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. Recent data suggest that the incidence is increasing, particularly to food. The lifetime prevalence of anaphylaxis is estimated to be between 0.5% and 2%. 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. Many reactions are not treated appropriately (discussed below), yet fatal anaphylaxis is (fortunately) a rare event, with a case fatality rate under 0.001%. Severe anaphylaxis, however, is unpredictable, and severe reactions may mimic more mild anaphylaxis reactions in the first instance. Delay in appropriate treatment almost certainly contributes to fatalities. 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. 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. 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. 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 (e.g., 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), 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. 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 (e.g., vomiting) would constitute anaphylaxis (as the gut is remote from the site of allergen exposure). 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
Myth 3: ‘No trigger for the reaction is identified, therefore it is not anaphylaxis’
Anaphylaxis is a **clinical** diagnosis. The most common trigger in young people is food: symptoms typically begin within 15–30 min of exposure and progress rapidly. Other triggers, such as medication or insect stings, are far less common in children. In around 20% of cases, no trigger is identified; this is known as idiopathic anaphylaxis. Many such reactions will be due to undisclosed or ‘hidden’ food allergens. Identifying the culprit allergen can be challenging and referral to an allergy specialist is advised: a thorough review of the circumstances surrounding the reaction including a detailed dietary history supported by ingredient lists is likely to be required. Of note, if a child is consuming a food regularly without problem, it is unlikely to be the cause. This might seem obvious, but dietary manipulation along these lines are often recommended by non-specialists for idiopathic, non-anaphylaxis reactions presenting with only skin symptoms: such episodes are generally due to immune activation (often viral-triggered) rather than allergen exposure.

**The most common food trigger for fatal anaphylaxis in children in the UK is milk, followed by peanut and tree nuts.** While there is broad public recognition of the risks posed by nuts, cow’s milk allergy is often perceived as being less severe. However, milk allergy persists into school age and is often associated with other coexisting atopies (such as asthma) and more severe reactions, particularly in the 30%–40% of milk-allergic children who are unable to tolerate milk in well-baked foods (such as biscuits or cakes). Such exposure often results in delayed reactions which mimic asthma; under such circumstances, it may not be obvious that the child has been exposed to milk. Therefore, **always consider anaphylaxis in someone with a known food allergy who has sudden breathing difficulty.**

Laboratory tests (such as mast cell tryptase, MCT) may support a diagnosis of anaphylaxis, but these are not specific for anaphylaxis, nor are results available quick enough to impact on acute management. Measuring MCT may be helpful where the cause of the reaction is unclear: a serum sample should be collected within 15–180 min of symptom onset, with a further convalescent sample at least 6 hours later. However, MCT is often not raised in food-induced reactions, even in the most severe and fatal reactions. In a Canadian study, only 19.2% of children presenting with anaphylaxis had elevated MCT; even with severe reactions (cyanosis, hypoxia, respiratory arrest, hypotension, loss of consciousness), MCT was only raised in 50% of cases. A negative MCT does not, therefore, rule out anaphylaxis.

**ACUTE MANAGEMENT**
**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
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.\(^6\)\(^ {10}\)\(^ {21}\)\(^ {23}\)\(^ {28}\) 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.\(^24\)\(^\) An alternative summary of anaphylaxis treatment, consistent with national and international guidelines, is shown in figure 2B.

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.\(^30\) A recent systematic review and meta-analysis included 27 studies with 4114 anaphylaxis cases, of whom 192 (4.7%) had biphasic reactions.\(^31\) 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).\(^32\) In reality, it is generally accepted that prolonged observation may not be required following a straightforward reaction in someone who already has a comprehensive history of severe reactions.
Review

MANAGING CHILDREN AT RISK OF ANAPHYLAXIS

Although research is 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 exposure (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.34 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 outcome.10 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. Healthcare 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

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Figure 3 Risk factors for severe reactions. Reproduced with permission from Dubois et al.34 BHR, bronchial hyperresponsiveness; NSAID, non-steroidal anti-inflammatory drugs; OIT, oral immunotherapy; EMS, emergency medical services.
Factors to be considered as part of the risk assessment on whether to prescribe epinephrine autoinjectors

| UK (BSACI) | Europe (EAACI) | Australia (ASCIA) | Evidence |
|------------|----------------|-------------------|----------|
| Previous history | Anaphylaxis and at risk of ongoing exposure | Anaphylaxis | Anaphylaxis and at ongoing risk of exposure | Previous anaphylaxis indicates potential for future reactions, although risk of fatal anaphylaxis remains low.1 15 |
| | Mild reaction to ‘trace’ amount of allergen | Mild reaction to ‘trace’ amount of allergen | Generalised urticaria alone without anaphylaxis due to insect sting in adults | No evidence that individuals who react to very low amounts of allergen are more likely to experience severe anaphylaxis.9 |
| | History of cofactors (eg, exercise) impacting on reaction severity | Venom allergy in adults with systemic symptoms | | Children with local or generalised skin rashes only to venom are at very low risk of anaphylaxis with subsequent stings.10 40 |
| Allergen-specific risk factors | High-risk allergens, for example, nuts | High-risk allergens, for example, nuts | High-risk allergens, for example, nuts, seafood | In the UK, cow’s milk and peanut/tree nuts are the most common cause of fatal anaphylaxis.2 |
| Patient-specific risk factors | Teenager/young adult | Teenager or young adult with a food allergy* | Teenagers and young adults with food allergy | Data suggests a specific vulnerability to severe outcomes from food-induced allergic reactions in teenagers and young adults.1 2 |
| | Food allergy* to high-risk allergens (eg, nuts) and other risk factors (eg, asthma) | Food allergy* and coexisting unstable or moderate–severe, persistent asthma | Food allergy* and coexisting unstable or moderate–severe, persistent asthma | Poor asthma control increases risk of severe reactions; most cases of fatal food-induced anaphylaxis have asthma, but asthma itself is poorly predictive of severe outcomes as it is so prevalent in food-allergic individuals.5 |
| | Raised baseline serum tryptase | Underlying mast cell disorders (eg, systemic mastocytosis or raised baseline serum tryptase) | Underlying mast cell disorders (eg, systemic mastocytosis or raised baseline serum tryptase) | Underlying mast cell disorders are a known risk factor for venom and idiopathic anaphylaxis.10 17 48 |
| | Limited access to emergency medical care, for example, remote location, social factors | Remote from medical help | Limited access to emergency medical care, for example, remote location, foreign travel | Remote access to medical support causes delays in emergency treatment. |

Factors in bold are specified as ‘absolute’ (EAACI) or ‘recommended’ (ASCIA) indications.

* Excluding pollen food allergy syndrome.

ASCIA, Australasian Society of Clinical Immunology and Allergy; BSACI, British Society for Allergy and Clinical Immunology; EAACI, European Academy of Allergy and Clinical Immunology.

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.17 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,18 in line with new Department of Health guidance for school children at risk of anaphylaxis19. 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.40 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.6 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.41 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.42 It must be noted that anaphylaxis morbidity/mortality is no lower in the USA compared with UK and Australia where epinephrine is only recommended for reactions with respiratory or cardiovascular involvement.16

**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.4 41 One-third of fatalities in the UK occur despite timely epinephrine administration.30 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 be the cause, 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...
Table 2  Common misconceptions in anaphylaxis and what current evidence reveals

| Common ‘myths’ | What evidence tells us |
|----------------|-----------------------|
| **Myth 1: Anaphylaxis often results in death** | Anaphylaxis can be life-threatening, but the majority of reactions do not result in severe outcomes |
| **Myth 2: There are no hives so it can’t be anaphylaxis** | Cutaneous symptoms (most commonly urticaria or ‘hives’) are absent in around 10% of anaphylaxis reactions |
| **Myth 3: No trigger for the reaction is identified, therefore it is not anaphylaxis** | In around 20% of cases, no trigger is identified; this is known as idiopathic anaphylaxis |
| **Myth 4: Epinephrine is dangerous** | Epinephrine given by intramuscular injection into the outer mid-thigh is very safe |
| **Myth 5: Antihistamines can be used to treat anaphylaxis initially; epinephrine is only needed if symptoms worsen** | There is insufficient evidence to support the use of corticosteroids prevent delayed or biphasic reactions in anaphylaxis |
| **Myth 6: Corticosteroids prevent delayed or biphasic reactions in anaphylaxis** | It is very difficult—if not impossible—to accurately predict who is at risk of severe anaphylaxis |
| **Myth 7: Only children who have had anaphylaxis need an epinephrine autoinjector** | Autoinjectors are underused to treat anaphylaxis in the community |
| **Myth 8: Epinephrine autoinjectors are overprescribed and overused in anaphylaxis** | Optimal management of food allergic patients and treatment of anaphylaxis has many facets and is not limited to a prescription for an epinephrine autoinjector |
| **Myth 9: Prescription of an epinephrine autoinjector in isolation is life-saving** | Both vaccines are safe to administer in egg-allergic children, including those with previous anaphylaxis to egg |

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 decomposition 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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