EAACI guidelines: Anaphylaxis (2021 update)

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EAACI anaphylaxis guideline

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ABSTRACT

Anaphylaxis is a clinical emergency which all healthcare professionals need to be able to recognise and manage. The European Academy of Allergy and Clinical Immunology Anaphylaxis multidisciplinary Task Force has updated the 2014 guideline. The guideline was developed using the AGREE II framework and the GRADE approach. The evidence was systematically reviewed and recommendations were created by weighing up benefits and harms. The guideline was peer-reviewed by external experts and reviewed in a public consultation. The use of clinical criteria to identify anaphylaxis is suggested with blood sampling for the later measurement of tryptase. The prompt use of intramuscular adrenaline as first line management is recommended with the availability of adrenaline autoinjectors to patients in the community. Pharmacokinetic data should be provided for adrenaline autoinjector devices. Structured, comprehensive training for people at risk of anaphylaxis is recommended. Simulation training and visual prompts for healthcare professionals are suggested to improve the management of anaphylaxis. It is suggested that school policies reflect anaphylaxis guidelines. The evidence for the management of anaphylaxis remains mostly at a very low level. There is an urgent need to prioritise clinical trials with the potential to improve the management of patients at risk of anaphylaxis.

KEY WORDS

Anaphylaxis; children; adults; guidelines

INTRODUCTION

This paper sets out the updated European Academy of Allergy and Clinical Immunology's (EAACI) guideline regarding the diagnosis, acute management and prevention of anaphylaxis. Anaphylaxis is a clinical emergency and all health care professionals need to be familiar with its recognition and management. Anaphylaxis is a life-threatening reaction characterised by acute onset of symptoms involving different organ systems and requiring immediate medical intervention.[1] Although the fatality rate due to anaphylaxis remains low,[2] the frequency of hospitalisation from food and drug-induced anaphylaxis has been increasing in recent years.[3]

The symptoms of anaphylaxis are highly variable.[4,5] Data from patients experiencing anaphylaxis revealed that skin and mucosal symptoms occur most frequently (>90% of cases) followed by symptoms involving the respiratory and cardiovascular systems (>50%). Food, drug and Hymenoptera venom are the most common elicitors of anaphylactic reactions.[5,6] The prevalence of the various causes of anaphylaxis are age-dependent and vary in different geographical regions. In Europe, typical causes of food-induced anaphylaxis in children are peanut, hazelnut, milk and egg and in adults, wheat, celery and shellfish; fruits such as peach are also typical causes of food-induced anaphylaxis in adults in some European countries such as Spain and Italy.[7,8] Venom-induced anaphylaxis is typically caused by wasp and bee venom[9]. Drug-induced anaphylaxis is typically caused by antibiotics and non-steroidal anti-inflammatory drugs.[10,11] Among antibiotics, beta-lactam antibiotics are the leading eliciting allergens.[12] At times there is an occupational cause[112]. Co-factors may be aggravating factors in anaphylaxis, examples are exercise, stress, infection, non-steroidal anti-inflammatory drugs and alcohol.[13-15] In some cases the cause is not obvious (idiopathic anaphylaxis) and investigations for rarer allergens or differential diagnoses should be considered.[16-18]

This guideline, updated from 2014,[19] provides evidence-based guidance to help manage anaphylaxis. The primary audience is clinical allergists (specialists and subspecialists), primary care, paediatricians, emergency physicians, anaesthetists

and intensivists, nurses, dieticians and other healthcare professionals. The guideline was developed by EAACI's Anaphylaxis Guideline Update task force (TF) and informed by a systematic review (SR).[20] Where published evidence was lacking, the findings of the review were supplemented with expert consensus opinion.

METHODOLOGY

This guideline was generated using the Appraisal of Guidelines for Research and Evaluation (AGREE II) approach[21,22] to ensure appropriate representation of the full range of stakeholders, a systematic search for and critical appraisal of, the relevant literature, and a systematic approach to formulating and presenting recommendations, with steps to minimise the risk of bias at each step. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach provided a structured way to evaluate evidence and potential recommendations.[23] The process commenced in September 2019 with a face-to-face discussion to agree the protocol and the key clinical areas. Regular webconferences took place through to November 2020 with additional email discussion to complete the guideline.

Clarifying the scope and purpose of the guidelines

This guideline provides evidence-based recommendations for the diagnosis, management and prevention of anaphylaxis in children and adults. It also highlights gaps where future research is required. Reactions to allergen immunotherapy are outside the scope of this guideline.[24]

Ensuring appropriate stakeholder involvement

The EAACI TF was drawn from 9 countries and included allergists (specialist and subspecialists), pediatricians, primary care, immunologists, emergency physicians, anaesthetists, dieticians, nurses, psychologist, education and patient organisation representatives. Methodologists took the lead in undertaking the SR, while clinical academics took the lead in formulating recommendations for clinical care.

Systematic review of the evidence

The SR aimed to assess the effectiveness of any approach for the immediate diagnosis, emergency management and prevention or long-term management of

anaphylaxis in children and adults.[20,25] It was undertaken by independent methodologists using GRADE Pro GDT (www.gradepro.org). Comparative studies were eligible for inclusion plus, in the case of diagnosis and adrenaline only, prospective case series with at least 20 participants were eligible. We continued to track evidence published after our SR cut-off date of 20th April 2020, and studies were considered by the TF chairs where relevant.

Evidence summaries for each question were prepared by methodologists, including assessments of the risk of bias and certainty of evidence.[26] TF members reviewed the summaries and provided feedback. The certainty of the evidence was assessed as high, moderate, low, or very low based on consideration of risk of bias, directness of evidence, consistency and precision of the estimates, and other considerations.[27]

Formulating recommendations

The TF used the GRADE approach to grade the strength and consistency of key findings from the SR,[20] which in turn contributed to formulating evidence-based recommendations for clinical care.[23] In generating recommendations, the TF evaluated the importance of the problem, desirable and undesirable effects, certainty of evidence, values, balance of effects, resources required, cost-effectiveness, equity, acceptability, and feasibility. All recommendations were agreed by consensus with a threshold of agreement set at 80%. Table 1 describes the conventions used in this guideline to describe the strength of recommendations and how this relates to policy and practice. Recommendations apply to all ages unless otherwise indicated.

TF members identified the resource implications of implementing the recommendations, barriers, and facilitators to the implementation of each recommendation, advised on approaches to implementing the recommendations, and suggested audit criteria that can help with assessing organizational compliance with each recommendation.

Table 1. Conventions used in Guideline wording

Strength and direction	Guideline wording	Implications for practice	Policy implications
Strong recommendation for an intervention	"The EAACI Task Force recommends …"	Most people in this situation should be offered the intervention	The recommendation can be adopted as a policy in most situations
Conditional recommendation for an intervention	"The EAACI Task Force suggests …"	Different choices will be appropriate for different people. Clinicians could help each patient make decisions consistent with the patient's preferences	Policies may differ depending on context and should be developed with the involvement of a wide range of stakeholders
Strong recommendation against an intervention	"The EAACI Task Force recommends against …"	Most people in this situation should not use this intervention	The recommendation can be adopted as a policy in most situations
Conditional recommendation against an intervention	"The EAACI Task Force suggests against …"	Different choices will be appropriate for different people. Clinicians could help each patient make decisions consistent with the patient's preferences	Policies may differ depending on context and should be developed with the involvement of a wide range of stakeholders
No recommendation	"There is no recommendation for or against using …"	Different choices will be appropriate for different people. Clinicians could help each patient make decisions consistent with the patient's preferences	Policies may differ depending on context and should be developed with the involvement of a wide range of stakeholders

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 guideline was made publicly available on the EAACI website for a 3-week period in February 2021 to allow a broader array of stakeholders to comment. All feedback was considered by the TF members and, where appropriate, final revisions were made in light of the feedback received. We will be pleased to continue to receive feedback on this guideline, addressed to the corresponding author.

Identification of evidence gaps

During the development of the guideline, areas where evidence is lacking were identified and gaps to fill prioritized.

Editorial independence and managing conflict of interests

The guideline development process was funded by EAACI. The funder did not have any influence on the guideline contents or on the decision to publish. TF members' conflicts of interest were declared at the start of the process and taken into account by the TF chairs, as recommendations were formulated. Specifically, anyone who had a potential financial conflict of interest was not able to be involved in final decisions about that recommendation (this did not apply to any task force members). Evidence about effectiveness was compiled independently by methodologists who had no conflict of interests. Additionally, final decisions about strength of evidence for recommendations were checked by the methodologists who had no conflict of interests.

Updating the guidelines

European Academy of Allergy and Clinical Immunology plans to update this guideline in 2026 unless there are important advances before then.

GUIDELINE RECOMENDATIONS

Table 2 summarises the guideline recommendations. The following sections explore these recommendations in more detail. The evidence is summarised narratively, with individual studies not described as these details can be found in our published SR.[20] The online supplement provides a detailed rationale with the relevant evidence for each recommendation (Online Supplement Tables S1-4).

Table 2. EAACI anaphylaxis guideline recommendations

Recommendation	Certainty of

	evidence
Diagnosing anaphylaxis in an emergency setting	
The EAACI task force **suggests** using clinical criteria, including rapid onset of multiple symptoms and signs, for identifying anaphylaxis in an acute context.	Very low
The EAACI task force **suggests** measuring serum tryptase half to two hours after the start of the reaction, and baseline tryptase at least 24 hours after complete resolution of symptoms, to support diagnosing anaphylaxis retrospectively.	Very low
Emergency management of anaphylaxis	
The EAACI task force **recommends** promptly using intramuscular adrenaline in the mid-thigh area as first-line management of anaphylaxis.	Very low
The EAACI task force **suggests** using adrenaline autoinjectors for the first-line management of anaphylaxis in the community.	Very low
The EAACI task force **recommends** that pharmacokinetic data should be provided for each adrenaline autoinjector product as they cannot be regarded as interchangeable.	Very low
The EAACI task force **suggests** prescribing 0.15mg adrenaline autoinjectors for children from 7.5kg to 25-30kg and 0.3mg adrenaline autoinjectors for children from 25-30kg, and at least 0.3mg adrenaline autoinjectors for adolescents and adults at risk of anaphylaxis.	Very low
Long-term management of anaphylaxis	
The EAACI task force **recommends** providing structured, comprehensive training to improve recognition of anaphylaxis and use of adrenaline autoinjectors in people at risk of anaphylaxis. This is in addition to basic instructions about autoinjector use.	Low
The EAACI task force makes **no recommendation** for or against using premedication with antihistamine to prevent anaphylaxis.	Very low
The EAACI task force **suggests** using premedication with subcutaneous adrenaline to prevent anaphylaxis when snake bite anti-venom is given to a patient.	Very low
The EAACI task force **suggests** that school policies reflect anaphylaxis guidelines but more research is needed to understand how guidelines and legislation in schools is best implemented.	Very low
Education and training for healthcare professionals	
The EAACI task force **suggests** using simulation training and visual prompts to improve healthcare professionals' recognition and management of anaphylaxis in emergency situations.	Very low

DIAGNOSIS OF ANAPHYLAXIS IN AN ACUTE CONTEXT

This section deals with making a diagnosis of anaphylaxis in a situation where someone has symptoms and signs of an acute allergic reaction. Further justification about each of the recommendations about diagnosing anaphylaxis is included in online supplement Table S1.

Making a diagnosis of anaphylaxis

The EAACI task force suggests using clinical criteria, including rapid onset of multiple symptoms and signs, for identifying anaphylaxis in an acute context.

Reason for recommendation: Anaphylaxis is a clinical emergency so the diagnosis needs to be made rapidly. Research suggests that National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network clinical criteria has high sensitivity.[28,29] (Box 1)

Strength of recommendation: This is a conditional recommendation as the evidence is of very low certainty and derives from case series or retrospective case-control studies.

Practical implications: Anaphylaxis has variable presentations, occasionally with no cutaneous involvement, and relatively low prevalence so it may not be easy to diagnose. Health care professionals require training in how to recognise anaphylaxis[30] (Box 1) and differentiate it from other diagnoses[31,32] (Box 2).

Box 1. 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

PEF, peak expiratory flow; BP, blood pressure. *Low systolic blood pressure for children is defined as <70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 x age]) from 1 to 10 years and <90 mmHg from 11 to 17 years.
Reproduced from Sampson et al[30] with permission.

Serum tryptase level may help to support the diagnosis later in the allergy consultation

The EAACI task force suggests measuring serum tryptase half to two hours after the start of the reaction, and baseline tryptase at least 24 hours after complete resolution of symptoms, to support diagnosing anaphylaxis respectively.

Reason for recommendation: Although measuring serum tryptase will not help to make a diagnosis of anaphylaxis in a clinical emergency, an elevated level within two hours of the reaction compared to a baseline value (measured before or after the reaction) can be helpful in confirming the diagnosis of anaphylaxis during subsequent allergy consultation.

Strength of recommendation: This is a conditional recommendation. Several studies have assessed the diagnostic accuracy of serum tryptase measurements for

anaphylaxis, but the evidence is of very low certainty, deriving from consecutive case series or case control studies.[33-35]

Practical implications: Taking the sample should not delay treating a patient with adrenaline where necessary. A sample taken later than two hours after the reaction may still demonstrate a raised tryptase level. A level of serum tryptase half to two hours after the start of the reaction (1.2 x baseline tryptase) + 2 µg/L supports a diagnosis of anaphylaxis.[36,37] A raised serum tryptase level can be associated with a mast cell disorder or hereditary alpha tryptasaemia[38-40], so it is important to compare with a baseline level at least 24 hours after complete resolution of a reaction. Also, serum tryptase is not always elevated in anaphylaxis, especially in children and with food triggers in all ages.[37] So failing to find an elevated tryptase level does not rule out anaphylaxis.

Box 2. Differential diagnosis of anaphylaxis

Skin or mucosal
- chronic remittent or physical urticaria and angioedema
- pollen food allergy syndrome (just oral symptoms)

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

Cardiovascular diseases
- vasovagal syncope
- pulmonary embolism
- myocardial infarction
- cardiac arrhythmias
- 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)
- dissociative disorder and conversion (e.g., globus hystericus)
- epilepsy
- cerebrovascular event
- psychoses
- factitious disorder

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

EMERGENCY MANAGEMENT OF ANAPHYLAXIS

In addition to the early use of adrenaline, the trigger should be removed where possible, posture should be optimised and assistance should be sought from emergency medical services in the community or the emergency team in hospital. To ensure adequate venous return patients experiencing anaphylaxis should lie flat with their legs raised. Where respiratory distress is the predominant presentation, patients may prefer to sit up with elevated legs. If pregnant, they can be placed on

their left side with the bed in a head-down position.[41] Where unconscious, patients can be placed in the recovery position. Avoid any abrupt change to a more upright posture.[42]

Further justification about each of the recommendations about managing anaphylaxis is included in online supplement Table S2. A checklist for managing anaphylaxis is presented in Box 3 and an algorithm approach to managing this clinical emergency is presented in Figure 1.

First line intervention: adrenaline

Route of administration

The EAACI task force recommends promptly using intramuscular adrenaline in the mid-thigh area as first-line management of anaphylaxis.

Reason for recommendation: Adrenaline has historically been used as first-line treatment for anaphylaxis, without evidence of serious harm. Early use of adrenaline appears to reduce the risk of biphasic reactions.[43-46] There is evidence that intramuscular adrenaline gives higher plasma levels than adrenaline via a metered dose inhaler.[47-50] The evidence comparing intramuscular with subcutaneous adrenaline is confounded by injection site but suggests that the former is associated with higher plasma adrenaline levels.[51,52] Injection mid-thigh gives higher levels than injection into deltoid.[52] There is little evidence of harm when adrenaline is given intramuscularly unlike with the intravenous dosing.[20]

Strength of recommendation: This is a strong recommendation in favour of adrenaline. The research evidence is of low certainty due to the challenges of undertaking randomised controlled trials in anaphylaxis. Given the totality of the evidence and clinical experience over many decades, the task force felt that a strong recommendation for the use of intramuscular adrenaline was appropriate.

Practical implications: Professionals who may need to manage anaphylaxis should be trained in how to promptly administer intramuscular adrenaline. The task force consider that adrenaline is best used early especially in patients who have had previous life-threatening reactions in similar circumstances (eg insect sting) although

346 our literature search did not focus on this and no relevant good quality evidence was
347 found. Assistance from colleagues should be sought early when managing a patient
348 with anaphylaxis. In severe reactions, especially involving the cardiovascular system,
349 intravenous fluids should also be given early with the second dose of intramuscular
350 adrenaline.[53] In some special circumstances, intramuscular adrenaline may not be
351 effective (eg refractory respiratory distress, hypotension) so intravenous adrenaline
352 should be used; this is likely to be more effective at reversing refractory
353 bronchospasm or hypotension. The use of intravenous adrenaline should be
354 restricted to healthcare professionals who are trained to use it and to monitored
355 settings such as the emergency room, operating theatres, or intensive care unit.
356 Patients on a beta-blocker may also respond poorly to adrenaline.

357 Adrenaline autoinjector or needle-syringe

358 *The EAACI task force suggests using adrenaline autoinjectors for the first-line*
359 *management of anaphylaxis in the community.*

360 *Reason for recommendation:* The benefits of using an autoinjector outweigh the risks
361 compared with using a (pre-filled) needle-syringe (online supplement Table S2).
362 Adrenaline autoinjectors are convenient, relatively safe, have a low risk of error and
363 are faster to administer compared to a needle-syringe approach. If autoinjectors are
364 also used to treat anaphylaxis in healthcare settings, the patient can practice using it
365 or at least observe how they are used and experience its effectiveness for managing
366 anaphylaxis.

367 *Strength of recommendation:* This is a conditional recommendation for using
368 autoinjectors because the certainty of evidence is very low due to the available trials
369 being at moderate or high risk of bias.[54,55]

Practical implications: A number of different adrenaline autoinjectors are available, each of which have slightly different mechanisms. Device specific training is therefore essential for each autoinjector and with further training if device is changed. Adrenaline autoinjectors are designed to be kept at 20-25°C and have a limited shelf life due to degradation of the adrenaline. Autoinjectors occasionally fail to deploy and the European Medicines Agency has stated that patients should have access to two devices[56] (see Table 3 for arguments for prescribing one or two devices). In many countries adrenaline autoinjectors are not available or not affordable or there are supply issues with adrenaline autoinjectors. In these circumstances a prefilled syringe is an alternative. Indications for the prescription of self-injectable adrenaline are described in Box 4.

Box 3. Checklist for managing an acute allergic reaction

1. Stay with patient
2. Remove the trigger (e.g. food, drug, venom)
3. Look for signs of anaphylaxis
4. Administer adrenaline if signs of anaphylaxis (eg breathing or circulatory problems)
5. Call for help
6. Lie flat with their legs raised unless in respiratory distress where patient may prefer to sit sit up with elevated legs
7. Repeat adrenaline if no improvement or worsening of symptoms 5-10 minutes after first administration
8. Do not forget oxygen, beta-2 agonist or i.v. fluids as indicated

Adrenaline is effective for all symptoms

Box 4. Indications for the prescription of self-injectable adrenaline

Table 3. Reasons for prescribing one or two adrenaline autoinjectors

Arguments for two autoinjectors	Arguments for one autoinjector
• European Medicines Agency recommends that two autoinjectors are prescribed[56] • About 10% patients require a second dose of adrenaline due to insufficient response to the first dose[58] • Rarely, an autoinjector will misfire or be injected in the wrong place56 • Where there is a likelihood of delayed medical assistance, eg remote location or travel	• Only needing to carry one device may improve adherence to carriage which is low • Most autoinjectors are not used and have to be replaced after 12-18 months when they expire • Most patients respond to one dose and second doses are usually administered by emergency services[57,58]

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Recommendation	Key references	Rationale
Absolute indications for adrenaline auto-injectors		
Previous anaphylaxis triggered by food, latex, or aeroallergens	59,60	High risk of recurrent anaphylaxis
Previous exercise-induced anaphylaxis	61	High risk of recurrent anaphylaxis
Previous idiopathic anaphylaxis	57	High risk of recurrent anaphylaxis
Co-existing unstable or moderate to severe, persistent asthma and a food allergy*	62,63	Asthma is a risk factor for experiencing anaphylaxis in the context of food allergy
Hymenoptera venom allergy in untreated patients with more than cutaneous/mucosal systemic reactions or high risk of re-exposure During and after VIT, in patients with more than cutaneous/mucosal systemic reactions if risk factors for relapse are present	24,64	High risk of recurrent anaphylaxis
Underlying systemic mastocytosis in adults with any previous systemic reaction. Children with very severe skin involvement (>50% body surface) and increased basal serum tryptase levels (>20ng/ml) and with blistering in the first three years of life.	65-68	Systemic mastocytosis is associated with a high risk of recurrent anaphylaxis and it is not possible to identify individual at risk patients
Consider prescribing adrenaline auto-injectors with any of the following additional factors (especially if more than one is present)		
Previous mild-to-moderate allergic reaction* to foods known to be associated with anaphylaxis in patient's region (eg peanut and/or tree nut, cow's milk, sea food depending on triggers for anaphylactic reactions at that location)	69,70, 113-116	Relatively high risk of experiencing anaphylaxis in the future with any peanut or tree nut allergy in many counties. Increasing number of fatal anaphylaxis with cow's milk in school age children and young adults. Seafood is an important hidden allergen in some countries.
Teenager or young adult with a food allergy with previous mild-to-moderate reactions*	71,72	This age group is at higher risk of experiencing anaphylaxis due to their life style or risk behaviours
Remote from medical help or prolonged travel abroad in the context of previous mild-to-moderate allergic reaction to a food, Hymenoptera venom, latex, or	73	Medical help may not be easily available during travel. Risks are more difficult to control due to language barriers and new foods.

aeroallergens		
Previous mild-to-moderate allergic reaction to traces of food*	[42,73,74]	Contact with a large amount of the food in the future may result in a more severe reaction
Hymenoptera venom or drug allergy in patients with more than cutaneous/mucosal systemic reactions and cardiovascular disease	[5,75]	Cardiovascular diseases appear to be associated with a greater risk of severe or fatal anaphylaxis (venom and drug anaphylaxis)
Oral immunotherapy for food allergy	[76]	Anaphylaxis is a known adverse effect of oral immunotherapy for food allergy

*Excluding pollen food allergy syndrome unless patient has previously experienced systemic symptoms. VIT: Hymenoptera venom immunotherapy. Supporting references taken from the anaphylaxis systematic review with additional ones taken from a specific review of the literature focused on indications.

Pharmacokinetic data for adrenaline autoinjectors and needle-syringe

The EAACI task force recommends that pharmacokinetic data should be provided for each adrenaline autoinjector product as they cannot be regarded as interchangeable. Reason for recommendation: Pharmacokinetic data are now available for many of the adrenaline autoinjector products. These data demonstrate that each type delivers very different plasma adrenaline levels. It had been thought that the length of the needle was critical to optimising the delivery of adrenaline. However, the pharmacokinetic data indicate that needle length does not dictate adrenaline plasma levels.[77] For example, when the same autoinjectors were used for adults with different skin to muscle depths (associated with body mass index), some devices have a similar plasma adrenaline profile in all[78] whereas there is marked blunting of the height of the early peak in overweight individuals in others.[79] (see online supplement Table S2). Plasma adrenaline levels may be more closely related to the force at which adrenaline is deployed from the device.[78]

Strength of recommendation: This is a strong recommendation for making pharmacokinetic data available. Only some pharmacokinetic data have been published in peer review journals and other data are available via information submitted to European medicine regulators. Given the marked differences in adrenaline profiles between different products and different patients they cannot be seen as interchangeable. The task force considered that these data should be made

available by companies for all adrenaline devices to help predict their likely clinical effectiveness.

Practical considerations: As we do not know what level of plasma adrenaline is needed to successfully treat anaphylaxis, the results of these pharmacokinetic studies need to be interpreted with some caution. A product that does not achieve similar plasma levels to other autoinjectors is of concern.

Dose of adrenaline

The EAACI task force suggests prescribing 0.15mg adrenaline autoinjectors for children from 7.5kg to 25-30kg and 0.3mg adrenaline autoinjectors for children from 25-30kg, and at least 0.3mg adrenaline autoinjectors for adolescents and adults at risk of anaphylaxis.

Reason for recommendation: There are no published data for children weighing under 15kg although the routinely advised intramuscular adrenaline dose is 0.01 mg/kg in healthcare settings. In the 2014 guideline we recommended using a 0.15mg adrenaline autoinjector for children from 7.5kg bodyweight on the basis that a mild overdose does not represent a major risk in otherwise healthy children.[32] There have been no reports of any adverse consequences of this approach and regulators have now licensed some autoinjectors down to 7.5kg in some European countries (eg Germany).[80] However, there is a danger that the needle will hit the underlying bone in small children.[81] We are aware of a 0.1mg adrenaline autoinjector product but this only appears to be available in the United States.[117] We identified only one study looking at plasma adrenaline levels with 0.15 and 0.3mg devices in children.[82] Similar plasma levels were seen but the 0.3mg dose was associated with more side-effects in children under 30kg. Alternatively, children may rapidly outgrow their dose and adverse effects need to be balanced against effectiveness. Countries within Europe vary as to whether a switch happens at 25 or 30kg for different devices. We therefore suggest using the 0.3mg dose only in children more than 25-30kg in weight. A 0.5mg dose gives a substantially higher plasma level than a 0.3mg dose with one device.[83] The optimal dose of adrenaline in anaphylaxis is not known

and 0.3mg devices have been found to be effective for treating anaphylaxis in most patients,[57] so the 0.3mg adrenaline dose is preferred.

Strength of recommendation: This is a conditional positive recommendation because it is based on small studies enrolling volunteers who were randomised to different adrenaline autoinjectors. It is uncertain what plasma adrenaline level is therapeutic in anaphylaxis, so it is difficult to make definitive recommendations.

Practical considerations: In the relatively rare case of an infant less than 7.5kg in bodyweight at risk of anaphylaxis, a prefilled syringe and adrenaline dose of 0.01 mg/kg can be used instead of an autoinjector. For adolescents and adult patients, a 0.3mg device is recommended although a higher 0.5mg device can be considered where a patient is overweight or has experienced a previous episode of life-threatening anaphylaxis. In a clinical setting, where a patient presents with severe anaphylaxis, a higher dose (eg 0.5mg or 0.3mg repeated for an older adolescent or adult) may be considered.

Other interventions

Our systematic review found no eligible randomised controlled trials assessing the effectiveness of other interventions for the acute management of anaphylaxis. It is recognised that some may be useful as concomitant therapy with adrenaline. These interventions are briefly described although no robust evidence is available.

Oxygen

Give high flow oxygen to a patient experiencing anaphylaxis.

Fluid support

Administer intravenous fluids early with first adrenaline dose to patients with cardiovascular involvement as adrenaline may not be effective without restoring the circulatory volume. Crystalloids are preferred given in boluses of 10 ml/kg (maximum 500ml per bolus) for children and 500ml in adults, repeated as needed. This should be repeated if lack of response. Fluid support could also be given in severe anaphylaxis with a respiratory presentation if a second dose of intramuscular adrenaline is required.

466 H1 and H2 antihistamines

467 Systemic antihistamines have only been demonstrated to relieve cutaneous
468 symptoms[84] and a possible effect on non-cutaneous symptoms remains
469 unconfirmed.[85]

470 Glucocorticoids

471 Glucocorticoids are commonly used in anaphylaxis as they are thought to prevent
472 protracted symptoms and possibly biphasic reactions but there is limited evidence of
473 their effectiveness and they may be deleterious in children.[85,86]

474 Inhaled Beta2-Agonists

475 In the case of predominant bronchial obstruction, inhaled ß-adrenoreceptor agonists,
476 (e.g. salbutamol) can be additionally administered (best using an oxygen driven
477 nebulizer or via metered dose inhaler using a “spacer”).

478 Inhaled adrenaline

479 In cases with suspected laryngeal/pharyngeal oedema inhaled administration of
480 adrenaline via a nebulizer together with oxygen is recommended. The systemic
481 absorption of inhaled adrenaline is negliable[48] and it should only be used as a
482 supplement to i.m. administration.

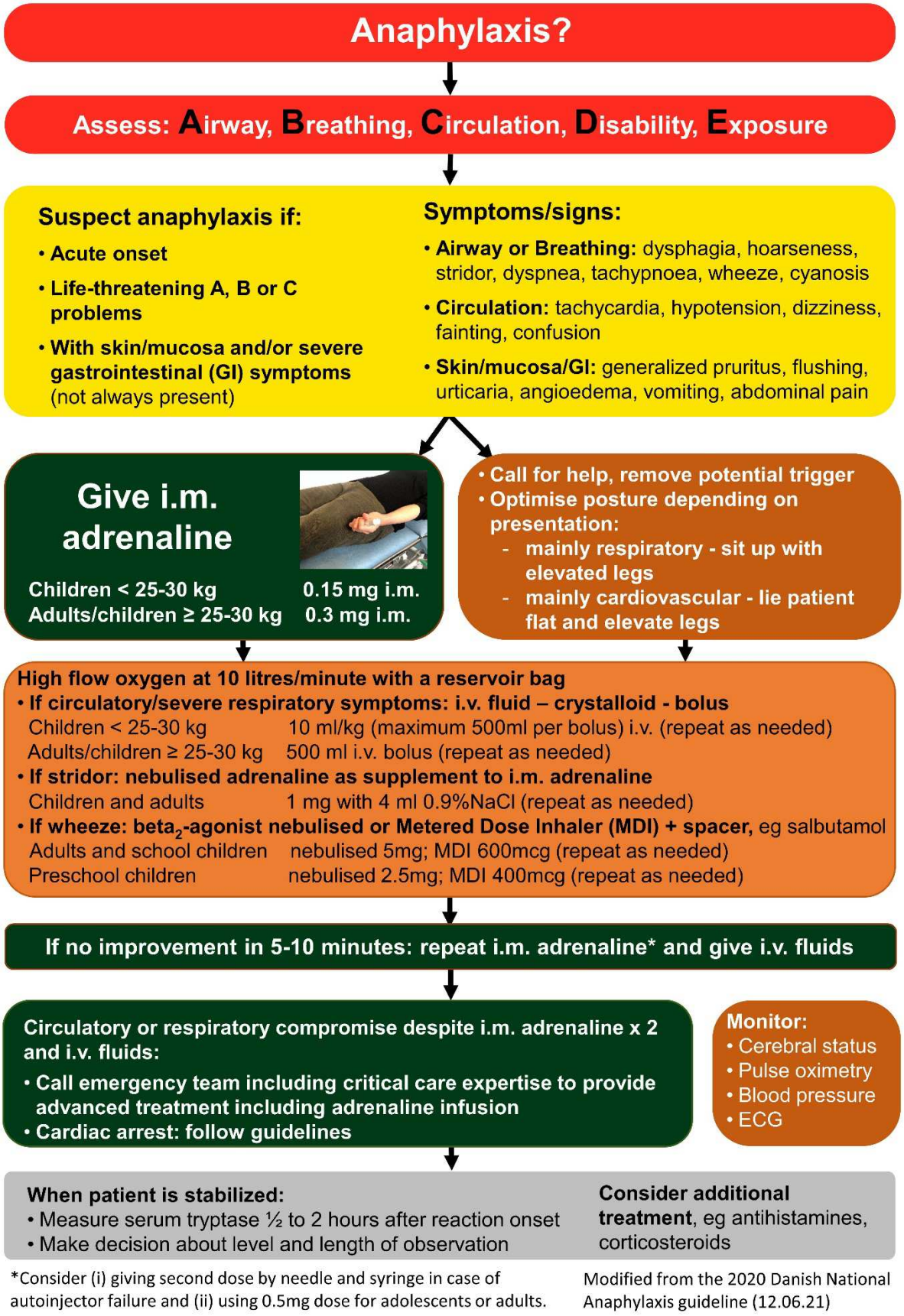
483

484 **Monitoring and discharge arrangements**

485 Patients with anaphylaxis are at risk of protracted reactions and of developing
486 biphasic reactions although the likelihood is low[85,87] (Table 4). The Task Force
487 suggest that they are monitored for 6-8 hours with respiratory compromise and at
488 least 12–24 hours with hypotension. Before discharge, assess the risk of future
489 reactions and prescribe adrenaline auto-injectors to those at risk of recurrence (Box
490 4). Provide patients with written advice covering allergen avoidance measures and
491 instructions for when and how to use the adrenaline autoinjector. Refer patients to an
492 allergy specialist to investigate possible triggers. This is particularly important for
493 idiopathic anaphylaxis where reactions to hidden allergens, such as alpha-gal or

drug excipients, can be examined. The allergist will also assess the risk of further reactions, and ensure that patients and caregivers are optimally equipped and trained to manage any further reactions. A specialist dietitian can provide helpful advice where the trigger is a food. Also signpost patients to local patient advocacy groups as sources of further information and ongoing support.

Figure 1. Schematic illustration of the initial management of anaphylaxis



501

502 **Table 4. Factors leading to need for prolonged observation following anaphylaxis**

Prolonged observation following anaphylaxis: factors to consider
Factors relating to the patient: • Reactions in individuals with severe asthma[88] • Patients presenting in the evening or at night, or those who may not be able to respond to any deterioration[88] • Patients in areas where access to emergency care is difficult[88] • Patients with a previous history of biphasic reactions[88]
Factors related to the reaction, potentially increasing the risk of a biphasic reaction: • With multi-organ involvement[87] • With a severe respiratory component[88] • Needing administration of >1 dose of epinephrine for the treatment of the initial anaphylaxis[85] • Caused by allergen with continued absorption of the allergen, eg food[88] • With unknown elicitor[85]

503 Supporting references taken from the anaphylaxis systematic review with additional ones from a
504 specific review of the literature focused one prolonged or biphasic reactions.

505

506

507 ## LONG-TERM MANAGEMENT OF ANAPHYLAXIS

508 The following sections detail the long-term management of patients at risk of
509 anaphylaxis. Further justification about each of the recommendations about
510 managing anaphylaxis is included in online supplement Table S3. A summary of
511 long-term management in the community is presented in Box 5. Boxes 6 and 7
512 provides examples of individualised paediatric emergency action plans.

Box 5. Summary of the long-term management in the community of patients at risk of anaphylaxis

Individualized management plan and emergency kit

- Provision of individualized management plan written clearly in simple, non-medical language; it must include:
  - personal identification data: name, address, contact number; also consider adding a photograph
  - details of the parents, guardian, or next of kin, allergist
  - family doctor and the local ambulance service
  - clear identification of the source of the allergens to be avoided and allergen avoidance advice
  - clear identification of any non-allergen triggers or cofactors (e.g. exercise) and avoidance advice
  - anaphylaxis emergency action plan
- Copy of plan must 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 (EMA recommends that patients have access to two devices)
  - fast-acting, non-sedating, antihistamine for treating cutaneous allergic reactions, where appropriate
- Implementation of the patient's management plan in the community (e.g. nursery, school university work)
- Advice to carry mobile phone (if appropriate)
- Discuss a form of medic alert notification
- Review of plan including doses with age and weight

Education and training

- Training of patients and caregivers, this must include:
  - instructions on appropriate allergen avoidance measures,
  - including consultation with an allergy dietitian, where appropriate if food is the trigger
  - instructions on prompt recognition of symptoms of anaphylaxis
  - training on when and how to use an adrenaline auto-injector, where appropriate and to carry them at all times
  - explanation of expiry of devices, reminders and process for renewal and storage
- Reinforcement with revision at regular intervals, possibly with asthma reviews
- Retraining on device if device switched
- Sign post patient support groups

Specific therapy

- Venom immunotherapy as appropriate
- Desensitization for drug allergy as appropriate

Other considerations

- Psychological support as required to patient and family/carers
- Ensure optimal management of co-morbidities such as rhinitis and asthma
- Support during transition to adulthood with good communication specialist units advice on at risk behaviour
- Log allergies in hospital and community medical records
- Re-referral or advice and guidance to allergy unit if new symptoms with foods or repeat admissions

EMA: European Medicines Agency.

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514

Box 6. Example of an individualised emergency action plan for a child

Action to take:
- Stay with the child, call or help if necessary
- Locate adrenaline autoinjectors
- Give long-acting, non-sedating antihistamine if required: medication _____, dose_____
- Phone parent/emergency contact: _____

Watch for signs of ANAPHYLAXIS (life-threatening allergic reaction)
Anaphylaxis may occur without skin symptoms: ALWAYS consider anaphylaxis in someone with known food allergy who has SUDDEN BREATHING DIFFICULTY

A: AIRWAY
- Persistent cough
- Hoarse voice
- Difficulty swallowing
- Swollen tongue

B: BREATHING
- Difficult or noisy breathing
- Wheeze or persistent cough

C: CIRCULATION
- Persistent dizziness
- Pale or floppy
- Suddenly sleepy
- Collapse/unconscious

IF ANY ONE (OR MORE) OF THESE SIGNS ABOVE ARE PRESENT:
1. Lie child flat with legs raised (if breathing is difficult, sit up with elevated legs)
2. Use Adrenaline autoinjector without delay (Device: ____, dose ____)
3. Dial ____ for ambulance and say ANAPHYLAXIS ("ANA-FIL-AX-IS")

*** IF IN DOUBT, GIVE ADRENALINE ***

AFTER GIVING ADRENALINE:
1. Stay with child until ambulance arrives, **do NOT** stand child up
2. Commence CPR if there are no signs of life
3. Phone parent/emergency contact
4. If no improvement after 5-10 minutes, give a further adrenaline dose using a second autoinjectable device, if available.

You can dial emergency number from any phone, even if there is no credit left on a mobile. Medical observation in hospital is recommended after anaphylaxis.

Adapted from British Society of Allergy and Clinical Immunology paediatric allergy action plans (https://www.bsaci.org/professional-resources/resources/paediatric-allergy-action-plans/, last accessed 26th September 2020).

How to give an adrenaline autoinjector:
- Instructions for how to give an adrenaline autoinjector differ between devices.
- Patients should receive training in how to use the auto-injector they are prescribed.

Instructions as to how to administer a particular autoinjector can be added to the "How to give an adrenaline autoinjector" box.

Box 7. Example of an individualised emergency action plan for a young person or adult

Mild/moderate reaction:
- Swollen lips, face or eyes
- Itchy/tingling mouth
- Hives or itchy skin rash
- Abdominal pain or vomiting

Action to take:
- Let others know, call for help if necessary
- Locate adrenaline autoinjectors
- Take long-acting, non-sedating antihistamine if required: medication _____, dose_____mg
- Watch for development of more severe symptoms

Watch for signs of ANAPHYLAXIS (life-threatening allergic reaction)
Anaphylaxis may occur without skin symptoms. If you have food allergy, ALWAYS consider anaphylaxis if you develop SUDDEN BREATHING DIFFICULTY

A: AIRWAY
- Persistent cough
- Hoarse voice
- Difficulty swallowing
- Swollen tongue

B: BREATHING
- Difficult or noisy breathing
- Wheeze or persistent cough

C: CIRCULATION
- Persistent dizziness
- Suddenly sleepy
- Collapse/unconsciousness

IF ANY ONE (OR MORE) OF THESE SIGNS ABOVE ARE PRESENT:
1. Lie flat with legs raised (if breathing is difficult, sit up with legs raised.bent)
2. Use Adrenaline autoinjector without delay (Device: _____, dose _____mg)
3. Dial ____ for ambulance and say ANAPHYLAXIS ("ANA-FIL-AX-IS")

*** IF IN DOUBT, GIVE ADRENALINE ***

AFTER GIVING ADRENALINE:
1. D**o NOT** stand up
2. CPR should be started if there are no signs of life
3. Phone emergency contact (_____)
4. If no improvement after 5-10 minutes, give a further adrenaline dose using a second autoinjectable device, if available.

You can dial emergency number from any phone, even if there is no credit left on a mobile. Medical observation in hospital is recommended after anaphylaxis.

Adapted from British Society of Allergy and Clinical Immunology paediatric allergy action plans (https://www.bsaci.org/professional-resources/resources/paediatric-allergy-action-plans/, last accessed 26th September 2020).

How to give an adrenaline autoinjector:
- Instructions for how to give an adrenaline autoinjector differ between devices.
- Patients should receive training in how to use the auto-injector they are prescribed.

Instructions as to how to administer a particular autoinjector can be added to the "How to give an adrenaline autoinjector" box.

Education to improve acute management

Education and training for patients at risk of anaphylaxis

The EAACI Task Force recommends providing structured, comprehensive training to improve knowledge and use of adrenaline autoinjectors in people at risk of anaphylaxis. This is in addition to basic instructions about autoinjector use.

Reason for recommendation: There is some evidence from research and clinical experience that repeated information and support helps patients feel more knowledgeable and confident about managing triggers and responding in an emergency.[89,90] (Box 5) (more details in Table S3).

Strength for recommendation: This is a conditional positive recommendation. Although there are randomised controlled trials about educating patients, the certainty of evidence was low. It is unclear what types of training and support are most effective.

Practical implications: Education is essential if patients at risk of anaphylaxis are to successfully recognise and manage future episodes. Many patient training approaches are available, including the use of adrenaline autoinjector training devices and online approaches.[71]

Other potential educational interventions

Some studies have also found that supporting patients to practise using an adrenaline_autoinjector or needle and syringe containing 0.9% saline can reduce anxiety or improve quality of life.[91,92] This approach may be helpful in anxious patients but requires adequate resources and preparation. More research focused on supervised self-injection with an adrenaline autoinjector with outcomes evaluated using disease-specific quality-of-life and self-efficacy measures is needed. In the case of anaphylaxis during an in-hospital based food/ drug challenge, patients and carers may be encouraged to administer their own adrenaline autoinjector to improve their confidence in this procedure.[93] It is also important for allergists to follow a patient's anaphylaxis management plan during a provocation challenge (eg giving im adrenaline with the first sign of anaphylaxis) to re-inforce this self-management approach.

Pharmacological approaches to prevent anaphylaxis

Premedication with antihistamine

The EAACI task force makes no recommendation for or against using premedication with antihistamine to prevent anaphylaxis.

Reason for no recommendation: We found insufficient evidence about the effectiveness of antihistamines in preventing anaphylaxis.[94,95] A recent meta-analysis that included observational studies and studies where the outcome was hypersensitivity not anaphylaxis concluded that antihistamines and or glucocorticoids may prevent index reactions to chemotherapy but not radio-contrast media (very low certainty evidence).[85]

Practical implications: Antihistamines are helpful at reducing reactions to allergen immunotherapy but this is outside the scope of the current guidelines.[96]

Premedication with adrenaline for snake bite anti-venom

The EAACI task force suggests using premedication with subcutaneous adrenaline to prevent anaphylaxis when snake bite anti-venom is given to a patient.

Reason for recommendation: There is some evidence that low dose, subcutaneous adrenaline can prevent anaphylaxis caused when snake anti-venom is given to a patient [97,98](more details in Table S3).

Practical implications: For this very specific scenario, pre-medication with low dose, subcutaneous adrenaline may be useful when a patient who has suffered a snake bite is treated with snake anti-venom. The task force found no evidence that antihistamines or hydrocortisone could prevent anaphylaxis associated with snake bite anti-venom (online supplement Table S3).

Approaches to prevent anaphylaxis in schools

Use of policy to improve management in schools

The EAACI task force suggests that school policies should reflect anaphylaxis guidelines but more research is needed to understand how guidelines and legislation in schools is best implemented.

Reason for recommendation: There is emerging evidence to support the value of school policies in improving the management of anaphylaxis in an education setting.[99] Anaphylaxis due to food allergy, occurs in schools more than in any other community location.[100,101] It may therefore be helpful to target secondary schools and community settings with educational support to help raise general awareness, empower adolescents to confidently self-manage food allergy and enable schools to develop protocols to minimise any adverse events if they occur (more details in Table S3).

Strength recommendation: This is a conditional positive recommendation because the certainty of the evidence is very low. Although there was only one study and it was at high risk of bias, we believe that schools need more support to prioritise systems to ensure that children at risk of anaphylaxis are protected in schools.

Practical implications: While there is some evidence to support a policy approach to improving the management of anaphylaxis in schools. For example, in a pilot study in two UK schools[102], full stakeholder involvement in toolkit development, based on EAACI guidelines, was found to raise awareness and empower pupils with/without allergies to self-manage effectively. However, there are barriers to the implementation of legislation[103]. Work needs to be done to understand how best to implement legislation and guidelines in schools, including how best to train schools staff.[104] Furthermore, standard allergy policies, such as those supplied by national or local authorities, may lack the school-specific practical solutions necessary for effective implementation. A similar approach may be helpful for pre-school care settings.

Other approaches

Other approaches researched to improve the management of anaphylaxis included nurses checking whether students were carrying autoinjectors[105] and availability of a

24-hour helpline.[106] None of these had sufficient evidence to warrant a recommendation.

EDUCATION AND TRAINING FOR HEALTHCARE PROFESSIONALS

Simulation training and visual prompts for healthcare professionals

The EAACI task force suggests using simulation training and visual prompts to improve healthcare professionals' recognition and management of anaphylaxis in emergency situations.

Reason for recommendation: Healthcare professionals are not well prepared to recognise and manage anaphylaxis.[107,108] Simulation-based training is well established across medicine and there is emerging evidence that it may help professionals recognise and react to anaphylaxis. (more details in Table S4). Similarly, there is some evidence that visual aids such as wallet sized prompt sheets or flow diagrams can help healthcare professionals understand and better manage anaphylaxis.[109-111]

Strength of recommendation: This is a conditional positive recommendation as the quantity and quality of available evidence is low. It is based on a number of small randomised controlled trials, the majority of which were at high risk of bias and focused on different endpoints so there was very low overall certainty in the evidence.

Practical implications: Simulation training is well established and accepted as a teaching method. Scenarios based on anaphylaxis could be included in simulation training programmes for healthcare professionals. With regards to visual aids, these need to be readily accessible to healthcare professionals who may encounter anaphylaxis in their practice. A number of modalities can be considered, for example wallet size prompt sheets, posters in emergency rooms or electronic apps.

SUMMARY, GAPS IN THE EVIDENCE AND FUTURE PERSPECTIVES

This guideline is intended to provide the best current evidence on the appropriate diagnosis and management of anaphylaxis both at the acute episode and in the long- term management. The diagnosis of anaphylaxis is still based on the clinical evaluation. In suspected reactions, measuring serum tryptase within the first 2 hours of reaction can help the allergist to subsequently make a diagnosis. Adrenaline is confirmed to be the first line treatment, to be administered intramuscularly and timely. Likewise, the provision of the adrenaline auto-injector is the cornerstone for the long term management. The task force recommends that pharmacokinetic data should be made available, especially for any new devices. The European Medicines Agency recommends " *that two auto-injectors are prescribed to any patient at-risk who should carry them all times.*"[56] Although this recommendation is valid in all the EU countries, the task force is aware that there are differences in implementation, availability of auto-injectors and reimbursement. Patients need an individualized plan for managing anaphylaxis as well as education. Health professionals, nursery staff and teachers also need training. We have considered the facilitators and barriers to implementing these recommendations (Table 5).

Strengths and limitations

A strength of this guideline is that it is informed by a balance of evidence and expert opinion. A comprehensive systematic review was undertaken evaluating the evidence according to well-established GRADE methods. We focused on randomised controlled trials to provide the highest quality available evidence. The review was led by independent methodologists with no conflicts of interest. It is a strength that the recommendations were also based on expert clinical and patient opinion, balancing benefits and harms and considering values and preferences. This included a range of countries, disciplines and clinical backgrounds, including primary care and patient organisations. So where the evidence was not clear or sufficient, a broad based consensus could be achieved.

A limitation of the guideline is that there is heterogeneity and gaps in existing knowledge, making it difficult to draw firm conclusions. Much of the research does

not use robust diagnostic criteria for anaphylaxis and there are other methodological weaknesses meaning that most recommendations are based on low or moderate certainty evidence. The heterogeneity in the studies, including different study populations, variations in interventions at different ages and duration, and varying definitions of anaphylaxis made it challenging to interpret the evidence. It was not appropriate to undertake meta-analysis to combine such heterogeneous studies.

Research gaps

There is much left to learn about diagnosing and managing anaphylaxis. Table 6 sets out key priorities. Where possible, evidence ought to be derived from double-blind, placebo-controlled randomised trials. Future studies would ideally include a harmonized definition and robust diagnostic criteria for anaphylaxis. High priority gaps are the need of biomarkers which can predict the level of risk for a given patient, the role of monoclonal antibodies in reducing the risk as well as getting evidence on the most adequate educational intervention or combination of interventions for prevention of the acute episode.

Conclusions

Implementing these recommendations would result in harmonization of the best standards of practice for anaphylaxis. The ultimate goal would be the development of an evidence- based, multifaceted and integrated patient-centric approach which may help to alleviate the burden of anaphylaxis amongst individuals and families and also reduce societal healthcare costs.

688 **Table 5. Considerations for implementing recommendations made in this guideline**

689

Topic	Barriers to implementation	Facilitators to implementation	Audit criteria	Resource implications
Using clinical criteria to identifying anaphylaxis in an emergency situation	Various definitions of anaphylaxis are still in place Lack of knowledge and experience	Training on validated list of rapid onset of signs and symptoms with accessible reminders (eg wallet, phone, internet)	Proportion of emergency settings in which the validated criteria is used	Cost of implementing standardized, validated, universal definition low
Measuring serum tryptase to support the diagnosis of anaphylaxis retrospectively	Lack of knowledge regarding tryptase in emergency department Tryptase sample should not delay acute diagnosis and treatment Lack of infrastructure for taking and analysing samples	Training about use of tryptase for emergency department staff Identification of laboratories with the relevant equipment	Proportion of anaphylaxis patients where tryptase is assessed	The cost of measuring tryptase, although low, needs to be taken into account
Healthcare professionals treating anaphylaxis with I.M. adrenaline and using the correct dosing	Differences in labelling of adrenaline (e.g. ratios 1:1000 or mass concentration 1mg/ml) Synonym epinephrine used in some countries Lack of training	Training healthcare professionals Standardization of labelling Add to mandatory annual training	Proportion of cases treated with I.M. adrenaline using the correct dosage	Resources needed for training and standardizing adrenaline
Use of adrenaline autoinjectors by patients	Lack of training Fear or embarrassment to use	Training patients and care givers with simulated scenarios Identify and treat needle phobia	Proportion of patients experiencing anaphylaxis who use an autoinjector	Autoinjectors are relatively expensive, most of not used and they have a relatively

	Not carrying AAI all times Needle phobia	Use of trainer devices Reminders to carry devices Access to training materials including online videos		short shelf-life
Education and training for patients and carers in anaphylaxis recognition and management	Training packages need to be developed and harmonized across regions Unclear which elements and structure are most beneficial Repeated training is likely to be of greater benefit	Patients and patient groups place great value on patient training Multiple different modalities of training can be developed (face-to-face, virtual) Online training already provided by commercial companies and patient organizations	Proportion of patients/ carers who have been offered and accessed a comprehensive training package after diagnosis	Training packages are costly to develop and implement, both financially and in terms of the time taken
Use of simulation training and visual prompts for healthcare professionals	Anaphylaxis specific simulation training packages need to be developed and validated Visual prompts need to be of a suitable format and kept updated and accessible	Simulation training is a well-established training modality Visual prompts are used for other medical emergencies Standardisation of devices where possible	Proportion of healthcare professionals who have received simulation training Proportion of healthcare professionals with access to visual management prompts	For simulation training costs can be high; also time-consuming For visual prompts, costs are low as these are inexpensive to produce
Use of policy to improve management in schools	Inaccessible clinically focussed documents Impractical standard allergy policies	Identification of specific needs and concerns in order to develop practical applications for schools that can be	Implementation of policy in school Proportion of students	Initially relatively high, but subsequently low once protocols are in

		implemented in real world context	who experience anaphylaxis	effect

708 **Table 6. Gaps in the evidence for managing anaphylaxis**

Gaps	Suggestion to address	Priority
Data comparing the pharmacokinetics of different adrenaline auto-injector devices	Clinical randomised controlled trial	High (1st)
Optimal dose and dosing intervals of intramuscular adrenaline in patients experiencing anaphylaxis	Clinical randomised controlled trial	High (2nd)
Clinical definition and diagnostic criteria for anaphylaxis that are easy to use in emergency situations.	Large community based studies to develop, validate and assess ease of use of criteria	High (3rd)
Identification of biomarkers to predict severity of anaphylaxis	Follow up of clinical cohorts at varying risks of anaphylaxis	Medium (4th)
Biomarkers for bedside testing to support diagnosis	Clinical cohorts experiencing anaphylaxis and similar presentations	Medium (5th)
Standardised severity grading for anaphylaxis	Clinical cohorts experiencing acute allergic reactions and consensus discussion	Medium (5th)
Role antihistamines, corticosteroids or adrenaline to prevent anaphylactic reactions in high risk situations	Large randomised controlled trials in high risk situations (i.e. re-administration of contrast media after a previous reaction)	Medium (7th)
Value of practising self-injection (using functioning adrenaline autoinjector devices) to a sub-group of patients that may be too anxious otherwise to use their auto-injector in real life.	Randomised controlled studies with outcomes focused on allergy specific quality of life, self-efficacy and anxiety	Medium (8th)
Role of second-and third line drugs in the treatment of anaphylaxis	Clinical randomised controlled trial	Medium (9th)
Identification of different endotypes of anaphylaxis which may benefit from different management	Analysis of large data sets considering different elicitors	Medium (10th)
More convenient routes of administration of adrenaline eg intranasal, inhalational, sublingual	Clinical randomised controlled trial, initially pharmacokinetic studies in well individuals, then randomised controlled trials in high risk patients or situations	Low (11th)

Effectiveness of smartphone based applications to improve recognition and management of anaphylaxis for patients	Community randomized controlled studies, with a focus on patient involvement in app development and patient engagement	Low (12th)
Best approach to implementing guidelines and legislation in schools	Qualitative methods (e.g. Interviews/focus groups) with students and staff to identify specific needs and concerns in order to develop practical applications Then large school based randomised controlled trial to assess the effectiveness of implementation	Low (13th)
Standardised questionnaires for quality of life for patients at risk of anaphylaxis from any elicitor	Analysis of large data sets from patients considering different elicitors	Low (14th)

Prioritisation was agreed by consensus within the guideline task force.

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AUTHOR CONTRIBUTIONS

Antonella Muraro, Graham Robert and Margitta Worm chaired the EAACI Anaphylaxis Guideline Task Force. Cherry Alviani, Victoria Cardona, Audrey DunnGalvin, Lene H. Garvey, Carmen Riggioni, Graham Roberts and Margitta Worm led the discussions for individual sections drafting the evidence table, recommendations and gaps for specific sections based on the underpinning systematic review and task force discussions which involved the authors. Graham Roberts, Antonella Muraro and Margitta Worm wrote the initial draft of the guideline. All authors participated in the discussion of the draft guideline, its revision and

approved the final version. Antonella Muraro chaired the EAACI Food Allergy and Anaphylaxis Guidelines Update; Graham Roberts coordinated the update of the guidelines supported by Ekaterina Khaleva; and Debra de Siva provided methodological support and advice as well as contributing to drafting sections.

CONFLICT OF INTERESTS

Professor Muraro reports grants and personal fees from Aimmune and personal fees from DVB, Mylan, ALK and Nestle outside the submitted work and was past President of EAACI.

Professor Worm reports grants and personal fees from Stallergens, HAL Allergie, Bencard Allergie, Allergopharma, ALK-Abello, Mylan Germany, Actelion Pharmaceuticals Deutschland, Biotest, AbbVie Deutschland, Lilly Deutschland Aimmune, DBV Technologies, Regeneron Pharmaceuticals, Sanofi Aventis, Leo Pharma, Novartis and Viatris, outside the submitted work and is past WAO co-chair of the anaphylaxis committee.

Dr. Alviani has nothing to disclose.

Dr. Cardona reports personal fees from Allergopharma and GSK and a grant from Thermofisher outside the submitted work and SLAAI chair anaphylaxis committee plus past WAO chair anaphylaxis committee.

Dr. DunnGalvin has nothing to disclose.

Dr. Garvey reports personal fees from Novo Nordisk, Merck, Lundbeck, Biomarin and Thermofisher Scientific outside the submitted work.

Dr. Riggioni has nothing to disclose.

Professor de Silva has no conflict to disclose in relation to the guideline. Her organisation received a grant from EAACI to conduct a systematic review, which was one of the tools the task force drew on tool when developing recommendations..

Dr. Angier reports BSACI member and Anaphylaxis Campaign scientific board member.

Dr. Arasi has nothing to disclose.

Professor Bellou has nothing to disclose.

Dr. Beyer reports grants and personal fees from Aimmune, grants and personal fees from ALK, grants and personal fees from Danone, grants and personal fees from DBV, grants and personal fees from Infectopharm, grants and personal fees from ThermoFisher, grants and personal fees from Hycor, grants from DST Diagnostic, Good Mills, Hipp, VDI, EU, German Research Foundation, BMBF and personal fees from Allergopharma, Bausch & Lomb, Bencard, Jenpharma, Mabylon, Mylan, Nestle, Novartis, and Nutricia outside the submitted work.

Dr. Bijlhout has nothing to disclose.

Dr Bilo reports personal fees from ALK, Allergy Therapeutics, Astra, GSK and Sanofi outside the submitted work.

Prof Dr Bindslev-Jensen reports research grants from Novartis outside the submitted work.

Dr Brockow reports personal fees from ThermoFisher and Mylan outside the submitted work.

Dr Fernandez-Rivas reports grants from ISCIII (Ministry of Science, Spanish Government), grants and personal fees from Aimmune and personal fees from Ga2len, DBV, Novartis, SPRIM, Diater, GSK, HAL Allergy and Thermofisher Scientific outside the submitted work.

Professor Halken has nothing to disclose.

Dr Jensen has nothing to disclose.

Dr. Khaleva has nothing to disclose.

Dr Michaelis has nothing to disclose.

Dr Oude Elberink reports grants from Pure IMS and Blueprint, support from Novartis, Behring, Viatric, Takeda and Sanofi outside the submitted work and is on the Advisory Board of PIMS Epinephrine.

Ms Regent reports she is employed by the Anaphylaxis Campaign, UK; the organisation received support from ALK-Abello and Mylan.

Dr Sanchez reports a personal fees from Aimmune Therapeutics outside the submitted work.

Dr Vlieg-Boerstra reports grants and personal fees from Nutricia and personal fees from Mead Johnson, Abbott and Marfo Food Groups outside the submitted work.

Professor Roberts reports he was Editor in Chief Clinical & Experimental Allergy until December 2020.

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