This study was approved by the clinical research ethics committee of the Necmettin Erbakan University (Date: 21.02.2020, number: 2020/2323), and written consent was obtained from all patients participating in the study.

Statistical analysis was performed using the IBM SPSS Statistics Version 22 (IBM Corporation, Armonk, NY, USA) software package. Normally distributed parameters were presented as mean  $\pm$ standard deviation, and data not normally distributed were expressed as median (minimum-maximum). Descriptive data were presented as frequencies and percentages and compared using a Chi-square or Fisher exact test. Comparisons of continuous variables between baseline characteristics were performed by independent Student-t or Mann-Whitney rank-sum tests, where appropriate.

## RESULTS

Seventy-eight patients [(Female (F): 22 (28.2%), Male (M): 56 (71.8%)] with the mean age of  $40.13 \pm 12.20$  (F:  $34.91 \pm 8.56$ , M:  $47.81 \pm 12.75$ ) years were included in the study. Sixty-eight patients (87.2%) had a history of anaphylaxis to bee sting before diagnosis of venom allergy and prescription of AAI. Venom immunotherapy was initiated in ten patients due to significant local reactions.

Thirty patients (38.5%) were on *Apis mellifera* (honey bee) immunotherapy, 38 patients (48.7%) were on *Vespula* spp. (yellow jacket) immunotherapy, and ten patients (12.8%) were on venom-specific immunotherapy with both species. The characteristics of the patients are summarized in Table 1. Following the venom allergy diagnosis, 70 patients (89.7%) were prescribed two AAIs and eight patients (10.3%) one AAI.

**Table 1. Demographic and laboratory properties of patients**

Parameters	Results
Current age, years (mean $\pm$ standard deviation)	40.13 $\pm$ 12.20
Gender, Female, n (%) Male, n (%)	22 (28.2) 56 (71.8)
Personal education level, • Primary school, n (%) • High school, n (%) • University, n (%)	36 (46.2) 16 (20.5) 26 (33.3)
Type of immunotherapy, n (%) • <i>Apis mellifera</i> • <i>Vespula</i> spp. • <i>Apis mellifera</i> + <i>Vespula</i> spp.	30 (38.5) 38 (48.7) 10 (12.8)
Concomitant diseases n (%) • Asthma • Allergic rhinitis • Atopic dermatitis	4 (5.1) 6 (7.7) 8 (10.3)
Eosinophil count, mm <sup>3</sup>	124.89 $\pm$ 69.14
Total IgE (IU/L), median (min-max)	122.15 (18.80–275)
Serum tryptase (ng/mL), median (min-max)	3.37 (1–49.2)

Ig: immunoglobulin

In addition to the AAI training provided by an allergy specialist, twenty-four patients (30.8%) watched training videos on the internet. Following the AAI training, 64 patients (82.1%) felt safe and qualified on this issue, whereas four patients (5.1%) reported anxiety and ten patients (12.8%) fear. AAI training was repeated for 12.8% of the patients at each visit.

Thirty-four patients (43.6%) were stung by a bee after immunotherapy initiation. No complaints were reported among 14 patients (41.2%) following a bee sting. However, 16 patients (47.1%) developed itching, urticaria, and angioedema, and 4 (11.7%) dizziness, blackout, and (pre-) syncope. Ten patients (29.4%) used AAI following a bee sting, whereas 24 patients (70.6%) did not use AAI.

However, six patients (17.7%) used an antihistamine drug as a self-medicine or antihistamine together with steroid treatment (2 out of 34 patients) instead of AAI.

All ten patients using AAI had used one single auto-injector, and none of the patients required a second administration. Of these patients, six patients (60%) reported no side effects related to the injector. In contrast, two patients (20%) reported pain, ache, and bleeding at the injection site, and two patients (20%) reported headaches following the administration.

Twenty-four patients did not use AAI following a bee sting. Four patients did not use AAI because they were not carrying it along with them, whereas six patients (25%) did not find it necessary because they were admitted to an emergency department. The Mini-survey is summarized in Table 2.

**Table 2. Questions and answers of the mini-survey**

Questions of Mini-survey	Answers
Have you had anaphylaxis before the adrenaline auto injector was prescribed? n (%)	Yes: 68 (87.2) No: 10 (12.8)
How many injectors were prescribed? n (%)	One: 8 (10.3) Two: 70 (89.7)
Have you been informed about the use of the AAI by anyone other than your doctor? n (%)	None: 44 (56.4) Pharmacist: 2 (2.6) Allergy Nurse: 6 (7.7) Internet/YouTube: 24 (30.8) Another patient: 2 (2.6)
Did you feel sufficient to use an adrenaline injector after injector training? n (%)	I felt, safe and sufficient: 64 (82.1) anxiety: 4 (5.1) fear: 10 (12.8)
Was adrenaline auto injector training done at every visit? n (%)	Yes: 10 (12.8) No: 68 (87.2)
Have you been stung by any bees during immunotherapy? n (%)	Yes: 34 (43.6) No: 44 (56.4)
Where did the bee sting take place? n (%)	Home: 8 (23.5) Work place: 2 (5.9) Garden: 16 (47.1) Other: 8 (23.5)

What kind of complaint did you have after the bee sting while immunotherapy continued? n (%)	No complaints: 14 (41.2) Pruritus, urticaria, angioedema: 16 (47.1) Dizziness, tinnitus, syncope: 4 (11.7)
Did you use the adrenaline auto-injector after the bee sting? n (%)	Yes: 10 (29.4) No: 24 (70.6)
Did you take a drug before applying an adrenaline auto-injector? n (%)	Yes: 6 (17.7) No: 28 (82.3)
Which drugs did you take, after the bee sting? n (%)	Antihistamines: 4 Steroids: 0 Anti-histamines + Steroids: 2 Salbutamol: 0
Who applied the adrenaline auto-injector? n (%)	Myself: 4 (40) My partner: 2 (20) My friend: 2 (20) Emergency staff: 2 (20)
Where did you apply the adrenaline auto-injector? n (%)	Work: 2 (20) Home: 4 (40) Social area: 4 (40)
What side effects did you see if you used it? n (%)	No adverse effect: 6 (60) Palpitation: 0 Pain/bleeding at the injection site: 2 (20) Nausea and vomiting: 0 Headache: 2 (20)
If you used it, how many have you used? n (%)	One: 10 (100) Two: 0
If you have not used it, what is your reason for not using it? n (%)	AAI was not with me: 4 (16.7) Since I went to the emergency room, I did not need to apply an AAI: 6 (25) I do not know exactly how to use AAI I took antihistamine/steroid drugs instead of applying AAI. My complaints were not serious. I did not need to use AAI: 14 (58.3)

AAI: Adrenaline Auto-Injector

Fifty-two (66.7%) patients correctly answered four questions regarding what to do following administering AAI, what cases and frequency they should have AAI prescribed, storage and transportation conditions of AAI,

and how to administer AAI. No significant differences were determined between those who correctly answered. It was not related to age, gender, personal atopy, and training provision on AAI at each visit (Table 3) (Table 4).

**Table 3. Comparison of patients who answered all questions about AAI use correctly with patients who did not**

	Patients who got full points (n: 52)	Patients who did not get full points (n: 26)	P
Gender, Female, n (%)	14 (26.9)	8 (30.8)	0.792
Age	39.0 ±13.14	42.38 ±9.61	0.248
Education status (high school and upper), n (%)	22 (42.3)	14 (53.8)	0.335
Patients who have had anaphylaxis before prescribing AAI, n (%)	46 (88.5)	22 (84.6)	0.724
Personal Atopy, n (%)	12 (23.1)	6 (23.1)	0.999
AAI training given at each visit	8 (15.4)	2 (7.7)	0.482
Patients stung by a bee during immunotherapy	18 (52.9)	16 (47.1)	0.031

AAI: Adrenaline Auto-Injector

Among the patients stung by a bee during immunotherapy, no difference between patients who gave and did not give full scores to the questions was determined regarding age, gender, and personal atopy. In contrast,

the rate of answering correctly to all questions of the patients who were administered AAI during anaphylaxis was significantly higher ( $p = 0.001$ ). These results are summarized in Table 5.

**Table 4. Binomial regression analysis demonstrating the relationship between baseline characteristics and getting full points from mini-survey**

Variables	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Age, year	1.024 (0.984–1.065)	0.245	1.010 (0.968–1.54)	0.635
Education status (high school and upper)	0.629 (0.244–1.621)	0.337	0.961 (0.317–2.916)	0.944
Stung by a bee during IT	3.022 (1.140–8.012)	0.026	3.022 (1.140–8.012)	0.026

IT: Immunotherapy

**Table 5. Features of patients stung by a bee during venom-specific immunotherapy**

	Patients who received full points (n: 18)	Patients who did not receive full points (n: 16)	P
Gender, Female, n (%)	4 (22.2)	6 (37.5)	0.329
Age	36.41 ±11.75	37.60 ±11.11	0.777
Education status (high school and upper), n (%)	6 (33.3)	6 (37.5)	0.800
Patients who have had anaphylaxis before prescribing AAI, n (%)	16 (53.3)	14 (46.7)	0.900
Personal Atopy, n (%)	4 (22.2)	6 (37.5)	0.329
AAI training given at each visit	2 (11.1)	2 (12.5)	0.900
Patients who administered AAI after stung by a bee	10 (55.6)	0	0.001

AAI: Adrenaline Auto-Injector

## DISCUSSION

Hymenoptera venom allergy is the most common cause of anaphylaxis in adults and the second most common after food in children. Moreover, it is an important cause of anaphylaxis-related mortality worldwide (17, 18). Adrenaline, however, is the indispensable first-line treatment and is life-saving (14). In our study, of the patients who received venom immunotherapy, 34 patients (43.6%) were stung by a bee after initiation of immunotherapy. Despite 20 patients (25.6%) who developed bee sting-related anaphylaxis, only 10 (12.8%) used AAI. These ratios revealed that approximately one-fourth of the patients prescribed with AAI had anaphylaxis within five years.

In our study, the rate of AAI use among the patients who were prescribed AAI was 12.8%. This rate is very low compared to the administration rate of AAI (29.9%) reported by Fleisher et al. (19). In another study from Turkey, the rate of AAI use was 6.84% (20). In the European Anaphylaxis Registry, the rate of AAI use (12%) in 2011 increased by up to 25% in 2014. Although there has been some increase in awareness and diagnosis of anaphylaxis and rates of AAI use, these rates are still below expected. Therefore, giving regular training to all clinicians, regardless of their specialty, that adrenaline is indispensable in treating anaphylaxis will increase awareness of this issue. In addition, the inclusion of patients and their relatives in these training may increase AAI usage rates.

Approximately 1–20% of cases of anaphylaxis have a biphasic pattern, i.e., after presenting symptoms disappear completely, and anaphylaxis symptoms recur in the absence of additional exposure in 1–20% of the patients (15, 21–23). Furthermore, some anaphylactic reactions may persist from hours to days, and in extreme conditions, weeks (3). Therefore, it is recommended to prescribe at least two AAIs for these patients (24). Song et al. reported that 82% of the patients who were prescribed two AAIs did not carry two AAIs with them (25). In our study, 89.7% of the patients were prescribed two AAIs.

Following training on AAI, anxiety and perturbation may develop because of both reinforced awareness on anaphylaxis and self-administration of AAI. Esenboga et al., in a study on a pediatric patient group (20), reported that of the family of the patients, 42.6% reported anxiety, and 15.4% felt fear following training on AAI. In our study, 5.1% reported anxiety, and 12.1% reported fear following AAI.

There may be mistakes made in AAI use, as it should be used only when necessary, and its administration includes some steps. Only 30–44% of the patients can appropriately administer AAI after prescription of the drug and attaining training (26). This makes training on AAI use essential. Although the use of the internet and smartphones has become popular, in our study, the rate of those watching training videos on AAI use on the internet was only 30.8%. In addition, training on AAI use by physicians at

each visit for only 10.8% of the patients is also a critical deficiency. Rate of those who correctly answered all questions regarding what to do following administering AAI, in what cases and frequency they should have AAI prescribed, storage and transportation conditions of AAI, and how to administer AAI was relatively low (66.7%). In another study on a pediatric patient group, these rates were  $\geq 85\%$  (20). The difference may result from our deficiency in training on AAI, and thus it is important for physicians and necessary to be corrected.

Bee sting-related anaphylaxis can occur at any place. Therefore, it is imperative that patients carry AAI with themselves continuously. Nevertheless, 30–70% of the patients do not carry AAI with them (26). Patients (16.6%) did not administer adrenaline following a bee sting because they did not have AAI along with them. In addition, in 6 (60%) out of 10 patients, AAI was administered by another person beyond themselves. Therefore, we believe that it is vital to train relatives (husband/wife, children, colleagues, etc.) of the patients at risk of anaphylaxis due to panic and hypotension, needle phobia, and risk of failure to administer AAI. In the International consensus on (ICON) anaphylaxis report, it was highlighted to train not only the patients at risk and their caregivers but also all clinicians, including the emergency department and primary physicians, and to spread this training to the whole society to increase awareness on anaphylaxis (16).

In all age groups, adrenaline administration may lead to side effects, including anxiety, palpitation, headache, and tremor, regardless of the route of administration. Nevertheless, there is no absolute contraindication for the use of adrenaline to treat anaphylaxis (4, 7). In our study, two patients (20%) had a headache, and two patients (20%) had palpitation, whereas 60% of the patients who used adrenaline did not report any side effects.

Adrenaline must be administered immediately after anaphylaxis is diagnosed. In anaphylaxis, delayed adrenaline administration is the leading cause of mortality (1, 27, 28). H1 antihistamines relieve itching, angioedema, and urticaria but are ineffective for stridor, shortness of breath, gastrointestinal symptoms, and hypotension (5). Albuterol, however, may be accompanied by adrenaline for patients with severe bronchospasm but does not resolve airway edema and treat hypotension or shock. Despite this, six (17.7%) out of 34 patients lost time on AAI administration following a bee sting by receiving

treatment with antihistamines and steroids. Retrospective design and relatively small study population are the most important limitations in our study.

In conclusion, although adrenaline treatment is the most vital treatment method in anaphylaxis, patients do not have sufficient awareness of the importance and vitalness of adrenaline treatment. It is imperative to train patients at risk and patient's relatives primarily by the physicians at appropriate intervals. The results of this study revealed the weaknesses of the practices in our clinic. Particularly the necessity of stepping up from patient enlightenment to "raising patients' awareness." Even though training on drug or device use is ideally provided, unfortunately, the studies on AAI use will not be very different unless consciousness and awareness of AAI administration are provided.

## Declarations

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This study was approved by the clinical research ethics committee of the Necmettin Erbakan University (Date: 21.02.2020, number: 2020/2323), and written consent was obtained from all patients participating in the study.

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