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Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology

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Abstract

Anaphylaxis is a clinical emergency, and all healthcare professionals should be familiar with its recognition and acute and ongoing management. These guidelines have been prepared by the European Academy of Allergy and Clinical Immunology (EAACI) Taskforce on Anaphylaxis. They aim to provide evidence-based recommendations for the recognition, risk factor assessment, and the management of patients who are at risk of, are experiencing, or have experienced anaphylaxis. While the primary audience is allergists, these guidelines are also relevant to all other healthcare professionals. The development of these guidelines has been underpinned by two systematic reviews of the literature, both on the epidemiology and on clinical management of anaphylaxis. Anaphylaxis is a potentially life-threatening condition whose clinical diagnosis is based on recognition of a constellation of presenting features. First-line treatment for anaphylaxis

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is intramuscular adrenaline. Useful second-line interventions may include removing the trigger where possible, calling for help, correct positioning of the patient, high-flow oxygen, intravenous fluids, inhaled short-acting bronchodilators, and nebulized adrenaline. Discharge arrangements should involve an assessment of the risk of further reactions, a management plan with an anaphylaxis emergency action plan, and, where appropriate, prescribing an adrenaline auto-injector. If an adrenaline auto-injector is prescribed, education on when and how to use the device should be provided. Specialist follow-up is essential to investigate possible triggers, to perform a comprehensive risk assessment, and to prevent future episodes by developing personalized risk reduction strategies including, where possible, commencing allergen immunotherapy. Training for the patient and all caregivers is essential. There are still many gaps in the evidence base for anaphylaxis.

Anaphylaxis is a clinical emergency, and all healthcare professionals should be familiar with its management. These guidelines have been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on Anaphylaxis and are part of the *EAACI Guidelines for Food Allergy and Anaphylaxis*. The guidelines aim to provide evidence-based recommendations for the recognition, risk assessment, and management of patients who have experienced, are experiencing, or are at risk of experiencing anaphylaxis. The primary audience is allergists but they are also likely to be of relevance to all other healthcare professionals (e.g., doctors, nurses, and paramedics) in emergency departments (ED), hospital, and primary care. Development of the guidelines has been informed by two systematic reviews of the epidemiology and clinical management of anaphylaxis (1, 2) with weaker forms of evidence being used where there were insufficient data or where high-level evidence is practically or ethically unobtainable. These guidelines build on the previous EAACI Position Paper on Anaphylaxis in Childhood (3) and are complementary to other current anaphylaxis guidelines (4–6). Distinctive features include a European focus and the placing of particular emphasis on the practical issues associated with long-term management.

Anaphylaxis is defined as a 'severe, life-threatening systemic hypersensitivity reaction' (7) (Box 1). This is characterized by being rapid in onset with potentially life-threatening

Box 1: Key terms

Anaphylaxis	Severe, potentially life-threatening systemic hypersensitivity reaction (6, 7). This is characterized by being rapid in onset with life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes
Adrenaline (epinephrine)	A drug with combined α- and β-agonist actions which result in (i) peripheral vasoconstriction, thereby reversing hypotension and mucosal edema; (ii) increased rate and force of cardiac contractions, thereby reversing hypotension; and (iii) reversal of bronchoconstriction and reduction in the release of inflammatory mediators
Adrenaline auto-injector	Device designed to be used by a nonmedical person to give a predefined dose of intramuscular adrenaline
Cofactors	Patient-related or external circumstances that are associated with more severe allergic reactions. They are also known as augmentation factors
Management plans	Lay summary of the clinical plan that patients should follow. It will have an emergency action plan with likely presenting symptoms and how to respond to each. It should also provide additional information such as avoidance advice if applicable and contact details for further advice from allergy clinic and patient support groups

Abbreviations

ACE inhibitor, angiotensin-converting enzyme inhibitor; AGREE II, Appraisal of Guidelines for Research & Evaluation; BP, blood pressure; EAACI, European Academy of Allergy and Clinical Immunology; ED, emergency departments; EIA, exercise-induced anaphylaxis; FDEIA, food-dependent, exercise-induced anaphylaxis; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; ICD, International Classification of Diseases Codes; IgE, immunoglobulin E; NSAID, nonsteroidal anti-inflammatory drugs; PEF, peak expiratory flow; VIT, Hymenoptera venom immunotherapy.

airway, breathing, or circulatory problems; it is usually, but not always, associated with skin and mucosal changes (5). These guidelines focus mainly on allergic anaphylaxis involving specific immunoglobulin E (IgE) but are also relevant to anaphylaxis involving other mechanisms.

Methods

These guidelines were produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach (8, 9), a structured approach to guideline production. This is designed to ensure appropriate representation of the full range of stakeholders, a careful search for and critical appraisal of the relevant literature, a systematic approach to the formulation and presentation of recommendations, and steps to ensure that the risk of bias is minimized at each step of the process. The process began in January 2012, ensuing over 18 months, with in detail discussion of the frame of guidelines for clinical practice, the main aims of the guidelines, the target conditions, agreeing the intended end-user for the recommendations, agreeing the intended end-user group, and ensuring adequate professional and lay representation in the guidelines development process. The process involved:

Clarifying the scope and purpose of the guidelines

The scope of these EAACI guidelines is multifaceted providing statements that assist clinicians in the management of anaphylaxis in daily practice; harmonizing the approach to this clinical emergency among stakeholders across Europe; and advocating for further research.

Ensuring appropriate stakeholder involvement

Participants in the Anaphylaxis Taskforce represented a range of 14 European countries, and disciplinary and clinical backgrounds, for example emergency physicians (A. B. Bellou), primary care (A. Sheikh), psychology (A. DunnGalvin), patient groups (F. Timmermans, L. Harada), and dietitians (B. J. Vlieg–Boerstra).

Systematic reviews of the evidence

The initial full range of questions that were considered important were rationalized through several rounds of iteration to agree to three key questions that were then pursued through two formal systematic reviews of the evidence (1, 2, 10, 11) (see Box 2).

Box 2: Key questions addressed in the two supporting systematic reviews (1, 2)

- What is the epidemiology (i.e., frequency, risk factors, and outcomes) of anaphylaxis and how do these vary by time, place, and person?
- What is the effectiveness of interventions for the acute management of anaphylaxis?
- What is the effectiveness of interventions for the long-term management of those at high risk of further episodes of anaphylaxis?

Formulating recommendations

We graded the strength and consistency of key findings from these systematic reviews to formulate evidence-linked recommendations for care (12) (Box 3). This involved formulating clear recommendations and making clear the strength of evidence underpinning each recommendation. Experts identified the resource implications of implementing the recommendations, barriers, and facilitators to the implementation of each recommendation, advice on approaches to implementing the recommendations and suggested audit criteria that can help with assessing organizational compliance with each recommendation (see Supporting Information Tables S1 and S2).

Box 3: Assigning levels of evidence and recommendations (12)

Level of evidence

Level I	Systematic reviews, meta-analysis, randomized controlled trials
Level II	Two groups, nonrandomized studies (e.g., cohort, case–control)
Level III	One group nonrandomized (e.g., before and after, pretest, and post-test)
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

Peer review and public comment

A draft of these guidelines was externally peer-reviewed by invited experts from a range of organizations, countries, and professional backgrounds. Additionally, the draft guidelines were made available on the EAACI Web site for a 3-week period in July 2013 to allow all stakeholders to comment. All feedback was considered by the Anaphylaxis Taskforce and, where appropriate, final revisions were made in light of the feedback received. We will be pleased to continue to receive feedback on these guidelines, which should be addressed to the corresponding author.

Identification of evidence gaps

The process of developing these guidelines has identified a number of evidence gaps and we plan in the future to formally prioritize these. We plan to draft outline research briefs that funders can use to commission research on these questions.

Editorial independence and managing conflict of interests

The production of these guidelines was funded and supported by EAACI. The funder did not have any influence on the guidelines production process, on its contents, or on the decision to publish. Taskforce members' conflict of interests were taken into account by the Taskforce Chair as recommendations were formulated.

Updating the guidelines

We plan to update these guidelines in 2017 unless there are important advances before then.

Epidemiology

A detailed description of the epidemiology of anaphylaxis can be found in the underpinning systematic review referred to above (1). The exact incidence and prevalence of anaphylaxis in Europe is challenging to establish due to a number of factors. The current definition of anaphylaxis is complex and difficult to use in epidemiological studies (13). Additionally, the World Health Organization's International Classification of Diseases codes (ICD-9 and current ICD-10) focus on anaphylactic shock and do not cover the full range of triggers, meaning that not all allergy cases are likely to be captured in routine data systems. ICD-11 is in development but still seems to miss major triggers (14). Additionally, anaphylaxis has an acute and unexpected onset, may vary in severity, and may resolve spontaneously (15). For all these reasons, underdiagnosis and under-reporting are likely to be common and as a result, epidemiological measures are likely to underestimate the true disease burden.

The results of 10 European studies suggest an incidence of 1.5–7.9 per 100 000 person-years (1) with studies from the UK showing an increase in admissions with anaphylaxis over the last two decades (1). Based on three European population-based studies, prevalence is estimated at 0.3% (95% CI, 0.1–0.5) (1). Overall, the case fatality rate for anaphylaxis is low, below 0.001% (1).

Key triggers include food, drugs, and stinging insects; in up to 20%, the elicitor is not identified. Their relative importance varies with age and geography studied. For ED presentations, drugs and foods are the most common elicitors of anaphylaxis, with age-related differences (1, 16). Foods are the most frequent cause of anaphylaxis in children, with pollen allergy and asthma being important risk factors (1). Drug- and Hymenoptera venom-triggered anaphylaxis are more common in adults than in children. Compared to males, adult females have a higher frequency of anaphylaxis (1) in general and specifically to plant foods and nonsteroidal anti-inflammatory drugs (NSAID) (1). Drugs are the most frequent cause of anaphylaxis in hospitalized patients (1). For anaphylaxis during anesthesia, neuromuscular blocking agents are the most frequent triggers in adult patients in most countries, with a higher incidence in females (1).

Clinical presentation and diagnosis

The clinical manifestations of anaphylaxis depend on the organ systems involved. Widely accepted criteria to help clinicians identify likely anaphylaxis (17, 18) (Box 4) emphasize the rapid onset of its multiple symptoms and signs. These criteria significantly improve the identification of anaphylaxis (19) and demonstrate excellent sensitivity (96.7%) and good specificity (82.4%) for the diagnosis of anaphylaxis in a retrospective ED study (20). Symptoms and signs of anaphylaxis usually occur within 2 h of exposure to the allergen (21), usually within 30 min for food allergy and even faster with parenteral medication or insect stings. In a large case series of fatal anaphylaxis, the median time from symptoms to arrest has been reported as 30, 15, and 5 min for food, insect venom, and parenteral medication, respectively (22).

Among the symptoms of anaphylaxis, cutaneous manifestations occur in most cases (23, 24). In a recent study describing a cohort of 2012 pediatric and adult patients with anaphylaxis, the skin was the most frequently affected organ (84%), followed by cardiovascular symptoms (72%) and respiratory symptoms (68%) (25). Anaphylaxis, however, can develop in the absence of cutaneous manifestations. Respiratory or cardiovascular symptoms or signs are the potentially life-threatening features of anaphylaxis (26). Respiratory symptoms occur more frequently in children, and cardiovascular symptoms predominate in adults (25–31). Nausea and vomiting may also be associated with anaphylaxis (22) (Fig. 1).

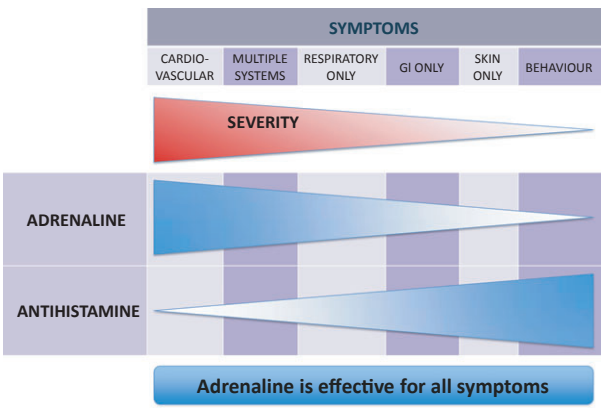

Figure 1 Symptoms associated with anaphylaxis. GI, gastrointestinal.

Biphasic anaphylactic reactions have been reported to develop in up to 20% of reactions (24, 32–34) although the evidence for this is of low quality. They usually occur within 4–12 of the first symptoms or signs and may be more severe. A delay in giving adrenaline (epinephrine), insufficient adrenaline, or failure to administer a glucocorticosteroid may increase the risk of biphasic reactions (33–37).

Anaphylaxis is a clinical diagnosis that builds on the criteria shown in Box 4. Retrospectively, the diagnosis may be supported if serum tryptase is elevated within a few hours after the reaction when compared with the patient's baseline levels; levels are often normal especially in food-triggered reactions in children (38). Evidence of IgE sensitization on skin prick (39) or *in vitro* testing may also aid the diagnosis; provocation testing, ideally with any potential cofactors (40), may be required if diagnostic doubt remains (26). Children may outgrow their food allergy, even if severe (41).

The differential diagnosis of anaphylaxis includes medical diseases, which affect the organ systems most frequently involved in anaphylaxis (Box 5).

Factors increasing the risk of severe allergic reactions

Risk factors for anaphylaxis include individual patient-related factors and circumstances (25, 26, 42–46) (Box 6). We do not have precise data on the magnitude of risk associated with each.

Concomitant diseases

Co-existing asthma is a risk factor for anaphylaxis and fatal anaphylaxis, especially if severe and uncontrolled (47, 48). Mast cell disorders, and probably underlying cardiovascular disease, are also associated with an increased risk of severe or fatal anaphylaxis (24, 49, 50).

Specific allergens

Patients with peanut and tree nut allergy are at an increased risk for a severe reaction (51). In patients with insect venom allergy, increased severity has been reported for older age, pre-existing cardiovascular disease, mast cell disorder, including mastocytosis and mast cell activation syndrome (52, 53), elevated baseline serum tryptase concentrations, concomitant treatment with a beta-adrenergic blocker and/or angiotensin-converting enzyme (ACE) inhibitor, and a previous severe reaction (54–57).

Cofactors

Cofactors increase the risk of an allergic reaction occurring or its severity. They have been described in nearly 20% of young patients in a prospective registry study (28) (Box 6) and include exercise, fever, acute infection, premenstrual status, and emotional stress. NSAID and alcohol also seem to enhance some food-allergic reactions (40). Exercise-induced anaphylaxis (EIA) and food-dependent, exercise-induced anaphylaxis (FDEIA) are more often seen in adults than in children. The association with exercise is crucial for the onset of symptoms or signs (58–60). The range of triggering physical activities and intensities is broad. EIA is not fully reproducible so that same exercise may not always result in anaphylaxis in a given patient.

Emergency management of anaphylaxis

Patients with anaphylaxis require immediate assessment using an Airway, Breathing, Circulation, Disability and Exposure approach. Problems should be treated as they are found and a call put out for emergency services (Box 7). Deaths result from upper airway, lower respiratory, and/or cardiovascular compromise so emergency management must focus on these

Box 4: Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips–tongue–uvula AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (e.g., dyspnea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin–mucosal tissue (e.g., generalized hives, itch-flush, swollen lips–tongue–uvula
   b. Respiratory compromise (e.g., dyspnea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or >30% decrease in systolic BP*
   b. Adults: systolic BP of <90 mmHg or >30% decrease from that person's baseline

Notes

PEF, peak expiratory flow; BP, blood pressure.
Reproduced from Sampson et al. (17) with permission (C).
*Low systolic blood pressure for children is defined as <70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 × age]) from 1 to 10 years and <90 mmHg from 11 to 17 years.

Box 5: Differential diagnosis of anaphylaxis (D)

Skin or mucosal
- chronic remittent or physical urticaria and angioedema
- pollen food syndrome

Respiratory diseases
- acute laryngotracheitis
- tracheal or bronchial obstruction (e.g., foreign substances, vocal cord dysfunction)
- status asthmaticus (without involvement of other organs)

Cardiovascular diseases
- vasovagal syncope
- pulmonary embolism
- myocardial infarction
- cardiac arrhythmias
- hypertensive crisis
- cardiogenic shock

Pharmacological or toxic reactions
- ethanol
- histamine, e.g. scombroid fish poisoning
- opiates

Neuropsychiatric diseases
- hyperventilation syndrome
- anxiety and panic disorder
- somatoform disorder (e.g., psychogenic dyspnea, vocal cord dysfunction)
- dissociative disorder and conversion (e.g., globus hystericus)
- epilepsy
- cerebrovascular event
- psychoses
- artifact (factitious disorder)
- Hoigné's syndrome
- coma, e.g. metabolic, traumatic

Endocrinological diseases
- hypoglycemia
- thyrotoxic crisis
- carcinoid syndrome
- vasointestinal polypeptide tumors
- pheochromocytoma

Adapted from Simons et al. (6) and Muraro et al. (3) with permission.

Box 6: Examples of risk factors and cofactors of anaphylaxis

Lifestyle factors
- physical exertion
- alcohol

Drugs
- NSAID
- ACE inhibitors
- β-blockers

Patient-specific factors
- adolescence, advanced age, and sex
- infections
- hormonal status
- psychogenic stress

Pre-existing conditions
- asthma and other IgE-dependent diseases
- cardiovascular disease
- mastocytosis and/or increased basal tryptase

manifestations. We recommend first-line treatment with intramuscular adrenaline before instituting other interventions as adrenaline is still underutilized in anaphylaxis (61) although it is potentially lifesaving. Cardiopulmonary resuscitation should be immediately instituted if cardiorespiratory arrest occurs. An overview is presented in Fig. 2 and check list in Box 8.

First-line intervention

Adrenaline

Adrenaline must be administered to all patients experiencing anaphylaxis; it should also be administered to those with clinical features that are likely to evolve into anaphylaxis (22, 45, 46, 62–64) (C). In an effort to increase the use of adrenaline, these guidelines place adrenaline as the first intervention for anaphylaxis. Adrenaline exerts effects on (i) α-1 receptors causing peripheral vasoconstriction, thereby reversing hypotension and mucosal edema; (ii) β-1 receptors by increasing both the rate and force of cardiac contractions, thereby reversing hypotension; and (iii) β-2 receptors reversing bronchoconstriction and reducing the release of inflammatory mediators (62). There are no absolute contraindications to treatment with adrenaline in a patient experiencing anaphylaxis; benefits outweigh the risks in the elderly and patients with pre-existing cardiovascular disease (6).

Adrenaline should be given by intramuscular injection into the mid-outer thigh (65, 66) (A). The safety profile of intramuscular adrenaline is excellent although patients may experience transient pallor, palpitations, and headache. Intramuscular adrenaline (1 mg/ml) should be given at a dose of 0.01 ml/kg of body weight to a maximum total dose of 0.5 ml (3). When using adrenaline auto-injectors, patients weighing between 7.5–25 kg should receive 0.15 mg dose with patients being moved to 0.3 mg dose at 25–30 kg (67). There are no data to inform us which patients should receive a 0.5-mg dose auto-injector, if this is available. The adrenaline dose can be repeated after at least a 5-min interval (D).

Patients who require repeated intramuscular doses of adrenaline may benefit from an adrenaline infusion (64) (D). Adrenaline infusion must be given by those experienced in the use of vasopressors in their daily clinical practice, for example anesthetists, ED, and critical care doctors. Intravenous adrenaline in patients with adequate circulation may cause life-threatening hypertension, myocardial ischemia, and arrhythmias. Patients who are given intravenous adrenaline should be monitored with continuous ECG, pulse oximetry, and frequent noninvasive blood pressures.

The use of subcutaneous or inhaled adrenaline in the treatment of anaphylaxis is not recommended (68, 69). One

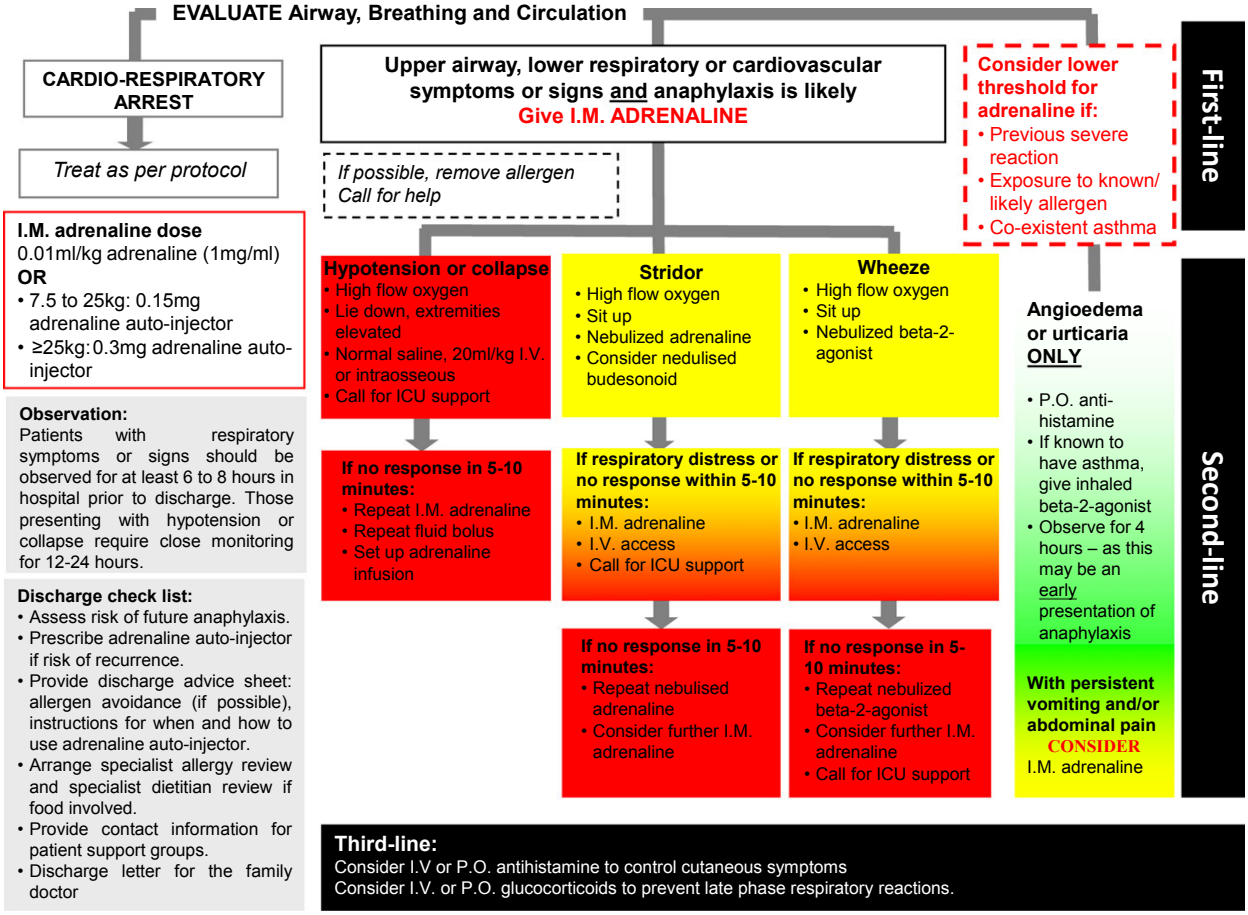

Figure 2 Schematic illustration of the initial management of anaphylaxis.

caveat is stridor from laryngeal edema where nebulized adrenaline (2–5 ml, 1 mg/ml) can be used in addition to intramuscular adrenaline (3) (D).

Second-line interventions

Removal of the trigger and call for help

The likely trigger of the anaphylaxis should be immediately removed, if possible (69) (D). Help should be called from the emergency medical services in the community or resuscitation team in hospital (69) (D).

Posture

Patients experiencing anaphylaxis should be kept still and positioned according to their presenting features: (i) with the most frequent presentation of respiratory distress, position sitting up (D); (ii) with circulatory instability, position lying on back with the lower extremities elevated to conserve the circulatory volume (45) (D); (iii) if pregnant, place semi-recumbent on the left side with lower extremities elevated (70) (D); and (iv) where unconscious, place in the recovery position (D). Patients should avoid sudden abrupt change to a more upright posture (D).

Oxygen

High-flow oxygen should be administered by face mask to all patients with anaphylaxis (D).

Fluid support

Intravenous fluids should be administered to patients with cardiovascular instability (71), as adrenaline may not be effective without restoring the circulatory volume (D). Crystalloids are the fluid of choice and should be given in boluses of 20 ml/kg (D).

Inhaled short-acting beta-2 agonists

Inhaled short-acting beta-2 agonists can be additionally given to relieve symptoms of bronchoconstriction in patients with anaphylaxis (22) (D). Although intramuscular adrenaline is first-line treatment in the emergency setting, in controlled circumstances in hospital with clinical staff experienced in managing anaphylaxis (e.g., oral food chal-

Box 7: Emergency management: recommendations

Recommendation	Evidence level	Grade	Key references
First-line intervention: adrenaline			
Adrenaline is potentially lifesaving and must therefore promptly be administered as the first-line treatment for the emergency management of anaphylaxis	IV	C	(22, 45, 46, 63, 64)
Earlier administration of adrenaline should be considered on an individual basis when an allergic reaction is likely to develop into anaphylaxis	V	D	Expert consensus
Adrenaline should be administered by intramuscular injection into the mid-outer thigh	I	B	(65, 66)
In patients requiring repeat doses of adrenaline, these should be administered at least 5 min apart	V	D	(66), expert consensus
With inadequate response to two or more doses of intramuscular adrenaline, adrenaline may be administered as an infusion by appropriately experienced intensive care, emergency department, and critical care physicians, with appropriate cardiac monitoring	IV	D	(64)
Second-line interventions			
Trigger of the anaphylaxis episode should be removed	V	D	Expert consensus
Help should be called promptly and simultaneously with patient's assessment	V	D	Expert consensus
Patients experiencing anaphylaxis should be positioned supine with elevated lower extremities if they have circulatory instability, sitting up if they have respiratory distress, and in recovery position if unconscious	V	D	(45)
High-flow oxygen should be administered by face mask to all patients with anaphylaxis	V	D	Expert consensus
Intravenous fluids (crystalloids) should be administered (boluses of 20 ml/kg) in patients experiencing cardiovascular instability	V	D	Expert consensus
Inhaled short-acting beta-2 agonists should additionally be given to relieve symptoms of bronchoconstriction	V	D	(22)
Third-line interventions			
Oral H1- (and H2)-antihistamines may relieve cutaneous symptoms of anaphylaxis	I	B	(73, 74)
Systemic glucocorticosteroids may be used as they may reduce the risk of late-phase respiratory symptoms. High-dose nebulized glucocorticoids may be beneficial for upper airway obstruction	V	D	Expert consensus
Monitoring and discharge			
Patients who presented with respiratory compromise should be closely monitored for at least 6–8 h, and patients who presented with circulatory instability require close monitoring for 12–24 h	V	D	Expert consensus
Before discharge, the risk of future reactions should be assessed and an adrenaline auto-injector should be prescribed to those at risk of recurrence	V	D	Expert consensus
Patients should be provided with a discharge advice sheet, including allergen avoidance measures (where possible) and instructions for the use of the adrenaline auto-injector. Specialist and food allergy specialist dietitian (in food anaphylaxis) follow-up should be organized. Contact information for patient support groups should also be provided	V	D	Expert consensus

lenge in an allergy clinic), mild wheeze may initially be treated with inhaled short-acting beta-2 agonists alone; intramuscular adrenaline should be given if there is no response within 5 min (D).

Third-line interventions

H1- and H2-antihistamines

Systemic antihistamines are commonly used in anaphylaxis but have only been demonstrated to relieve cutaneous symptoms in studies where only a minority of participants were experiencing anaphylaxis (72). The combination of systemic H1- and H2-antihistamines may confer additional benefits over-and-above systemic H1-antihistamines alone in relieving some cutaneous symptoms in those experiencing acute allergic reactions (73, 74). There are case reports that intravenous antihistamines may cause hypotension; this may be related to the speed of administration (75). Oral H1- (and H2)-antihistamines are therefore only recommended for the relief of cutaneous symptoms of anaphylaxis (B).

Box 8: Checklist for managing anaphylaxis

1. Stay with patient
2. Look for signs of anaphylaxis
3. Administer adrenaline if signs of anaphylaxis
4. Repeat adrenaline as necessary
5. Other treatments as indicated (e.g., oxygen, beta-2 agonist, fluids, antihistamine, corticosteroid)
6. Look for trigger (e.g., food, drug, venom)

Adrenaline is effective for all symptoms

Glucocorticosteroids

Oral or intravenous glucocorticosteroids are commonly used in anaphylaxis and are thought to possibly prevent protracted anaphylaxis symptoms, particularly in patients with concomitant asthma, and also biphasic reactions; however, this has not been proven and they have a slow onset of action. Oral or parenteral glucocorticosteroids may be given once first- and second-line therapies have been administered (D). High doses of nebulized budesonide may be effective for airway edema (D); this is therefore recommended for patients presenting with stridor.

Other potential treatments

Glucagon

Parenteral administration of glucagon may be useful in treating patients with anaphylaxis who are unresponsive to adrenaline, particularly in those taking beta-blockers (76) (D).

Monitoring and discharge arrangements

Patients who presented with respiratory compromise should be closely monitored for at least 6–8 h, and patients who presented with hypotension require close monitoring for at least 12–24 h (D). Before discharge, the risk of future reactions should be assessed and an adrenaline auto-injector prescribed to those at risk of recurrence (D). Patients should be provided with a discharge advice sheet, including allergen avoidance measures (where possible), instructions for when and how to use the adrenaline auto-injector; referral to an allergy specialist to investigate possible triggers, assess and, where possible, to intervene to minimize the risk of further reactions, and ensure that patients and caregivers are optimally equipped and trained to manage any further reactions; and, if food is involved, referral to a specialist dietitian (D). Contact information for patient support groups should ideally be provided to signpost sources of further useful information.

Long-term management of anaphylaxis

The long-term management of patients who have experienced anaphylaxis starts with the confirmation of triggering allergens using validated *in vivo* and/or *in vitro* tests interpreted in light of a detailed allergy history. Preventive strategies to avoid recurrence include allergen avoidance (3) and allergen immunotherapy where possible should be implemented. Finally, education should be provided covering self-treatment of anaphylaxis recurrence in the community, and management of relevant concomitant diseases (6) (Box 9). An allergy specialist dietitian can help identify food triggers and provide avoidance advice. Patients should be carefully instructed about hidden allergens, cross-reactions to other allergens, and situations that constitute a special hazard such as eating out (see Food Allergy Guidelines for further details) (77) (Box 9). Most recommendations are based on expert opinion (Box 10).

Box 9: Summary of the long-term management in the community of patients at risk of anaphylaxis

- Provision of individualized management plan written clearly in simple, nonmedical language; it should include:
  - personal identification data: name and address; contact details of the parents, guardian, or next of kin, allergist, family doctor and the local ambulance service; and preferably a photograph
  - clear identification of the source of the allergens to be avoided and allergen avoidance advice
  - clear identification of any nonallergen triggers or cofactors, such as exercise, and avoidance advice
  - anaphylaxis emergency action plan
- Copy of plan should be kept by the patient, any caregivers, school staff, and family doctor.
- Provision of emergency kit with copy of anaphylaxis emergency action plan and medications for self-treatment, e.g.
  - adrenaline auto-injector for treating anaphylaxis, where appropriate
  - fast-acting, nonsedating, antihistamine for treating cutaneous allergic reactions, where appropriate
- Venom immunotherapy and desensitization in drug allergy as appropriate
- Training of patients and caregivers, this should include:
  - instructions on appropriate allergen avoidance measures, including consultation with an allergy dietitian, where appropriate
  - instructions on prompt recognition of symptoms of anaphylaxis
  - training on when and how to use an adrenaline auto-injector, where appropriate
  - reinforcement with revision at regular yearly intervals
- Psychological support as required
- Implementation of the patient's management plan in the community (e.g., nursery, school)

Anaphylaxis management plans

Anaphylaxis management plans should cover avoidance advice, contact details for advice plus an anaphylaxis emergency action plan with likely presenting symptoms, and how to respond to each. Studies have shown that after the inception of a management plan, accidental reactions are less

Box 10: Long-term management: recommendations

Recommendation	Evidence level	Grade	Key references
Anaphylaxis management plan			
An anaphylaxis management plan should be used from the time of diagnosis to prevent future reactions, and aid recognition and treatment of any further reactions	III	C	(79, 80)
Venom immunotherapy			
Subcutaneous venom immunotherapy is recommended in venom-allergic patients with a previous episode of anaphylaxis and adults with systemic cutaneous reactions	I	A	(56, 90–93)
Training			
Training in the recognition and management of anaphylaxis should be offered to all patients and caregivers of children at risk of anaphylaxis ideally from the time of diagnosis	V	D	(3, 6)
Training in the recognition and management of anaphylaxis, including the use of adrenaline auto-injectors, should be offered to all professionals dealing with patients at risk of anaphylaxis	IV	C	(115)
Training packages should be developed with the target groups	V	D	Expert consensus
Training should cover allergen avoidance, symptoms of allergic reactions, when and how to use an adrenaline auto-injector, and what other measures are needed within the context of an anaphylaxis management plan	V	D	(3, 6, 79, 125)
Training may involve more than one session to allow revision, an interactive scenario-based approach, a standardized program with manual and educational material and simulation tools. Content and language should be tailored to be understood and memorized	V	D	(3, 126)
Psychological interventions			
Educational interventions should ideally incorporate psychological principles and methods to address anxiety so that children and families may function well at home, at school/work, and socially despite their risk of future reactions and should ideally be part of their educational training. This can be done in a group format. Some patients, with severe anxiety of ongoing duration, may need more in-depth one-to-one psychological intervention	V	D	(110, 123, 124)

Box 11: Example of an individualized anaphylaxis emergency action plan

If **you think you/your child/other are having an anaphylactic reaction** after possible contact with an allergic trigger
Or after possible contact with an allergic trigger, any of the following symptoms may indicate that you/your child/other is experiencing an anaphylactic reaction

Airway problems	swelling of tongue
	swelling/tightness in the throat
	difficulty swallowing
	difficulty talking and/or hoarse voice
Breathing problems	difficulty breathing
	noisy breathing, wheeze, and/or persistent cough
Reduced consciousness	feeling faint, dizziness, confused state, or loss of consciousness pale and floppy (young children)

Then
1. **Immediately administer adrenaline auto-injector** into the upper outer thigh
2. **Call an ambulance** stating that the patient is having an anaphylactic reaction
3. Lay person having the reaction down (with legs up if possible); if there is difficulty in breathing, allow them to sit up but not stand
4. If no improvement after 5 min, administer a second adrenaline auto-injector.

When in doubt, administer the adrenaline auto-injector

Notes

This is only one example of an anaphylaxis action plan. The plan should be individualized, for example patients with previous rapid-onset life-threatening anaphylaxis may be instructed to use their self-injectable adrenaline earlier in the development of any subsequent allergic reaction.

common, at least in children with peanut or tree nut allergies (78, 79). A management plan used by a multidisciplinary allergy clinic had a positive effect on parental knowledge of avoidance measures and emergency treatment of reactions in another study (80). Anaphylaxis management plans should be used from diagnosis to aid recognition and treatment of any further reactions and should be regularly updated (81, 82) (C) (Box 11).

Indications for adrenaline auto-injectors

There are six absolute indications for a prescription of an adrenaline auto-injector (Box 12): (i) previous anaphylaxis with food, latex, aeroallergens such as animals or other unavoidable triggers (C); (ii) EIA (C); (iii) previous idiopathic anaphylaxis (C); (iv) co-existent unstable or moderate to severe, persistent asthma with food allergy (C); (v) venom allergy in adults with previous systemic reactions (unless receiving maintenance VIT) and children with more than systemic cutaneous reactions (C); and (vi) underlying mast cell disorder and any previous systemic reaction (C). The asthma indication is extrapolated from data emerging from retrospective studies (15, 83–86). There are a large number of relative indications based on case series or expert consensus (Box 12). As a guide, the presence of one should lead to the consideration of the prescription of an adrenaline auto-injector; in the presence of two or more, strong consideration should be given to prescription; a specialist allergy review may help to balance the advantages and disadvantages of prescribing. Prescription practices differ considerably (87), and there may be additional local indications such as lipid-transfer protein sensitization in the Mediterranean region.

There are no high-quality data to help decide how many adrenaline auto-injectors should be available to individual patients. The percentage of patients who required a further dose of intramuscular adrenaline after the administration of an auto-injector was 0–15–32% in different patient groups (15, 61, 83, 84, 88, 89) (Box 13) with the additional adrenaline given by healthcare professionals in over 80% of cases. Co-existent asthma was found to be a risk factor for additional adrenaline in one study (84). The challenge is therefore to identify the patients who need to have access to more than one auto-injector. Indications for two auto-injectors are suggested in Box 14. There may also be practical, psychological, or policy considerations as to why a specific patient needs more than one auto-injector.

Immunomodulatory approaches

Venom immunotherapy

Systematic reviews (90–92) and meta-analyses (93) have demonstrated the effectiveness of subcutaneous venom immunotherapy (VIT) in children and adults (A). Patients treated with VIT have a better health-related quality of life

Box 12: Indications for prescription of an adrenaline auto-injector

Recommendation	Evidence level	Grade	Key references
Absolute indications for at least one adrenaline auto-injector			
Previous anaphylaxis triggered by food, latex, or aeroallergens	IV	C	(127, 128)
Previous exercise-induced anaphylaxis	IV	C	(58)
Previous idiopathic anaphylaxis	IV	C	(61)
Co-existing unstable or moderate to severe, persistent asthma and a food allergy*	IV	C	(15, 83–86)
Venom allergy in adults with previous systemic reactions (not receiving maintenance VIT) and children with more than cutaneous/mucosal systemic reactions	IV	C	(56, 129, 130)
Underlying mast cell disorders or elevated baseline serum tryptase concentrations together with any previous systemic allergic reactions to insect stings, even in VIT-treated patients	IV	C	(52, 56, 103, 130)
Consider prescribing at least one adrenaline auto-injector with any of the following additional factors (especially if more than one is present)			
Previous mild-to-moderate allergic reaction* to peanut and/or tree nut	IV	C	(51,79)
Teenager or young adult with a food allergy*	IV	C	(22, 45, 46, 63, 131)
Remote from medical help and previous mild-to-moderate allergic reaction to a food, venom, latex, or aeroallergens	V	D	(131); Expert consensus
Previous mild-to-moderate allergic reaction to traces of food*	V	D	(22, 45, 46, 63, 131)

Notes

*Excluding pollen food syndrome (oral allergy syndrome).

Box 13: Rate of usage of adrenaline auto-injectors by patients

Reference	Study design	Auto-injector prescription	Used an auto-injector during follow-up*	Reactions where initial intramuscular adrenaline dose was followed by additional doses**
(61)	Retrospective clinic population	All	4% (41/969) over a 12-month period	32% (13/41)
(88)	Retrospective clinic population	All	22% (15/68) over a 20-month period	15% (2/13)
(89)	Prospective clinic population	Not all	3% (23/785) over an average of 48 months	0% (0/23)
(84)	Prospective clinic population	Not all	19% (78/413) over an average of 24 months	19% (18/95)
(15)	Patient survey	Not all	27% (500/1885)	18% (90/500)
(83)	Patient survey	Not all	35% (22/63)	18% (4/22)

Notes
*Refers to individual patients.
**Refers to individual allergic reactions (often more than one per patient). Additional doses were usually given by a healthcare professional.

than those just provided with an adrenaline auto-injector (94, 95). Subcutaneous VIT is therefore recommended in venom allergy for both children and adults with anaphylaxis plus adults with systemic cutaneous reactions (A). Some children with cutaneous sting reactions, where VIT is not indicated, may benefit from having access to an auto-injector (56). The recent systematic review has found VIT to only be cost-effective in populations at high risk of further exposure (93), but the analysis did not incorporate quality of life (96). Rush protocols (i.e., over a few days) are as equally efficacious as slower regimens (97). More adverse effects have been reported with an ultra-rush (few hours) compared to a rush protocol (52) and with rush compared to cluster protocols (98).

Drug desensitization
Drug desensitization is defined as the induction of a temporary state of clinical tolerance of a compound responsible for a hypersensitivity reaction. It is undertaken by administering increasing doses of the medication concerned (e.g., antibiotic, insulins, sulfonamides, chemotherapeutic and biological agents) over a short period of time (from several hours to a few days), until the total cumulative therapeutic dose is achieved and tolerated. It should only be used by trained doctors when alternatives are less effective, not available, or contraindicated after considering the risks and benefits. It is mainly undertaken in IgE-mediated reactions, but also in reactions where drug-specific IgE levels have not been demonstrated (e.g., acetyl salicylic acid). Desensitization induces a temporary tolerant state, which can only be maintained by continuous administration of the medication.

Food oral immunotherapy
There are currently no established oral immunotherapy treatment protocols for food-induced anaphylaxis. Recent data suggest that immunotherapy may increase the amount of a tolerated dose over time (99). Significant systemic side-effects can occur, and currently, these protocols are not recommended in clinical practice [see related Food Allergy Guidelines (77)].

Prophylaxis

Adrenaline admixture with snakebite antivenom
The use of subcutaneous adrenaline alone as a premedication with snakebite antivenom reduces the risk of anaphylaxis to the snake antivenom administration (100, 101) (A). The use of hydrocortisone alone does not reduce severe adverse reaction to snake antivenom (102) (A).

Pharmacological interventions for the prevention of anaphylaxis to iodinated contrast media
The routine use of prophylactic systemic premedication (H1- and/or H2-antihistamines or glucocorticosteroids) cannot be recommended in unselected people undergoing procedures with radiocontrast media as they do not prevent life-threatening reactions (103) (A). There are no available data to support the use of premedication in patients with a previous reaction to another allergen (104).

Training

Who should be trained
As anaphylaxis usually occurs in the community (105–107), all patients at risk of anaphylaxis and their caregivers should be provided with educational resources and training to be able to self-manage reactions ideally from the time of diagnosis (D) (Box 9). Adolescent patients require particular attention given the challenges associated with this period of life (108–111).

Box 14: Suggested indications for prescription of a second adrenaline auto-injector

Suggested indications for prescribing a second auto-injector for the patient to carry include:	Evidence level	Grade	Key references
Co-existing unstable or moderate to severe, persistent asthma and a food allergy*	IV	C	(84)
Co-existing mast cell diseases and/or elevated baseline tryptase concentration	IV	C	(129, 130)
Lack of rapid access to medical assistance to manage an episode of anaphylaxis due to geographical or language barriers	V	D	Expert consensus
Previous requirement for more than one dose of adrenaline prior to reaching hospital	V	D	Expert consensus
Previous near fatal anaphylaxis	V	D	Expert consensus
If available auto-injector dose is much too low for body weight	V	D	Expert consensus

Notes
*Excluding pollen food syndrome (oral allergy syndrome).

What training should cover
Training should cover patient-specific avoidance strategies at home, in the social environment and when traveling (112) (D), recognition of symptoms and warning signals, when and how to administer self-injectable adrenaline and other measures needed to manage the reaction (e.g., call for help, positioning) (D). Training should emphasize the need to continually carry the auto-injector where one has been prescribed (113) (D).

How they should be trained
Several studies indicate that for most patients, the standard prescription and formal instruction on how to prevent and treat anaphylaxis by a physician are insufficient to achieve compliance with respective practical measures, including carrying an adrenaline auto-injector (114) and appropriately using it (61). This is compounded by the inability of many clinicians to correctly use an adrenaline auto-injector (3, 115). Training should be offered to all professionals dealing with patients at risk of anaphylaxis (C). Educational training has been shown to be clinically effective in chronic allergic diseases such as asthma and atopic eczema or dermatitis (116, 117). Patient education programs are especially effective when using a written action plan (118), a multidimensional and multidisciplinary approach (119), or involved repeated regular medical reviews (120) in other conditions. A multidisciplinary approach (80) and the provision of educational printed and online materials for food allergy (121) have both been shown to improve knowledge, correct use of auto-injectors, and reduce reactions using a before-and-after study design. Repeated instructions on how to use an adrenaline auto-injector improved correct use in one center (122) (see Supporting Information Table S3).

Psychological interventions

Information about the future risk of anaphylaxis may lead to stress and anxiety in patients and caregivers (110, 123, 124). Research suggests that this should be addressed by alleviating uncertainty using psychological principles and methods to maximize quality of life as part of the educational training (123) (Box 11) (D). This can be done in a group format. Some patients, with severe anxiety of ongoing duration, may need more in-depth one-to-one psychological intervention (123) (D) (see Supporting Information Table S4).

Summary and future perspectives

Anaphylaxis is an important clinical emergency which all healthcare professionals should be able to recognize and manage. Anaphylaxis is a clinical diagnosis based on a constellation of presenting features. Allergy tests are usually helpful in accurately identifying the trigger. First-line treatment is intramuscular adrenaline, which may be repeated if required. Second-line interventions include removing the trigger, calling for help, correct positioning of the patient, high-flow oxygen, intravenous fluids, inhaled short-acting bronchodilators, and nebulized adrenaline. The evidence base for these and other potential interventions is neither comprehensive nor robust. Patients should be monitored after recovery to observe for possible biphasic reactions. Before discharge, an assessment should be made of the risk of further reactions; where appropriate, the patient should be equipped with an adrenaline auto-injector. The absolute indications for an adrenaline auto-injector are (i) previous anaphylaxis with food, latex, aeroallergens such as animals, and other unavoidable triggers; (ii) previous EIA; (iii) previous idiopathic anaphylaxis; (iv) co-existent unstable or moderate to severe, persistent asthma with food allergy; (v) untreated venom allergy in adults with previous systemic reactions (unless on maintenance VIT) and children with more than systemic cutaneous reactions; and (vi) underlying mast cell disorder and any previous systemic reaction. Specialist allergy follow-up is essential to investigate possible triggers as well as potential cofactors, to perform a risk assessment, prevent future episodes by developing personalized risk reduction strategies, including allergen immunotherapy where indicated, as well as a personalized emergency response plan for future allergic reactions. Patients with food allergy should also have advice from a dietitian. Training the patient and caregivers is

Box 15: Anaphylaxis: gaps in the evidence

Gap	Plan to address	Priority
Anaphylaxis epidemiology and clinical presentation		
Clinical definition and diagnostic criteria for allergic anaphylaxis that are easy to use in practice by emergency room medical staff	Consensus process	2
Universally accepted, epidemiological definition and associated coding criteria to allow accurate modeling of anaphylaxis cases	Consensus process	3
Accurate estimation of the incidence, prevalence, burden, and mortality rate of anaphylaxis in different populations across Europe	Application of new definition and criteria plus study of routine clinical diagnostic data	4
Clearer understanding of the magnitude of risk factors for future occurrence of anaphylaxis	Large prospective cohort studies of patients at risk of anaphylaxis	1
Emergency management		
First-line intervention: adrenaline		
Optimal dose and dosing intervals of intramuscular adrenaline in patients experiencing anaphylaxis	Pharmacokinetics studies	1
Role of other routes of adrenaline (e.g., inhaled, sublingual) in anaphylaxis	Randomized controlled trials	2
Data comparing the pharmacokinetics of different adrenaline auto-injector devices	Randomized controlled trials	4
Second-line interventions		
Role of second-line drugs in the treatment of anaphylaxis, namely oxygen and inhaled beta-2 agonists	Randomized controlled trials	5
Comparative efficacies of crystalloids and colloids in the treatment of cardiovascular instability during anaphylaxis	Randomized controlled trials	6
Third-line interventions		
Role of third-line interventions in the treatment of anaphylaxis, namely H1-antihistamines and systemic glucocorticosteroids	Randomized controlled trials	3
Long-term management, training, and psychological interventions		
Anaphylaxis management plans		
Multiple different anaphylaxis management plans and emergency action plans in use	Consensus process with all stakeholders	5
Evidence on the effectiveness of anaphylaxis management plans, particularly in different subgroup (e.g., age, allergy type, different risk levels)	Pragmatic large randomized controlled trials	2
Evidence on the utility of management plans (e.g., with quality of life questionnaires)	Pragmatic randomized controlled trials	7
Adrenaline auto-injectors		
Who should have an adrenaline auto-injector and how many should they have access to?	Large prospective studies, well-phenotyped participants, clear criteria for anaphylaxis	1
Whether a stock supply of adrenaline auto-injectors in locations such as schools might improve the management of anaphylaxis in the community?	Large cluster randomized controlled trials	8
Venom immunotherapy		
It is unclear if venom immunotherapy is able to prevent fatal reactions, because of the rarity of this outcome	Controlled studies would be unethical	
Cost-effective evaluation of the treatment in relation to quality of life rather than survival rate	Health economic analysis	9
Comparative studies on the effect of different build-up protocols (traditional versus rush and ultra-rush) with the same extract focusing on safety	Randomized controlled trials comparing approaches	10
Prophylactic interventions		
Studies to compare the effectiveness of prophylactic premedication to prevent life-threatening reactions due to iodinated contrast media in patients with a history of a previous immediate reactions or potential risk factors for reactions	Large randomized controlled trial	11
Studies looking at the impact of other immunomodulatory interventions on reducing the risk of further episodes of anaphylaxis, for example monoclonal anti-IgE (e.g., omalizumab)	Randomized controlled trials to assess	

Box 15: (Continued)

Gap	Plan to address	Priority
Training		
Evidence on the efficacy of training of patients and direct caregivers/parents of children and other groups such as teachers, day care workers, nurses, and physicians	Randomized controlled trial to assess the impact of training	3
Evidence on the optimal content, trainers (e.g., physicians, allergy specialist dietitians), duration, repetition and format of training and whether it should vary for patients of different ages and different future risk	Development of training program with stakeholders and formal assessment of effectiveness	4
Psychological interventions		
Short- and long-term efficacy of different psychological interventions and their influence on quality of life, knowledge, anxiety, compliance with carriage of in-date adrenaline auto-injectors, performance in an emergency situation, and social functioning in at-risk patients and their caregivers and how differing personalities impact the efficacy of the interventions	Randomized controlled trial assessing the impact of approach	6

essential and should cover avoidance strategies, recognition of symptoms and warning signals, when and how to administer medication including self-injectable adrenaline. Other professionals within health care, education, and childcare should also be trained to recognize and appropriately manage anaphylaxis.

Two recent, related EAACI systematic reviews of the anaphylaxis literature (1, 2) have revealed a lack of high-quality evidence in this area preventing the development of firm recommendations. It is important that these gaps are prioritized to maximize the benefit of future research to patient care (132). Large prospective cohort studies of patients at risk of anaphylaxis in real-life settings are required to provide a clearer understanding of the magnitude of risk associated with each factor to allow us to personalize avoidance advice and auto-injector prescription (Box 15). For patients experiencing anaphylaxis, we need further pharmacokinetic studies to determine the optimal dose and dosing interval, especially for adult patients (Box 15). Further work on other routes of adrenaline administration should be encouraged as adjuvants to intramuscular adrenaline. Additionally, randomized controlled studies are required to assess the effectiveness of systemic glucocorticosteroids in preventing late manifestations of anaphylaxis and whether the addition of antihistamines improves the respiratory and/or cardiovascular features of anaphylaxis. Finally, we need evidence to assess the effectiveness of training and anaphylaxis management plans in improving outcome in patients (Box 15).

Expert Panel

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Author contributions

Antonella Muraro, Chair of the EAACI Food Allergy and Anaphylaxis Guidelines Initiative, has steered and coordinated the publication. Graham Roberts facilitated the anaphylaxis guidelines group and edited the guidelines document with support from Margitta Worm. M. Beatrice Bilò, Knut Brockow, Montserrat Fernández Rivas, Alexandra F. Santos, Zaraquiza Zolkipli, and Aziz Sheikh coordinated drafting of the evidence table, recommendations,

gaps, and text for specific sections. Sangeeta Dhami and Sukhmeet Panesar undertook the supporting systematic reviews under the supervision of Aziz Sheikh. All authors participated in the discussion of the evidence table, recommendations, gaps, and specific sections and approved the final version.

Conflicts of interest

Graham Roberts has provided scientific advice for Danone and ALK-Abelló; Thermo Fisher and ALK-Abelló have provided consumables for his research activities. Antonella Muraro has provided scientific advice for Meda. Margitta Worm has provided scientific advice for ALK-Abelló. M. Beatrice Bilò has provided scientific advice for Meda. Knut Brockow has provided scientific advice for ALK-Abelló, Meda, Thermo Fisher, and Stallergenes. Montserrat Fernández Rivas has provided scientific advice to GSK; ALK-Abelló has provided consumables for her research activities. Carsten Bindslev-Jensen has received funding from Thermo Fisher, HAL, Stallergenes, and Anergis, ALK, Novartis, MSD, Schering-Plough for his research activities. Victoria Cardona has provided scientific advice for ALK-Abelló. Pascal Demoly has provided scientific advice for Stallergenes, ALK-Abelló, Circassia, Allergopharma, Chiesi, Menarini, and Pierre Fabre Médicament; Tony DuBois has provided scientific advice for ALK-Abelló and received funding from ALK-Abelló to support his research activities. Audrey DunnGalvin has received funding from Novartis for her research. Philippe Eigenmann has provided scientific advice for Danone, Novartis, ALK, DBV technologies, and Stallergenes; he has received funding for research activities from LETI, Nestlé, and Thermo Fisher. Susanne Halken has provided scientific advice for ALK-Abelló. Marek Jutel has been an investigator for clinical studies led by Allergopharma, Stallergenes, Novartis, GSK, and Medimmune. Franziska Ruëff has been an investigator for clinical studies led by Allergopharma, HAL, Novartis, and Pierre Fabre and has received travel grants and honoraria as a speaker from ALK-Abelló, Bencard, HAL, Novartis, and Thermo Fisher. Frans Timmermans has received unrestricted grants from ALK-Abelló, MSD, MEDA for the activities of European Anaphylaxis Taskforce – Nederlands Anafylaxis Netwerk which he manages. Berber Vlieg–Boerstra has provided scientific advice for Danone and Mead Johnson; she has received research grants from Nutricia Advanced Medical Nutrition and ALK-Abelló. Sukhmeet Panesar, Sangeeta Dhami, and Aziz Sheikh have received funding for coordinating guidelines production and generating the systematic reviews from EAACI. Aziz Sheikh has provided scientific advice to ALK-Abelló, Meda, Lincoln Medical, Thermo Fisher, Pfizer, and Stallergenes; he is on the Anaphylaxis Campaign UK's Scientific Committee, World Allergy Organization's Anaphylaxis Special Committee, UK Resuscitation Council's Anaphylaxis Committee, and the BSACI's Standard of Care Committee. Laurie Harada works for Anaphylaxis Canada whose educational activities have been supported by Pfizer and Sanofi. Alexandra F. Santos, Zaraquiza Zolkipli, Cezmi Akdis, Kirsten Beyer, Abdul Bellou, Gideon Lack, Bodo Niggemann, Andy Clark, and Thomas Werfel have no conflict of interests.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Emergency management recommendations: barriers and facilitators to implementation, audit criteria and resource implications of recommendations.

Table S2. Long-term management recommendations: barriers and facilitators to implementation, audit criteria and resource implications of recommendations.

Table S3. Training recommendations: barriers and facilitators to implementation, audit criteria and resource implications of recommendations.

Table S4. Psychological intervention recommendations: barriers and facilitators to implementation, audit criteria and resource implications of recommendations.

References

1. Panesar SS, Javad S, De Silva D, Nwaru BI, Hickstein L, Muraro A et al. The epidemiology of anaphylaxis in Europe: a systematic review. *Allergy* 2013;**68**:1353–1361.
2. Dhami S, Panesar SS, Roberts G, Muraro A, Worm M, Bilò B et al. Management of anaphylaxis: a systematic review. *Allergy* 2014;**69**:159–167.
3. Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. *Allergy* 2007;**62**:857–871.
4. Soar J, Perkins GD, Abbas G, Alfonzo A, Barelli A, Bierens JJLM et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 8. Cardiac arrest in special circumstances: electrolyte abnormalities, poisoning, drowning, accidental hypothermia, hyperthermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution. *Resuscitation* 2010;**81**:1400–1433.
5. Soar J, Pumphrey R, Cant A, Clarke S, Corbett A, Dawson P et al. Emergency treatment of anaphylactic reactions – guidelines for healthcare providers. *Resuscitation* 2008;**77**:157–169.
6. Simons FER, Ardusso LRF, Bilo MB, El-Gamal YM, Ledford DK, Ring J et al. World Allergy Organization guidelines for the assessment and management of anaphylaxis. *J Allergy Clin Immunol* 2011;**127**:587–593.
7. 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.
8. Agree Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Saf Health Care* 2003;**12**:18–23.
9. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *Can Med Assoc J* 2010;**182**:E839–E842.

10. Panesar SS, Nwaru B, Hickstein L, Rader T, Hamadah H, Ali D et al. The epidemiology of anaphylaxis in Europe: protocol for a systematic review. *Clin Transl Allergy* 2013;**3**:9.
11. Dhami S, Panesar SS, Rader T, Muraro A, Roberts G, Worm M et al. The acute and long-term management of anaphylaxis: protocol for a systematic review. *Clin Transl Allergy* 2013;**3**:14.
12. Oxford Centre for Evidence-based Medicine. Levels of Evidence and Grades of Recommendation. 2013. http://www cebm net/index aspx?o = 1025. Last accessed 25 March 2013.
13. Simons FER, Ardusso LRF, Bilò MB, El-Gamal YM, Ledford DK, Ring J et al. World allergy organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J* 2011;**4**:13–37.
14. Tanno LK, Ganem F, Demoly P, Toscano CM, Bierrenbach AL. Undernotification of anaphylaxis deaths in Brazil due to difficult coding under the ICD-10. *Allergy* 2012;**67**:783–789.
15. Simons FER, Clark S, Camargo CA Jr. Anaphylaxis in the community: learning from the survivors. *J Allergy Clin Immunol* 2009;**124**:301–306.
16. Moro Moro M, Tejedor Alonso MA, Esteban Hernandez J, Mugica Garcia MVM, Rosado Ingelmo A, Vila Albelda C. Incidence of anaphylaxis and subtypes of anaphylaxis in a general hospital emergency department. *J Investig Allergol Clin Immunol* 2011;**21**:142–149.
17. 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.
18. Sampson HA, Munoz-Furlong A, Bock SA, Schmitt C, Bass R, Chowdhury BA et al. Symposium on the definition and management of anaphylaxis: summary report. *J Allergy Clin Immunol* 2005;**115**:584–591.
19. Harduar-Morano L, Simon MR, Watkins S, Blackmore C. Algorithm for the diagnosis of anaphylaxis and its validation using population-based data on emergency department visits for anaphylaxis in Florida. *J Allergy Clin Immunol* 2010;**126**:98–104.
20. Campbell RL, Hagan JB, Manivannan V, Decker WW, Kanthala AR, Bellolio MF et al. Evaluation of national institute of allergy and infectious diseases/food allergy and anaphylaxis network criteria for the diagnosis of anaphylaxis in emergency department patients. *J Allergy Clin Immunol* 2012;**129**:748–752.
21. de Silva IL, Mehr SS, Tey D, Tang MLK. Paediatric anaphylaxis: a 5 year retrospective review. *Allergy* 2008;**63**:1071–1076.
22. Pumphrey RSH. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000;**30**: 1144–1150.
23. Bohlke K, Davis RL, DeStefano F, Marcy SM, Braun MM, Thompson RS. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. *J Allergy Clin Immunol* 2004;**113**:536–542.
24. Brown SGA. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 2004;**114**:371–376.
25. Worm M, Edenharter G, Rueff F, Scherer K, Pfohler C, Mahler V et al. Symptom profile and risk factors of anaphylaxis in Central Europe. *Allergy* 2012;**67**:691–698.
26. Simons FER, Ardusso LR, Bilo MB, Dimov V, Ebisawa M, El-Gamal YM et al. 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis. *Curr Opin Allergy Clin Immunol* 2012;**12**:389–399.
27. Steele R, Camacho-Halili M, Rosenthal B, Davis-Lorton M, Aquino M, Fonacier L. Anaphylaxis in the community setting: determining risk factors for admission. *Ann Allergy Asthma Immunol* 2012;**109**: 133–136.
28. Hompes S, Kohli A, Nemat K, Scherer K, Lange L, Rueff F et al. Provoking allergens and treatment of anaphylaxis in children and adolescents – data from the anaphylaxis registry of German-speaking countries. *Pediatr Allergy Immunol* 2011;**22**:568–574.
29. Braganza SC, Acworth JP, McKinnon DRL, Peake JE, Brown AFT. Paediatric emergency department anaphylaxis: different patterns from adults. *Arch Dis Child* 2006;**91**:159–163.
30. Vetander M, Helander D, Flodstrom C, Ostblom E, Alfven T, Ly DH et al. Anaphylaxis and reactions to foods in children – a population-based case study of emergency department visits. *Clin Exp Allergy* 2012;**42**:568–577.
31. Beyer K, Eckermann O, Hompes S, Grabenhenrich L, Worm M. Anaphylaxis in an emergency setting – elicitors, therapy and incidence of severe allergic reactions. *Allergy* 2012;**67**:1451–1456.
32. Douglas DM, Sukenick E, Andrade WP, Brown JS. Biphasic systemic anaphylaxis: an inpatient and outpatient study. *J Allergy Clin Immunol* 1994;**93**:977–985.
33. Ellis AK, Day JH. Incidence and characteristics of biphasic anaphylaxis: a prospective evaluation of 103 patients. *Ann Allergy Asthma Immunol* 2007;**98**:64–69.
34. Lee JM, Greenes DS. Biphasic anaphylactic reactions in pediatrics. *Pediatrics* 2000;**106**:762–766.
35. Sampson HA. Fatal food-induced anaphylaxis. *Allergy* 1998;**53**:125–130.
36. Lieberman P. Biphasic anaphylactic reactions. *Ann Allergy Asthma Immunol* 2005;**95**:217.
37. Mehr S, Liew WK, Tey D, Tang MLK. Clinical predictors for biphasic reactions in children presenting with anaphylaxis. *Clin Exp Allergy* 2009;**39**:1390–1396.
38. Sala-Cunill A, Cardona V, Labrador-Horrillo M, Luengo O, Esteso O, Garriga T et al. Usefulness and limitations of sequential serum tryptase for the diagnosis of anaphylaxis in 102 patients. *Int Arch Allergy Immunol* 2013;**160**:192–199.
39. Heinzerling L, Mari A, Bergmann KC, Bresciani M, Burbach G, Darsow U et al. The skin prick test – European standards. *Clin Transl Allergy* 2013;**3**:3.
40. Cardona V, Luengo O, Garriga T, Labrador-Horrillo M, Sala-Cunill A, Izquierdo A et al. Co-factor-enhanced food allergy. *Allergy* 2012;**67**:1316–1318.
41. Vlieg-Boerstra BJ, Duiverman EJ, Van Der Heide S, Bijleveld CMA, Kukler J, Dubois AEJ. Should children with a history of anaphylaxis to foods undergo challenge testing? *Clin Exp Allergy* 2008;**38**:1935–1942.
42. Mertes PM, Alla F, Trechot P, Auroy Y, Jougla E, Groupe d'Etudes des Reactions Anaphylactoides P. Anaphylaxis during anesthesia in France: an 8-year national survey. *J Allergy Clin Immunol* 2011;**128**:366–373.
43. Park HJ, Kim SH. Factors associated with shock in anaphylaxis. *Am J Emerg Med* 2012;**30**:1674–1678.
44. Moneret-Vautrin DA. Drugs as risk factors of food anaphylaxis in adults. [French] Facteurs de risque d'anaphylaxie alimentaire severe Role confirme de certaines classes de medicaments. *Med Sci* 2010;**26**:719–723.
45. Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. *J Allergy Clin Immunol* 2007;**119**:1018–1019.
46. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *J Allergy Clin Immunol* 2007;**119**:1016–1018.
47. Calvani M, Cardinale F, Martelli A, Muraro A, Pucci N, Savino F et al. Risk factors for severe pediatric food anaphylaxis in Italy. *Pediatr Allergy Immunol* 2011;**22**:813–819.

48. Gonzalez-Perez A, Aponte Z, Vidaurre CF, Rodriguez LAG. Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. *J Allergy Clin Immunol* 2010;**125**:1098–1104.
49. Triggiani M, Patella V, Staiano RI, Granata F, Marone G. Allergy and the cardiovascular system. *Clin Exp Immunol* 2008;**153**:7–11.
50. Wimazal F, Geissler P, Shnawa P, Sperr WR, Valent P. Severe life-threatening or disabling anaphylaxis in patients with systemic mastocytosis: a single-center experience. *Int Arch Allergy Immunol* 2012;**157**:399–405.
51. Vander Leek TK, Liu AH, Stefanski K, Blacker B, Bock SA. The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. *J Pediatr* 2000;**137**:749–755.
52. Rueff F, Przybilla B, Bilo MB, Muller U, Scheipl F, Aberer W et al. Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum tryptase-a study of the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity. *J Allergy Clin Immunol* 2009;**124**:1047–1054.
53. Hamilton MJ, Hornick JL, Akin C, Castells MC, Greenberger NJ. Mast cell activation syndrome: a newly recognized disorder with systemic clinical manifestations. *J Allergy Clin Immunol* 2011;**128**:147–152.
54. Bilo MB. Anaphylaxis caused by Hymenoptera stings: from epidemiology to treatment. *Allergy* 2011;**66**:35–37.
55. Rueff F, Przybilla B, Dugas-Breit S. Mastocytosis – clinical symptoms. *Allergologie* 2009;**32**:214–223.
56. Golden DB, Moffitt J, Nicklas RA, Freeman T, Graft DF, Reisman RE et al. Stinging insect hypersensitivity: a practice parameter update 2011. *J Allergy Clin Immunol* 2011;**127**:852–854.
57. Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy* 2008;**63**:226–232.
58. Shadick NA, Liang MH, Partridge AJ, Bingham C, Wright E, Fossel AH et al. The natural history of exercise-induced anaphylaxis: survey results from a 10-year follow-up study. *J Allergy Clin Immunol* 1999;**104**:123–127.
59. Tewari A, Du TG, Lack G. The difficulties of diagnosing food-dependent exercise-induced anaphylaxis in childhood – a case study and review. *Pediatr Allergy Immunol* 2006;**17**:157–160.
60. Aihara Y, Takahashi Y, Kotoyori T, Mitsuda T, Ito R, Aihara M et al. Frequency of food-dependent, exercise-induced anaphylaxis in Japanese junior-high-school students. *J Allergy Clin Immunol* 2001;**108**:1035–1039.
61. Noimark L, Wales J, Du Toit G, Pastacaldi C, Haddad D, Gardner J et al. The use of adrenaline autoinjectors by children and teenagers. *Clin Exp Allergy* 2012;**42**:284–292.
62. Westfall TC. Adrenergic agonists and antagonists. In: Chabner BA, Brunton LL, Knollmann BC, editors. *Goodman and Gilman's the Pharmacological Basis of Therapeutics*. New York: Mc Graw-Hill, 2006: 215–268.
63. Bock SA, Muoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;**107**:191–193.
64. Soreide EB. Severe anaphylactic reactions outside hospital: etiology, symptoms and treatment. *Acta Anaesthesiol Scand* 1988;**32**:339–342.
65. Simons FER, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol* 1998;**101**:33–37.
66. Simons FER, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *J Allergy Clin Immunol* 2001;**108**:871–873.
67. Simons FER, Gu X, Silver NA, Simons KJ. EpiPen Jr versus EpiPen in young children weighing 15 to 30 kg at risk for anaphylaxis. *J Allergy Clin Immunol* 2002;**109**:171–175.
68. Simons FER, Gu X, Johnston LM, Simons KJ. Can epinephrine inhalations be substituted for epinephrine injection in children at risk for systemic anaphylaxis? *J Allergy Clin Immunol* 2000;**106**:1040–1044.
69. Simons FER, Sheikh A. Anaphylaxis: the acute episode and beyond. *BMJ* 2013;**346**:602.
70. Simons FER, Schatz M. Anaphylaxis during pregnancy. *J Allergy Clin Immunol* 2012;**130**:597–606.
71. Perel P, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev* 2012;**6**:CD000567.
72. Nurmatov UB, Rhatigan E, Simons FER, Sheikh A. H2 antihistamines for the treatment of anaphylaxis with and without shock: a systematic review. *Ann Allergy Asthma Immunol* 2014;**112**:126–131.
73. Runge JW, Martinez JC, Caravati EM, Williamson SG, Hartsell SC. Histamine antagonists in the treatment of acute allergic reactions. *Ann Emerg Med* 1992;**21**:237–242.
74. Lin RY, Curry A, Pesola GR, Knight RJ, Lee HS, Bakalchuk L et al. Improved outcomes in patients with acute allergic syndromes who are treated with combined H1 and H2 antagonists. *Ann Emerg Med* 2000;**36**:462–468.
75. Ellis BC, Brown SG. Parenteral antihistamines cause hypotension in anaphylaxis. *Emerg Med Australas* 2013;**25**:92–93.
76. Thomas M. Best evidence topic report. Glucagon infusion in refractory anaphylactic shock in patients on beta-blockers. *Emerg Med J* 2005;**22**:272–273.
77. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C et al. EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy. *Allergy* 2014;**69**:1008–1025.
78. Ewan PW, Clark AT. Long-term prospective observational study of patients with peanut and nut allergy after participation in a management plan. *Lancet* 2001;**357**:111–115.
79. Ewan PW, Clark AT. Efficacy of a management plan based on severity assessment in longitudinal and case-controlled studies of 747 children with nut allergy: proposal for good practice. *Clin Exp Allergy* 2005;**35**:751–756.
80. Kapoor S, Roberts G, Bynoe Y, Gaughan M, Habibi P, Lack G. Influence of a multidisciplinary paediatric allergy clinic on parental knowledge and rate of subsequent allergic reactions. *Allergy* 2004;**59**:185–191.
81. Choo K, Sheikh A. Action plans for the long-term management of anaphylaxis: systematic review of effectiveness. *Clin Exp Allergy* 2007;**37**:1090–1094.
82. Nurmatov U, Worth A, Sheikh A. Anaphylaxis management plans for the acute and long-term management of anaphylaxis: a systematic review. *J Allergy Clin Immunol* 2008;**122**:353–361.
83. Uguz A, Lack G, Pumphrey R, Ewan P, Warner J, Dick J et al. Allergic reactions in the community: a questionnaire survey of members of the anaphylaxis campaign. *Clin Exp Allergy* 2005;**35**:746–750.
84. Jarvinen KM, Sicherer SH, Sampson HA, Nowak-Wegrzyn A. Use of multiple doses of epinephrine in food-induced anaphylaxis in children. *J Allergy Clin Immunol* 2008;**122**:133–138.
85. Manivannan V, Campbell RL, Bellolio MF, Stead LG, Li JT, Decker WW. Factors associated with repeated use of epinephrine for the treatment of anaphylaxis. *Ann Allergy Asthma Immunol* 2009;**103**:395–400.
86. Rudders SA, Banerji A, Corel B, Clark S, Camargo CA Jr. Multicenter study of repeat epinephrine treatments for food-related anaphylaxis. *Pediatrics* 2010;**125**:e711–e718.

87. Johnson MJ, Foote KD, Moyses HE, Roberts G. Practices in the prescription of adrenaline autoinjectors. *Pediatr Allergy Immunol* 2012;**23**:124–127.
88. Gold MS, Sainsbury R. First aid anaphylaxis management in children who were prescribed an epinephrine autoinjector device (EpiPen). *J Allergy Clin Immunol* 2000;**106**:171–176.
89. Clark AT, Ewan PW. Good prognosis, clinical features, and circumstances of peanut and tree nut reactions in children treated by a specialist allergy center. *J Allergy Clin Immunol* 2008;**122**:286–289.
90. Boyle RJ, Elremeli M, Hockenhull J, Cherry MG, Bulsara MK, Daniels M et al. Venom immunotherapy for preventing allergic reactions to insect stings. *Cochrane Database Syst Rev* 2012;**10**:CD008838.
91. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of Hymenoptera venom hypersensitivity: a meta-analysis. *Clin Ther* 2000;**22**:351–358.
92. Watanabe AS, Fonseca LAM, Galvao CES, Kalil J, Castro FFM. Specific immunotherapy using Hymenoptera venom: systematic review. *Sao Paulo Med J* 2010;**128**:30–37.
93. Hockenhull J, Elremeli M, Cherry MG, Mahon J, Lai M, Darroch J et al. A systematic review of the clinical effectiveness and cost-effectiveness of Pharmalgen for the treatment of bee and wasp venom allergy. *Health Technol Assess* 2012;**16**:III–IV, 1.
94. Oude Elberink JNG, De Monchy JGR, Van Der Heide S, Guyatt GH, Dubois AEJ. Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. *J Allergy Clin Immunol* 2002;**110**:174–182.
95. Oude Elberink JNG, van der Heide S, Guyatt GH, Dubois AEJ. Analysis of the burden of treatment in patients receiving an EpiPen for yellow jacket anaphylaxis. *J Allergy Clin Immuno* 2006;**118**:699–704.
96. Rueff F, Bilo MB, Cichocka-Jarosz E, Muller U, Elberink HO, Sturm G. Immunotherapy for Hymenoptera venom allergy: too expensive for European health care? *Allergy* 2013;**68**:407–408.
97. Golden DBK, Valentine MD, Kagey-Sobotka A, Lichtenstein LM. Regimens of Hymenoptera venom immunotherapy. *Ann Intern Med* 1980;**92**:620–624.
98. Mosbech H, Muller U, Behalf of the Study Group. Side-effects of insect venom immunotherapy: results from an EAACI multicenter study. *Allergy* 2000;**55**:1005–1010.
99. Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschorner J, de Oliveira LCL et al. Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol* 2010;**126**:83–91.
100. Habib A. Effect of pre-medication on early adverse reactions following antivenom use in snakebite. *Drug-Safety* 2011;**34**:869–880.
101. de Silva HA, Pathmeswaran A, Ranasinha CD, Jayamanne S, Samarakoon SB, Hittharage A et al. Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial. *PLoS Med* 2011;**8**:e1000435.
102. Gawarammana IB, Kularatne SA, Dissanayake WP, Kumarasiri RP, Senanayake N, Ariyasena H. Parallel infusion of hydrocortisone +/- chlorpheniramine bolus injection to prevent acute adverse reactions to antivenom for snakebites. [Erratum appears in Med J Aust. 2004 Apr 19;180(8):428]. *Med J Aust* 2004;**180**:20–23.
103. Tramer MR, von Elm E, Loubeyre P, Hauser C. Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review. *BMJ* 2006;**333**:675–681.
104. Brockow K, Ring J. Anaphylaxis to radiographic contrast media. *Curr Opin Allergy Clin Immunol* 2011;**11**:326–331.
105. Mehl A, Wahn U, Niggemann B. Anaphylactic reactions in children – a questionnaire-based survey in Germany. *Allergy* 2005;**60**:1440–1445.
106. Clark S, Bock SA, Gaeta TJ, Brenner BE, Cydulka RK, Camargo CA. Multicenter study of emergency department visits for food allergies. *J Allergy Clin Immunol* 2004;**113**:347–352.
107. Grabenhenrich L, Hompes S, Gough H, Rueff F, Scherer K, Pfohler C et al. Implementation of anaphylaxis management guidelines: a register-based study. *PLoS ONE* 2012;**7**:e35778.
108. MacKenzie H, Roberts G, van Laar D, Dean T. Teenagers' experiences of living with food hypersensitivity: a qualitative study. *Pediatr Allergy Immunol* 2010;**21**:595–602.
109. Monks H, Gowland MH, MacKenzie H, Erlewyn-Lajeunesse M, King R, Lucas JS et al. How do teenagers manage their food allergies? *Clin Exp Allergy* 2010;**40**:1533–1540.
110. DunnGalvin A, Gaffney A, Hourihane JOB. Developmental pathways in food allergy: a new theoretical framework. *Allergy* 2009;**64**:560–568.
111. Worth A, Regent L, Levy M, Ledford C, East M, Sheikh A. Living with severe allergy: an Anaphylaxis Campaign national survey of young people. *Clin Transl Allergy* 2013;**3**:2.
112. Barnett J, Botting N, Gowland M, Lucas J. The strategies that peanut and nut-allergic consumers employ to remain safe when travelling abroad. *Clin Transl Allergy* 2012;**2**:12.
113. Macadam C, Barnett J, Roberts G, Stiefel G, King R, Erlewyn-Lajeunesse M et al. What factors affect the carriage of epinephrine auto-injectors by teenagers? *Clin Transl Allergy* 2012;**2**:3.
114. 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.
115. Sicherer SH, Forman JA, Noone SA. Use assessment of self-administered epinephrine among food-allergic children and pediatricians. *Pediatrics* 2000;**105**:359–362.
116. Guevara JP, Wolf FM, Grum CM, Clark NM. Effects of educational interventions for self management of asthma in children and adolescents: systematic review and meta-analysis. *BMJ* 2003;**326**:1308–1309.
117. Staab D, Diepgen TL, Fartasch M, Kupfer J, Lob-Corzilius T, Ring J et al. Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: multicentre, randomised controlled trial. *BMJ* 2006;**332**:933–938.
118. Ducharme FM, Bhogal SK. The role of written action plans in childhood asthma. *Curr Opin Allergy Clin Immunol* 2008;**8**:177–188.
119. Lagger G, Pataky Z, Golay A. Efficacy of therapeutic patient education in chronic diseases and obesity. *Patient Educ Couns* 2010;**79**:283–286.
120. Powell H, Gibson PG. Options for self-management education for adults with asthma. *Cochrane Database Syst Rev* 2003;**1**:CD004107.
121. Sicherer SH, Vargas PA, Groetch ME, Christie L, Carlisle SK, Noone S et al. Development and validation of educational materials for food allergy. *J Pediatr* 2012;**160**:651–656.
122. Segal N, Garty BZ, Hoffer V, Levy Y. Effect of instruction on the ability to use a self-administered epinephrine injector. *Isr Med Assoc J* 2012;**14**:14–17.
123. Manassis K. Managing anxiety related to anaphylaxis in childhood: a systematic review. *J Allergy* 2012, doi: 10.1155/2012/316296.
124. Akeson N, Worth A, Sheikh A. The psychosocial impact of anaphylaxis on young people and their parents. *Clin Exp Allergy* 2007;**37**:1213–1220.

125. Vickers DW, Maynard L, Ewan PW. Management of children with potential anaphylactic reactions in the community: a training package and proposal for good practice. *Clin Exp Allergy* 1997;**27**: 898–903.
126. Patel BM, Bansal PJ, Tobin MC. Management of anaphylaxis in child care centers: evaluation 6 and 12 months after an intervention program. *Ann Allergy Asthma Immunol* 2006;**97**:813–815.
127. Anagnostou K, Harrison B, Iles R, Nasser S. Risk factors for childhood asthma deaths from the UK Eastern Region Confidential Enquiry 2001-2006. *Prim Care Respir J* 2012;**21**:71–77.
128. Hourihane JO, Kilburn SA, Dean P, Warner JO. Clinical characteristics of peanut allergy. *Clin Exp Allergy* 1997;**27**:634–639.
129. Bonifazi F, Jutel M, Bilo BM, Birnbaum J, Muller U, Hypersensitivity EIGoIV. Prevention and treatment of hymenoptera venom allergy: guidelines for clinical practice. *Allergy* 2005;**60**:1459–1470.
130. 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.
131. Sicherer SH, Simons FER. 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.
132. Papadopoulos N, Agache I, Bavbek S, Bilo B, Braido F, Cardona V et al. Research needs in allergy: an EAACI position paper, in collaboration with EFA. *Clin Transl Allergy* 2012;**2**:21.