EAACI guideline: Anaphylaxis (2020 update)

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SHORT TITLE

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.

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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 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, the most frequent causes of food-induced anaphylaxis in children are peanut, hazelnut, milk and egg and in adults, wheat, celery and shellfish.[7,8] Venom-induced anaphylaxis is mainly caused by wasp and bee venom[9]. The main causes of drug-induced anaphylaxis are antibiotics and non-steroidal anti-inflammatory drugs.[10,11] Among antibiotics, beta-lactam antibiotics are still the leading eliciting allergens.[12] 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 causes or mast cell activation syndromes 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

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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 & 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 XXX 2020 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 specialists, 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

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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

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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.

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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 adrenaline autoinjector devices as they cannot be regarded as interchangeable devices.	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, 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.	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

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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).

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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 9 age]) from 1 to 10 years and <90 mmHg from 11 to 17 years.
Reproduced from Sampson et al. (Sampson 2006) with permission.

Reference: Sampson 2006[30]

<u>Serum tryptase level may help to support the diagnosis later in the allergy consultation</u>

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 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. A number of 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 at the time of reaction above (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.

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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)
- 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

Adapted from Simons et al. (2011) and Muraro et al. (2007) with permission.

References: Simons 2011[31], Muraro 2007[32]

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 semi-recumbent on the left side with the legs elevated.[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

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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 our literature search did not focus on this and no relevant good quality evidence was found. Assistance from colleagues should be sought early when managing a patient with anaphylaxis. In severe reactions, especially involving the cardiovascular system, intravenous fluids should also be given early with the second dose of intramuscular adrenaline.[53] In some special circumstances, intramuscular adrenaline may not be effective so intravenous adrenaline should be used. The use of intravenous adrenaline should be restricted to healthcare professionals who are trained to use it and to monitored settings such as the emergency room, operating theatres or intensive care unit.

Adrenaline autoinjector or needle-syringe

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

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

Strength of recommendation: This is a conditional recommendation for using autoinjectors because the certainty of evidence is very low due to the available trials 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 2 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 up with legs elevated
7. Repeat adrenaline if no improvement or worsening of symptoms 5-10 minutes after first administration
8. Do not forget other treatments as indicated (e.g., oxygen, beta-2 agonist, i.v. fluids, antihistamine, corticosteroid)

Adrenaline is effective for all symptoms

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 (EMA)	Only needing to carry one device may improve adherence to carriage which is low
About 10% patients require a second dose of adrenaline due to insufficient response to the first dose (Ierodiakonou 2020)	Most autoinjectors are not used and have to be replaced after 12-18 months when they expire
Rarely, an autoinjector will misfire or be injected in the wrong place (EMA)	Most patients respond to one dose and second doses are usually administered by emergency services (Ierodiakonou 2020, Noimark 2012)
Where there is a likelihood of delayed medical assistance, eg remote location or travel	

References: Noimark 2012[57], Ierodiakonou 2020[58], EMA 2012[56]

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

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
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 or 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 peanut and/or tree nut	69,70	Relatively high risk of experiencing anaphylaxis in the future with any peanut or tree nut allergy
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, venom, latex, or aeroallergens	73	Medical help may not be easily available during travel. Risks are more difficult to control due to language barriers and new foods.
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
Cardiovascular disease	5,75	Cardiovascular diseases appear to be associated with a greater risk of severe or fatal 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

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Pharmacokinetic data for adrenaline autoinjectors and needle-syringe

The EAACI task force recommends that pharmacokinetic data should be provided for adrenaline autoinjector devices as they cannot be regarded as interchangeable devices.

Reason for recommendation: Pharmacokinetic data are now available for many of the adrenaline autoinjectors. These data demonstrate that each autoinjector 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 speed 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 devices and different patients they cannot be seen as interchangeable devices. 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 device that does not achieve similar plasma levels to other autoinjectors is of concern.

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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, 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 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 increasing the risk of side effects.[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 may also be appropriate.

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 to patients with cardiovascular involvement as adrenaline may not be effective without restoring the circulatory volume. Crystalloids are preferred given in boluses of 20 ml/kg for children, and in adults 500ml initial bolus. 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.

H1 and H2 antihistamines

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

Glucocorticoids

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

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Inhaled Beta2-Agonists

In the case of predominant bronchial obstruction, inhaled ß-adrenoreceptor agonists, (e.g. salbutamol) can be additionally administered (best using an oxygen driven nebulizer or using a “spacer” for children).

Inhaled adrenaline

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

Monitoring and discharge arrangements

Patients with anaphylaxis are at risk of protracted reactions and of developing biphasic reactions although the likelihood is low[85,87] (Table 4). the Task Force suggest that they are monitored for 6-8 hours with respiratory compromise and at least 12–24 hours with hypotension. Before discharge, assess the risk of future reactions and prescribe adrenaline auto-injectors to those at risk of recurrence (Box 4). Provide patients with written advice covering allergen avoidance measures and instructions for when and how to use the adrenaline autoinjector. Refer patients to an allergy specialist to investigate possible triggers, assess risk of further reactions, and ensure that patients and caregivers are optimally equipped and trained to manage any further reactions. Involve a specialist dietitian where the trigger is a food. Also signpost patients to local patient advocacy groups as sources of further information and ongoing support.

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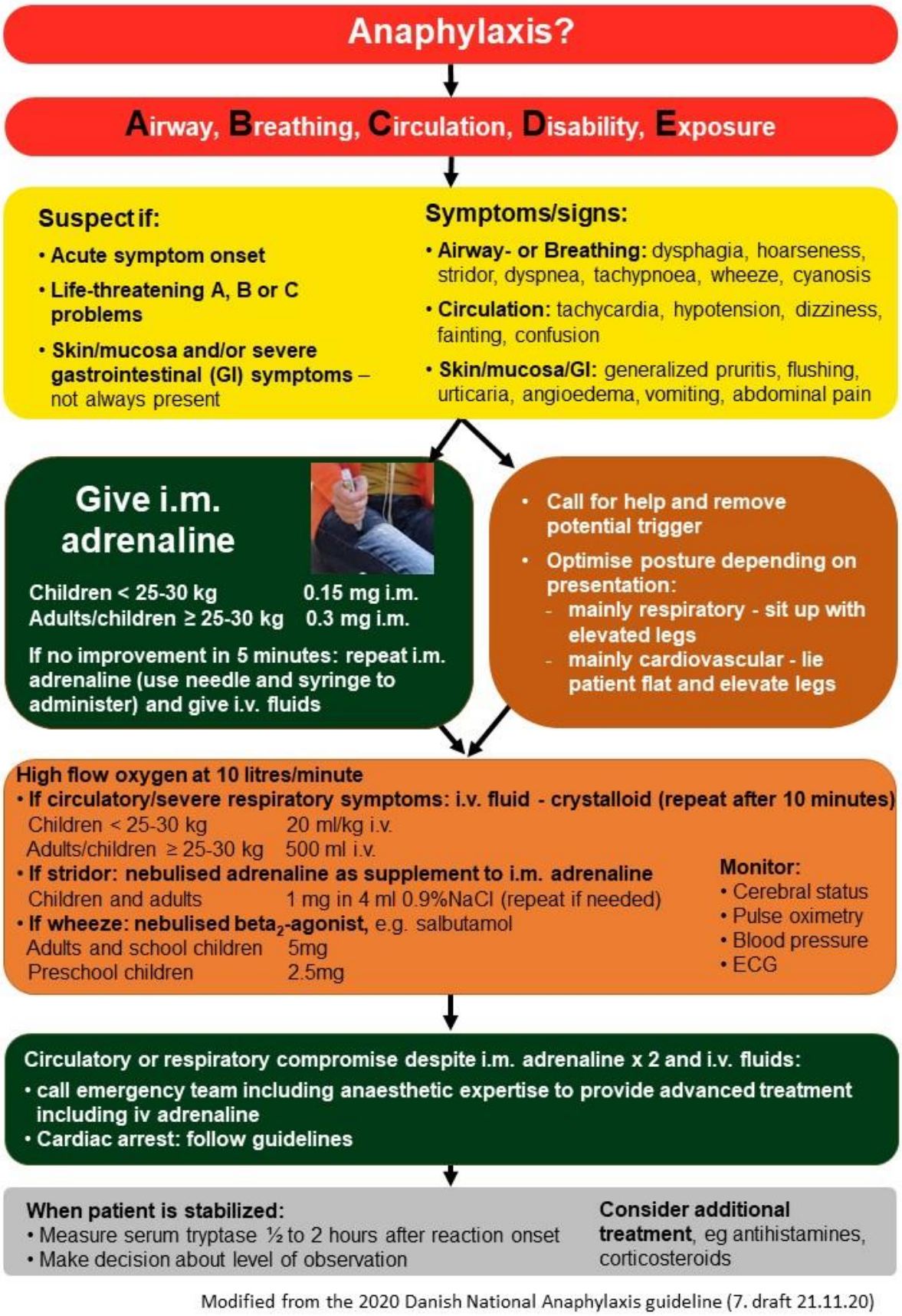
Figure 1. Schematic illustration of the initial management of anaphylaxis



Modified from the 2020 Danish National Anaphylaxis guideline (7. draft 21.11.20)

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 (UK resus council 2016) • Patients presenting in the evening or at night, or those who may not be able to respond to any deterioration (UK resus council 2016) • Patients in areas where access to emergency care is difficult (UK resus council 2016) • Patients with a previous history of biphasic reactions (UK resus council 2016)
Factors related to the reaction, potentially increasing the risk of a biphasic reaction • with multi-organ involvement (Kraft 2020) • with a severe respiratory component (UK resus council 2016) • needing administration of >1 dose of epinephrine for the treatment of the initial anaphylaxis (US practice parameter 2020) • caused by allergen with continued absorption of the allergen, eg food (UK resus council 2016) • with unknown elicitor (US practice parameter 2020)

References: Kraft 2020[87], UK resus council 2016[88], US practice parameter 2020[85]

LONG-TERM MANAGEMENT OF ANAPHYLAXIS

The following sections detail the long-term management of patients at risk of anaphylaxis. Further justification about each of the recommendations about managing anaphylaxis is included in online supplement Table S3. A summary of long-term management in the community is presented in Box 5. Box 6 provides an example of an individualised paediatric emergency action plan.

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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, nonmedical 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
  - 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 medi alert
- 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

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

Mild/moderate reaction:

- Swollen lips, face or eyes
- Itchy/tingling mouth
- Hives or itchy skin rash
- Abdominal pain or vomiting
- Sudden change in behaviour

Action to take:

- Stay with the child, call for help if necessary
- Locate adrenaline autoinjector(s)
- Give antihistamine: 10mg loratidine tablet
- Phone parent/emergency contact: 0238 XXXX XXX

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, allow child to sit)
2. Use Adrenaline autoinjector without delay (XXX, dose 0.3mg)
3. Dial XXX 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 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.

How to give a Anapen/Emerade/Epipen/Jext autoinjector:

Areas labelled as XXXX are patient, device or country specific. 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).

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 empty syringe and needle 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]

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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 may decrease skin symptoms in the case of a hypersensitivity reaction so can be used to manage reactions. Antihistamines are also 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.

Reason for recommendation: There is some evidence that low dose, subcutaneous adrenaline can prevent anaphylaxis caused by snake anti-venom but this is sparse and from Asia[97,98](more details in Table S3).

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

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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.

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 RCTs, 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.

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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

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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.

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Table 5. Considerations for implementing recommendations made in this guideline

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 Not carrying AAI all times Needle phobia	Training patients and care givers with simulated scenarios Identify and treat needle phobia Use of trainer devices Reminders to carry devices Access to training materials including online videos	Proportion of patients experiencing anaphylaxis who use an autoinjector	Autoinjectors are relatively expensive, most of not used and they have a relatively 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	Patients and patient groups place great value on patient training Multiple different modalities of training can be developed (face-to-face, virtual)	Proportion of patients/carers who have been offered and accessed a	Training packages are costly to develop and implement, both financially and in terms of the time taken

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	Repeated training is likely to be of greater benefit	Online training already provided by commercial companies and patient organizations	comprehensive training package after diagnosis	
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 implemented in real world context	Implementation of policy in school Proportion of students who experience anaphylaxis	Initially relatively high, but subsequently low once protocols are in effect

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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)

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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.

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 ALK, grants from GAP study and personal fees from Aimmune, DBV Technologies, Regeneron Pharmaceuticals, Sanofi Aventis, Leo Pharma, Mylan, ARLA and Nestle outside the submitted work and is WAO co-chair anaphylaxis committee.

Dr. Alviani has nothing to disclose.

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Dr. Cardona reports personal fees from ALK, Allergopharma, Allergy Therapeutics, Diater, LETI and Thermofisher outside the submitted work and SLAAI chair anaphylaxis committee, past WAO chair anaphylaxis committee.

Dr. DunnGalvin reports grants from Aimmune Therapeutics, National Children's Research Centre Ireland, DBV Technologies, SafeFood Ireland and Atlanta Clinical Trials in Food outside the submitted work.

Dr. Garvey reports personal fees from Novo Nordisk, Merck 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.

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Ms Regent reports she is employed by the Anaphylaxis Campaign, UK.

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

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EAACI Anaphylaxis Guideline Online Supplement

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Table S1. Diagnosis of 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.			
Evidence of effectiveness (from systematic review)	Balance of benefits and harms	Values or preferences that may impact	Feasibility and costs
Our recommendation is justified because there are positive trends in the evidence, even though we cannot be certain. It is difficult to draw conclusions based on the research evidence alone because the certainty of evidence is very low. One retrospective case-control study (Brighton Case definition[1]) and one consecutive case series (NIAID/FAAN clinical criteria[2]) found that clinical criteria as defined in Brighton Case definition and NIAID/FAAN clinical criteria had sensitivities at 0.681 and 0.671 – 95.1%, and specificities at 0.790 and 0.704 – 70.8% respectively (Erlewyn-Jeunesse 2010[1], Loprinzi Brauer 2016[2]). A retrospective case-control study involving 214 emergency department patients showed a sensitivity of 96.7% for the NIAID/FAAN criteria with 82.4% specificity. (Campbell 2012[3]) The sensitivities vary between the studies but are highest for the NIAID/FAAN clinical criteria in the latest and largest study. The specificity is lower in both studies but still reasonable.	We suggest the use of clinical criteria, such as those defined by NIAID/FAAN or the Brighton Case definition, as they both show a high sensitivity which is important to identify and treat rapidly all possible cases of anaphylaxis	The definitions are designed for different types of cases. The NIAID/FAAN definition was designed to clarify clinical diagnosis and provide standardization in research. The Brighton definition was designed for ascertaining cases of anaphylaxis occurring as an adverse event following immunisation. Studies have investigated these definitions in an emergency setting (Erlewyn-Jeunesse 2010[1], Loprinzi Brauer 2016[2]). The Task Force prefer the NIAID/FAAN definition as sensitivity is slightly higher and the criteria more easily applicable in an emergency setting. Additionally, the NIAID/FAAN criteria is easier to use and has been extensively for many years. In contrast, the Brighton Case definition is much more complicated to use in an emergency setting.	This is likely to be feasible with training and at low cost.

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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.			
Evidence of effectiveness (from systematic review)	Balance of benefits and harms	Values or preferences that may impact	Feasibility and costs
Our recommendation is justified because there are positive trends in the evidence, whilst the certainty of evidence is very low. It is difficult to draw conclusions based on the research evidence alone . Peak serum tryptase (obtained within the first two hours of reaction) is often but not always elevated in anaphylaxis, a normal level is not uncommon and does not rule out anaphylaxis. Two consecutive case series found that serum tryptase measurements (total, peak, delta) are not accurate enough to diagnosis anaphylaxis in the acute situation (Brown 2004[4], Sala-Cunhill 2013[6]). Serum tryptase is more frequently associated with more severe anaphylaxis and positively correlates to the grades of severity of anaphylaxis (Sala-Cunhill 2013[6], Francis 2017[5]). Serial tryptase measurements increased diagnostic accuracy. An increase in tryptase of 2.0 µg/L or greater had a sensitivity of 73% and specificity of 98% (Brown 2004[4]). Serum tryptase concentrations 1-2 hours after the reaction is significantly higher than later measurements (Sala-Cunill 2013[6]).	An increase in serum tryptase as compared with a baseline value supports the diagnosis of anaphylaxis, whereas a negative result is not reliable for the diagnosis. One study found that the most effective algorithm is achieved when the acute total tryptase levels is greater than ([1.2×baseline tryptase] + 2] µg/L to be considered a clinically significant rise. Using this algorithm achieved 94% positive predictive value (PPV) and 53% negative predictive value (NPV) (Vitte 2019[7]).	Different measures are used in the studies (total, peak, delta), no value is conclusively more useful. Blood for tryptase can be taken once first line therapy has been given.	Our recommendation is justified because It is likely feasible and the moderate cost to measure tryptase. It may help diagnose anaphylaxis retrospectively in cases where the diagnosis is not obvious and may also raise the suspicion of a potential underlying mast cell disease.

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Table S2. Emergency management of anaphylaxis

The EAACI task force recommends promptly using intramuscular adrenaline in the mid-thigh area as first-line management of anaphylaxis.			
Evidence of effectiveness (from systematic review)	Balance of benefits and harms	Values and preferences	Feasibility and costs
Our recommendation is justified because there is evidence for the superiority of IM adrenaline over other routes of administration while there are minimal safety concerns with this route. *Use of adrenaline in anaphylaxis* Two case control studies (n = 269) compared adrenaline versus no adrenaline on the incidence of biphasic reactions in children. Adrenaline was associated with an absolute reduction in biphasic reactions of 9% and 18%, respectively compared to children who did not receive adrenaline (Mehr 2009[8], Manuyakorn 2015[9]). *Early/prompt use of adrenaline in anaphylaxis* One case control study (n=384) found that early adrenaline administration was associated with no absolute reduction (0%) in ICU admission. (Fleming 2015[10]) One consecutive case series (n=430) found that early adrenaline administration was associated with an absolute reduction in the risk of biphasic reactions of 23%. (Liu 2020[11]) *IM better than inhaled route* Two randomised trials and two non-randomised trials (n=79), three in adults and one in children, suggest that inhalation did not consistently deliver a therapeutically appropriate dose of adrenaline	*Use of adrenaline in anaphylaxis* High quality evidence is lacking due to ethical and feasibility issues of studying the effect of adrenaline in anaphylaxis in controlled studies. The benefits considered to outweigh the risks because the treatment has shown to work in clinical practice through several decades and there is universal consensus at a global level to use adrenaline as first line treatment in anaphylaxis. The pathophysiology of anaphylaxis and the mechanism of action of adrenaline supports its use in this situation. Retrospective studies have found benefits from adrenaline for the acute management of anaphylaxis in the form of reduced admission rates, faster recovery, fewer biphasic reactions and fewer admissions to ICU (Ko 2016[19], Cardona 2017[20]) Studies from fatality registries have shown a higher mortality in patients who either did not receive adrenaline or had delayed treatment (Pumphrey 2000[13]). *Potential benefit of early use* Studies suggests that early use of adrenaline is associated with prevention of hypotension (Ko	Adrenaline is universally recommended in guidelines as the first-line therapy for anaphylaxis. (EAACI 2014[24],WAO 2015 update[25], AAAAI practice parameter 2020[26], UK resus council 2012[27]) Some laypeople and clinicians may be hesitant about using adrenaline given the potential impact of the drug. These beliefs are not supported by evidence when used via intramuscular route. In severe reactions treatment with adrenaline should be complimented by concomitant administration of fluids and help should be called early.	*Feasibility* In most parts of the world it is feasible to have adrenaline available in community and hospital settings and schools. It is feasible to have adrenaline available for inhalation for patients with upper airway obstruction. The use of inhaled adrenaline as first line treatment is not feasible unless a portable device with high delivery in few breaths is made available. Devices with better bioavailability are being developed. It is feasible to have IV adrenaline available in acute settings with monitoring and specialists used to diluting and administering IV adrenaline.

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compared to intramuscular or subcutaneous injection. Risk of adverse effects was higher on inhalation and children could not inhale sufficient doses. (Breuer 2013[12]; Simons 2000[13]; Heilborn 1986[14]; Foucard 1997[15]) *IM better than SC route* Two trials (n=30) compared intramuscular versus subcutaneous injection of adrenaline in children and young adults. Intramuscular adrenaline was associated with an absolute increase of mean plasma adrenaline concentration in one study but it was confounded by using different injection sites (thigh versus arm)(Simons 1998[16]). In the other, intramuscular and subcutaneous adrenaline in arm gave similarly low mean plasma adrenaline concentration (Simons 2001[17]). *IM better than IV route* One consecutive case series (n=301) in children and adults found that intravenous bolus administration was associated with a 13% increase in the incidence of adrenaline overdose (OR 61.3, 95% CI 7.5 to infinity) and an 8% increase in the incidence of cardiovascular events compared with intramuscular administration (OR 7.5, 95% CI, 1.6 to 35.3, (Campbell 2015[18]).	2016[19]), decreased rates of hospitalization (Fleming 2015[10]), and increased survival. *Inhaled as supplementary to im adrenaline* Whilst sufficient plasma levels of adrenaline cannot be achieved by the inhaled route, there are beneficial local effects in reducing airway oedema. Nebulised adrenaline inhalation can be used as a supplement to intramuscular adrenaline in cases of symptoms or signs of upper airway obstruction. *Intramuscular route* There is very little evidence of harm when intramuscular adrenaline is correctly used, but harm may include local vascular injury especially if accidently injected into a digit (Anshien 2019[21]). Intramuscular injection into the mid-thigh area (vastus lateralis muscle) is preferred as it achieves better plasma levels than the arm (deltoid muscle) (Simons 2001[17]) and it is easier to identify (Duvauchelle 2018[22]; Worm 2020[23]). Potential harms from adrenaline include overdose which may lead to cardiac arrythmias, cardiac ischaemia and death. Groups that may be particularly at risk of harm include elderly patients with ischaemic heart disease. The risk of overdose is significantly higher when administered intravenously (Campbell 2015[18]). *Intravenous adrenaline in special circumstances* As correct dilution and intravenous administration of adrenaline requires training, the use of IV adrenaline should be restricted to be used in special settings, in monitored		

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	patients by health care professionals with this competence.		

The EAACI task force suggests using adrenaline autoinjectors for the first-line management of anaphylaxis in the community.			
Evidence of effectiveness (from systematic review)	Balance of benefits and harms	Values and preferences	Feasibility and costs
Our recommendation is justified because there are positive trends in the evidence identified in the systematic review. It is difficult to draw conclusions based on the research evidence alone because the certainty of evidence is very low. *Administration and accuracy may be better with an autoinjector* One non-randomised trial with health professionals tested an autoinjector or a syringe (not pre-filled) having been trained in the use of AAI (Asch 2017[28]). It showed that using an autoinjector reduced the time to administration by an average of 70 seconds compared to a syringe and resulted in fewer administration errors (statistically significant, confidence intervals not reported) (Very low certainty of evidence). As an alternative, prefilled syringe might be used for treatment of anaphylaxis. One RCT in caregivers of children at risk of anaphylaxis found that a prefilled syringe (n=57) was associated with a 61% absolute increase in the proportion who successfully completed administration of adrenaline compared to autoinjector	*Generalisation of evidence to acute anaphylaxis* Assessments in these studies did not occur in the acute setting of anaphylaxis, and therefore, findings may not be directly transferable to the real-life situation where levels of stress are likely to be higher and risk of error greater. *Potential problems with autoinjectors* Potential harms from adrenaline autoinjector use include technical issues that may lead to errors in administration (Muck 2010[36], Simons 2010[37]). Data suggests that there could be accidental injections (Anshien 2019[21]) or lacerations (Brown 2016[38]). However, newer/modified models of adrenaline autoinjectors can slightly reduce the risk of unintentional injuries. AAI should be stored at 20°C to 25°C (68°F to 77°F), therefore, adrenaline stored outside the recommended temperature range may not provide the labelled dose (Rachid 2016[39]). Similarly, the concentration and bioavailability of expired AAI may decrease over time (Simons 2000[40]). Physicians	*Autoinjectors differ and require specific training* There are different devices of autoinjectors. Some patients may prefer Epipen/Jext with protective caps and shielding at the opposite end to needle, Anapen with a needle protection cap and a safety cap that require activation for use (depressing a red button with the thumb- a syringe mechanism) and needle stays exposed, or Emerade with a direct injection but no protective cap. Therefore, there are different instructions on how to use different AAI and therefore requires regular training. AAI can be	*Autoinjectors are not universally available* Adrenaline autoinjectors are only available in some countries (Tanno 2020[41]). The cost of AAI varies based on the dosage and whether it is branded or generic. In addition, AAI require replacing before expiratory day. In some countries where AAI are not available or lack of affordability, prefilled syringes with adrenaline may be an alternative. In emergency departments adrenaline autoinjectors, prefilled syringe and/or vials of adrenaline are available. The use of pre-filled syringes with adrenaline can also be considered in times of AAI

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(Epipen) (n=56) (OR 4.07, 95% CI 1.29 to 12.86)(Suwan 2018[29])(low certainty). Time to adrenaline administration was the same in both groups. *Current autoinjectors more likely to be correctly used and have less adverse effects* Seven randomised trials, two non-randomised controlled trials and one consecutive case series have examined the usability of autoinjectors (SR supplement S5h[30]). The modifications included in the current generation of adrenaline autoinjectors may slightly increase the proportion of people correctly using the devices (low certainty)(Arga 2012[31]; Bakirtas 2011[32]; Umasunthar 2015[33]; Robinson 2014[34]; Guerlain 2010[35]) and decrease the time taken to administer adrenaline (low certainty) (Arga 2012[31]; Bakirtas 2011[32]). The new autoinjectors may also reduce unintentional injuries (very low certainty, statistically significant, confidence intervals not reported) (Arga 2012[31]; Bakirtas 2011[32]).	should emphasize the importance of restocking expired AAI to patients. *Conclusion* We suggest adrenaline autoinjector for the first-line treatment of anaphylaxis. We suggest that patients at risk of anaphylaxis should have access to adrenaline autoinjectors. The benefits outweigh the risks because AAI is easy to use, convenient, relatively safe, results in low risk of errors in dosing and faster to administer compared to syringe and needle. Moreover, newer/ modified models of adrenaline autoinjectors may slightly increase the proportion of people correctly using the devices and reduce the time taken to administer adrenaline.	self-administered or administered by another individual upon onset of symptoms. *Use by healthcare professionals* It may also be useful for healthcare professionals to use AAI for first line management of anaphylaxis as it demonstrates to patients how the autoinjector is used and its effectiveness (use same device as patient has). They HCP do need to be trained.	shortage. Potential limitations include accidental needle pricks, unintentional disconnection of the needle from the syringe and premature release of adrenaline, However, high rate of participants (adults, adolescents and caregivers) successfully administrated prefilled syringe (Moss 2018[42]) and there was a significantly higher failure rate in the administration of the EpiPen trainer compared to the Symjepi (prefilled syringe) in adolescents (Moss 2018[43]). Prescription of pre-filled adrenaline should come with verbal and written instructions (patient leaflet) as well as specific training with a dummy syringe. Based on the SRs, syringes filled with 1 mg/mL adrenaline are stable and sterile for 90 days (Parish 2016[44], 2019[45])

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The EAACI task force recommends that pharmacokinetic data should be provided for adrenaline autoinjector devices as they cannot be regarded as interchangeable devices.			
Evidence of effectiveness (from systematic review)	Balance of benefits and harms	Values and preferences	Feasibility and costs
Our recommendation is justified because of the pharmacokinetic data now available for adrenaline autoinjectors demonstrate that they deliver very different plasma adrenaline levels which is not necessarily related to needle length. These data are not references in our systematic review (de Silva 2020[30]) as most data are not published or only recently published. Plasma adrenaline levels are used as outcomes in many of these studies but we do not know adrenaline's the therapeutic plasma level *Needle length may be too short for overweight adults but too long for infants* Different adrenaline autoinjectors have different needle lengths: 0.15mg dose: anapen 12.7mm, emerade 16.0mm, epipen 12.7mm, jext 13.0mm; 0.3mg dose: anapen 12.7mm, emerade 25.0mm, epipen 15.0mm, jext 15.0mm; 0.5mg dose: emerade 25.0mm (Schwirtz 2012[46], Song 2016[47]). A number of studies have measured the distance between skin and muscle. Two consecutive case series in adults found that needle length of 14mm or 15mm may be too short to reach the muscle for one to two fifths of women (very low certainty, confidence intervals not reported) (Song 2005[48]; Tsai 2014[49]).	*Injection exceed needle length* A study assessing the injection depth of adrenaline autoinjectors injected into ballistic gelatin gave injections depths of 28.87 mm (SD 0.73) for Jext, 29.68 mm (2.08) for EpiPen, and 18.74 mm (1.25) for Anapen demonstrating delivery exceeds needle length (Schwirtz 2012[46]). However, a study using porcine tissue blocks has demonstrated that the fascia lata prevents fluid traveling from a subcutaneous injection into the underlying muscle (Diacono 2015[50]). *Needle length does not dictate adrenaline plasma levels* One randomized, open label, cross-over study compared adrenaline plasma levels when 0.3mg was delivered by an anapen with a 7.5mm needle or a syringe with a 25mm needles (Duvauchelle 2018[22]). Plasma levels were significantly higher with the anapen despite the shorter needle. One unpublished open label, randomized, cross-over study (n=40) has compared adrenaline plasma levels between emerade, epipen and jext with 0.3mg adrenaline dose (Emerade unpublished[51]). The concentration-time graphs suggest, qualitatively, that the three devices have very different pharmacokinetics for the first peak (5-10 minutes) with levels highest for epipen and lowest for emerade. The second peak (40-60 minutes) is similar for all three devices). This study also looked at pharmacokinetics in adults with skin to muscle distance (STMD) of <15, 15-20 and >20mm. Qualitatively there is blunting of the first peak in adults with larger STMD which is most marked with emerade and least	Different adrenaline autoinjectors are available in different countries. There is a constant process of development in these devices. Although they have a number of different internal mechanisms, currently available devices have the same long cylinder appearance. They are activated in slightly different ways so patients may prefer one over the others.	The pharmacokinetic data has only been published in peer reviewed journal for two autoinjectors (Duvauchelle 2018[22], Worm 2020[23]). There is therefore limited ability to question the available data, it is also not readily comparable. Within Europe, the adrenaline autoinjector devices are similarly priced.

These studies are only proxies as the important parameter is plasma adrenaline level after injection.	with epipen. This is despite emerade having a much longer needle. Another open label, randomized, cross-over study (n=35) has compared adrenaline plasma levels in adults with different STMD with 0.3mg epipen autoinjector confirming that these are similar with adults with different STMD (Worm 2020[23]). A further unpublished open label, randomized, cross-over study (n=24) has compared adrenaline plasma levels in adults with different STMD with 0.3mg jext autoinjector (Jext SMPC[52]). These data suggest that those with >20mm STMD have delayed absorption. Lastly, a randomized, open-label, crossover study (n=30) compared a 0.3mg dose of adrenaline with an anapen (Duvauchelle 2018[22]). There was a qualitatively slower increase in adrenaline plasma levels in the overweight female compared to normal weight male adults. *Different autoinjectors deliver adrenaline at different rates* Adrenaline autoinjectors have different mechanisms (Frew 2011[53]). Anapen has a syringe based mechanism with a fixed needle and a weak spring. Epipen, jext and emerade are cartridge devices (Diacono 2015[50]) with moving needles and strong springs. Emerade, epipen and jext all deliver adrenaline at a much higher velocity and much quicker than anapen (18-21 versus 4m/s and 110-170 versus 1500ms respectively)(Diacono 2015[50]).		

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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, adolescents and adults at risk of anaphylaxis.			
Evidence of effectiveness (from systematic review)	Balance of benefits and harms	Values and preferences	Feasibility and costs
0.15mg dose better <30kg body weight A randomized, double-blind, parallel-group study has assessed adrenaline plasma levels and adverse effects in 10 children 15-30kg at risk of anaphylaxis who received either a 0.15 or 0.3mg old type epipen (Simons 2002[54]). Levels were similar but palpitations, headaches and nausea were only seen with the 0.3mg dose. *0.15mg autoinjector may give IO dose with <15kg weight* A consecutive case series found that 29% of children under 15kg may be at risk of having an autoinjector injected into bone with a needle length of 13mm (very low certainty, CI not reported) (Kim 2014[55]).	*0.15mg adrenaline autoinjector from 7.5kg to 30kg weight* *There are no published data for <15kg weight.* The routinely advised IM adrenaline dose is 0.01 mg/kg in health care settings. In 2007, the EAACI anaphylaxis position paper recommend using 0.15mg adrenaline autoinjectors for children from 7.5kg on the basis that a mild overdosing of a child did not seem to represent a major risk in otherwise healthy children (Muraro 2007[56]). This was in the context of firstly not knowing what is a therapeutic adrenaline serum concentration and secondly knowing that parents take a long time to prepare and administer an injection when given a needle, syringe and vial (Simons JACI 2001[17]). There have been no case reports of adverse events in the last decade. Given the favorable benefit/risk ratio of adrenaline with anaphylaxis in young children, 0.15mg adrenaline autoinjectors can be used down to 7.5kg body weight. While there is a possibility of an IO injection, this is associated with good bioavailability of adrenaline and so is acceptable in a life-threatening situation. Care should be exercised where a child may be more at risk of adverse effects, for example with coexisting cardiac disease. *0.3mg adrenaline autoinjector from 30kg weight* A randomized, open-label, cross-over study has assessed 0.3 and 0.5mg adrenaline doses administer using a needle and syringe into mid-thigh (Duvauchelle 2018[22]). In early peak of adrenaline was substantial higher with the 0.5mg dose. Both doses were well tolerated. An unpublished open label, randomized, cross-over study (n=40) has compared adrenaline plasma levels between 0.3 and 0.5mg emerade advice (Emerade unpublished[51]). The concentration-time graphs suggest that the 0.5mg doses gives substantially higher levels, this is especially marked in the first 20 minutes after injections with adults with higher STMD. Both doses were well tolerated. A further study available only currently only in abstract form, compared 0.3 and 0.5mg emerade doses in a randomized, single-blind, cross-over study in	Families may have different views on the use of an adrenaline autoinjector off label in small children. Where there are concerns, families may prefer to have access to a needle, syringe and vial of adrenaline. They will need to be trained to use this approach. The setting may influence decisions about an appropriate dose. While the use 0.3mg dose adrenaline autoinjector may be deemed appropriate for a community setting, within a clinical setting a decision may be made to give a higher 0.01mg/kg (maximum 0.5mg) IM dose for a patients presenting with severe anaphylaxis. *Different licenses in different countries* Junior 0.15mg adrenaline autoinjectors are generally licensed for use from 15kg body weight although it is from 7.5kg for some (eg Germany 7.5 to 25kg and Spain 7.5 to 30kg for epipen).	Junior 0.15mg adrenaline autoinjector devices are available. The alternative is a needle, syringe and ampoule of adrenaline. Although these items will be cheaper and have a similar shelf life, it is much quicker to give an autoinjector (Simon JACI 2002[54]). At present, most adrenaline autoinjector devices are 0.3mg. Only emerade and anapen have a 0.5mg version which has currently been withdrawn. It is therefore difficult to access anything but a 0.3mg device. While there are some data comparing plasma adrenaline levels with 0.3 and 0.5mg devices, we do not know what is the therapeutic level of adrenaline.

	teenagers at risk of anaphylaxis (Patel 2020[57]). The 0.5mg gave statistically higher plasma levels. Both doses were well tolerated. Data collected with the Emerade device shows there were lower adrenaline plasma levels in the first 20 minutes post injection in adults with higher skin to muscle depth (Emerade, unpublished[51]). Jext seems to have similar characteristics (Jext SMPC[52]) but this is not seem with epipen and jext (Worm 2020[23]). The level at which adrenaline achieves its therapeutic actions in anaphylaxis is not known. Within intensive care settings, adrenaline doses are titrated to clinical parameters with a wide range of dosages used. So there may not be one universal dose. 0.3mg adrenaline autoinjectors are effective for treating anaphylaxis in most patients (Noimark 2012[58]). A dose of 0.3mg seems to be effective in most patients, The European Medicines Agency has mandated that a second autoijector should be available in case of no response for device failure (EMA[59]). Given the adrenaline plasma levels do not rise as rapidly with adults with larger skin to muscle depth with anapen or emerade, consideration should be given to prescribing a 0.5mg device or an alternative 0.3mg device. Consideration should also be given to any risk factors for adverse effects with adrenaline which may be exacerbated with the higher plasma levels.		

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Table S3. 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.			
Evidence of effectiveness (from systematic review)	Balance of benefits and harms	Values and preferences	Feasibility and costs
Our recommendation is justified because there is moderate evidence to support this recommendation, coupled with the combined expertise of the taskforce which recognises the value and importance of education One moderate size RCT (Brockow 2015[60]) found that face to face education training sessions (two three-hour group sessions one week apart) improved anaphylaxis knowledge at 3 months and improved competence in adrenaline autoinjector use. A small RCT (Fernandez-Mendez 2017[61]) found face-to face training was associated with faster recognition of anaphylaxis and faster, more accurate delivery of adrenaline autoinjector compared to online training packages.	The Task Force recommend the use of educational training in the management of anaphylaxis. Benefits include improved recognition and management of anaphylaxis in different groups, including parents, carers and teachers (Polloni 2020[62]). Patient groups place value on face-to-face training. Potential benefits of electronic applications are likely to include the portability and accessibility of apps, particularly to younger patients. Use of medical apps has bene found to be of benefit in other conditions, particularly for adolescents and young people (EAACI AYA guidelines[63]). Other studies (Davidson 2017[64]) have demonstrated that apps can improve anaphylaxis quality of life and improvement in management. More research is required in the field of anaphylaxis Risks may include an increase in patient/ carer anxiety if highly anxious at base line and subjected to repeated training- account must be taken of patient individuality and training tailored to their needs. Training modalities- either face-to-face or online need to be tailored to individual preferences	Everyone requires a basic level of training in self-management upon diagnosis. Repeated training is likely to be of greater benefit as long as patient individuality is taken account of. Multiple opportunities for training are likely to arise during the patient journey, and online training programmes are also provided by patient organization and commercial companies. The structure and the approach to training needs to be harmonised across clinics and regions. We are not recommending one form over another, a duration of training or recommending who provides the training or which app to use. Further research is warranted to clarify which elements and structure make for an effective training package, incorporating patients' views on this.	Our recommendation is justified because basic training is essential to all patients/ carers, and it is feasible and beneficial to deliver training. The cost is likely to vary depending on the length and size of the training package delivered and amount of staff training required. For the patients/ carers, time and engagement is required. Governing bodies should take into account the essential nature of patient education and funding for this should be considered. .

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The EAACI task force makes no recommendation for or against using premedication with antihistamine to prevent anaphylaxis.			
Evidence of effectiveness (from systematic review)	Balance of benefits and harms	Values and preferences	Feasibility and costs
Our recommendation is justified because it is uncertain whether antihistamines prevent medication induced anaphylaxis since certainty of the evidence is very low. This is based on two RCT showing that a combination of an anti-H1+anti-H2 lowered the number of adverse reactions to plasma derivatives or histamine infusion. One RCT showed a reduction of systemic reactions by dimethpyrindene + cimetidine vs placebo before plasma substitute (n=50)(0% vs 24%, p<0.05). (Lorenz 1977[65]). A cross-over RCT showed that cimetidine + promethazine prior to intravenous infusion of histamine prevented tachycardia, fall of blood pressure and cutaneous reactions vs promethazine alone vs placebo in 8 volunteers. Promethazine alone was only associated with partial reductions (Tryba 1984[66]).	We make no recommendation on the use antihistamines to prevent medication-induced anaphylaxis. Benefits could be the potential reduction of anaphylaxis induced by some medications, but the studies are limited to very specific situations. In addition, there is much more evidence that skin reactions such as urticaria or pruritus can be reduced. A recent meta-analysis (Practice Parameters, Shaker 2020[26]) showed that antihistamines and/or glucocorticoids may prevent index reactions to chemotherapy but not to radio-contrast media (certainty of evidence very low). Studies included were mainly observational, retrospective and outcomes included hypersensitivity or infusion related reactions, some of which were not consistent with anaphylaxis. Potential risks include that the use of anti-histamines may theoretically mask initial symptoms of reactions which may suddenly progress in severity, or worsen central nervous system symptoms if first-generation antihistamines are used. Also, it may give a false sense of reassurance to healthcare professionals who may lower their alertness upon the appearance of a reaction.	Premedication may confer patients a feeling of safety. Antihistamines may decrease skin symptoms in case of a hypersensitivity reaction. Antihistamines may reduce hypersensitivity reactions due to allergen immunotherapy (EAACI IT guideline[67,68]) but this was outside the scope of the current guideline.	Feasible, low-cost intervention

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The EAACI task force suggests using premedication with subcutaneous adrenaline to prevent anaphylaxis when snake bite anti-venom is given.			
Evidence of effectiveness (from systematic review)	Balance of benefits and harms	Values and preferences	Feasibility and costs
Our recommendation is justified because there is some evidence that adrenaline can prevent anaphylaxis caused by snake antivenom, although the certainty of evidence is very low. Two RCT showed that low-dose subcutaneous adrenaline reduced adverse reactions to anti-venom. In a RCT (N=105), adrenaline was associated with fewer severe reactions (0% vs 8% placebo, p=0.04) (Premawardhena 1999[69]). In another RCT (n=1007), compared with placebo, adrenaline significantly reduced severe reactions to antivenom by 43% (p<0.001) at one hour. Adding hydrocortisone to adrenaline negated the effect of adrenaline (de Silva 2011[70]).	We suggest for the use of adrenaline for preventing anaphylaxis associated with snake antivenom despite the beneficial effects shown in these two RCTs is based on very low certainty of evidence. Potential benefits are shown by the two studies but it is unclear whether the benefit is superior to treatment of a reaction. Potential risks may be associated with the use of adrenaline, but in these studies, low-dose subcutaneous adrenaline there were no relevant side-effects in the studies included.	The use of of snake antivenom is a very specific situation, and prevention of anaphylaxis by adrenaline may not be applicable in contexts that do not use antivenoms at high risk of reaction. There is no evidence that the use of prophylactic subcutaneous adrenaline is superior to the use of intramuscular adrenaline to treat an anaphylactic reaction, if it occurs	Feasible, low-cost intervention

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The use of antihistamines and hydrocortisone to prevent anaphylaxis associated when snake bite antivenom is given			
Evidence of effectiveness (from systematic review)	Balance of benefits and harms	Values and preferences	Feasibility and costs
There is some limited evidence that antihistamines or hydrocortisone cannot prevent anaphylaxis caused by snake antivenom, although the certainty of evidence is very low. Two RCT showed that hydrocortisone did not induce a relevant reduction of adverse effects of anti-venom. In a RCT (N=1007), hydrocortisone and promethazine had no significant effect (de Silva 2011[70]). Another RCT (N=52) showed no difference in the number of moderate and severe reactions between hydrocortisone, hydrocortisone plus chlorpheniramine and placebo (p>0.05) (Gawarammana 2004[71]). Two RCT showed that promethazine had no significant effect on anaphylaxis incidence due to snake anti-venom. A RCT did not show significant difference in the incidence of anaphylaxis by promethazine versus placebo (Fan 1999[72]). Another RCT (N=1007) did not show any effect of promethazine on anaphylaxis incidence (p = 0.378) (de Silva 2011[70]).	The balance of the evidence would suggest against the use of antihistamines and hydrocortisone to prevent anaphylaxis associated with snake antivenom. The task force felt that this did not reach the priority to be included as a recommendation. Potential benefits are the anti-inflammatory effect of corticosteroids. Potential risks are the well-known side effects associated with the use of costicosteroids, especially in high dose and long-term schedules. Nevertheless, in the two RCT there was no difference in the number of adverse effects attributed to hydrocortisone versus placebo or other medications. Potential benefits are the capacity of antihistamines to reduce some of the effects of histamine released during an allergic reaction. Potential risks are that anti-histamines may potentially mask initial symptoms of reactions which may suddenly progress in severity. In the two RCT no information was provided regarding side-effects	The effect of other corticosteroids or antihistamines, or other administration schedules remains unknown.	Feasible, low-cost intervention

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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.			
Evidence of effectiveness (from systematic review)	Balance of benefits and harms	Values and preferences	Feasibility and costs
Our recommendation is justified because there is some evidence to support the value of school policies in improving the management of anaphylaxis. The certainty of the evidence is very low, there is a high risk of bias and publication bias is uncertain. One case control study which observed the adrenaline autoinjector technique of staff and using a standardised checklist and independent assessors. One case control study which compared policies from 112 schools in a region with (cases) and in 4 regions without (controls) legislation. Despite training, sub-optimal technique commonly observed. However, in the legislated environment staff more likely to demonstrate accurate technique, (39% scoring 4/4) vs 26% ($p<0.002$) in non-legislated environments. (Cicutto 2012[73]). Policy consistency with Canadian anaphylaxis guidelines was significantly better ($p = 0.009$) in legislated (Mean 8.8, SD 4.4) vs non-legislated (Mean 6.1,SD 4.4) environments (Cicutto 2012[73]).	Although there is insufficient evidence about benefits and harms, it is likely that the benefits would outweigh any harms. Fidelity to training protocol is central since this would impact level of risk. Differences in legislation (and enforcement) would impact comparability within and across studies.	Policies in a legislated environment more likely to include: clauses on reducing allergen exposure; regular employee training; individual plans for at risk students. However, significant gaps exist in both environments	Likely feasible in terms of cost. Costs could be minimised if regular evaluation conducted as part of general education outcomes audit. There is evidence (Morris 2011[74]) there are barriers to implementation of guidelines/legislation and therefore emphasize more research is needed to understand how guidelines and legislation in schools is best implemented and can support staff to demonstrate accuracy in technique and increase confidence levels of school staff in using an autoinjector.

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Financial incentives for carrying adrenaline autoinjectors			
Evidence of effectiveness (from systematic review)	Balance of benefits and harms	Values and preferences	Feasibility and costs
The certainty of the evidence is very low, there is a high risk of bias and publication bias is uncertain. One small RCT study has looked at this recruiting mostly female participants via emergency department (Cannuscio 2015[75]). The group receiving a (greater) financial incentive carried autoinjectors at 54% of check-ins compared to 27% for control group (p = 0.023). But there was no true control group. The control group received a (smaller) financial reward to take part so the study was not comparing financial reward with no reward (both groups were compensated).	Although it is important to have financial support through government health policy so that at least one auto-injector can be carried at all times to reduce risk of death, the task force felt that individual financial incentives to carrying auto-injectors were unethical. Groups that may be particularly at risk of harm are young people who are least likely to be self- motivated to carry an auto-injector and are also at high risk of anaphylaxis. The risks outweigh any potential benefits because financial incentives may override/harm real world motivation to carry an auto-injector to protect against the risk of accidental reactions.	This is a short -term study and therefore we do not know whether people in the financial incentive group continued to carry their autoinjectors once the study ended and the financial incentive was removed. This provides a serious ethical issue because carrying an auto-injector may have become associated with payment, and once that payment was removed, no other incentive (e.g. self-management strategy) was put in place.	Costs would prove quite substantial over time.

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School nurse checks of carrying adrenaline autoinjectors			
Evidence of effectiveness (from systematic review)	Balance of benefits and harms	Values and preferences	Feasibility and costs
There is insufficient evidence resulting in very low certainty of the evidence. There is a high risk of bias, including potential confounders, and publication bias is uncertain. Only one non-randomised controlled trial has compared school nurses checking students, combined with education, three times during the year to see whether they were carrying their auto-injectors versus no checks during the year. There was no significant difference between groups in whether students were carrying their autoinjector at the final check of the year (61% students in intervention group vs 76% in the control group ($p = 0.189$) (Spina 2012[76]).	Although there is insufficient evidence about benefits and harms. Given the uncertainty the task force decided not to make a recommendation. Groups that may be particularly at risk of harm may be the school nurses themselves since they may be held accountable if some checks were not performed or held to be insufficient in some way in relation to a reaction encountered by a student. Students may also be at risk of harm since they must become self- motivated to carry an auto-injector and to self-manage risk of anaphylaxis. The risks may therefore outweigh any potential benefits.	Adolescents and young people may not be happy being 'checked' regularly and this may abrogate normal development of autonomy. If the intervention was developed and carried out with input from the students themselves, then it may minimise the limitations noted above.	Likely feasible in terms of cost.

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Helpline to improve health related quality of life and service use for patients at risk of anaphylaxis			
Evidence of effectiveness (from systematic review)	Balance of benefits and harms	Values and preferences	Feasibility and costs
The certainty of the evidence is very low with moderate risk of bias and uncertain publication bias is uncertain. In one RCT study the intervention group was given a direct access 24 hour helpline number (6 months) to ring in the event of a suspected serious allergic reaction. The helpline was associated with a mean absolute improvement of 1.6 points on a validated food allergy quality of life scale at 12 months (Kelleher, 2013[77]). However, no statistically significant difference in use of health services for allergic events or anaphylaxis due to limited number of severe reactions occurring during the study.	Since a 24-hour helpline is available, any risk in reaction management appears low and is supported by the study findings. Potential risk for patients if helpline is not operated correctly.	The apparent security provided by 24-hour access to expert guidance, and not just the actual contact and guidance given, was sufficient to have a significant impact on quality of life and confidence in management.	In the study the phone line personnel operated it on a voluntary basis. The task force felt that this would not be financially possible in clinical practice.

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Table S4. 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.			
Evidence of effectiveness (from systematic review)	Balance of benefits and harms	Values and preferences	Feasibility and costs
Our recommendation is justified because although the certainty of the evidence is very low on the use of simulation-based training to aid anaphylaxis recognition and management for medical students, simulation is a well-established and validated teaching modality for other medical emergencies. One small RCT demonstrated an improvement in anaphylaxis management following sim-based training compared to a lecture (McCoy 2011[78]). One further small RCT found screen-based simulation was not better than a lecture (Tan 2008[79]) For visual prompts, it is difficult to draw conclusions on the research evidence alone because the certainty of evidence is very low**,** based on three small RCT on the use of visual aids to improve the knowledge and skill of healthcare professionals. One small RCT found that studying a wallet sized prompt sheet improved anaphylaxis recognition and adrenaline auto-injector brand knowledge (Hernandez-Trujillo 2013[80]). Another small RCT found that using a short visual aid-based algorithm was associated with faster recognition of anaphylaxis, but not with accuracy of diagnosis (Joshi 2014[81]). Finally, an RCT the use of a visual aid flowchart during a simulated scenario was associated with an improvement in time to adrenaline	It is the task-forces' experience that health care professionals require further training in the recognition and management of anaphylaxis. Benefits include an opportunity to enhance and consolidate knowledge using a more practical and less didactic approach, with a closer approximation to real-life scenarios. The anaphylaxis studies have both focused on medical students, with short timeframes and no real world outcome measures. Simulation is also a well-established and internationally used form of teaching in medical training. There is also evidence of benefit in the use of simulation for the management of other emergency conditions (Whitmore 2019[83]; Gilfoyle 2017[84]). The benefits of visual aids include faster recognition of anaphylaxis and improved management in high stress situations, where errors are more likely to occur. There are no obvious risks associated with the use of prompt sheets, although prompt sheets need to be easily accessible and updated when necessary.	Simulation is widely used during medical training and a well validated form of teaching and likely to be beneficial. Consideration should be given to the inclusion of other healthcare professionals within the simulation training. The use of visual aids is of most benefit to healthcare professionals who are likely to encounter anaphylaxis in their practice and is not recommended for all healthcare practitioners. Other forms of prompts, for example posters or the use of electronic apps, may also be useful.	It is feasible for simulation training to be used as it is well-established and accepted as teaching method. The costs are variable but can be high, including development of the training package, use of equipment and training of staff. It is time-consuming to run for both staff and students. Again, it is feasible for the visual aids to be available to clinical staff, as either portable prompt sheets or located in relevant clinical areas for rapid reference. The cost is likely to be low as these are inexpensive to produce.

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administration and a trend towards less errors in administration (Gardner 2018[82]).			

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