Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

Allergy

POSITION PAPER

Self-medication of anaphylactic reactions due to Hymenoptera stings—an EAACI Task Force Consensus Statement

M. B. Bilò[1], E. Cichocka-Jarosz[2], R. Pumphrey[3], J. N. Oude-Elberink[4], J. Lange[5], T. Jakob[6], P. Bonadonna[7], J. Fernandez[8], M. Kosnik[9], A. Helbling[10], H. Mosbech[11], R. Gawlik[12], M. Niedoszytko[13], V. Patella[14], V. Pravettoni[15], R. Rodrigues-Alves[16], G. J. Sturm[17,18] & F. Rueff[19]

[1]Allergy Unit, Department of Internal Medicine, University Hospital, Ancona, Italy; [2]Department of Pediatrics, Jagiellonian University Medical College, Krakow, Poland; [3]Immunology, Central Manchester University Hospitals, Manchester, UK; [4]Department of Allergology, GRIAC Research Institute, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [5]Department of Pediatric Pulmonology and Allergy, Medical University of Warsaw, Warsaw, Poland; [6]Department of Dermatology and Allergology, Justus Liebig University Gießen, University Medical Center Gießen and Marburg GmbH, Gießen, Germany; [7]Allergy Unit, Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy; [8]Allergy Service, Department of Clinical Medicine, Alicante University Hospital, UMH, Alicante, Spain; [9]University Clinic of Respiratory and Allergic Disease, Golnik, Slovenia; [10]Division of Allergology, University Clinic of Rheumatology, Immunology and Allergology, University Hospital/Inselspital, Bern, Switzerland; [11]Allergy Unit, Department of Dermatology and Allergy, Copenhagen University Hospital Gentofte, Hellerup, Denmark; [12]Department of Internal Medicine, Allergy and Clinical Immunology, Silesian University of Medicine, Katowice, Poland; [13]Department of Allergology, Medical University of Gdansk, Gdansk, Poland; [14]Division and School of Allergy and Clinical Immunology, ASL Salerno and University of Naples Federico II, Naples, Battipaglia Hospital, Salerno, Italy; [15]Clinical Allergy and Immunology Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [16]Allergy and Clinical Immunology Division, Divino Espirito Santo Hospital, Ponta Delgada, Portugal; [17]Ambulatory for Allergy and Clinical Immunology, Vienna; [18]Department of Dermatology, Medical University of Graz, Graz, Austria; [19]Department of Dermatology and Allergology, Ludwig-Maximilian University, Munich, Germany

To cite this article: Bilò MB, Cichocka-Jarosz E, Pumphrey R, Oude-Elberink JN, Lange J, Jakob T, Bonadonna P, Fernandez J, Kosnik M, Helbling A, Mosbech H, Gawlik R, Niedoszytko M, Patella V, Pravettoni V, Rodrigues-Alves R, Sturm GJ, Rueff F. Self-medication of anaphylactic reactions due to Hymenoptera stings—an EAACI Task Force Consensus Statement. *Allergy* 2016; **71**: 931–943.

Keywords
adrenaline; anaphylaxis; hymenoptera; immunotherapy; insect venom allergy.

Correspondence
Maria Beatrice Bilò, Allergy Unit, Department of Internal Medicine, University Hospital, Ancona, Italy.
Tel.: +39 071 5963804
Fax: +39 071 5963253
E-mail: mariabeatrice.bilo@ospedaliriuniti.marche.it

Accepted for publication 4 April 2016

DOI:10.1111/all.12908

Edited by: Pascal Demoly

Abstract

An anaphylactic reaction due to a Hymenoptera sting is a clinical emergency, and patients, their caregivers as well as all healthcare professionals should be familiar with its recognition and acute management. This consensus report has been prepared by a European expert panel of the EAACI Interest Group of Insect Venom Hypersensitivity. It is targeted at allergists, clinical immunologists, internal medicine specialists, pediatricians, general practitioners, emergency department doctors, and any other healthcare professional involved. The aim was to report the scientific evidence on self-medication of anaphylactic reactions due to Hymenoptera stings, to inform healthcare staff about appropriate patient self-management of sting reactions, to propose indications for the prescription of an adrenaline auto-injector (AAI), and to discuss other forms of medication. First-line treatment for Hymenoptera sting anaphylaxis is intramuscular adrenaline. Prescription of AAIs is mandatory in the case of venom-allergic patients who suffer from mast cell diseases or with an elevated baseline serum tryptase level and in untreated patients with a history of a systemic reaction involving at least two

Abbreviations
AAI, adrenaline auto-injector; ACE, angiotensin-converting enzyme; BST, baseline serum tryptase; EAACI, European Academy of Allergy and Clinical Immunology; ED, Emergency Department; GRADE, The Grading of Recommendations Assessment, Development and Evaluation; HVA, hymenoptera venom allergy; i.m., intramuscular; i.v., intravenous; ISA, insect sting anaphylaxis; s.c., subcutaneous; SAR, systemic allergic reaction; VIT, venom immunotherapy.

different organ systems. AAI prescription should also be considered in other specific situations before, during, and after stopping venom immunotherapy.

Systemic IgE-mediated reactions to Hymenoptera stings may range from mild symptoms limited to the skin (e.g. generalized pruritus, urticaria) to a fully developed cardiovascular shock with a potentially fatal outcome. Several clinical classifications are in use and reported elsewhere (1). There is a common agreement that the term anaphylaxis is used only for a severe form of a systemic immediate type reaction if there is involvement of skin or mucosal tissue and respiratory or cardiovascular or gastrointestinal symptoms (2–7). It is generally assumed that treatment with adrenaline before the reaction becomes severe improves the chance of survival (8–11). Unfortunately, in fatal and near-fatal sting reactions, the time to shock or cardiac/respiratory arrest is short (median 12 min) (8) meaning that timely therapeutic intervention is essential. Today, in many countries, AAIs have become the mainstay of anaphylaxis self-management. Although AAIs appear to be a simple solution, patients are faced with many problems.

It is now 20 years since the original EAACI position paper on the emergency treatment of allergic reactions to Hymenoptera stings was published (12), and subsequent reports of suboptimal management indicate that an update on this topic is necessary. The objectives of the present document are as follows:

1 To summarize the scientific evidence on which this position paper is based.
2 To inform healthcare staff about appropriate self-management of patients following an anaphylactic reaction to a sting.
3 To propose indications for the prescription of an AAI.
4 To discuss other forms of medication.

This consensus report is targeted at allergists, clinical immunologists, internal medicine specialists, pediatricians, general practitioners, emergency department (ED) doctors, and any other healthcare professional involved.

Materials and methods

This consensus document was prepared by a European Academy of Allergy and Clinical Immunology (EAACI) Task Force, European expert panel of 18 members of the EAACI Interest Group on Insect Venom Hypersensitivity. Data on doctors' intervention, adrenaline's features, and indications for the prescription of an AAI are based on current English literature using a MEDLINE and EMBASE search. The authors used the GRADE system of evaluation to translate the results of this research into evidence-based recommendations (13) (Box 1).

In June 2012, the expert panel discussed the first written draft version of the document. A revised draft was discussed in December 2012 and then in 2013, 2014, and 2015, to achieve group consensus. All issues that received the agreement of ≥94% of the experts were included in the final draft; the same agreement was accepted for an absolute indication for AAI prescription. The authors suggest an update of this consensus document in 2020 unless there are important advances before then.

Anaphylaxis due to insect stings

Definition, pathogenesis, and clinical features

Insect sting anaphylaxis is 'a serious life-threatening generalized/systemic hypersensitivity reaction which is rapid in onset and might cause death' (2–7) as a consequence of an insect sting.

The pathophysiology of insect sting anaphylaxis (ISA) primarily involves crosslinking of IgE with aggregation of FcεRI on mast cells and basophils, which results in a sudden release of preformed and newly generated cell-derived mediators (14, 15).

Possible alternative or concomitant mechanisms are not completely understood (16), but some evidence shows concomitant activation of complement and activation of the plasma contact system (17, 18).

At the onset of an individual anaphylactic episode, its course is unpredictable and can result in different clinical patterns (19, 20): (i) spontaneous resolution due to endogenous counter regulation, (ii) biphasic response, (iii) protracted reaction, and (iv) fatal (usually <6 h after sting). ISA may present with prodromal signs and symptoms or as a fully developed reaction (Table 1). In children, about 60% of systemic reactions (SARs) are mild and restricted to the skin, whereas in adults, respiratory, or cardiovascular symptoms occur in about 70% of SARs (1). Table 2 shows the risk factors for severe anaphylactic reaction due to insect stings.

Patient's recognition

Patients should be taught which symptoms may forecast a major reaction following a sting in the majority of cases (Table 1) (21).

In the case of a first event of ISA, a patient may not be aware of its recognition and risk. Unfortunately, around 67% of UK fatal sting reactions occur the first time the patient reacts (22), limiting the effectiveness of all efforts to prevent fatal reactions. Therefore, widespread information and education of anaphylaxis and its treatment are essential.

Self-treatment of systemic allergic sting reactions

All patients with a previous SAR due to a Hymenoptera sting should be prescribed emergency medications and advised to carry them, especially during the Hymenoptera season (5, 23).

Aspiration of adrenaline from a vial is time-consuming and the delay may prevent the beneficial effects of the drug; therefore, AAIs are recommended (23) (grade of

Box 1: Levels of evidence and recommendations (13)

Level of evidence	
Level I	Systematic reviews, meta-analysis, randomized control trials
Level II	Two groups, nonrandomized studies (e.g., cohort, case–control)
Level III	One-group nonrandomized (e.g., before and after, pretest and posttest)
Level IV	Descriptive studies that include analysis of outcomes (single-subject design, case series)
Level V	Case reports and expert opinion that include narrative literature, reviews, and consensus statements
Grades of recommendation	
Grade A	Consistent level I studies
Grade B	Consistent level II or III studies or extrapolations from level I studies
Grade C	Level IV studies or extrapolations from level II or III studies
Grade D	Level V evidence or troublingly inconsistent or inconclusive studies at any level

Table 1 Symptoms and signs of anaphylaxis due to insect sting

Skin	
Prodromal	Feeling of warmth, itching [may occur in areas such as external auditory canals, palms, soles, or groin], and 'hair standing on end' [piloerection]
Developed	Flushing [erythema], urticaria, angioedema
Oral	
Prodromal	Itching or tingling of lips, tongue, or palate, metallic taste
Developed	Edema of lips, tongue, uvula
Respiratory	
Prodromal	Nose (Itching, Congestion, Rhinorrhea, And Sneezing) Dysphonia, hoarseness Lower airways (shortness of breath (dyspnea), chest tightness, deep or repetitive cough)
Developed	Stridor, wheezing, and cyanosis
Gastrointestinal	
Prodromal	Nausea, laryngeal—itching and 'tightness' in the throat
Developed	Abdominal pain [colic, cramps], vomiting,diarrhea†, and dysphagia
Cardiovascular	
Prodromal	Feeling of faintness or dizziness; tunnel vision, difficulty hearing
Developed	Syncope, chest pain, palpitations, tachycardia, bradycardia or other dysrhythmia, hypotension*, and cardiac arrest, loss of consciousness, Kounis syndrome type I/II/III
Neurologic	Anxiety, apprehension, sense of impending doom, sopor, stupor Headache†, and confusion; seizures† Children may become irritable, cease to play, or have other sudden behavioral changes, urinary or fecal incontinence†
Ocular	Itching, erythema and edema, tearing, and conjunctival erythema
Other	Uterine cramps and premature bleeding in women and girls

*Low systolic blood pressure is defined as <70 mmHg from 1 month to 1 year, < [70 mmHg + 2× age in years)] from 1 to 10 years, <90 mmHg from 11 to adulthood) or greater than 30% decrease from that person's baseline systolic pressure in all groups.
†Very rare.

recommendation D). Several AAI preparations for immediate self-application are commercially available (24–26) (see specific section).

Patients experiencing anaphylaxis should be advised of other interventions needed to manage the reaction. They should be advised to call for help, if possible, and adjust their position according to their leading symptoms: When respiratory distress is leading, they should sit or remain seated, and when symptoms of circulatory instability are leading, they should lie down on their back with the lower extremities elevated (9) (grade of recommendation D).

In addition, patients may receive a set of tablets containing an adequate dose of a rapidly effective nonsedating oral antihistamine (e.g. levocetirizine 10 mg, cetirizine 20 mg, or double dose for children according to the age) and corticosteroids (e.g. prednisone: for adults 50–100 mg and 1–2 mg/kg body weight in children) (4, 6, 12, 27). For mild SARs, oral antihistamines and corticosteroids are a sufficient treatment. Systemic allergic reactions due to field stings did not occur in patients on VIT taking oral antihistamines and corticosteroids right after the sting before any symptoms have occurred (28). However, their use should not delay self-

Table 2 Risk factors for severe systemic reactions due to insect stings

- Absence of skin symptoms such as urticaria/angioedema during anaphylaxis
- Time interval < 5 min from sting to onset of symptoms
- Age over 65 years
- Usually bee venom, in mast cell disorders wasp venom
- Systemic reactions (the higher the grade the higher the risk)
- Adult patients suffering from mastocytosis: indolent systemic mastocytosis without skin lesions (gene expression), patients with an elevated basal serum tryptase (BST) level
- Cardiac comorbidities and concurrent cardiovascular medication (e.g., ACE inhibitors)*

*Not confirmed by all studies.

treatment with an AAI if one is carried and extracutaneous symptoms occur. Delayed injection of adrenaline in anaphylaxis is reported to be associated with mortality (8–11) and biphasic reactions (29) (grade of recommendation D).

Patients with asthma should be advised to carry their inhaled short-acting beta-2-agonist and to use as many inhalations as needed if respiratory difficulty follows a sting (30) (grade of recommendation D). Any patient referred following a sting SAR should be given written recommendations for the avoidance of insect stings as well as a written personalized emergency action (Tables 3 and 4).

Table 3 Recommendations for patients allergic to Hymenoptera venom

- Allergic beekeepers are strongly advised to stop beekeeping before achieving immunoprotection by venom immunotherapy.
- Avoid staying in open spaces among plants in bloom (e.g. meadows, orchards), especially when there are mature, ripe fruits on the ground.
- Refrain from eating fruit, sweet jam and jelly, ice-cream and sandwiches outdoors (wasps).
- Keep trash can lids tightly closed, store leftover food in tightly closed containers (wasps).
- Remember, the smell of sweat, any fragrances, and deodorants attract insects, even insect/mosquito repellents.
- Walking barefoot increases the risk of a sting.
- Recommended colors of garments are white, green and beige (brightly colored garments attract insects) (bees)
- While staying at places with an increased risk of exposure to honey bees or wasps, wear long slacks, long-sleeved shirts, hats, and possibly also gloves.
- Do not drink from unattended beer, coke, or other beverages' cans
- In case of an attack by wasps or bees, cover your head.
- Do not kill insects without reason—there may be others around.
- Stings are common when working near nests, when attention is focused on the work. Look for signs of nests before starting window cleaning, hedge cutting, trimming, and so on.
- Queen wasps may hibernate in gloves and boots: check these before first use in the winter, even if they were stored in drawers or cupboards.

First-line medications

Adrenaline

Even though there is no evidence from prospective, randomized, or quasi-randomized trials on the effectiveness of adrenaline for the emergency management of anaphylaxis mainly due to practical and ethical reasons (31), there is a universal agreement that adrenaline is the mainstay of therapy to halt the progression of anaphylaxis and to reverse potentially life-threatening cardiopulmonary manifestations (26, 31–35) (grade of recommendation C).

Routes of administration and dosage

There have been no prospective human studies performed during the management of anaphylaxis to evaluate the bioavailability and optimal dose of adrenaline given subcutaneously (s.c.), intramuscularly (i.m.), or intravenously (i.v.) (31, 36). However, according to studies performed in healthy children and adults, adrenaline should be injected by the i.m. route and preferentially in the mid-anterolateral thigh as soon as anaphylaxis is diagnosed or strongly suspected (4, 6, 19, 37) (grade of recommendation A). Given the potentially life-threatening outcome of anaphylaxis, there are no absolute contraindications for the use of adrenaline in the elderly and in patients with preexisting cardiovascular disease or for use in infants or children (6, 20, 37, 38). Intramuscular adrenaline should be given at a dose of 10 μg per kg of body weight but not exceeding a maximum of 300 μg in children and 500 μg in adults (4, 20, 37). Depending on the severity of the episode and the response to the initial injection, the dose should be repeated every 5–15 min, as needed (37). Because of the potential harm from the use of i.v. adrenaline (39), guidelines generally recommend that the i.v. route has to be given in a resuscitation

Table 4 Principles of self-management immediately after a sting for patients and caregivers

1. Remove a stinger (if venom sac is still attached).
2. After a sting, immediately take in emergency medication pills in doses prescribed by the physician (antihistamines, glucocorticosteroids).
3. If after a sting, you develop any of the symptoms listed below, despite the administration of medication, you must use an adrenaline auto-injector: After a sting, you develop intense coughing, hoarseness, labored breathing, wheezing, problems with swallowing saliva, speech disturbances, weakness, intense rash, and edema (especially if involving the lips and tongue).
4. Call for help.
5. Sit up if respiratory distress does occur or to lay on back with the lower extremities elevated if you experience symptoms of circulatory instability happen.
6. Following a sting, do not stay alone.

area in cases that do not respond to initial treatment with i.m. adrenaline and where cardiac or respiratory arrest is considered imminent (40).

Although the use of inhaled adrenaline is not recommended in any form of anaphylaxis, in the event of stridor from laryngeal edema, nebulized adrenaline (2–5 ml, 1 mg/ml) can be used in addition to i.m. adrenaline (grade of recommendation D).

Negative outcomes

No prospective studies performed during the management of anaphylaxis in humans are available to assess the incidence of adverse effects to adrenaline (31). When adrenaline has been given in an excessive dose, an inadequately diluted i.v. dose, or an overly rapid rate of infusion, it has been associated with the induction of fatal cardiac arrhythmias, myocardial infarction, and pulmonary edema (8, 39, 41–43). Individuals thought to be particularly at risk of adverse effects of adrenaline include elderly patients and patients with hypertension, arteriopathies, or known ischemic heart disease (8, 9). These patients may also be at increased risk of cardiac problems due to the anaphylactic episode itself (43–45). It is difficult, particularly in retrospect, to dissect potentially adverse effects of adrenaline from the known effects of anaphylaxis (8, 38, 41, 46).

Antihistamines

Systemic and oral anti-H1 antihistamines can be useful in treating mild sting reactions (those limited to skin manifestations, itching, urticaria, angioedema, as well as eye and nasal symptoms) (47) (grade of recommendation B). No high-quality evidence from randomized, controlled trials exists to support the use of H1-antihistamines and H2-antihistamines in the treatment of anaphylaxis (47, 48). Despite the lack of evidence, it is still recommended in guidelines for the management of anaphylaxis (49).

Glucocorticosteroids

There is no evidence from randomized, controlled trials to confirm the effectiveness of glucocorticoids in the treatment of anaphylaxis (50, 51).

They potentially relieve protracted anaphylaxis symptoms and are thought to prevent biphasic anaphylaxis (4, 6, 50, 52), although these effects have never been proven (grade of recommendation D). Other drugs suggested as second-line medications in the treatment of anaphylaxis were described elsewhere (37).

ED doctor intervention

Few studies have examined the management of ISA in the ED or the emergency medical transport system. The results demonstrated that patients with ISA continue to receive care discordant with the guidelines for the emergency management of anaphylaxis. Only a few of the patients received a prescription for AAI or referral to an allergy specialist at ED discharge (53–55). Pharmacological treatment of anaphylaxis by ED doctors is not within the scope of this document. However, some practical suggestions are provided below.

1 Because anaphylaxis is often misdiagnosed in ED, it is essential that the clinical record is complete (e.g. blood pressure, pulse, and oxygen saturation).
2 Record the daily medication and any additional self-medication taken on the day of the sting, in particular ACE inhibitor or beta-blocker.
3 Record any additional risk factors for reaction severity such as upright position following onset of shock, supine position in late pregnancy, and so on.
4 For diagnosis of doubtful reactions, collect blood (ideally within 1–2 h but no later than 4 h from the onset of symptoms) for serum tryptase testing (3 ml clotted sample, serum separated and frozen).
5 Patient should be observed for a minimum of 6 h preferably up to 24 h from the beginning of the reaction (37) (grade of recommendation D). In case of patients with a history of biphasic ISA, comorbidities or other risk factors the time of observation should be thoroughly documented.
6 After emergency treatment for suspected ISA, prescribe the patient (or, as appropriate, their parent and/or care givers) an AAI that is appropriate for age and body mass (56). Patients must receive a referral to a specialist allergy service.

Self-injectable adrenaline

Currently available adrenaline auto-injectors

Adrenaline auto-injectors currently available in Europe are designed to deliver a single dose of 0.15 or 0.3 mg adrenaline in a sterile solution i.m. into the vastus lateralis muscle of the thigh. In addition, Anapen® and Emerade® are available in a 0.5 mg version (Table 5).

A redesigned EpiPen® was introduced in some countries in 2011 and 2012.

The correct administration sequences for EpiPen®, Jext®, Anapen®, and Emerade® are reported in Box 2.

EpiPen and Jext are cartridge-based AAIs, whereas Anapen and Emerade are syringe-based AAIs (24). In previous studies addressed to comparison between cartridge-based devices (Jext and EpiPen) and syringe-based Anapen, Jext performed better than EpiPen® or Anapen® following mechanical stress designed to mimic real-world use (57). A more recent paper showed that most subjects correctly demonstrated all steps in the use of the redesigned EpiPen® and Anapen® both prior to and after training on use; however, after 3 months, significantly more participants correctly demonstrated use of EpiPen® compared to Anapen® (58). On the other hand, digital injection was more common at 1 year with the old version of EpiPen® than Anapen® (59). Recently published results of comparison between Emerade®, Jext®, and EpiPen® indicated that the Emerade® is an intuitive, easy-to-use AAI, its administration took less time in

Table 5 Currently available adrenaline autoinjectors in Europe (doses and exposed needle length)

Adrenaline autoinjector	Single dose children weight <25 kg	Single dose adults and children weight ≥25 kg	Single dose adults
Cartridge-based AAI			
EpiPen®	0.15 mg (13 mm)	0.30 mg (15 mm)	
Fastjekt® (Italy and Germany)	0.15 mg (13 mm)	0.30 mg (15 mm)	
Altellus® (Spain)	0.15 mg	0.30 mg	
Cartridge-based AAI			
Jext®	0.15 mg (13 mm)	0.30 mg (15 mm)	
Syringe-based AAI			
Anapen®	0.15 mg (7 mm)	0.30 mg (7 mm)	0.50 mg (7 mm)
Emerade®	0.15 mg (16 mm)	0.30 mg (25 mm)	0.50 mg (25 mm)

comparison with the other AAIs, and its instruction was easy to be followed (60).

The shelf life may differ between AAI devices due to storage at pharmacies, retailers, and producers. Among European products, EpiPen® is available as a twin pack of two devices.

Other AAIs, TwinJect, Adrenaclick, and Auvi-Q, with two dosages (0.3 and 0.15 mg), are available in the USA only (in 2015). TwinJect® is a syringe-based device that contains two doses of adrenaline (24). Auvi-Q® was designed to be intuitive to use and reduce the potential for use-related errors, by including audible and visible cues for use. For most devices, patients are instructed to hold the device in place for 10 s after firing. A recent *ex vivo* study on adrenaline absorption suggested, however, that holding the device in place for 1 s might be just as effective (61).

Dosage of AAI and needle length

The availability of only two fixed doses of adrenaline represents a problem especially for infants and children allergic to food, as ISA is extremely rare in infants. When using AAI, patients weighing between 7.5 and 25 kg should receive a 0.15 mg dose while those at 25–30 kg should move to 0.3 mg (6, 7, 26). Even in infants, a 0.15 mg dose is suggested in community settings (62, 63). However, a large proportion of children <15 kg prescribed an AAI is at risk of having the auto-injector administered into bone. Therefore, AAIs should be prescribed with appropriate counseling in this population (64).

Regardless of the design of the AAI, crucial for efficacy is its needle length, which determines whether the adrenaline goes intramuscularly or subcutaneously (Table 5). The use of currently available AAIs in many women and overweight or obese children may result inadvertently in the s.c. rather than the i.m. deposition (65–68). Even the most recently licensed Emerade® 0.5 mg and 0.3 mg auto-injectors with an exposed needle length of 25 mm cannot ensure an i.m. injection in all patients (65).

It is recommended to replace the AAI when the solution is discolored or contains a precipitate, and when expiration date is nearing. However, in the first aid treatment of anaphylaxis, if the only AAI available is outdated but free of precipitate, it could be used in preference to no adrenaline injection at all, because it might still have some beneficial effects (69).

Side-effects associated with AAIs

Patients and physicians are sometimes reluctant to use adrenaline early in the course of anaphylaxis because of concerns of potential adverse effects (31). In a study on the burden of the EpiPen® in insect venom-allergic patients, only 20% were concerned about side-effects, while 60% were not after receiving adequate EpiPen® instruction (70). What might be expected about five minutes after i.m. administration of the proper dose are sensation of cold (shivering), trembling, and elevation of the heartbeat. There are no reports about significant adverse effects, such as ventricular arrhythmias, hypertensive crisis, and pulmonary edema, in neither adults nor children using AAIs for the treatment of anaphylaxis.

Because of difficulties inherent to patient's emergency self-injections, the prospect of rapidly disintegrating sublingual tablets is a welcome one.

Indication for prescription of an adrenaline auto-injector

An individual experiencing respiratory or cardiovascular symptom after exposure to a known allergen in the community should receive an AAI immediately and should be instructed in its use (6).

The first quandary for the physician is to determine which patients who have not actually experienced anaphylaxis as such might also be at risk of anaphylaxis and might also benefit from the prescription of an AAI (71). In this context, the field of HVA is very peculiar as the prescription of an AAI may be indicated not only in untreated patients with a history of SARs, but also in some already treated with venom immunotherapy (VIT) and in some even after stopping VIT. One concern that might be raised about lowering the threshold for prescribing AAIs is that this may lead to unnecessary adverse effects on the patients' quality of life, because some may view the prescription as the physicians' confirmation of a potentially deadly disease.

Some indications for AAI prescription to patients with HVA have been suggested so far (5, 6, 23, 72). In clinical

Box 2: Step-by-step self-administration of adrenaline autoinjectors (AAI) according to manufactures' recommendations

	EPIPEN/FASTJEKT/ALTELLUS	JEXT	EMERADE	ANAPEN
STEP 1	Grasp your pen in your dominant hand (the one you use to write with) with the orange tip pointing downward	Grasp the JEXT injector in your dominant hand (the one you use to write with) with your thumb closest to the yellow cap	Grasp the Emerade injector in your dominant hand (the one you use to write with)	Grasp the Anapen injector in your dominant hand (the one you use to write with)
STEP 2	Form fist around the unit (orange tip down). Then pull off the blue safety release	Pull off the yellow cap with your other hand	Remove the needle shield	Remove the black safety cap from the needle
STEP 3	Hold orange tip near outer thigh	Leg should be immobilized before use. It is not necessary to remove trousers	Leg should be immobilized before use. It is not necessary to remove trousers	Remove the protective cap from the red button
STEP 4	Leg should be immobilized before use. It is not necessary to remove trousers	Place the black injector tip against your outer thigh, holding the injector at a right angle (approx. 90°) to the thigh	Place and press Emerade against outer side of your thigh, holding the injector at a right angle (approx. 90°) to the thigh	Leg should be immobilized before use. It is not necessary to remove trousers.
STEP 5	Swing and firmly push against outer thigh at a right angle (approx. 90°) until it clicks	Push the black tip firmly into your outer thigh until you hear a 'click' confirming the injection has started, then keep it pushed in	Press the white tip firmly into your outer thigh until you hear a 'click' confirming the injection goes to the muscle	Place your Anapen needle against the skin of the anterolateral thigh and press the red button. In emergency, in slender individuals, the medication may be injected through thin clothing. Considerably dirty skin at the site of the planned injection should first be cleaned
STEP 6	Hold your EpiPen/Fastjekt/ Altellus at the site of injection for 10 s (a slow count to 10)	Hold the injector firmly in place against the thigh for 10 s (a slow count to 10) then remove. The black tip will extend automatically and hide the needle	Hold Emerade against the thigh for about 5 s (a slow count up to 5) then remove. The white tip will extend automatically and hide the needle	Hold your Anapen at the site of injection for 10 s (a slow count to 10)
STEP 7	Remove unit from thigh (the orange needle cover will extend to cover needle). Massage the injection site for 10 s	Massage the injection area for 10 s	Gently massage the injection site afterward	

- Call for help (ask for an ambulance and say 'anaphylaxis'). If you are unable to make the call, get someone else to call for you.
- Do this immediately after using your first pen if you have more than one, even if you now feel better.
- Do this immediately if you would have used your pen but find you do not have it with you.
- If the reaction is obviously severe, do not delay using the first pen until after the call for help.

practice, these indications differ from country to country and between physicians in the same country, indicating that AAI prescription is a decision that often is made on a case-to-case basis and should include a thorough discussion of the issues involved.

To generate a recommendation for AAI indications in different HVA patients, a questionnaire has been prepared and an analysis of the results has been completed by the HVA expert panel (Table 6). Table 7 reports a summary of the recommendations for AAI prescription in patients suffering from HVA that were generated by the expert panel.

Indication for AAI prescription in untreated patients with SAR

According to the available data on the natural history of insect sting allergy in adults, the risk of recurrence of a SAR following a subsequent sting ranges from 20% to 70% (30).

Table 6 AAI prescription according to natural history and risk factors of HVA (before, during, and after VIT): results from the HVA expert panel

VIT	Systemic reaction (severity)	Children (percentage of answer)	Adults (percentage of answers)	Patients with mast cell diseases (Defined as increased baseline serum tryptase level and/or diagnosis of mastocytosis) (percentage of answers)
BEFORE	Dermal reactions	YES: 40%	YES: 44%	Children/adults: YES
		NO*: 60%	NO*: 56%	100%
	More than dermal reactions	YES: 100%	YES: 100%	
DURING	Dermal reactions	YES: 20%	YES: 31%	Children/adults: YES
		NO: 80%	NO: 69%	100%
	More than dermal reactions	YES†: 100%	YES†: 100%	
AFTER	Dermal reactions	YES: 13%	YES: 13%	Children/adults: YES
		NO: 87%	NO: 87%	100%
	More than dermal reactions	YES‡: 94%	YES‡: 100%	

*Except in the case of high sting exposure which can increase the risk of later progression of SR severity grade.
†If risk factors of VIT failure present.
‡If risk factors for relapse present.

Table 7 Hymenoptera venom-allergic reactions: recommendation for adrenaline auto-injector prescription

Absolute indications
- Children and adults with underlying mast cell disorders or elevated baseline serum tryptase level who experienced any previous systemic reactions, before starting immunotherapy, during, and after stopping VIT (evidence level IV; grade of recommendation C)
- Untreated children and adults with more than cutaneous/mucosal systemic reactions or high risk of reexposure (evidence level IV; grade of recommendation C)
- VIT-treated children and adults with more than cutaneous/mucosal systemic reactions, if risk factors of VIT failure are present (evidence level V; grade of recommendation D)
- After stopping VIT, children and adults with more than cutaneous/mucosal systemic reactions, if risk factors for relapse are present (evidence level V; grade of recommendation D)

Consider prescribing adrenaline auto-injector
- Previous mild (cutaneous) sting reaction and remote from medical help (evidence level V; grade of recommendation D)
- After stopping VIT, children and adults with cutaneous/mucosal systemic reactions, only if continuing risk of multiple stings, short VIT duration (< 3 years) or no restings during VIT (evidence level V; grade of recommendation D), or ACE inhibitor therapy (evidence level IV; grade of recommendation C)

Children with generalized symptoms limited to the skin and mucosa are considered as a low risk group as they have a chance of <10% of a subsequent anaphylactic reaction (73), while those with severe systemic reactions remain at a level of risk as high as 40% after 10 years, and as high as 30% after 20 years (30).

Taking into account these factors, some guidelines (5, 23, 72) state that AAIs should be prescribed for any type of SAR, provided that allergic sensitization has been confirmed by skin testing and/or serum-specific IgE antibodies. The recent EAACI Guidelines on Anaphylaxis (6) state that absolute indications for the prescription of an AAI are as follows: 'venom allergy in adults with SAR (not receiving maintenance VIT) and children with more than cutaneous/mucosal systemic reactions' as well as 'underlying mast cell disorders or elevated baseline serum tryptase (BST) together with any previous systemic allergic reactions to insect stings, even in VIT treated patients'. Adrenaline prescription should also be considered in the case of 'remote from medical help and previous mild-to-moderate allergic reaction to food, venom, latex, or aeroallergens' (6).

According to the EAACI expert panel on HVA, adults as well as children with mast cell diseases or elevated BST that have experienced a SAR after an insect sting need an AAI prescription (evidence level IV; grade of recommendation C) (Tables 6 and 7). This is also the case when patients have reached the VIT maintenance dose, because of an increased risk of a SAR despite VIT with maintenance dose (74, 75) and the possibility that a SAR may also occur after a sting of an insect of which the venom was not used for VIT (76). There is also a full agreement on AAI prescription in untreated adults and children with more than skin reactions (evidence level IV; grade of recommendation C) (Tables 6 and 7).

As for patients with only skin reactions, more than 50% of experts believe that there is no need of an AAI prescription not only in children but also in adults. The only exceptions are cases with high sting exposure (e.g. beekeepers), which can increase the risk of a later progression of SAR severity grade (Table 6).

Criteria for prescribing an AAI should also consider the quality-of-life issue in the individual patient, because an AAI may be perceived as a burdensome and unsuitable treatment, as reported for the majority of vespid venom-allergic patients with a history of a SAR (77).

Indication for AAI prescription in VIT-treated patients

AAI should always be prescribed until the standard protective maintenance dosage has been reached (78). Its

prescription during the maintenance phase of VIT remains a controversial issue (5, 72).

According to the HVA expert panel, there is a full agreement on AAI prescription in treated adults and children with mast cell disorders or elevated BST (evidence level IV; grade of recommendation C), and in patients with more than a dermal reaction if risk factors of VIT failure are present (severe pre-VIT anaphylactic reaction, severe honeybee allergy, anaphylactic reaction during VIT or if VIT efficacy has not been proven by sting challenge or infield sting) (evidence level V; grade of recommendation D) (5, 23, 27, 72) (Tables 6 and 7) or if the patient is on ACE inhibitor therapy (79).

As for patients with only skin reactions, about 70–80% of experts believe that there is no need of an AAI prescription in children as well as in adults (Table 6). The only exceptions are cases with high sting exposure (e.g. beekeepers). There may be additional practical or medico-legal considerations as to why some experts do prescribe AAIs in some of these patients.

Indication for AAI prescription after stopping VIT

Because of the risk, even if small, of resting reactions, self-administered emergency medications, including AAIs, should be discussed when stopping VIT (23, 72, 80). According to the HVA expert panel, there is a full agreement on AAI prescription after stopping VIT in adults and children with mast cell disorders and/or elevated BST (who should usually have prolonged VIT) (evidence level IV; grade of recommendation C), and in adults with more than a dermal reaction if risk factors for relapse are present (e.g. severe honeybee allergy, severity of pre-VIT anaphylactic reaction, anaphylactic reaction during VIT) (81) (evidence level V; grade of recommendation D) (Tables 6 and 7). In children with a more than cutaneous SAR and in children with risk factors for relapse the vast majority, but not all, of the experts suggest an AAI prescription.

Concerning patients with only dermal reactions (who usually will not receive VIT), more than 80% of experts believe that there is no need of an AAI prescription in children as well as in adults (Table 7), although the continuing risk of multiple stings related to occupational activities (72), as well as a short VIT duration and absence of efficacy documentation during VIT (expert panel) should be considered.

AAI prescription in patients with anaphylactic sting reactions and negative testing for venom-specific IgE

Even though IgE-negative anaphylaxis has been reported by several investigators, epidemiological data are scarce (82–84). The percentage seems to be very low when additional diagnostic tests are performed (e.g., basophil activation test, component-resolved diagnostics). The prescription of an AAI is indicated in patients with underlying mast cell disorders (72, 85, 86).

It is also indicated in healthy subjects with a documented anaphylactic sting reaction until second allergy work-up within 6 weeks to 3 months later is not performed. The allergy work-up aims to detect positive venom-specific IgE (which were previously negative) due to the boostering effect of the sting.

Large local reactions

Less than 10% of patients with a history of a large local reaction will develop a SAR when next stung, either by a sting challenge or infield sting (87, 88). According to the vast majority of authors (89) and the HVA expert panel, this risk is considered negligible, making the prescription of an AAI unnecessary (72).

Indication for prescription of a second adrenaline auto-injector

Up to 32% of allergic patients required a further dose of intramuscular adrenaline after the administration of an AAI (6). The EAACI expert panel agree with the indications for prescription of a second AAI suggested by the EAACI Anaphylaxis Guidelines (6): patients with mast cell diseases and/or raised BST, previous requirement for more than one dose of adrenaline prior to reaching hospital, previous near-fatal anaphylaxis, lack of rapid access to medical assistance to manage an episode of anaphylaxis due to geographical or language barriers.

Even though it is unclear whether adrenaline administration with auto-injectors may be influenced by a patient's body weight (90), the recent Anaphylaxis Guidelines suggest a second AAI prescription if available AAI dose is inappropriate for body weight (6).

Patient's compliance and general education

Many studies have shown that compliance with carrying AAI at all times and the ability to correctly administer it are both poor in most patients independent of the cause of anaphylaxis (91–95).

Few studies have been performed in HVA patients. In one of these studies, only 18% of bee-allergic beekeepers carried an AAI (96). Less than 30% of HVA patients carried it at all times (97). Patients who have not reached the VIT maintenance dose showed a better compliance with carrying the EpiPen® (97).

Many HVA patients are unsure when to use their AAI (68) or await for the development of other symptoms before taking any further action (97) despite the instruction of the use tablets immediately after sting and to use AAI if symptoms appear (Table 4) (68). Only 22% of the patients said that they would immediately administer their EpiPen® (97). Moreover, the majority of the self-medication units were found to be expired when systematically analyzed on follow-up visits of insect venom-allergic patients in a large allergy outpatient clinic (98).

Therefore, patients and their caregivers should be taught why, when, and how to inject adrenaline and should be equipped with a personalized written anaphylaxis emergency action plan (7) that helps them to recognize anaphylaxis symptoms, instructs them to inject adrenaline

promptly, then seek medical assistance, along with appropriate allergen-specific risk reduction measures (Tables 1, 3 and 4).

Unfortunately, healthcare providers and school personnel have also been shown to be deficient in knowledge concerning the correct administration of AAIs. The above-mentioned findings indicate that further general education is urgently needed.

Conclusions and future perspectives

Hymenoptera sting allergy remains a significant cause of morbidity and mortality all over the world. Currently, there is no way to predict the precise risk of anaphylaxis in vulnerable individuals.

For patients with SARs, prevention of future severe anaphylactic reactions goes through the correct use of adrenaline by the emergency doctors, the prescription of an AAI and most importantly teaching the patient proper techniques for self-administration of adrenaline, and the referral to an allergist for diagnosis and prescription for VIT. However, patients, their caregivers as well as healthcare providers have demonstrated a lack of knowledge on how to use AAIs.

Thus, our efforts should focus on how to improve the general education. Innovative and easy-to-reach methods of education as well as multidimensional approaches are required, especially for adolescents at risk of anaphylaxis to encourage and support self-management of the allergy and reduce risk taking in this group of patients (89, 99). A better partnership between allergists and emergency physicians would also be helpful (56, 100).

Authors' contribution

The EAACI Interest Group on Venom Hypersensitivity proposed the Task Force, which was accepted by the EAACI Executive Committee. MBB facilitated the guidelines group and edited the document. MBB, C-JE, PR, and O-EH coordinated drafting of the text for specific sections. All authors reviewed, discussed, and approved the final version of this manuscript.

Funding

M. Beatrice Bilò has received lecture fees from Alk, Denmark, and Meda-Pharma, Germany. Gunter Sturm has received lecture fees from Meda, ALK, and Bencard. Ewa Cichocka-Jarosz, Joanna Lange, Javier Fernandez, Marek Niedoszytko, Arthur Helbling, Radosław Gawlik and Mitja Kosnik declare no conflict of interests. Tilo Jakob has received lecture and consulting fees from ALK-Abelló, Thermo Fisher Scientific and Allergy Therapeutics and research grants from Thermo Fisher Scientific, Germany. R. Rodrigues-Alves has received lecture fees from Bial, GSK, Leti, Menarini, and MSD. Holger Mosbech has been in advisory boards for ALK, Denmark. Franziska Ruëff has participated in clinical studies for Novartis, HAL. She is a paid lecturer for HAL, ALK-Abello, Novartis, and advisor for Bencard, and ALK-Abelló, Denmark. Valerio Pravettoni has received a consultancy fee from ALK, Denmark.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Bilò BM, Rueff F, Mosbech H, Bonifazi F, Oude-Elberink JN. EAACI Interest Group on Insect Venom Hypersensitivity. Diagnosis of hymenoptera venom allergy. *Allergy* 2005;**60**:1339–1349.
2. Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;**113**:832–836.
3. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A et al. Second symposium on the definition and management of anaphylaxis: summary report: second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. *J Allergy Clin Immunol* 2006;**117**:391–397.
4. Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G et al. EAACI Task Force on Anaphylaxis in Children. The management of anaphylaxis in childhood: position paper of the European Academy of Allergology and Clinical Immunology. *Allergy* 2007;**62**:857–871.
5. Golden BK, Moffitt J, Nicklas RA. Stinging insect hypersensitivity: a practice parameter update 2011. *J Allergy Clin Immunol* 2011;**127**:852–854.
6. Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernandez-Rivas M et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy* 2014;**69**:1026–1045.
7. Simons FE, Ardusso LR, Bilò MB, Cardona V, Ebisawa M, El-Gamal YM et al. International consensus on (ICON) anaphylaxis. *World Allergy Organ J* 2014;**30**:7–9.
8. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000;**30**:1144–1150.
9. Pumphrey RSH, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999–2006. *J Allergy Clin Immunol* 2007;**119**:1018–1019.
10. Greenberger PA, Rotskoff BD, Lifschultz B. Fatal anaphylaxis: postmortem findings and associated comorbid diseases. *Ann Allergy Asthma Immunol* 2007;**98**:252–257.
11. Bock SA, Muñoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001–2006. *J Allergy Clin Immunol* 2007;**119**:1016–1018.
12. Müller U, Mosbech H, Blaauw P, Dreborg S, Malling HJ, Przybilla B et al. Emergency treatment of allergic reactions to Hymenoptera stings. *Clin Exp Allergy* 1991;**21**:281–288.
13. Oxford Centre for Evidence-based Medicine. Levels of Evidence and Grades of Recommendation. http://www.cebm.net/index.aspx?o=1025 (accessed 25th March 2013) 2013.
14. Hsu FI, Boyce JA. Biology of mast cell and their mediators. In: Allergy I. editor. *Middleton's Allergy principles and practice*, 7th edn. St. Louis, Missouri: Mosby Elseviere; 2009.
15. Stone SF, Brown SGA. Mediators released during human anaphylaxis. *Curr Allergy Asthma Rep* 2012;**12**:33–41.

16. Brown SG. Anaphylaxis: clinical concepts and research priorities. *Emerg Med Australas* 2006;**18**:155–169.
17. Sala-Cunill A, Björkqvist J, Senter R, Guilarte M, Cardona V, Labrador M et al. Plasma contact system activation drives anaphylaxis in severe mast cell-mediated allergic reactions. *J Allergy Clin Immunol* 2015;**135**:1031–1043.
18. Sala-Cunill A, Cardona V. Biomarkers of anaphylaxis, beyond tryptase. *Curr Opin Allergy Clin Immunol* 2015;**15**:329–336.
19. Simons FER. Risk assessment in anaphylaxis: current and future approaches. *J Allergy Clin Immunol* 2007;**120**(Suppl. 1): S2–S24.
20. Tse V, Rylance G. Emergency management of anaphylaxis in children and young people: new guidance from Resuscitation Council (UK). *Arch Dis Child Educ Pract Ed* 2009;**94**:97–101.
21. Simons E, Sicherer SH, Simons FE. Timing the transfer of responsibilities for anaphylaxis recognition and use of an epinephrine auto-injector from adults to children and teenagers: pediatric allergists' perspective. *Ann Allergy Asthma Immunol* 2012;**108**:321–325.
22. Pumphrey R. Anaphylaxis: can we tell who is at risk of a fatal reaction? *Curr Opin Allergy Clin Immunol* 2004;**4**:285–290.
23. Bonifazi F, Jutel M, Bilò BM, Birnbaum J, Muller U. Prevention and treatment of hymenoptera venom allergy: guidelines for clinical practice. *Allergy* 2005;**60**:1459–1470.
24. Frew AJ. What are the 'ideal' features of an adrenaline (epinephrine) auto-injector in the treatment of anaphylaxis? *Allergy* 2011;**66**:15–24.
25. Rudders SA, Banerji A. An update on self-injectable epinephrine. *Curr Opin Allergy Clin Immunol* 2013;**13**:432–437.
26. Song TT, Lieberman P. Epinephrine in anaphylaxis: doubt no more. *Curr Opin Allergy Clin Immunol* 2015;**15**:323–328.
27. Przybilla B, Ruëff F. Insect stings: clinical features and management. *Dtsch Arztebl Int* 2012;**109**:238–248.
28. Ruëff F, Przybilla B, Biló MB, Müller U, Scheipl F, Seitz MJ et al. Clinical effectiveness of hymenoptera venom immunotherapy: a prospective observational multicenter study of the European academy of allergology and clinical immunology interest group on insect venom hypersensitivity. *PLoS One* 2013;**8**:e63233.
29. Lee JM, Greewes DS. Biphasic anaphylactic reactions in pediatrics. *Pediatrics* 2000;**106**:762–766.
30. Golden DB. Insect sting allergy and venom immunotherapy: a model and a mystery. *J Allergy Clin Immunol* 2005;**115**:439–447.
31. Sheikh A, Shehata YA, Brown SG, Simons FE. Adrenaline for the treatment of anaphylaxis: cochrane systematic review. *Allergy* 2009;**64**:204–212.
32. Alrasbi M, Sheikh A. Comparison of international guidelines for the emergency medical management of anaphylaxis. *Allergy* 2007;**62**:838–841.
33. Simons FE, Sheikh A. Evidence-based management of anaphylaxis. *Allergy* 2007;**62**:827–829.
34. Simons FE. Emergency treatment of anaphylaxis. *BMJ* 2008;**336**:1141–1142.
35. Sheikh A, Simons FE, Barbour V, Worth A. Adrenaline auto-injectors for the treatment of anaphylaxis with and without cardiovascular collapse in the community. *Cochrane Database Syst Rev* 2012;**8**: CD008935.
36. Simons FE, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol* 1998;**101**:33–37.
37. Simons FER, Ardusso LRF, Bilò MB, El-Gamal YM, Ledford DK, Ring J et al. World Allergy Organization anaphylaxis guidelines: summary. *J Allergy Clin Immunol* 2011;**127**:587–593.
38. Lieberman P, Simons FE. Anaphylaxis and cardiovascular disease: therapeutic dilemmas. *Clin Exp Allergy* 2015;**45**:1288–1295.
39. Campbell RL, Bellolio MF, Knutson BD, Bellamkonda VR, Fedko MG, Nestler DM et al. Epinephrine in anaphylaxis: higher risk of cardiovascular complications and overdose after administration of intravenous bolus epinephrine compared with intramuscular epinephrine. *J Allergy Clin Immunol Pract* 2015;**3**:76–80.
40. Soar J, Pumphrey R, Cant A, Clarke S, Corbett A, Dawson P et al. Working Group of the Resuscitation Council (UK). Emergency treatment of anaphylactic reactions–guidelines for healthcare providers. *Resuscitation* 2008;**77**:157–169.
41. Brown AFT. Therapeutic controversies in the management of acute anaphylaxis. *J Acc Emerg Med* 1998;**15**:89–95.
42. Montanaro A, Bardana EJ Jr. The mechanisms, causes, and treatment of anaphylaxis. *J Investig Allergol Clin Immunol* 2002;**12**:2–11.
43. Macdougall CF, Cant AJ, Colver AF. How dangerous is food allergy in childhood? The incidence of severe and fatal allergic reactions across the UK and Ireland. *Arch Dis Child* 2002;**86**:236–239.
44. Brown SG. Cardiovascular aspects of anaphylaxis: implications for treatment and diagnosis. *Curr Opin Allergy Clin Immunol* 2005;**5**:359–364.
45. Kounis NG. Serum tryptase levels and Kounis syndrome. *Int J Cardiol* 2007;**114**:407–408.
46. Marone G, Bova M, Detoraki A, Onorati AM, Rossi FW, Spadaro G. The human heart as a shock organ in anaphylaxis. *Novartis Found Symp* 2004;**257**:133–149.
47. Sheikh A, Ten Broek V, Brown SGA, Simons FER. H1-antihistamines for the treatment of anaphylaxis: cochrane systematic review. *Allergy* 2007;**62**:830–837.
48. Nurmatov UB, Rhatigan E, Simons FE, Sheikh A. H2-antihistamines for the treatment of anaphylaxis with and without shock: a systematic review. *Ann Allergy Asthma Immunol* 2014;**112**:126–131.
49. Ring J, Beyer K, Biedermann T, Bircher A, Duda D, Fischer J et al. Guideline for acute therapy and management of anaphylaxis: S2 Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Association of German Allergologists (AeDA), the Society of Pediatric Allergy and Environmental Medicine (GPA), the German Academy of Allergology and Environmental Medicine (DAAU), the German Professional Association of Pediatricians (BVKJ), the Austrian Society for Allergology and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Anaesthesiology and Intensive Care Medicine (DGAI), the German Society of Pharmacology (DGP), the German Society for Psychosomatic Medicine (DGPM), the German Working Group of Anaphylaxis Training and Education (AGATE) and the patient organization German Allergy and Asthma Association (DAAB). *Allergo J Int* 2014;**23**:96–112.
50. Choo KJL, Simons FER, Sheikh A. Glucocorticoids for the treatment of anaphylaxis: cochrane systematic review. *Allergy* 2010;**65**:1205–1211.
51. Choo KJ, Simons FE, Sheikh A. Glucocorticoids for the treatment of anaphylaxis. *Evid Based Child Health* 2013;**8**:1276–1294.
52. Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol* 2010;**126**:477–480.
53. Clark S, Long AA, Gaeta TJ, Camargo CA Jr. Multicenter study of emergency department visits for insect sting allergies. *J Allergy Clin Immunol* 2005;**116**:643–649.
54. Clark S, Camargo CA Jr. Emergency treatment and prevention of insect-sting anaphylaxis. *Curr Opin Allergy Clin Immunol* 2006;**6**:279–283.
55. Manivannan V, Hyde RJ, Hankins DG, Bellolio MF, Fedko MG, Decker WW et al. Epinephrine use and outcomes in

anaphylaxis patients transported by emergency medical services. *Am J Emerg Med* 2014;**32**:1097–1102.
56. Fineman SM, Bowman SH, Campbell RL, Dowling P, O'Rourke D, Russell WS et al. Addressing barriers to emergency anaphylaxis care: from emergency medical services to emergency department to outpatient follow-up. *Ann Allergy Asthma Immunol* 2015;**115**:301–305.
57. Schwirtz A, Seeger H. Comparison of the robustness and functionality of three adrenaline auto-injectors. *J Asthma Allergy* 2012;**5**:39–49.
58. Robinson MN, Dharmage SC, Tang ML. Comparison of adrenaline auto-injector devices: ease of use and ability to recall use. *Pediatr Allergy Immunol* 2014;**25**:462–467.
59. Umasunthar T, Procktor A, Hodes M, Smith JG, Gore C, Cox HE et al. Patients' ability to treat anaphylaxis using adrenaline autoinjectors: a randomized controlled trial. *Allergy* 2015;**70**:855–863.
60. Knibb R, Morton K. Accuracy in use of adrenalin auto-injectors in a simulated emergency situation: a comparison of JEXT®, EpiPen® and Emerade®. *Clin Transl Allergy* 2015;**5**(Suppl. 3):O5.
61. Baker TW, Webber CM, Stolfi A, Gonzalez-Reyes E. The TEN study: time epinephrine needs to reach muscle. *Ann Allergy Asthma Immunol* 2011;**107**:235–238.
62. Simons FE, Sampson HA. Anaphylaxis: unique aspects of clinical diagnosis and management in infants (birth to age 2 years). *J Allergy Clin Immunol* 2015;**135**:1125–1131.
63. Halbrich M, Mack DP, Carr S, Watson W, Kim H. CSACI position statement: epinephrine auto-injectors and children < 15 kg. *Allergy Asthma Clin Immunol* 2015;**11**:20.
64. Kim L, Nevis IF, Tsai G, Dominic A, Potts R, Chiu J et al. Children under 15 kg with food allergy may be at risk of having epinephrine auto-injectors administered into bone. *Allergy Asthma Clin Immunol* 2014;**10**:40.
65. Song TT, Nelson MR, Chang JH, Engler RJ, Chowdhury BA. Adequacy of the epinephrine autoinjector needle length in delivering epinephrine to the intramuscular tissues. *Ann Allergy Asthma Immunol* 2005;**94**:539–542.
66. Stecher D, Bulloch B, Sales J, Schaefer C, Keahey L. Epinephrine auto-injectors: is needle length adequate for delivery of epinephrine intramuscularly? *Pediatrics* 2009;**124**:65–70.
67. Bhalla MC, Gable BD, Frey JA, Reichenbach MR, Wilber ST. Predictors of epinephrine autoinjector needle length inadequacy. *Am J Emerg Med* 2013;**31**:1671–1676.
68. Tsai G, Kim L, Nevis IF, Dominic A, Potts R, Chiu J et al. Auto-injector needle length may be inadequate to deliver epinephrine intramuscularly in women with confirmed food allergy. *Allergy Asthma Clin Immunol* 2014;**10**:39.
69. Rachid O, Simons FE, Wein MB, Rawas-Qalaji M, Simons KJ. Epinephrine doses contained in outdated epinephrine auto-injectors collected in a Florida allergy practice. *Ann Allergy Asthma Immunol* 2015;**114**:354–356.
70. Oude Elberink JN, van der Heide S, Guyatt GH, Dubois AE. Analysis of the burden of treatment in patients receiving an EpiPen for yellow jacket anaphylaxis. *J Allergy Clin Immunol* 2006;**118**:699–704.
71. Sicherer SH, Simons FE. Quandaries in prescribing an emergency action plan and self-injectable epinephrine for first-aid management of anaphylaxis in the community. *J Allergy Clin Immunol* 2005;**115**:575–583.
72. Krishna MT, Ewan PW, Diwakar L, Durham SR, Frew AJ, Leech SC et al. Diagnosis and management of hymenoptera venom allergy British Society for Allergy and Clinical Immunology (BSACI) guidelines. *Clin Exp Allergy* 2011;**41**:1201–1220.
73. Golden DB, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM. Outcomes of allergy to insect stings in children, with and without venom immunotherapy. *N Engl J Med* 2004;**351**:668–674.
74. Dubois AE. Mastocytosis and Hymenoptera allergy. *Curr Opin Allergy Clin Immunol* 2004;**4**:291–295.
75. Niedoszytko M, de Monchy J, van Doormaal JJ, Jassem E, Oude Elberink JN. Mastocytosis and insect venom allergy: diagnosis, safety and efficacy of venom immunotherapy. *Allergy* 2009;**64**:1237–1245.
76. Reimers A, Muller U. Fatal outcome of a vespula sting in a patient with mastocytosis after specific immunotherapy with honeybee venom. *Allergy Clin Immunol Int J WAO Org* 2005;**17**:68–70.
77. Oude-Elberink J, de Monchy J, van der-Heide S, Guyatt GH, Dubois AE. Venom immunotherapy improves health related quality of life in patients allergic to yellow jacket venom. *J Allergy Clin Immunol* 2002;**110**:174–182.
78. Simons FE, Edwards ES, Read EJ Jr, Clark S, Liebelt EL. Voluntarily reported unintentional injections from epinephrine auto-injectors. *J Allergy Clin Immunol* 2010;**125**:419–423.
79. Ruëff F, Vos B, Oude Elberink J, Bender A, Chatelain R, Dugas-Breit S et al. Predictors of clinical effectiveness of Hymenoptera venom immunotherapy. *Clin Exp Allergy* 2014;**44**:736–746.
80. Bilò BM, Brianzoni FM, Napoli G, Bonifazi F. Insect sting anoxic encephalopathy after stopping venom immunotherapy. *Allergy* 2006;**61**:268–269.
81. Bilò BM, Bonifazi F. Hymenoptera venom immunotherapy. *Immunotherapy* 2011;**3**:229–246.
82. Golden DB, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM. Insect sting allergy with negative venom skin test responses. *J Allergy Clin Immunol* 2001;**107**:897–901.
83. Kontou-Fili K. Patients with negative skin tests. *Curr Opin Allergy Clin Immunol* 2002;**2**:353–357.
84. Ebo DG, Hagendorens MM, Bridts CH, De Clerck LS, Stevens WJ. Hymenoptera venom allergy: taking the sting out of difficult cases. *J Investig Allergol Clin Immunol* 2007;**17**:357–360.
85. Ruëff F, Dugas-Breit S, Przybilla B. Stinging Hymenoptera and mastocytosis. *Curr Opin Allergy Clin Immunol* 2009;**9**:338–342.
86. Bonadonna P, Zanotti R, Müller U. Mastocytosis and insect venom allergy. *Curr Opin Allergy Clin Immunol* 2010;**10**:347–353.
87. Bilò MB, Bonifazi F. The natural history and epidemiology of insect venom allergy: clinical implications. *Clin Exp Allergy* 2009;**39**:1467–1476.
88. Sturm GJ, Kranzelbinder B, Schuster C, Sturm EM, Bokanovic D, Vollmann J et al. Sensitization to Hymenoptera venoms is common, but systemic sting reactions are rare. *J Allergy Clin Immunol* 2014;**133**:1635–1643.
89. Golden DB. Insect sting anaphylaxis. *Immunol Allergy Clin North Am* 2007;**27**:261–272.
90. Rudders SA, Geyer BC, Banerji A, Phipatanakul W, Clark S, Camargo CA Jr. Obesity is not a risk factor for repeat epinephrine use in the treatment of anaphylaxis. *J Allergy Clin Immunol* 2012;**130**:1216–1218.
91. Simons FE, Clark S, Camargo CA Jr. Anaphylaxis in the community: learning from the survivors. *J Allergy Clin Immunol* 2009;**124**:301–306.
92. Kastner M, Harada L, Waserman S. Gaps in anaphylaxis management at the level of physicians, patients, and the community: a systematic review of the literature. *Allergy* 2010;**65**:435–444.
93. Soller L, Fragapane J, Ben-Shoshan M, Harrington DW, Alizadehfar R, Joseph L et al. Possession of epinephrine auto-injectors by Canadians with food

allergies. *J Allergy Clin Immunol* 2011;**128**:426–428.
94. DeMuth KA, Fitzpatrick AM. Epinephrine autoinjector availability among children with food allergy. *Allergy Asthma Proc* 2011;**32**:295–300.
95. Song TT, Worm M, Lieberman P. Anaphylaxis treatment: current barriers to adrenaline auto-injector use. *Allergy* 2014;**69**:983–991.
96. Richter AG, Nightingale P, Huissoon AP, Krishna MT. Risk factors for systemic reactions to bee venom in British beekeepers. *Ann Allergy Asthma Immunol* 2011;**106**:159–163.
97. Goldberg A, Confino-Cohen R. Insect sting-inflicted systemic reactions: attitudes of patients with insect venom allergy regarding after-sting behavior and proper administration of epinephrine. *J Allergy Clin Immunol* 2000;**106**:1184–1189.
98. Fischer J, Knaudt B, Caroli UM, Biedermann T. Factory packed and expired – about emergency insect sting kits. *J Dtsch Dermatol Ges* 2008;**6**:729–733.
99. Nwaru BI, Sheikh A. Anaphylaxis in adolescents: a potential tripartite management framework. *Curr Opin Allergy Clin Immunol* 2015;**15**:344–349.
100. Desai SH, Jeong K, Kattan JD, Lieberman R, Wisniewski S, Green TD. Anaphylaxis management before and after implementation of guidelines in the pediatric emergency department. *J Allergy Clin Immunol Pract* 2015;**3**:604–606.