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EAACI Anaphylaxis Guideline Online Supplement

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EAACI anaphylaxis guideline

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CONTENTS

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 NIAID/FAAN criteria have been criticised and modified criteria have been proposed by World Allergy Organisation (Cadona[85]). These modified criteria have not been validated.	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.

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.

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 compared to intramuscular or subcutaneous	*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 2016[19]), decreased rates of hospitalization (Fleming 2015[10]), and increased survival.	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 2021[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.

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]).	*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 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 (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	*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 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	*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 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	*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 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

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]).	proportion of people correctly using the devices and reduce the time taken to administer adrenaline.	how the autoinjector is used and its effectiveness (use same device as patient has). The HCP do need to be trained.	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])

The EAACI task force recommends that pharmacokinetic data should be provided for each adrenaline autoinjector product as they cannot be regarded as interchangeable.			
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 different adrenaline autoinjector products 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 autoinjector products 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	Different adrenaline autoinjector products are available in different countries. There is a constant process of development in these autoinjectors. 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 autoinjector products (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.	Emerade® and least 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 autoinjector products 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]).		

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

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. .

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 RCTs 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 AIT guideline[67,68]) but this was outside the scope of the current guideline.	Feasible, low-cost intervention

The EAACI task force suggests using premedication with subcutaneous adrenaline to prevent anaphylaxis when snake bite anti-venom is given to a patient.			
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 anti-venom, although the certainty of evidence is very low. Two RCTs 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 anti-venom 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 giving snake anti-venom to a patient. However, 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 anti-venom is a very specific situation, and prevention of anaphylaxis by adrenaline may not be applicable in contexts that do not use anti-venoms 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

The use of antihistamines and hydrocortisone to prevent anaphylaxis associated with snake bite antivenom			
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 anti-venom, although the certainty of evidence is very low. Two RCTs 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 RCTs 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 anti-venom. 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

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.

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.

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.

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. Given the uncertainty of the evidence the task force decided not to make a recommendation.	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.

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