Myths, facts and controversies in the diagnosis and management of anaphylaxis

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ABSTRACT
Anaphylaxis is a serious systemic allergic reaction that is rapid in onset and may cause death. Despite numerous national and international guidelines and consensus statements, common misconceptions still persist in terms of diagnosis and appropriate management, both among healthcare professionals and patient/carers. We address some of these misconceptions and highlight the optimal approach for patients who experience potentially life-threatening allergic reactions.

INTRODUCTION
Anaphylaxis is a serious systemic allergic reaction that is rapid in onset and may cause death.1,2 Recent data suggest that the incidence is increasing, particularly to food.3,4 The lifetime prevalence of anaphylaxis is estimated to be between 0.5% and 2%.5 Despite numerous national and international guidelines, misconceptions continue to persist among both healthcare professionals and patients/carers, which result in under-recognition and suboptimal management of this medical emergency. In this review, we address some of these misconceptions and highlight areas of best practice.

Myth 1: ‘Anaphylaxis often results in death’
Anaphylaxis can be life-threatening, but in reality the majority of reactions do not result in severe outcomes.6–8 Many reactions are not treated appropriately (discussed below), yet fatal anaphylaxis is (fortunately) a rare event, with a case fatality rate under 0.001%.8 Severe anaphylaxis, however, is unpredictable, and severe reactions may mimic more mild anaphylaxis reactions in the first instance.9 Delay in appropriate treatment almost certainly contributes to fatalities.10 Therefore, it is critical that all anaphylaxis reactions are treated as a medical emergency.

While hospitalisations in the UK and elsewhere due to anaphylaxis have increased over the last two decades, there has been no increase in fatalities.11–14 For the food-allergic individual, the incidence of fatal anaphylaxis is 1.81 per million person years—less than death due to accidental causes or murder.15 Nonetheless, this needs to be interpreted appropriately: allergic individuals (and their parents) perceive risk very differently: a ‘one in a million’ risk may be acceptable in terms of public health but with respect to their own child, parents will consider their child to be the ‘one in a million’ who will die from anaphylaxis.16 Indeed, the adverse impact of a diagnosis of food allergy on health-related quality of life is greater than that seen in diabetes and other chronic diseases. These data are perhaps best framed in the context of safety-netting: just as we manage everyday risks (such as driving, with safety standards on cars, airbags and crumple zones, adhering to a highway code), can we help our patients and their families take a similar approach to the food allergy, with safety-netting allowing affected individuals to lead as normal a life as possible?

DIAGNOSIS OF ANAPHYLAXIS
Anaphylaxis has been defined as a systemic or multi-organ allergic reaction; however, not all systemic reactions are anaphylaxis. For example, many reactions have only cutaneous manifestations (eg, generalised urticaria)—clearly a systemic phenomenon, but (in the absence of other symptoms) not anaphylaxis according to most guidelines. In practice, anaphylaxis in the UK (and also Australia) is characterised by the presence of ‘Airway/Breathing/Circulation’ (respiratory or cardiovascular) symptoms as part of an allergic reaction. Skin or mucosal changes alone are not a sign of an anaphylactic reaction.

There are two areas of potential controversy: the most common criteria to diagnose anaphylaxis are those developed by the National Institute of Allergy and Infectious Diseases (NIAID) and subsequently adopted by the World Allergy Organisation (box 1),1 which were designed to capture 95% of cases. However:

1. According to criterion 2, skin and gut symptoms together constitute anaphylaxis. However, the prevailing consensus in the UK (and Australia) with respect to food-induced reactions is that skin and gut symptoms, in the absence of respiratory or cardiovascular symptoms, are not anaphylaxis.17 For food, gastrointestinal symptoms are caused by the presence of local allergen in the gut rather than a systemic reaction. This is in contrast to venom-induced reactions, where the presence of gastrointestinal symptoms (eg, vomiting) would constitute anaphylaxis (as the gut is remote from the site of allergen exposure).18 There is also no consensus as to what constitutes persistent gut symptoms. This distinction is important, as many food-induced reactions are classified as anaphylaxis in the USA (and therefore should be treated with epinephrine), but not in the UK and Australia, something important to consider when making comparisons to US data.

2. Fatal (and in our experience, near-fatal) anaphylaxis reactions often present as acute bronchoconstriction without any other symptoms being
Epinephrine can either be injected using a needle–syringe (using an epinephrine auto-injector; EAI) or an intramuscular (IM) syringe. Epinephrine given by IM injection into the outer mid-thigh is very safe and starts to work within minutes. Epinephrine is the first-line treatment for anaphylaxis according to all guidelines. It has both α-sympathomimetic and β-sympathomimetic actions, causing peripheral vasoconstriction, increased cardiac output and bronchodilation; importantly, it is the only drug that inhibits the further release of inflammatory mediators from mast cells and basophils.

Myth 4: ‘Epinephrine is dangerous’
Epinephrine given by intramuscular injection into the outer mid-thigh is very safe and starts to work within minutes. Epinephrine can either be injected using a needle–syringe (using 1:1000 epinephrine, which results in a lower volume, less painful
Review

**Figure 1** Allergy Action Plan from the British Society for Allergy and Clinical Immunology/Royal College of Paediatrics and Child Health (available at www.sparepensinschools.uk or http://www.bsaci.org/about/pag-allergy-action-plans-for-children).

Injection than if using 1:10 000) or by autoinjector device (eg, Emerade, EpiPen, Jext). Where an autoinjector is used, note that both EpiPen and Jext are only available in 150 µg and 300 µg doses, which means that the 300 µg is effectively an underdose in someone over 30 kg (this may explain why some patients require a second epinephrine dose). Younger children should be transitioned to a 300 µg dose when their body weight is >25 kg, and some centres advocate doing so from 20 kg. Around 10%–20% of patients report transient effects including pallor, anxiety, palpitations, dizziness and headache (although these symptoms may also be due to the reaction and/or the patient’s own endogenous epinephrine production).
Epinephrine is underused in the treatment of anaphylaxis, both prehospital and in emergency departments. Further intramuscular doses of epinephrine should be administered in the event of persisting respiratory or cardiovascular symptoms. Epinephrine can and should be repeated after 5 min; the administration of other medication such as antihistamines or steroids must not cause delay or distraction, as these are not first-line (or even second-line) treatments for anaphylaxis.

Myth 5: ‘Antihistamines can be used to treat anaphylaxis initially; epinephrine is only needed if symptoms worsen’

Histamine is only one of many inflammatory mediators released during anaphylaxis. Oral antihistamines take around 30 min for onset of effect; intravenous chlorphenamine has a faster onset, but can cause hypotension. Antihistamines are not effective against anaphylaxis: their prophylactic use during controlled immunotherapy does not prevent anaphylaxis, and any apparent response during acute management of reactions is most likely due to the patient’s own endogenous epinephrine. Antihistamines have now been relegated to third-line therapy in international guidelines; their use is limited to the relief of cutaneous symptoms and should never delay the administration of epinephrine or fluid resuscitation during patient stabilisation.

Myth 6: ‘Corticosteroids prevent delayed or biphasic reactions in anaphylaxis’

Historically, corticosteroids have been used to prevent protracted and biphasic reactions (the latter defined as a recurrence of symptoms within 72 hours of initial anaphylaxis, without re-exposure to the trigger). However, this has never been tested in a randomised clinical trial; more recent evidence has cast doubt over their efficacy. A recent systematic review and meta-analysis included 27 studies with 4114 anaphylaxis cases, of whom 192 (4.7%) had biphasic reactions. Steroid administration did not affect the likelihood of a late phase reaction (OR 1.52, 95% CI 0.96 to 2.43). In fact, there was a non-significant trend towards increased risk, although this is probably because steroid use was more common with severe reactions. Biphasic reactions were more common where hypotension was present at initial reaction (OR 2.18, 95% CI 1.14 to 4.15), but this is unusual in food-induced anaphylaxis. The median time to onset of biphasic symptoms was 11 (range 0.2–72) hours, that is, 50% of reactions occurred >11 hours after initial reaction. This is relevant because current guidance from the National Institute for Health and Care Excellence recommends patients over 16 years are observed for 6–12 hours after anaphylaxis (children under 16 should be admitted). In reality, it is generally accepted that prolonged observation may not be required following a straightforward reaction in someone who already has a comprehensive

Figure 2 Acute management of anaphylaxis. (A) Current UK Resuscitation Council algorithm. (B) Suggested amended algorithm by the authors, which emphasises the need for further doses of intramuscular epinephrine in the event of ongoing anaphylaxis symptoms and incorporates a low-dose epinephrine infusion protocol used widely in Australia and Spain (with permission, from Brown SG, Emerg Med Australas. 2006;18:155–69).
MANAGING CHILDREN AT RISK OF ANAPHYLAXIS

Although research in ongoing into potential treatments for food allergy, the mainstay of management remains dietary avoidance and provision of a management plan/rescue medication in the event of accidental reactions.

Myth 7: ‘Only children who have had anaphylaxis need an epinephrine autoinjector’

Allergy skin prick tests and/or allergen-specific IgE blood tests do not predict reaction severity, and anaphylaxis can occur in patients with high, low and even negative tests. A recent European Consensus concluded that it is very difficult if not impossible to accurately predict who is at risk of severe anaphylaxis: a number of risk factors acting together are involved (figure 3).9

Clearly someone with previous anaphylaxis is at risk of subsequent anaphylaxis. However, most children who present with anaphylaxis as their initial reaction do not experience further anaphylaxis. Ewan and Clark followed up 747 allergic children, of whom 220 had initial anaphylaxis to peanut/tree nuts; 25% had further accidental reactions over a median 3-year follow-up, with only one experiencing further anaphylaxis.33 Other studies report a higher rate of anaphylaxis in those with initial mild reactions. In a UK survey of 969 young people attending allergy clinics, 48% had experienced an accidental reaction in the previous year, with 245 (25%) having anaphylaxis.6 However, the occurrence of anaphylaxis is likely to depend on a number of factors, including dose or level of exposure34 (figure 3). In a unique study of 89 children with suspected peanut allergy, Wainstein et al demonstrated that up to 75% will have anaphylaxis if exposed to sufficient peanut at challenge.35 Thus, lack of prior anaphylaxis is more likely due to insufficient exposure rather than some inherent lack of predisposition. Importantly, there are no data indicating that allergic reactions get worse with each subsequent exposure. Nor is there any evidence to suggest that anaphylaxis risk ‘runs in the family’.

Various risk factors for severe anaphylaxis have been proposed, based on limited case series of fatal anaphylaxis. Interestingly, food-induced anaphylaxis is most common in the 0–5 age group, but death from anaphylaxis in this age group is rare.2 Teenagers and young adults appear to have an age-dependent predisposition towards severe outcomes, which cannot be easily explained by risk-taking behaviours.2 Asthma is considered a risk factor; however, in the UK Fatal Anaphylaxis Registry, 22% of cases did not have a prior diagnosis of asthma.2 Around 50% of children with food allergies have asthma: the vast majority will never have a severe allergic reaction, thus asthma has poor predictive value for severe reactions (although this does not negate the imperative to improve asthma control in food-allergic individuals as a means of reducing risk).9

Delays in treating with epinephrine are a risk factor for fatal outcome10 36: it is this, as well as our inability to predict severe reactions, which drives the provision of epinephrine autoinjectors. A summary of recent guidelines on who should be prescribed autoinjectors is summarised in table 1. Health-care professionals must consider the patient/family preference: if prescription boosts patient confidence and allows them to lead a less restrictive life, then autoinjectors should be part of the management plan. However, this requires actual carriage: the autoinjectors need to be available at all times, otherwise prescription is pointless.

Controversy exists over the number of autoinjectors to be prescribed. The BSACI and ASCIA in general recommend one device (for school children, one device for home and a second for school, while in the USA, physicians will generally prescribe two devices).10 17 In 2014, following an extensive review of epinephrine autoinjectors prompted by a coronial inquest, the Medicines and
Healthcare products Regulatory Agency (MHRA) issued guidance that individuals at risk of anaphylaxis should carry two epinephrine autoinjectors at all times due to ‘uncertainties about the site of drug delivery and the speed of epinephrine action within the body’, which, together with device misuse or malfunction, might result in a second dose being needed. The BSACI guidance (issued after the 2014 statement) recommends a single device on the basis that one dose is usually effective for most reactions. The MHRA recently reiterated its policy, in line with new Department of Health guidance for school children at risk of anaphylaxis. The MHRA review also addressed a concern that in some individuals (predominantly adolescent and adult women), the needle length in some autoinjectors may be insufficient to deliver an intramuscular (rather than subcutaneous) injection, although data to inform this are limited. At the current time, prescribing practice remains divided among UK healthcare professionals.

Myth 8: ‘Epinephrine autoinjectors are overprescribed and overused in anaphylaxis’

Autoinjectors are underused to treat anaphylaxis in the community. In a study of infants aged 3–15 months with anaphylaxis (US definition), epinephrine was administered in under one-third, most commonly because the caregiver did not recognise the severity of reaction or the autoinjector was not available. In a UK study, only 16.7% of young people used an autoinjector to treat anaphylaxis, the most common reason being they did not recognise that the reaction needed treatment with epinephrine. A Scottish study among adolescents with previous anaphylaxis reported a number of barriers to the effective use of autoinjectors, including failure to recognise anaphylaxis, uncertainty and fear over how and when to use the autoinjector, and lack of carriage due to size/design. In the USA, these issues have led to some management plans (by FARE) offering the suggestion to use an epinephrine autoinjector for all reactions regardless of severity, but this remains controversial and is not accepted as standard practice among many healthcare professionals.

Myth 9: ‘Prescription of an epinephrine autoinjector in isolation is life-saving’

Optimal management of food-allergic patients and treatment of anaphylaxis has many facets and is not limited to a prescription for an epinephrine autoinjector. Improving patient/carer knowledge on the recognition and treatment of anaphylaxis, and addressing the complex psychosocial dimensions of allergic emergencies, form the cornerstone of successful anaphylaxis management. One-third of fatalities in the UK occur despite timely epinephrine administration. Epinephrine autoinjectors potentially buy valuable minutes while an emergency medical response is summoned. Such devices need to be prescribed as part of a comprehensive management plan, which includes advice on dietary avoidance and on when to administer epinephrine. Patients and their families need to be told to use their autoinjector in the event of any respiratory symptoms, where anaphylaxis might cause the irascible, irrespective of severity. Patients with asthma may not realise the importance of this; they may perceive mild wheezing following food allergen exposure as equivalent to their routine symptoms. Patients and their families need to be provided with more...
constructive strategies and support’ than merely being told to ‘use your pen’.42

The BSACI management plans are available for download online (http://www.bsaci.org/about/pag-allergy-action-plans-for-children) and were recently updated to take into account changes in UK-wide legislation allowing the use of ‘spare’ epinephrine autoinjectors in schools. The BSACI plans, correctly completed, meet the requirements of the legislation and UK healthcare professionals are encouraged to use these plans where possible. Further information is available online (www.sparepensinschools.uk).

Correct positioning of the patient is important in anaphylaxis,8 23 something highlighted in MHRA guidance. Case series have highlighted the potential for a change in posture (eg, from sitting or lying to standing) to trigger decompensation and fatal event in some patients. Lying the patient supine with the lower limbs elevated will increase venous return and cardiac output. Patients with respiratory symptoms can be allowed to sit if this improves comfort, with their lower limbs elevated where possible. Sudden standing must be avoided, and patients with anaphylaxis must not be instructed to walk to a first aid room to use their autoinjector, as this may increase the risk of death.8 23 36

**Myth 10: ‘MMR and influenza vaccination are contraindicated in patients with previous anaphylaxis to egg’**

A common misconception is that the influenza and measles, mumps, rubella (MMR) vaccines cannot be given to egg-allergic children, in particular those with previous anaphylaxis. The MMR vaccine is grown in chick fibroblast cell lines and does not contain detectable egg protein. Egg allergy, however severe, is not a contraindication.43 Influenza vaccines are prepared from viruses grown in embryonated hen’s eggs and can contain very low levels of ovalbumin. However, recent data have confirmed that both injected and intranasal forms of the vaccine are safe in egg-allergic children, including those with previous anaphylaxis.23 36 43 The ‘Green Book’36 and US guidelines44 now advise that these vaccines can be administered in primary care (or, in the case of the intranasal vaccine, schools), with the usual precautions taken for any vaccination. The only exception is those with previous life-threatening reactions to egg requiring intensive care, in whom there is little safety data (such reactions to egg are vanishingly rare); in any event, these patients (and their carers) may be better reassured if the vaccine is administered in hospital.

In contrast, yellow fever vaccine does contain small amounts of egg protein and has been reported to trigger anaphylaxis in some egg-allergic individuals. Desensitisation protocols for use in specialist centres are available,47 but administration is complicated by the need for such centres to be authorised to provide WHO certification. Currently, the authors are aware of only one UK paediatric centre (Evelina Hospital, London) where WHO certification can be issued following successful administration.

**CONCLUSIONS**

Anaphylaxis is a severe, potentially life-threatening systemic allergic reaction, which constitutes a clinical emergency. Common misconceptions regarding anaphylaxis are summarised in **table 2**. Prompt assessment and management are essential, as delays in treatment are associated with fatal outcomes. Anaphylaxis is primarily a clinical diagnosis: patients/carers and health professionals must be appropriately trained to recognise and institute appropriate treatment with intramuscular epinephrine, as part of a comprehensive management plan. Epinephrine is the first-line treatment for anaphylaxis, but is underused. Changes in posture have been documented as a trigger for decompensation and fatal anaphylaxis. New management plans incorporating this advice, and which allow the use of ‘spare’ autoinjectors in schools, are available from the BSACI and via www.sparepensinschools.uk website.

**Correction notice** This paper has been corrected since it was published Online First. The BSACI(RCPCH) has just updated its Allergy Plans and so figure 1 has been replaced with the new plan.

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**Patient consent** Not required.
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