

BSACI guideline: prescribing an adrenaline auto-injector

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Summary

This guidance for the prescription of an adrenaline auto-injector has been prepared by the Standards of Care Committee (SOCC) of the British Society for Allergy and Clinical Immunology (BSACI). There is insufficient quality evidence-based data in some areas, including the question of how often a second dose is required, and the optimal dose and absorption after subcutaneous vs. intramuscular injection. Thus, indications for adrenaline (which are partly opinion based) in guidelines from different countries vary slightly. The guideline is based on evidence as well as on expert opinion and is for use by both adult physicians and paediatricians practising allergy. During the development of these guidelines, all BSACI members were included in the consultation process using a web-based system. Their comments and suggestions were carefully considered by the SOCC. Evidence from randomized controlled trials is lacking in anaphylaxis for ethical reasons. Consensus was reached by the experts on the committee. Included in this guideline are aetiology, risk of recurrence and management of anaphylaxis (after treatment of the acute episode), including allergen avoidance and written treatment plans. There are sections on dose and absorption of adrenaline, and adrenaline auto-injectors, including indications for their prescription, risk assessment for the number required and training in their use. The guidelines are not intended to be prescriptive, and clinicians should use their clinical judgement. Finally, we have made recommendations for potential areas of future research.

Keywords adrenaline, anaphylaxis, auto-injector, British Society for Allergy and Clinical Immunology, epinephrine, guideline, Standards of Care Committee, tryptase
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Executive summary

- Adrenaline is the first-line treatment for anaphylaxis. It should be used in patients with significant airway involvement or hypotension, occurring as part of an anaphylactic (IgE- or non-IgE-mediated) reaction.
- An adrenaline auto-injector should be prescribed for those at risk of anaphylaxis.
- An auto-injector allows early administration of adrenaline as this improves outcome. It should be seen as a first-aid measure combined with calling for help (ambulance/emergency medical services).
- After acute anaphylaxis, an adrenaline auto-injector should be prescribed in the Emergency Department or primary care and an allergy referral immediately triggered (NICE guidance).
- Specialist allergy experience is required to make a risk assessment to determine the continuing need for an adrenaline auto-injector. This requires accurate diagnosis of the aetiology, assessment of severity and future risk, including consideration of the amount of allergen involved in previous reactions and the ease of avoiding the trigger. Certain co-factors increase the risk of anaphylaxis, for example asthma in the case of food allergy, raised baseline serum tryptase and the age of the patient.
- Patients at risk of anaphylaxis that should be considered for long-term provision of an adrenaline auto-injector include those
 - who have suffered a severe systemic reaction where the allergen cannot be easily avoided

- who are allergic to high-risk allergens, for example nuts with other risk factors (such as asthma), even if the reaction was relatively mild
 - who had a reaction in response to trace amounts of allergen/trigger
 - who cannot easily avoid the allergen
 - with continuing risk of anaphylaxis (e.g. food-dependent exercise-induced)
 - with idiopathic anaphylaxis
 - with significant co-factors (e.g. asthma in food allergy, raised baseline serum tryptase)
- A recent MHRA drug safety update (2014) recommended that people who have been prescribed an AAI should carry two; however, normally only one auto-injector is required for self-administration during a reaction. For children, two should usually be prescribed one each for school and for home. Exceptions, when two pens may be required in one kit, that is giving the option of administering two doses, include obesity, remoteness from medical help, a previous life-threatening reaction or if two doses were *required* (as distinct from *given*) in a short time period for previous reactions, or other assessment of risk.
 - Assessment of patients who never suffered anaphylaxis but considered to be at risk of anaphylaxis can be difficult and requires expertise. Many of the patients prescribed an AAI are in this category. Guidance is provided.
 - Patients, parents or carers should be trained in both when and how to use the auto-injector device at the time of prescribing and the training reinforced when the device is dispensed by the pharmacist and during allergy clinic appointments. Pharmacists should be encouraged to undertake device training at every opportunity.
 - Prescribing an adrenaline auto-injector is only one step in managing anaphylaxis risk. It should be combined with specialist allergy advice on avoidance of triggers, a written treatment plan and re-training in the use of the auto-injector. In the case of children, education of parents/carers and school staff is required.
 - Successful prevention of anaphylaxis, thus not needing to use the auto-injector, should not be taken to mean the auto-injector prescription is not required or will not be required in the future.
 - Carrying adrenaline long term is not required if the trigger can be avoided, even when the reaction was severe, for example oral prescription drugs, injection-administered drugs, foods which are avoidable, for example prawns (depending on setting) or in venom allergy patients who have been desensitized, unless there are additional risk factors.
 - Adrenaline auto-injectors should be discontinued if the original prescription was inappropriate, the

allergy resolves or after successful venom immunotherapy except when there are additional risk factors such as raised baseline tryptase, risk of multiple stings or occupational hazard. Discontinuation should be considered if the allergy becomes less severe, for example milk allergy of initial severity requiring an AAI, but now partially resolved.

- Prescribing an auto-injector cannot be a substitute for allergy referral.

Introduction

This guidance for the prescription of an adrenaline auto-injector has been prepared by the Standards of Care Committee (SOCC) of the British Society for Allergy and Clinical Immunology (BSACI) for use by allergy specialists. It is intended to be used for management of patients considered at risk of anaphylaxis.

Anaphylaxis is more easily reversed in early adrenaline administration, and this is part of the 'first-aid' approach [1–3]. Hence, adrenaline auto-injectors are available for self-administration early in the development of anaphylaxis, particularly in the most severe reactions. Clinical experience in allergy clinics demonstrates rapid reversal of anaphylaxis after early treatment, for example during immunotherapy and drug challenge, and by anaesthetists treating drug-induced anaphylaxis during anaesthesia. Delayed administration of adrenaline is a feature in fatal and near-fatal anaphylaxis [4–6]. The provision of an adrenaline auto-injector must be part of an overall management plan focused on preventing further reactions by avoiding triggers.

Prescribing practice both nationally and internationally remains inconsistent with a lack of clear consensus on who should be provided with an AAI. An auto-injector should be prescribed not only to 'cover risk' but also should form part of an overall management plan formulated once diagnosis has been confirmed. Referral to an Allergy Clinic will allow identification of triggers and provide appropriate advice on future prevention and training in the use of the auto-injector. There is evidence that this reduces the risk of further reactions.

Whilst an adrenaline auto-injector device can be life-saving, unnecessary prescription may have unforeseen consequences. The widespread prescription of AAI, for example in schools, means that these could be less associated with risk, by some patients or carers. Less attention might then be focused on children with the highest risk of anaphylaxis. Caregivers, teachers and families also face the additional burden of carrying medical equipment wherever the child goes. Additionally, the universal availability of an auto-injector adrenaline device may encourage individuals to be less compliant with avoidance measures. Carrying an

auto-injector may be a source of anxiety and limit activities and career choice. All of this must be balanced with the primary concern of patient safety.

Methods

Evidence for the recommendations was obtained from literature searches of MEDLINE/PubMed/EMBASE, NICE and the Cochrane library. The experts' knowledge of the literature and hand searches as well as papers suggested by experts consulted during the development stage was also used. Where evidence was lacking, a consensus was reached amongst the experts on the committee. The methodology followed the BSACI guideline production manual (available at <http://www.bsaci.org/Guidelines/bsaci-guidelines-and-SOCC>). Conflict of interests were recorded by the BSACI. None jeopardized unbiased guideline development. During the development of the guidelines, all BSACI members were consulted using a web-based system and their comments carefully considered by the SOCC. BSACI provided the necessary resources for production of this guideline.

Definition of anaphylaxis

Anaphylaxis is a severe allergic-type reaction usually of rapid onset with either airway involvement or hypotension typically with cutaneous features [1, 7], although features may vary. With parenteral allergens, such as insect stings or IV drugs, hypotension may be the only or dominant symptom and patients can present with sudden loss of consciousness. This contrasts with foods where airway involvement is dominant (laryngeal oedema and/or asthma) [1]. Idiopathic anaphylaxis can be of slower onset with evolution over an hour or longer, beginning with pruritus then erythema/urticaria often including gastrointestinal features followed by hypotension [8]. A US definition is more detailed defining three different sets of criteria, all of which are incorporated in the shorter Resuscitation Council of UK definition [7, 9]. In dealing with suspected anaphylaxis in the emergency setting where patients/parents will self-treat, for practical purposes, a simple definition is required.

Treatment of anaphylaxis

Adrenaline is the first-line treatment for anaphylaxis and is recommended in the major guidelines including those of the Resuscitation Council UK, World Allergy Organization (WAO) and European Academy of Allergy and Clinical Immunology [7, 10–15], yet adrenaline is underused. In addition, the WAO Committee believes adrenaline for self-injection is under-prescribed [11].

Aetiology of anaphylaxis

This may be IgE-mediated (e.g. due to food, some drugs, venom, latex, occupational agents) or non-IgE-mediated, for example idiopathic, some drugs, physical or related to mastocytosis (Table 1). The commonest causes in adults are food, drugs, venom and idiopathic [16]. In children, the main cause is food allergy [17–19].

Triggers for more severe reactions

Fatal reactions in the United Kingdom are due to drugs (about 50% of those whose cause was identified), foods (about 25%) and venom (about 25%) [20]. Rapid-onset reactions occur within minutes with IV drugs, for example those given at induction of anaesthesia, antibiotics and NSAIDs. However, oral antibiotics may rarely cause anaphylaxis within 5–10 min. Oral NSAIDs and aspirin may cause severe reactions in 30 min. Of foods, peanut allergy has been reported in the USA as the commonest cause of fatal and near-fatal reactions [4]. Subsequent data have shown that Brazil and cashew nut are both likely to cause more severe reactions than peanut [21, 22]. Whilst milk allergy mostly resolves, children with persistent allergy often have severe anaphylaxis even on minor exposure.

Risk of recurrence of anaphylaxis

The prevalence of recurrent anaphylactic reactions ranged from 21.3% to 34.8% [19, 23, 24] from three retrospective studies and from 30% to 42.8% from two prospective studies [25, 26]. In 25% to 72% of cases, the recurrent episode was likely to be due to the same allergen that caused the first anaphylactic reaction [19]. The risk of recurrence depends on the cause of the anaphylaxis and the quality of management provided. Mullins and colleagues, in Australia, found that 172

Table 1. Causes and frequency of different types of anaphylaxis

Cause or type	Frequency
Foods	Common
Drugs	Common
Venom (bee or wasp stings)	Common
Idiopathic	Common
Raised baseline serum tryptase	Common
Food-dependent exercise-induced	Uncommon
Physical	
Pressure	Rare
Cold	
Heat	
Exercise	
Latex	Rare
Auto-immune	Rare

patients had experienced 584 previous reactions (about three episodes per patient) and that in any one year, 1 in 12 patients who had suffered anaphylaxis were experiencing recurrence [25].

In idiopathic anaphylaxis, as there is no identifiable trigger to avoid, there is a higher risk of recurrence. Clinical experience suggests that prophylaxis with regular daily antihistamines in individuals with frequent episodes can reduce or prevent further episodes in a proportion of patients, but the risk remains.

Historically, nuts have been difficult to avoid and recurrent allergic reactions are common. Bock and Atkins [5] found 50% of children with a diagnosis of peanut allergy had an accidental ingestion within the past year. Vander Leek et al. [27] found an annual incidence rate of 33%, and Yu et al. [28] reported a rate of 14%. Sicherer [29] found a follow-up reaction rate for peanut and tree nut allergy of 55% over 5.4 years. High-quality management from a specialist allergy clinic can greatly reduce the severity and frequency of further nut-induced reactions to a 3% annual incidence rate [30–32]. Further reactions were minor, requiring oral antihistamines only or no treatment, and anaphylaxis was rare [31].

Referral to an allergist

A number of authors recommend referral to an allergist for diagnosis of the aetiology of the anaphylaxis and its management [33–35]. This has been endorsed for UK practice by the NICE anaphylaxis guideline (2011: <http://guidance.nice.org.uk/CG134>).

All patients with anaphylaxis or allergy with the potential to develop anaphylaxis should be referred to an allergist. However, due to the lack of NHS allergy services across the UK, opportunities for referral will vary and allergy clinics will have differing expertise and competences. It is important to have specialist level referral in cases of severe reactions, diagnostic difficulty, suspected drug-induced, venom anaphylaxis, recurrent anaphylaxis and when several foods are implicated (Box 1).

Management plan approach

Who should carry adrenaline?

This decision is part of overall management and the steps outlined in Fig. 1, and amplified below. An accurate diagnosis of the cause of anaphylaxis is a prerequisite (Table 1). A risk assessment is then required to determine who is likely to have a further anaphylactic reaction, and this informs which patients should carry

Box 1. Quality Standards in anaphylaxis

Early (to be met at the time of treatment of an anaphylactic episode or as soon as possible afterwards)

- 1 Measure serum tryptase (timed sample according to NICE guidance)
- 2 Provision of adrenaline auto-injector
- 3 Training and education in use of adrenaline auto-injector
- 4 Advice on avoidance of suspected trigger
- 5 Referral to an allergy clinic

Later (in allergy clinic, following recovery from anaphylaxis)

- 1 Diagnosis of anaphylaxis – confirm or exclude
- 2 Diagnosis of aetiology

History

Appropriate investigation: tailored to the suspected causes, includes skin prick tests if appropriate, may include drug or food challenge

Exclusion of causes (required to reach diagnosis of idiopathic anaphylaxis)

- 3 Identification of other potential cross-reacting triggers (drugs and foods)
- 4 Recommendation of safe substances, for example drugs
- 5 Management plan

Avoidance advice

Written treatment plan to include medication to self-administer

Training (when and how to use drugs including adrenaline auto-injector; training must be device specific)

Education of patient/parents/carers/school staff

- 6 Optimize asthma management
- 7 Medic alert advice including wording, if appropriate

For drug allergy, a 'Drug Allergy Notification' for patient to carry.

Allergy alert in hospital records, including computer alerts

- 8 Further management to reduce future episodes, for example specialist dietary advice, desensitization, regular antihistamines
- 9 Provide information on patient support groups
- 10 Expertise required experience and knowledge of all causes of anaphylaxis; ability to investigate and interpret results.

Longer term (in allergy clinic or primary care)

- 1 Monitoring
 - Of further reactions (device specific)
 - Identify if resolution has occurred – may require further investigation with skin prick test and other tests
- 2 Device: review of dose and retraining (device specific). Revise written treatment plan. Management plan review to include dose changes in children. Update school training.
- 3 Monitor asthma control and manage/adjust therapy

References

NICE Guideline: Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode. (clinical guideline 134) 2011 <http://guidance.nice.org.uk/CG134>.

BSACI Standards of Care guidelines: www.bsaci.org (drug allergy [8]; beta lactam allergy [36]; anaphylaxis during anaesthesia [37]; venom allergy [38]; peanut allergy (manuscript in preparation), egg allergy [39]).

adrenaline (Table 2). The main principles on which this assessment is based include severity, likelihood of avoidance of the allergen/trigger, co-factors which increase the risk of further anaphylaxis (e.g. raised baseline serum tryptase or asthma) (Fig. 2 and Table 3). Social circumstances and geographic factors should also be considered.

Confirming the diagnosis and identifying the cause

The aetiology of anaphylaxis must be identified, before deciding whether continued prescription of an adrenaline auto-injector is required (Table 1). This requires assessment in an allergy clinic with expertise in all types of anaphylaxis. Identification of the allergen/trigger responsible for previous allergic reactions is vital to safeguard the patient. It is also important to rule out other allergens, which are not responsible to avoid possible malnutrition or use of more costly and in some cases less-effective alternative drugs.

The diagnosis of anaphylaxis is usually evident from the history and may be supported by records of acute observations, for example blood pressure, oxygen saturation, wheeze, erythema, urticaria, rash, or angioedema and an elevated acute serum tryptase level is helpful. The next step is to determine the type of anaphylaxis and identify triggers. Diagnosis is primarily clinical from a detailed history, including symptom pattern and

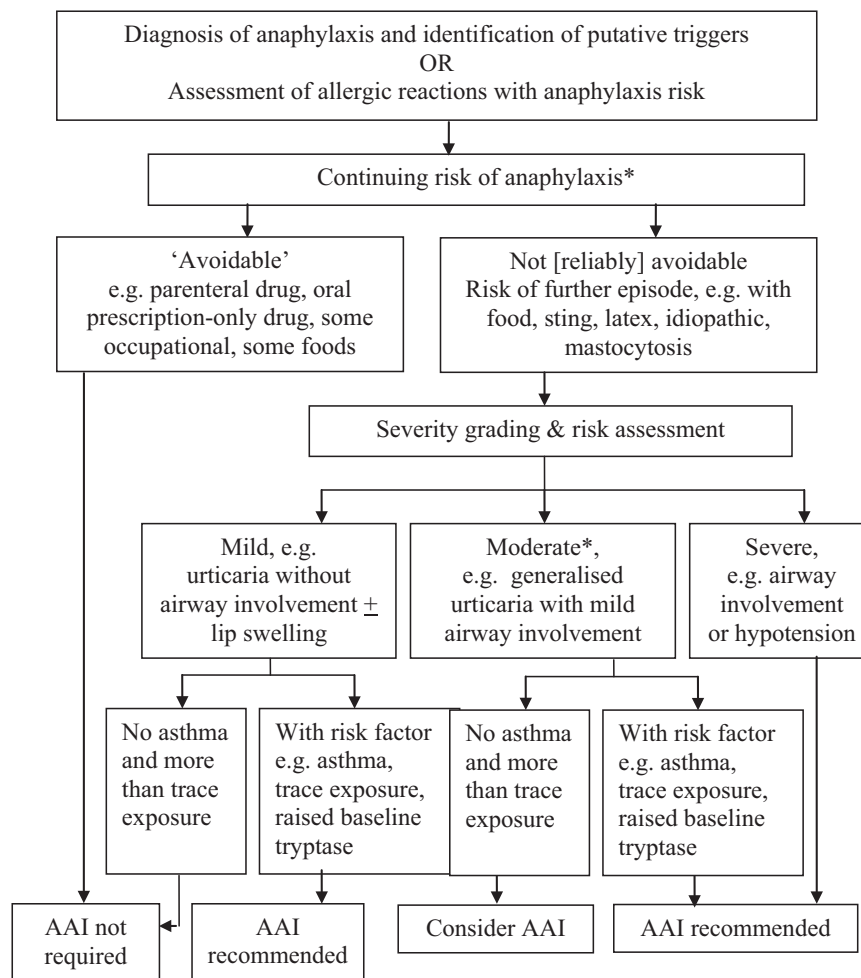


Fig. 1. When to prescribe adrenaline for patient administration. (AAI, adrenaline auto-injector).

* in the absence of additional risk factors, GI symptoms in infants and young children do not usually require adrenaline auto-injectors.

Table 2. Factors to consider when making a risk assessment

Factor	Examples influencing risk
Previous reactions	Severity Amount of allergen and route of exposure Which allergen Rapidity of onset Age: teenagers/young adults for foods, elderly
Allergen and/or likelihood of recurrence	Ease of avoidance Risk of severe reaction Idiopathic anaphylaxis
Comorbidities	Asthma control Raised baseline serum tryptase/mast cell activation disorder/mastocytosis
Presence of serum-specific IgE to epitopes associated with severe reactions	Peanut ara h 1/2/3 and 9
Medication	Betablockers, ACE inhibitors
Occupational risk	
Venom allergy	Bee keeper, beekeeper's family or neighbour, roofer, gardener, jam worker, fruit picker, bakery worker
Inhalant antibiotic allergy	Nurse, pharmacist
Remoteness from medical help	Rural location, travel abroad or hobby (sailing, mountain climbing)
Social and personal circumstances	Single parent with young children; living alone

timing of events in relation to potential triggers. Skin prick tests and sometimes intradermal tests, are required. Confirmation of a trigger may also involve excluding suspected triggers. In the case of drug allergy, more complex tests are required [8, 37] and may require provocation testing. Further investigations are required to phenotype the non-IgE-mediated reactions. Physical triggers such as heat, cold and exercise will need consideration (Box 2). Co-factors such as concomitant infection and exercise may also play a role. If the cause is avoidable, adrenaline is not required (Fig. 1).

Risk assessment for future allergic reactions

It is necessary to consider those who have had anaphylaxis, and those who might be at risk of anaphylaxis although have not yet had a severe reaction, for example nut allergy, mastocytosis. In patients who have never had anaphylaxis but might be considered at risk, AAI are often prescribed, but are indicated only in some. Risk assessment is essential to inform the need for self-held adrenaline. This should be based on severity of the allergy and the likelihood of recurrence (Table 2). Co-factors leading to severe reactions and

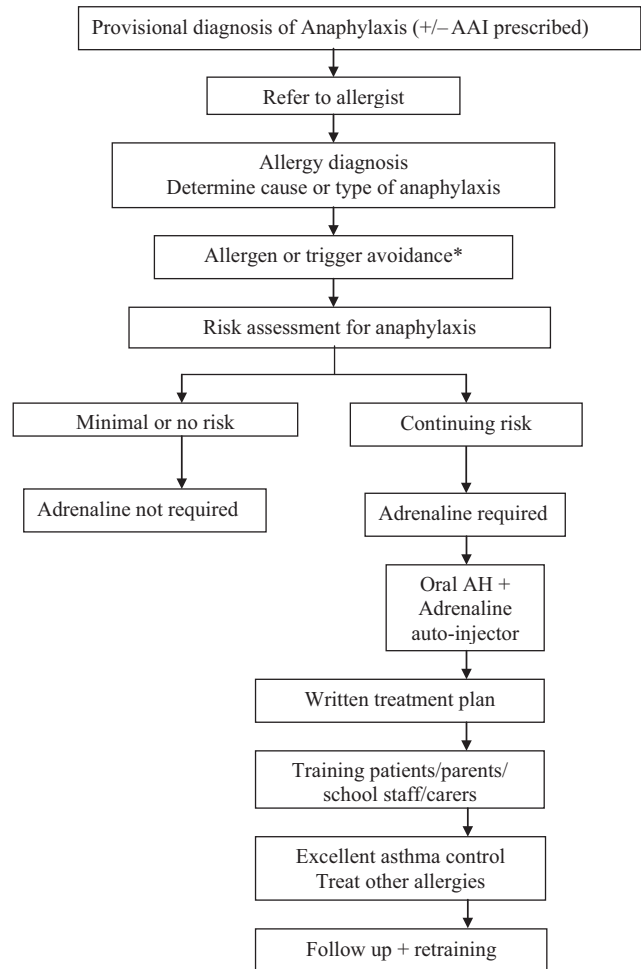


Fig. 2. Management approach in allergy clinic. * or plan for desensitization, but remainder of management plan is required until desensitization achieved. AH, antihistamine (quick acting, non-sedative).

Table 3. Avoidability of allergic triggers

Easily avoidable	More difficult to avoid	Not avoidable	No identifiable trigger but may be ameliorated by medication
IV drugs	Food, for example	Bee or wasp sting	Idiopathic anaphylaxis
Oral prescription drugs	-Peanut		Mastocytosis and mast cell activation disorder
Food*, for example	-Tree nuts		
	-Soya		
	-Milk		
	-Shellfish	Latex	
	-Fish	Panallergens (e.g. LTP)	
	-Kiwi	Cold	
	-Other fruits	Pressure	

*Depends on setting, for example shellfish in Asia difficult to avoid, and patient's circumstances.

Box 2. Correct allergen avoidance advice

- Avoidance advice should be provided for food allergens, drugs including antibiotics, latex, exercise and food plus exercise. Avoidance advice is also essential for cold and pressure-induced anaphylaxis.
- For venom allergy, avoidance advice has much less impact, but still needs providing.
- If allergen-specific advice is appropriate, advice on avoidance of related allergens may be required, for example cross-reacting drugs
- Advice on the 'real' risk of future reactions
- Education of family members should be considered, extended to schools, grandparents or other guardians of young children.
- Specialist allergy clinics have their own exclusion diet sheets drawn up with dietetic advice, but this must be combined with detailed verbal explanations. Advice from an allergy-trained dietician is required for children who require long-term exclusion of a nutritionally important food, for example milk.
- For food allergy:
 - Advice on reading ingredients labels, how to handle risk of accidental contamination and understand 'may contain traces' labelling.
 - Age- and circumstance-specific avoidance warning is required for toddlers, schoolchildren, grandparents and teenagers as well as birthday parties, school playground/handouts/food swapping and eating out/takeaways/alcohol [31]
 - Identify and communicate high-risk situations

geographic issues should also be considered. An AAI should not be required to treat isolated urticaria or angioedema not involving the airway (e.g. excluding tongue angioedema). Patients should understand the risk factors that have led to the prescription of an AAI.

Severity and allergen-specific factors

This should be based on the severity of the worst ever previous reaction:

- 1 Indicators of 'higher' risk: wheeze, stridor, change in voice pitch, drooling, drowsiness, hypotension in previous reaction
- 2 Previous mild generalized reaction to ingestion of very small amounts of allergens meaning future exposure to larger amount may cause a severe reaction.
- 3 Allergen specific: in allergy to nuts, 38% of the worst reaction to date will involve airway narrowing with 8% having severe dyspnoea, but it is mild in the majority. It is important to appreciate that these reactions have resulted from uncontrolled exposure because families were previously unaware of the diagnosis. Further reactions, once diagnosis is made and specialist management implemented, are mostly mild [30–32]. There is evidence in a large UK cohort

of children that previous mild peanut and nut allergic reactions do not become more severe over time, but other data from USA show that patients who have had a mild reaction may then have a more severe one [27]. It is not known if this is due to ingestion of a larger dose (failure to avoid), co-factors or due to a real increase in sensitivity. In a small minority, subsequent reactions may increase in severity because the severity of the index reaction was not accurately defined or because of co-factors. These findings support the need for specialist management. Within the nuts, Brazil nut is more likely to cause severe reactions than peanut (in two of three compared with one of three) and cashew is also more severe than peanut (for cashew, the risk (odds ratio) of a severe reaction is increased 25 times, of wheeze eight times, and need for IM adrenaline 13 times) [21, 40]. However, peanuts remain important because they are the commonest nut causing allergy and the most difficult to avoid. Egg and milk allergy are usually mild and resolve. However, in a minority milk allergy is severe and remains the most common cause of fatal anaphylaxis in infants [20, 41]. A recent study of practice in Italy found that in addition to the severity of the reaction, the causative allergen was also considered when deciding when to prescribe an auto-injector [42]. Although the nature of the allergen is important, the decision on whether to prescribe an AAI must also take into account other factors such as ease of avoidance, severity of previous reactions and presence of asthma.

- 4 Persistence or resolution of allergy: allergens likely to resolve, for example egg allergy, are less likely to require an adrenaline auto-injector unless the reaction was particularly severe, which applies only to a tiny minority [39].
- 5 Component-resolved testing: molecular characterization of IgE responses can be a useful diagnostic adjunct where there is a supportive clinical history. Examples of food allergen molecular components commonly tested include Ara h 2 (primary peanut allergy), omega 5 gliadin (wheat-dependent exercise-induced anaphylaxis) and lipid transfer proteins such as peach Pru p 3 (systemic reactions to fruits). These tests have limited value, however, in predicting likely *severity* of future reactions. Many other component tests are available although relatively few have been validated in clinical studies.

Age-specific risk factors

Teenagers and young adults tend to suffer food-induced anaphylaxis more than young children. Possible reasons are that they become less risk-averse, begin to drink alcohol and are newly independent.

Asthma

The major adverse feature in food allergy is respiratory compromise rather than hypotension, and the severity and control of the underlying asthma affects the risk for severe food-induced reactions [43]. A UK study of fatal reactions showed that all reactions thought to have been due to food caused difficulty breathing and led to respiratory arrest in 86% [6]. Of fatal anaphylactic reactions to foods, all but one was known to have asthma [4]. Asthma is associated with an increased incidence of anaphylaxis, and this occurs even with mild asthma although the relative risk is higher with severe asthma [44]. Mullins found that having asthma was not a risk factor for recurrence of anaphylaxis but was a risk factor for severity of reactions [25].

Asthma occurs in about 76% of adults and children with nut allergy and is likely representative of food allergy more generally [31, 40, 43]. Asthma which requires regular inhaled corticosteroids is considered to be a risk factor, whereas minor intermittent asthma/wheezing is not, for example only after a URTI [31]. It has also been suggested from population-based data on 8000 subjects in USA that food allergy could be an under-recognized risk factor for problematic asthma [45].

Raised baseline serum tryptase

An elevated baseline serum tryptase (without the features of mastocytosis) is known to increase the frequency and severity of systemic reactions to bee and wasp stings. It is also likely that there is an increased risk for idiopathic reactions [46].

Can allergen be avoided?

When allergen(s) are avoided, for example drugs (to which this particularly applies) and certain foods, adrenaline should not be required unless there is an additional risk factor.

Remoteness from medical help and social factors

This increases risk, as the time to receive medical help will be longer, so the threshold for prescribing adrenaline should be lower. Similarly, social and personal factors need to be considered, for example a single mother with young children, or a person living alone or who is infirm.

Provision of emergency medication

The indication for adrenaline will be linked to risk assessment. The allergist should lead on advice, but

must consider and discuss patient and/or parental views.

Written treatment plan

An emergency treatment plan should be provided. Examples are attached, which can be used as proformas, which are then tailor made to the patient [Appendices A1–A5]. Different plans are required according to the age of the patient, for example adult, child and older child, so that medication doses and the recommended device are appropriate. The treatment plan should also include oral antihistamines. This is because subsequent reactions (depending on aetiology) may be less severe, for example if exposed to a smaller amount of allergen which should be the case in most patients with food allergy who were provided with appropriate advice, but then suffered inadvertent exposure. If symptoms are mild to moderate, initially, oral antihistamines should be given at the onset of the reaction to all patients, an approach demonstrated to be effective, for example, in a large series of nut allergy [31]. Oral antihistamines are not first-line treatment for treating severe and rapid-onset reactions as may occur after some hymenoptera stings when adrenaline should be first administered. An alternative standard plan is available through the BSACI Paediatric Allergy Group, but this suggests two AAIs should be available and does not include antihistamines, which are an important part of management of reactions after identification of aetiology (<http://www.bsaci.org/about/pag-allergy-action-plans-for-children>).

The use of self-administered adrenaline for all 'allergic' reactions, for example urticaria, rather than for severe symptoms, is discouraged [47].

Dose

The precise physiological dose of adrenaline as a treatment for anaphylaxis is not known. Kinetic studies have been performed, but the therapeutic range for plasma adrenaline is not known; furthermore, the pharmacodynamics and tissue and receptor levels will be more relevant. The dose of adrenaline is therefore empirical.

The dose when self-administered from auto-injectors is shown on Table 4 and for different age groups in Box 3. An AAI delivering 0.5 mg has recently become available.

Recommended doses of adrenaline when administered by medical staff are shown in Box 4. Standard practice for healthcare professionals, particularly in the hospital setting, is to use a vial of adrenaline, syringe and needle, and administer intramuscularly in the upper outer quadrant of the buttock.

Table 4. Adrenaline devices for self-injection licensed in United Kingdom

Device	Mechanism	Doses	Needle length	Needle gauge	Retractable or shielded needle	Shelf life	Distributor
EpiPen	Cartridge	0.3 mg	15 mm	21	Yes (shield)	18 months*	Meda Pharmaceuticals Ltd.
EpiPen Junior		0.15 mg	13 mm	21			
Jext (300)	Cartridge	0.3 mg	15 mm	21	Yes (shield)	18 months*	ALK Abello
Jext (150)		0.15 mg	13 mm	21			
Emerade	Triple Spring (pre-filled syringe)	0.5 mg	25 mm	23	Yes (shield)	30 months*	Bausch & Lomb
		0.3 mg	25 mm	23	Yes (shield)	30 months*	Lome Ltd
		0.15 mg	16 mm	23	Yes (shield)	30 months*	
Minijet** (not an auto-injector)	Self-assembly	1 mg	1.5 inch	21	No		UCB Pharma

Data from SPC; *from point of manufacture; **no longer recommended for self-injection in the United Kingdom. Note Anapen, AAI withdrawn in United Kingdom.

Box 3. Doses of adrenaline available for self-administration

Group	Dose adrenaline
Adult or child > 12 years*	0.5 mg
Adult, adolescent or child > 30 kg	0.3 mg
Children 15–30 kg**	0.15 mg
Children < 15 kg (unlicensed)	0.15 mg

*0.3 mg more appropriate for a smaller child > 12 years.
 **0.3 mg may be more appropriate for some children, for example over 25 kg.

Box 4. The British National Formulary (BNF) and the Resuscitation Council UK [7] dosages of adrenaline to be administered intramuscularly by healthcare professionals†

Age	Dose and volume using 1 mg/mL adrenaline (= 1 in 1000)
Adult or child > 12 years*	0.5 mg (= 0.5 mL)
Children aged 6–12 years	0.3 mg (= 0.3 mL)
Children < 6 years**	0.15 mg (= 0.15 mL)

†Using syringe, needle and vial of adrenaline 1 in 1000 strength.
 *0.3 mg if child small or pre-pubertal.
 **RCUK recommended dose for 6 months–6 years.

Auto-injector adrenaline delivery devices

Adrenaline auto-injectors should be easy and safe to use, deliver adrenaline to the muscle, readily available in appropriate doses, stable at a range of temperatures and with a long shelf life [48]. Ideally, they should also be small and portable, but a device incorporating all these features has not developed yet. Devices available for self-administration licensed in the United Kingdom are shown in Table 4.

The main difference between the auto-injector devices is the type of delivery system, which is either

cartridge based or a syringe delivery system [48]. The cartridge device has a compression force delivering the adrenaline deeper than the needle length [49]; however, it is now apparent that this is only if the needle tip has penetrated the fascia and the delivery was intramuscular [50].

Absorption. The needle length, depth reached by the needle tip and thickness of subcutaneous fat determine the site of delivery of adrenaline [51, 52]. There is limited data on absorption. One study compared three sites of injection and showed that absorption was greater from intramuscular injection in the thigh, than either by subcutaneous or by intramuscular injection into the deltoid [50]. Thus, intramuscular (IM) absorption is greater from the thigh (vastus lateralis muscle) than the arm (deltoid), presumably related to muscle bulk and perfusion [52]. In two separate studies in adults, the time to peak level after IM administration was 10 min and after subcutaneous administration, 5 min [52, 53]. After subcutaneous adrenaline in adults, peak levels were > 400 pg/mL (units converted), and 400 pg/mL results in marked beta-2 activity and broncho-dilation [53]. In children, comparing IM (thigh) and subcutaneous (arm) administration, time to peak was similar around 8 min, but absorption was variable after subcutaneous, and the area under the curve was greater for IM [51]. Intramuscular administration in the thigh thus appears preferable. More data on absorption from AAIs are needed and have been requested by the European Medicines Agency.

If the AAI needle tip only reaches the subcutaneous tissue, the deep fascia of the thigh prevents fluid from entering the muscle [50]. The depth of subcutaneous fat will influence whether the dose from an auto-injector is delivered into the muscle [2]. Although the intramuscular route rather than the subcutaneous route is recommended, there are no studies that directly compare clinical effectiveness of the two routes in anaphylaxis.

Patients, parents or carers should be trained in the use of their auto-injector at the time of prescribing, and training reinforced when the pharmacist dispenses device. Pharmacists should be encouraged to undertake device training at every opportunity. The public can obtain Trainer devices for Emerade, EpiPen and Jext. It is essential for patients to practise with a trainer device regularly to maintain technique. Retraining (formalized and documented) should be a component of each hospital allergy follow-up appointment. Adrenaline auto-injectors have an expiry date, and for some devices, (Emerade, EpiPen, Jext) patients can register for a reminder when the auto-injector needs replacing. With some devices, patients can check that the solution remains clear and colourless. Anapen has been withdrawn in the United Kingdom.

The Minijet is an older non-automatic device that requires assembly, and patients were required to inject either one half or one-third of the volume in the syringe, with the risk of incorrect dosage. This device is therefore not used and has been superseded by other devices, which automatically deliver a fixed dose.

Auto-injector dose for infants and children

The BNF lower cut-off for the junior strength auto-injector is a weight of 15 kg, but there are infants < 15 kg at risk of anaphylaxis who require an adrenaline auto-injector. A practical approach taken by specialists is to recommend the junior auto-injector (0.15 mg adrenaline) from age six months. This is supported by Simons, for children weighing > 7.5 kg if there is a high risk of accidental exposure [54]. Below this age, avoidance should be possible and cover most of those at risk. The auto-injector containing 0.3 mg can be used in a child over 30 kg, as well as adults.

Evidence for effectiveness of auto-injectors

A Cochrane review found many studies relating to anaphylaxis and adrenaline auto-injector use but no randomized controlled trials [55]. The authors concluded that the use of adrenaline auto-injectors in anaphylaxis is based on the best available information at present. There is no evidence from randomized controlled trials for the effectiveness of adrenaline auto-injectors in the emergency treatment of anaphylaxis in the community.

Evidence for efficacy of adrenaline

Allergists treating reactions in clinic, for example anaphylaxis induced during a diagnostic challenge or by immunotherapy, have extensive experience and recognize the beneficial effect of a single timely dose of adrenaline. This is delivering adrenaline IM using a

vial, syringe and needle. The same prompt response to adrenaline administration is evident in the anaesthetic records of patients who developed anaphylaxis during anaesthesia. This is supported by consensus statements (WAO [56], UK Resuscitation Council [7], EAACI [14]). In clinical practice, the very large number of reports of benefit from patients, although anecdotal, is compelling.

Interaction with tricyclic antidepressants and other drugs

Tricyclic antidepressants such as imipramine inhibit reuptake of directly acting sympathomimetic agents and theoretically may potentiate the effect of adrenaline, increasing the risk of development of hypertension and cardiac arrhythmias. It is not known whether this occurs in practice. Patients on these drugs should not be denied adrenaline in anaphylaxis, but adrenaline use should be restricted to severe reactions and there should be caution with dose. This also applies to monoamine oxidase inhibitors given, because of the risk of hypertensive crisis. Similarly, adrenaline should not be unnecessarily withheld because patients are on betablockers, ACE inhibitors, or have cardiovascular disease.

Risk assessment for number of adrenaline auto-injectors

There is no good evidence that issuing two AAIs is necessary or cost-effective in most cases. After an episode in A&E, awaiting proper risk assessment, the normal practice would be to issue one device.

The decision to recommend one or more AAIs at each site must be individualized with each patient and requires a thorough risk assessment. Most patients will only require one injection of adrenaline to treat an episode of anaphylaxis and therefore only require carrying one device. Two adrenaline auto-injectors should be considered when other factors are present, but this should be based on specialist risk assessment. These include, for example, a previous life-threatening reaction, a previous *requirement* for two doses within a short period during a reaction, obesity or geographical isolation. Essential is that patients should carry their device at all times, are trained in how and when to use it and to use it early when adrenaline is indicated. Carrying two devices does not replace allergen avoidance, education and training. The decision of how many additional settings to provide adrenaline for (e.g. school/early year's settings) should be discussed between the clinician and the patient/family.

Reviewing the literature on the use of two doses of adrenaline, most studies are of poor quality. Table 5 summarizes the relevant literature. Studies, which are

Table 5. Data on the use of more than one dose of adrenaline for self-treatment

Author	Design Setting and Aim	Disease	Number of subjects	Age	Duration and follow-up years	Severity pre-intervention	Criteria for use of adrenaline	Incidence of further reactions	Severity of further reactions	No. (%) using adrenaline	No (%) using \geq 2 doses adrenaline	Comments and criticisms of study
Clark and Ewan [31]	Prospective studies Incidence and severity of further reactions and self-use of adrenaline	Nut	785	Children Median 68 m	5.3 years 3640 patient-years	Mild 516 (66%) Mod 224 (29%) Severe 45 (5%)	Respiratory difficulty or symptoms of hypotension	3.1% annual incidence rate for all severities	Most were mild requiring no treatment or oral antihistamine. Mild 92 pts Mod 21 Severe 1 (0.1%)	1/785 (0.001%) 1/1 (100%) Effective Self Rx AAI	0	Prospective Low incidence severe reactions. Patients trained in when to use adrenaline As above
Ewan and Clark [40]	Prospective studies Incidence and severity of further reactions and self-use of adrenaline	Nut	615 longitudinal 112 case-controlled	Children Mean 6.3 years (range 10 month-15 years)	Median 3.3 years 25 906 patient-months	Mild 64% Severe 36%	Respiratory difficulty or symptoms of hypotension	For whole cohort 0.07 reactions/person year	Most were mild Severe 1/615 (0.2%)	2/615 (0.3%) 1/1 (100%) severe reactions Adrenaline effective	0	As above
Ewan and Clark [30]	Prospective studies Incidence and severity of further reactions and self-use of adrenaline	Nut	567	All ages Median 7.5 years (range 7 months-65 years)	13 610 patient-months	Mild, 277 (51.4%) Mod severe 262 (48.6%)	Respiratory difficulty or symptoms of hypotension	15% overall incidence, of reduced severity	Mild, 62 pts (10.9%) Mod severe 26 pts (4.6%) [anaphylaxis]	9/567 (0.16%) always effective 9/9 (100%) severe	0	As above
Uguz et al. [60]	Retrospective self-reported questionnaire of allergic reactions in community via patient support group (not all had been prescribed adrenaline)	Any Food implicate in 89%	109 (126 reactions)	All ages (69% children)	6 months	All	NK	100% (126 reactions in 109 patients)	Varied	10/88 (11%) 12/38 (31%) adults Adrenaline used in 35% of severe rxns; in 13% of non-severe rxns; where AAI available	1/88 (1.1%) in children 3/38 (7.9%) in adults	No data on need for vs. use of Second dose of adrenaline Higher use in adults Under treatment of severe reactions; over treatment of mild reactions Few were self-treatment. In about half of all patients 1st (or only) dose adrenaline administered by HCP
Jarvinen et al. [59]	Retrospective questionnaire to new or follow-up patients attending tertiary centre.	Food (but history suggestive of food in only 51%)	413	Children Median 4.5 years	6 months Recall period median 24 m	N/A	NK	N/A	Severity score similar in groups receiving 1 or 2 doses adrenaline	84/413 (20%)	12/95 (13%) of reactions had 2 doses 6/95 (6%) had 3 doses	

(continued)

Table 5 (continued)

Author	Design Setting and Aim	Disease	Number of subjects	Age	Duration and follow-up years	Severity pre-intervention	Criteria for use of adrenaline	Incidence of further reactions	Severity of further reactions	No. (%) using adrenaline	No (%) using \geq 2 doses adrenaline	Comments and criticisms of study
Noimark et al. [61]	Retrospective self-reported questionnaire of patients attending 14 UK paediatric allergy clinics. Entry criterion was the prescription of AAL [having at least one reaction in previous year was not entry criterion]	Any Mostly food	Total 969 466 of whom had a reaction in last year; 245 of which were 'anaphylaxis'	Children and teenagers to age 18 years	1 year	N/A	NK (definition was mild: included tight throat, or itchy throat, or wheeze, any of which may have been mild)	466 (48%) had reactions 245 (25%) had 'anaphylaxis'	25% had anaphylaxis (definition included mild symptoms only)	41/969(4.2%) 41/466(8.7%) 41/245(16.7%)	13/969 (1.3%) 13/466 (2.7%) 13/245 (5.3%) In 9/13 health prof admin at least one dose	In 83% of anaphylaxis, adrenaline was not used (treated with AH) Mild definition used for anaphylaxis meant low threshold for adrenaline Reactions treated with adrenaline need not have been severe. Indications for prescription of adrenaline not clear.
Van der Leek et al. [27]	Prospective	Peanut	83 (53 with 5 years f/u)	Children Median 2.4 years	Median 5.9 years	Mild 73% Severe 27%	No data	60/83 (72%) further reaction	31/83 (37%) severe further reaction	No data	No data	Discrepancies between data in text and tables. Data from tables used. -Definition anaphylaxis used meant low threshold for adrenaline - Commonest symptoms cutaneous, gastro only. -Delay to
Rudders et al. [74]	Retrospect ED case chart review of food-related rxns in USA by diagnostic code 2001-06 from 2 EDs. Aim: to establish frequent of use of > 1 dose adrenaline before or in ED	Food	605 pt charts equivalent to 1255 pts	Children Median 5.8 y	6 years	52% had anaphylaxis (USA FAAN definition)	2 systems involved, for example rash + vomiting or hypo alone	NR	52% had anaphylaxis (USA FAAN definition)	34% before ED 44% over course of Rx	Pre-ED 3% of those with anaphylaxis [2% of all pts] 34% not self admin In ED 1% of those with anaphylaxis [0.3% of all pts]	

(continued)

Table 5 (continued)

Author	Design Setting and Aim	Disease	Number of subjects	Age	Duration and follow-up years	Severity pre-intervention	Criteria for use of adrenaline	Incidence of further reactions	Severity of further reactions	No. (%) using adrenaline	No (%) using \geq 2 doses adrenaline	Comments and criticisms of study
Oren et al. [75]	One ED in USA retrospective case review	Food	34 with acute allergic reactions	Children and adults median 6 years	1 year	19 had anaphylaxis	N/A	N/A	N/A	12/19 (63%)	3/19 (16%)	No data on indications for second dose
Gold and Sainsbury [76]	Retrospective telephone questionnaire of children with anaphylaxis from specialist allergy service prescribed AAI	All allergens	94 prescribed AAI	6 years	1477 pt-months Mean 20 months	68 had anaphylaxis	N/A	37/68 (54%) had 121 reactions 0.98 episodes per pt-year	45/121 anaphylaxis 76/121 non-anaphylaxis	AAI used in 13/45 (29%) anaphylaxis AAI used in 15/121 reactions (12%)	0	Over course of Rx, 6% of those with anaphylaxis [3% of all pts] used in ED; -Adrenaline mostly given sub cut
Braganza [77]	Retrospective, case review, Paediatric attending single teaching hospital ED Australia Aim: incidence and treatment	Any	526 GR	Children Median age 4.1 years; severe anaphylaxis 5.9 years	3 years		Anaphylaxis 57 of whom 28 severe	N/A	N/A	15 (26.3%) 16 (39.3%) of severe anaphylaxis	Presume none – not noted	AAI usually used in venom anaphylaxis; but in only 9–14% of food anaphylaxis

Rxn, reaction; gastro, gastro-intestinal; resp, respiratory; ED, emergency department; paed, paediatric; pt, patient; f/u, follow-up; AAI, adrenaline auto-injector; HCP, healthcare professional.

informative, should have prospective design, recent patient recall, evidence of the clinical features of the reaction being treated and a sufficiently robust definition of anaphylaxis, but these criteria are difficult to achieve.

Early data that two doses of adrenaline may be required came from two retrospective studies of treatment of reactions to immunotherapy, largely to inhaled allergens, and were not self-treatment [57, 58]. One study was in the form of a letter, and no information was provided on whether the second dose was *needed*, rather than just *given*. Many studies are retrospective and self-reported, without clinician confirmation of the clinical circumstances and others included milder symptoms, for example urticaria, which would not constitute anaphylaxis according to the UK definition [7]. The study often quoted as showing patients requiring two doses of adrenaline was a retrospective questionnaire in patients with food allergy in the USA, which recorded the patients *receiving* two doses rather than actually *requiring* two doses [59]. In some cases, the symptoms recorded were mild (e.g. oral pruritus) and did not fulfil indications for even a single dose. Another self-reported questionnaire study sent to members of the UK patient support group, the Anaphylaxis Campaign, also indicated two doses were used in 25% of adults (three subjects). However, this study lacks data to show two doses were indicated [60]. A recent study where there was repeat use of adrenaline in food allergy was a self-reported questionnaire with retrospective recall, with no corroborated data on the indication [61].

In nut allergy, where recurrent and severe reactions are common, there is no evidence from large prospective follow-up cohorts that two devices are required routinely (data on over 1000 patients, one cohort followed over 4000 patient-years) and one dose was effective [30–32] (Table 5). Of note, in this study, avoidance advice, one component of managing anaphylaxis risk, prevented further severe reactions.

A recent MHRA drug safety update [62] recommended that individuals who need an AAI should in fact carry two. It is important to remember that the aim of self-management is the early and correct administration of adrenaline. In the majority of cases, only one dose will be required and should be combined with calling for help. A second dose is rarely necessary and, if needed, can be given by paramedics or in the Emergency Department.

Incorrect administration technique: inability to use auto-injector

Studies have shown that only one-third to one half of patients are able to demonstrate correct technique of

use: this is a major problem. In addition, most doctors in primary and secondary care are uncertain how to use the device, and in the USA, three quarters of healthcare professionals who teach patients were unable to demonstrate correct technique [63]. It is therefore important for clinicians who regularly prescribe adrenaline auto-injectors to be aware of the correct technique and to train patients as an integral part of allergy care. The use of trainer pens and the advent of company websites and videos including that of the Anaphylaxis Campaign may improve standards. The NICE quality standard on anaphylaxis includes education in adrenaline auto-injector use [64].

Posture

The written treatment plan provided by the allergist should state that when breathing is the dominant problem in anaphylaxis, the patient should sit up (the commonest problem is food-induced anaphylaxis). Whereas if hypotension has occurred, the patient should be kept lying flat, ideally with legs elevated; however, if there is loss of consciousness or vomiting, the patient should be in the recovery position.

Device failure

If there is failure of the device due to inability to administer, there is no evidence or reason to believe that the patient will be able to correctly administer a second device. Inherent device failure is extremely rare. User error rather than device failure is often to blame and reflects inadequate training. The solution is to train and retrain patients correctly rather than gaining false security by prescribing more devices. Training will increase patient safety.

Training families in the entire management plan

As many carers as possible should be involved. Educational materials such as written guidance on avoidance, use the auto-injector, written treatment plan, obtaining a trainer pen should be provided to enable trained parents to teach other family members (especially grandparents) not present at the consultation. Teenagers are at higher risk [31], perhaps because of peer-pressure and consumption of alcohol reducing the ability to avoid food allergens. The median age of death in food-induced anaphylaxis is 20 years, whereas with bee or wasp stings, it is about 50 years [20].

Community link: schools and early year's settings

It is essential to develop a strong link between the allergy service provider and the community paediatric

service [65]. The ideal working model is to have allergy-trained paediatric nurses out in the community. The allergist should have a system in place to contact the community paediatric team whenever a new treatment plan is issued. A visit to the school can then be arranged to undertake training in:

- 1 The recognition of acute allergic reactions, including understanding of different levels of severity.
- 2 Allergen avoidance.
- 3 The correct use of the auto-injector.

Annual re-training is required. Visits should provide advice for both teachers and catering staff. It is essential that the person conducting the visit has the appropriate knowledge base in allergy. The Anaphylaxis Campaign has produced a web-based training aid for schools (<http://www.anaphylaxis.org.uk/information/health-professionals/administering-adrenaline.aspx>). Generic provision of AAI within schools has been proposed, with potential cost savings [66].

Maintaining good asthma control

In patients at risk of anaphylaxis, it is important to aim for excellent asthma control in order to minimize the risk of exacerbation and consequent life-threatening anaphylaxis on inadvertent allergen ingestion. A definition of good asthma control should be provided for patients and parents because of asthma severity and day-to-day control, which is often poorly appreciated by carers. For example, regularly using ≥ 2 puffs salbutamol a few times per week when otherwise well (i.e. without URTI) is inadequate control. Awareness of when to start preventer inhalers is important in seasonal asthma when no treatment is required out of season and similarly with other intermittent predictable triggers. Increased vigilance is particularly important in teenage years when compliance with asthma medication and food avoidance is likely to slip. Therefore, an important part of the allergy consultation is monitoring, managing and providing training in asthma control.

An enquiry into asthma deaths reveals that seasonal and non-seasonal allergy may be an important cause and was usually unrecognized in life despite conventional asthma care over many years [67, 68].

Evidence on current prescribing

In the United Kingdom, there is inconsistency in prescription of AAI, poor training, lack of compliance and follow-up [69]. This probably reflects a lack of knowledge of allergy in primary and secondary care. Wide regional variation in adrenaline auto-injector prescribing is observed in Australia, and although this may be related to variation in incidence of anaphylaxis, it is

more likely due to variation of prescribing practice [70]. United Kingdom prescribing of auto-injectors has increased considerably in recent years, but there are neither data on whether the prescribing is appropriate nor the proportion of those at-risk receiving adrenaline auto-injectors. About 201 000 patients received a prescription for an adrenaline auto-injector in a 12-month period, 2009–2010 (73% were a repeat prescription and 27% initial prescription). Auto-injectors are on occasions used as a substitute for allergy referral and too often as an 'end-point' rather than the starting point in the management of anaphylaxis.

Use vs. need for an adrenaline auto-injector

Not needing to use an auto-injector has been used as an argument against the need for provision, but this does not mean the device should not be available. Avoidance, where appropriate, should be first line, and if effective, no further reactions will occur. Hospital Episode Statistics (HES) data for England 2009/2010 show there were 3349 emergency events coded as anaphylaxis; although all episodes of anaphylaxis are not captured by HES, it is not possible to verify whether the diagnostic label was correctly applied in every case. There is no data on how many of the auto-injectors prescribed are used, but clinician information suggests this is extremely low. However, the better the avoidance advice, the lower the likely use of adrenaline. Therefore, in the at-risk patient, the provision of an adrenaline auto-injector remains a requirement and lack of use of auto-injectors should not be taken as a surrogate for lack of need and is a flawed argument against appropriate prescribing. Appropriate prescribing need not mean a reduction in overall numbers of adrenaline auto-injectors required [71].

Auto-injector repeats prescription

Patients themselves deciding not to obtain repeat prescriptions may indicate that perhaps the original provision of an adrenaline auto-injector was inappropriate. Of 14 677 patients in a large HMO who received a prescription for EpiPen or EpiPen Jr between 2000 and 2006, 6776 (46%) obtained a repeat prescription at least once [72]. In a cohort followed for 5 years or more, 25% repeated their prescription on multiple occasions but only 11% obtained repeat prescriptions at each expiry. Infants and children to age 12 years were more likely to receive a repeat prescription (63%) compared with teenagers and adults (40%). The most common ICD-9 codes that were linked to the initial adrenaline dispensing were allergic disorder (37%), miscellaneous anaphylaxis/angioedema (23%), hymenoptera/insect bite or sting (14%) and specific or non-specific food allergy

(11%). A total of 79% of patients with a food-related ICD-9 code and 59% of patients with an insect sting-related ICD-9 code obtained a repeat prescription at least once.

Unintended adrenaline injections

In the USA, the public can self-report unintentional auto-injector injections to two databases. From 1994 to 2007, 15 190 unintentional injections from adrenaline auto-injectors were reported to US Poison Control Centers of which 60% occurred from 2003 to 2007 [2]. The number is increasing annually. Those unintentionally injected had a median age of 14 years, and 85% were injected in a home or other residence. By contrast, from 1969 to 2007, only 105 unintentional injections from auto-injectors were reported to MedWatch. Forty percent took place during attempts to treat allergic reactions; 13% occurred during self-training or inspection of the device and 11% when disposing of the device. Almost half of all events were managed onsite or in a non-healthcare facility. In most, clinical effects were described as minor or minimal. However, the study only captured voluntary reports and did not present data on the number of devices prescribed over the study period.

Data from the manufacturers of adrenaline auto-injectors in the United Kingdom suggest few unintended self-injections occur. This is also the experience of the major allergy centres.

Prescribing for specific anaphylaxis phenotypes

Raised baseline serum tryptase and mastocytosis. Raised baseline serum tryptase occurs in 8–10% of patients with systemic reactions to hymenoptera venom [73] and in some patients with idiopathic anaphylaxis and other conditions. The allergic reaction is the usual reason for identifying the abnormal tryptase level. Many of these patients have mast cell activation disorder and not mastocytosis. They are at increased risk of further systemic reaction, although in idiopathic anaphylaxis this is often ameliorated by medical therapy. In venom allergy, patients with raised levels of baseline serum tryptase are at increased risk of more severe (grade 3 and 4) reactions [38].

Cold urticaria/anaphylaxis—cold exposure, for example chilling of the skin by weather or sea swimming, can induce anaphylaxis. Appropriate diagnosis and avoidance advice are required and warming up usually effective treatment. Prescription of an adrenaline auto-injector is rarely required.

Exercise-induced reactions—some of these can be managed with oral antihistamines and inhaled salbutamol

although adrenaline may be required in severe cases. However, food-dependent exercise-induced anaphylaxis is more likely to be severe, requiring adrenaline. In many cases, the frequency of reactions can be reduced by identifying the food and avoidance before exercise.

When to stop adrenaline auto-injector prescription

There are situations when prescription of an AAI is no longer required. This will require explanation with the patient, as this may present difficulties for the patient and doctor. These include the following:

- Resolution, for example, of food allergy;
- After successful venom immunotherapy (maintenance dose tolerated) if no other risk factors;
- When initial prescription was inappropriate;
- When the initial diagnosis has been clarified, and the identified triggers show that an AAI is not required.

Summary

Adrenaline is the first-line treatment for anaphylaxis. It should be used in patients with significant airway involvement or hypotension, occurring as part of an anaphylactic reaction. An auto-injector allows early administration of adrenaline, improving outcome. Its use should be combined with calling for an ambulance. Following the acute event, an adrenaline auto-injector should be prescribed and an allergy referral immediately triggered (NICE guidance).

Specialist allergy experience is required to make a risk assessment to determine the continuing need for an adrenaline auto-injector, allergy advice on avoidance of triggers, a written treatment plan and re-training in the use of the auto-injector.

Despite recent advances, there are many areas of practice where further clinical data would be valued, including the number of doses of adrenaline required, studies of sites and routes of administration, patient risk and co-factors for severe and fatal reactions, measures to prevent anaphylaxis, benefits of generic adrenaline provision in schools and optimizing use of autoinjectors.

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These *guidelines* inform the prescription of adrenaline auto-injectors. Adherence to these guidelines does not constitute an automatic defence for negligence, and

conversely, non-adherence is not indicative of negligence. It is anticipated that these guidelines will be reviewed 5 yearly.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A1
Example of emergency treatment plan for a child (with Jext Junior)

PRIVATE & CONFIDENTIAL

To the parents of: _____ Copy to: _____ *GP Details*

EMERGENCY TREATMENT OF ALLERGIC REACTIONS _____ **Jext Junior**
 _____ **(150)**

..... **Date of birth:**

..... is allergic to It is important that avoids completely. It is essential that the ingredients of all foods eaten are checked carefully, (for example, nuts can be hidden in foods as nut oils or essences).
 Treatment of Allergic Reactions: This depends on their severity.

Mild reactions

Itching of the skin, rash, swelling, e.g. of the lips, or nausea.
 Treatment – give antihistamine mixture, e.g. cetirizine syrup teaspoons (... mg) or Piriton syrup ... teaspoons (... mg) immediately. Take to a doctor if necessary.

Moderate reactions

If there is difficulty in breathing or tightness in the throat give antihistamine as above and take to a doctor or A & E Department quickly.

Severe reactions

The symptoms are:
 (i) Marked difficulty in breathing or choking (a feeling of closing up of the throat) and/or
 (ii) Floppiness, collapse or loss of consciousness.

Treatment

- (1) Immediately send someone to call an ambulance. Say this is an emergency a case of anaphylactic (pronounced ana-fi-lac-tic) shock with collapse.
- (2) If there is collapse or if there is difficulty in breathing is severe immediately give an injection of adrenaline from the auto-injector in his/her treatment pack. This is a Jext Junior syringe which delivers a fixed dose of 0.15 mL of 1/1000 strength (equivalent to 0.15 mg). This can be injected into the front or side of the thigh. If faint should be kept lying down on his/her side.

(INSERT CONS/REG DETAILS)

Appendix A2

Example of emergency treatment plan for an older child (with EpiPen)

Insert Hospital Header

PRIVATE & CONFIDENTIAL

To the parents of:	Copy to:	GP Details
EMERGENCY TREATMENT OF ALLERGIC REACTIONS		EpiPen Older Child

..... Date of birth:

..... is allergic to It is important that avoids completely. It is essential that the ingredients of all foods eaten are checked carefully, (for example, nuts can be hidden in foods as nut oils or essences).

Treatment of Allergic Reactions: This depends on their severity.

Mild reactions

Itching of the skin, rash, swelling, e.g. of the face.

Treatment – take antihistamine, e.g. cetirizine syrup 2–4 teaspoons (10–20 mg) or Piriton syrup 2–4 teaspoons (4–8 mg)

Take to a doctor if necessary.

Moderate reactions

If there is mild difficulty in breathing or slight tightness in the throat, give the antihistamine as above and take to a doctor or Accident & Emergency Department quickly.

Severe reactions

The symptoms are:

- (i) Difficulty in breathing or choking (a feeling of closing up of the throat) and/or
- (ii) Floppiness, collapse or loss of consciousness.

Treatment

- (1) Immediately send someone to call an ambulance. Say this is an *emergency* a case of anaphylactic (pronounced ana-fi-lac-tic) shock with collapse.
- (2) If there is collapse or the difficulty in breathing is worse or gets worse, immediately give an *injection of adrenaline* from the pre-loaded syringe (EpiPen) in his/her treatment pack. This delivers a fixed dose of 0.3 mL of 1/1000 strength. This can be injected into the front or side of the thigh. If faint should be kept lying down on his/her side.

(INSERT CONS/REG DETAILS)

Appendix A3**Example of emergency treatment plan for an older child (with Jext)***[Insert hospital header]*

PRIVATE & CONFIDENTIAL

Patient details	Copy to	GP details
EMERGENCY TREATMENT OF ALLERGIC REACTIONS		Jext older child

..... is allergic to It is important that avoids ... completely. It is essential that the ingredients of all foods eaten are checked carefully, (for example, nuts can be hidden in foods as nut oils or essences).

Treatment of Allergic Reactions: This depends on their severity.

Mild reactions

Itching of the skin, rash, swelling, e.g. of the face.

Treatment – take antihistamine, e.g. cetirizine syrup 2–4 teaspoons (10–20 mg) or Piriton syrup 2–4 teaspoons (4–8 mg).

Take him/her to a doctor if necessary.

Moderate reactions

If there is mild difficulty in breathing or slight tightness in the throat, give the antihistamine as above and take him/her to a doctor or Accident & Emergency Department quickly.

Severe reactions

The symptoms are:

- (i) Difficulty in breathing or choking (a feeling of closing up of the throat) and/or
- (ii) Floppiness, collapse or loss of consciousness.

Treatment

- (1) Immediately send someone to call an ambulance. Say this is an *emergency* a case of anaphylactic (pronounced ana-fi-lac-tic) shock with collapse.
- (2) If there is collapse or the difficulty in breathing is worse or gets worse, immediately give an *injection of adrenaline* from the auto-injector (Jext) in the treatment pack. This delivers a fixed dose of 0.3 mL of 1/1000 strength (equivalent to 0.3 mg). This can be injected into the front or side of the thigh. If faint should be kept lying down on his/her side.

[INSERT CONSULTANT/REGISTRAR DETAILS]

Appendix A4**Example of an emergency treatment plan for an adult (with Jext)***(Insert Hospital Header)*

Hospital No:

NHS No:

Clinic Date:

Typed:

PRIVATE & CONFIDENTIAL

Insert patient's name and address

Copy to:

*Insert GP name
and address*

EMERGENCY TREATMENT OF ALLERGIC REACTIONS

Jext (300)

(Insert patient's name) is allergic to It is important that avoids . . . completely. It is essential that the ingredients of all foods eaten are checked carefully, (for example, nuts can be hidden in foods as nut oils or essences).

Treatment of Allergic Reactions: This depends on their severity.

Mild reactions

Itching of the skin, rash, swelling, e.g. of the face.

Treatment – take antihistamine, e.g. cetirizine 2 tablets (20 mg).

Go to a doctor if necessary.

Moderate reactions

If there is mild difficulty in breathing or slight tightness in the throat, take the antihistamine as above and go to a doctor or Accident & Emergency Department quickly.

Severe reactions

The symptoms are:

- (i) Difficulty in breathing or choking (a feeling of closing up of the throat) and/or
- (ii) Floppiness, collapse or loss of consciousness.

Treatment

- (1) Immediately send someone to call an ambulance. Say this is an *emergency* a case of anaphylactic (pronounced ana-fi-lac-tic) shock with collapse.
- (2) If there is collapse or the difficulty in breathing is worse or gets worse, immediately give an *injection of adrenaline* from the auto-injector (Jext) in your treatment pack. This delivers a fixed dose of 0.3 mL of 1/1000 strength (equivalent to 0.3 mg). This can be injected into the front or side of the thigh. If you faint you should be kept lying down on your side.

(INSERT CONS/REG DETAILS)

Appendix A5**Example of an emergency treatment plan for an adult (with Emerade)***(Insert Hospital Header)*

Hospital No:

NHS No:

Clinic Date:

Typed:

PRIVATE & CONFIDENTIAL

Insert patient's name and address

Copy to:

*Insert GP name
and address*

EMERGENCY TREATMENT OF ALLERGIC REACTIONS

Emerade 500

(Insert patient's name) is allergic to ... It is important that ... avoids ... completely. It is essential that the ingredients of all foods eaten are checked carefully, (for example, nuts can be hidden in foods as nut oils or essences).

Treatment of Allergic Reactions: This depends on their severity.

Mild reactions

Itching of the skin, rash, swelling, e.g. of the face.

Treatment – take antihistamine, e.g. cetirizine 2 tablets (20 mg).

Go to a doctor if necessary.

Moderate reactions

If there is mild difficulty in breathing or slight tightness in the throat, take the antihistamine as above and go to a doctor or Accident & Emergency Department quickly.

Severe reactions

The symptoms are:

- (i) Difficulty in breathing or choking (a feeling of closing up of the throat) and/or
- (ii) Floppiness, collapse or loss of consciousness.

Treatment

- (1) Immediately send someone to call an ambulance. Say this is an *emergency* a case of anaphylactic (pronounced ana-fi-lac-tic) shock with collapse.
- (2) If there is collapse or the difficulty in breathing is worse or gets worse, immediately give an *injection of adrenaline* from the auto-injector (Emerade) in your treatment pack. This delivers a fixed dose of 0.5 mL of 1/1000 strength (equivalent to 0.5 mg). This can be injected into the front or side of the thigh. If you faint you should be kept lying down on your side.

(INSERT CONS/REG DETAILS)