



Anaphylaxis: Clinical concepts and research priorities

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Abstract

Anaphylaxis is a severe immediate-type hypersensitivity reaction characterized by life-threatening upper airway obstruction bronchospasm and hypotension. Although many episodes are easy to diagnose by the combination of characteristic skin features with other organ effects, this is not always the case and a workable clinical definition of anaphylaxis and useful biomarkers of the condition have been elusive. A recently proposed consensus definition is ready for prospective validation. The cornerstones of management are the supine position, adrenaline and volume resuscitation. An intramuscular dose of adrenaline is generally recommended to initiate treatment. If additional adrenaline is required, then a controlled intravenous infusion might be more efficacious and safer than intravenous bolus administration. Additional bronchodilator treatment with continuous salbutamol and corticosteroids are used for severe and/or refractory bronchospasm. Aggressive volume resuscitation, selective vasopressors, atropine (for bradycardia), inotropes that bypass the β -adrenoreceptor and bedside echocardiographic assessment should be considered for hypotension that is refractory to treatment. Management guidelines continue to be opinion- and consensus-based, with retrospective studies accounting for the vast majority of clinical research papers on the topic. The clinical spectrum of anaphylaxis including major disease subgroups requires clarification, and validated scoring systems and outcome measures are needed to enable good-quality prospective observational studies and randomized controlled trials. A systematic approach with multicentre collaboration is required to improve our understanding and management of this disease.

Key words: *aetiology, anaphylaxis, classification, diagnosis, drug therapy, physiopathology.*

Introduction

Anaphylaxis is a severe reaction within the spectrum of generalized immediate-type hypersensitivity, characterized in its most critical form by life-threatening

upper airway obstruction bronchospasm and hypotension. Most episodes are easy to diagnose clinically; however, case definition has been problematic for researchers and clinicians alike and acute management is based largely on extrapolation and anecdote.¹ The

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present paper aims to provide a clinically focused review of reaction features (including case definition), pathophysiology and ED management. Clinical research priorities will also be proposed.

Clinical presentation

Recognition

Table 1 provides a summary of the clinical features of anaphylaxis, derived from retrospective studies and personal observation of reactions induced under experimental conditions.²⁻⁷ When closely observed, virtually all patients experiencing anaphylaxis in adult studies are noted to have some skin manifestation of systemic mediator release.^{4,6} However, these features can be transient and difficult to detect; skin features were not recorded in up to 20% of cases in some retrospective studies.^{5,7} Absent or overlooked skin features might

occur more often in the paediatric population where respiratory features predominate,⁷ and in adults sudden cardiovascular collapse with circulatory shock and cardiac arrest might occur prior to any other skin manifestation.^{3,5,6} Around 50% of deaths do not display diagnostic features of anaphylaxis at post-mortem.⁸ Anaphylaxis must be considered as a differential for any acute-onset respiratory distress, bronchospasm, hypotension or cardiac arrest.

Differential diagnosis

The many causes of hypotension should be considered in shocked patients. Isolated rashes/urticaria and angioedema should not be assumed to be anaphylaxis. Rashes might instead represent various forms of acute and chronic urticaria or post-viral syndromes, and isolated angioedema is frequently angiotensin-converting enzyme-induced, or due to hereditary or acquired C1 esterase deficiency. These might require specific inves-

Table 1. Clinical features of anaphylaxis²⁻⁷

General
Anxiety, malaise, weakness, feeling of impending doom
Paresthesia (hands, lips/mouth and tongue), dry mouth, abnormal taste in the mouth
Cutaneous, subcutaneous and mucosal tissues
Nasal congestion, rhinorrhoea, conjunctival erythema, tearing
Itch – often localized to the palms or soles, groin, armpit, face/eyes or nose
Flushing (erythema, typically most noticeable on the face, neck and upper trunk), urticaria (typical skin wheals and erythema), periorbital oedema
Angioedema of the tongue, lips, ears, neck and other areas of the body
Gastrointestinal/abdominal
Nausea, vomiting, abdominal pain including uterine contraction pain, diarrhoea
Respiratory
Upper airway oedema causing difficulty speaking and/or swallowing, hoarse voice, stridor
Chest or throat tightness/pain, dyspnoea, tachypnoea, bronchospasm, cough
Hypoxaemia/central cyanosis
Cardiovascular
Tachycardia associated with vasodilation and relative reduction in blood pressure, particularly diastolic blood pressure
Systolic hypotension with either tachycardia or a relative bradycardia
Diaphoresis and circulatory failure (capillary refill >2 s) with pallor and/or peripheral cyanosis
T inversion and/or ST depression in multiple leads (with or without chest pain), arrhythmias
Cardiogenic shock and pulmonary oedema†
Cardiac arrest
Neurological
Throbbing headache
Dizziness/presyncope, visual loss, loss of consciousness, incontinence‡
Confusion§

†Cardiogenic shock and pulmonary oedema appear to be uncommon, and are probably more likely to occur in those with underlying cardiac disease. ‡These features are usually, but not always, associated with hypotension and poor cerebral perfusion.⁵ §Confusion appears to have a strong association with hypoxaemia rather than hypotension.⁵

tigation to determine the underlying cause. Scombroid fish poisoning might appear identical to anaphylaxis, and dystonic reactions (causing an apparent 'swelling of the tongue' and stridor) and panic attacks (causing dyspnoea) can be confused with anaphylaxis. Conversely, however, clinicians must take care not to erroneously diagnose dyspnoea and bradycardia as anxiety.

Case definition

Relevant definitions from the World Allergy Organization (WAO) are presented in Box 1.⁹ Although a useful concept, the WAO definition of anaphylaxis can be problematic as the term 'life-threatening' has different meanings to different doctors. A recent meeting in the USA sponsored by the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) worked on a consensus definition to satisfy epidemiological, research and clinical needs.¹⁰ The definition from that meeting is presented in Box 2. Three alternate criteria are provided.

The first of these describes a typical and unequivocal episode of anaphylaxis with typical skin features and evidence of airway or cardiovascular involvement, which might be diagnosed *irrespective* of a history of allergen exposure. The second and third criteria recognize the potential for reactions without prominent skin features, reactions with prominent gastrointestinal features that have a significant correlation with severe anaphylaxis,⁵ and reactions that present only with hypotension. However, other conditions might present in similar ways; therefore, these criteria also require exposure to a likely or known allergen to reduce the likelihood of 'false positive' diagnoses. Although this is a sensible probability-based approach to case definition, emergency guidelines must not be rigidly linked to it, because life-saving treatment might be withheld or delayed if allergen exposure is not identified. In 15–32% of severe reactions a likely cause is not identified.^{4,5,7} Thus, it is important to initiate treatment for any suspected case of anaphylaxis with cardiovascular or respiratory compromise, even if consensus diagnostic criteria are not met.

Box 1. Definitions according to the World Allergy Organization⁹

Hypersensitivity	Objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons
Allergy	Hypersensitivity initiated by specific immunological mechanisms (antibody or cell mediated). When other mechanisms can be proven, the term non-allergic hypersensitivity should be used. Cell-mediated allergy produces a delayed response to allergen
Atopy	A personal and/or familial tendency to become sensitized and produce IgE antibodies in response to ordinary exposures of commonly encountered environmental allergens. This results in the development of asthma, rhinoconjunctivitis or eczema. Note that an allergic IgE response on its own does <i>not</i> define the condition of atopy
Anaphylaxis	A severe, life-threatening generalized or systemic hypersensitivity reaction. This might be subclassified as <i>allergic</i> (e.g. mediated by IgE, IgG or immune complexes) or <i>non-allergic</i> . Allergic anaphylaxis mediated by IgE antibodies is referred to as <i>IgE-mediated anaphylaxis</i>

Box 2. A consensus working definition of anaphylaxis derived from the Second NIAID/FAAN Symposium¹⁰

A reaction might be classified as anaphylaxis if it satisfies any one of the following three definitions:

1. Acute-onset illness (minutes to hours) with involvement of skin and/or mucosa (*generalized* hives, pruritus or flushing, swollen lips and/or tongue) AND AT LEAST ONE OF THE FOLLOWING:
Respiratory compromise (dyspnoea, wheeze, bronchospasm, stridor, hypoxaemia) OR
Hypotension or associated symptoms of end-organ dysfunction (e.g. collapse, syncope, incontinence)
2. Two or more of the following within minutes to a few hours of exposure to a *likely* allergen for that patient:
Skin or mucosal involvement as above
Airway compromise as above
Hypotension or associated symptoms as above
Persistent gastrointestinal symptoms (e.g. cramping abdominal pains, vomiting)
3. Hypotension within minutes to several hours following exposure to a *known* allergen for that patient
Absolute: 0–1 year <70 mmHg; 1–10 years <(70 + 2 × age) mmHg; ≥11 years <90 mmHg
Relative: ≥30% drop from baseline

Patterns of organ involvement

Some patients are atopic, particularly those with food allergy, and tend to present first during childhood or adolescence. Lethal reactions to foods occur at a median age of 22–24 years, usually have a dominant respiratory component (bronchospasm and hypoxia), and appear to be mostly confined to people with a history of asthma.^{11–13} Because of this dominant respiratory pattern, children, who are more likely to present with food allergy, appear less likely than adults to exhibit skin features.^{4,8} However, the retrospective ED chart reviews on which this observation is based are difficult to interpret because of the potential for incomplete documentation, presentation bias with children being more likely to present with milder illness, and diagnostic overlap between asthma and anaphylaxis.

In contrast, lethal reactions to insect venoms and various drug (iatrogenic) causes occur at median ages of 55–67 years, with cardiovascular collapse more likely to be the sole reaction feature.¹² Venom allergy is more common in the greater than 35 years old age group, in whom the risk of a severe (hypotensive) reaction is also higher when a reaction occurs.¹⁴ Unlike food allergy, the incidence of atopy in venom and drug allergic people appears to be no greater than in the general population although, as with food allergy, a history of asthma might predispose to respiratory compromise.^{14,15}

Severity grading

A number of severity grading systems based on clinical reasoning rather than statistical analyses of the relationships between individual reaction features are reviewed in detail elsewhere.¹⁶ Approaches range from simple descriptions of key symptoms^{17,18} to complex 'two or more' rules,¹⁹ sums of scores,²⁰ or physiological parameters that might not be available when assessing a reaction that has occurred outside a monitored environment.⁴ Weighting cardiovascular compromise above

respiratory compromise is a common approach but is not supported by observations that death might be due to respiratory compromise, cardiovascular compromise or both.¹²

A recent retrospective analysis of 1149 reactions using multivariate analysis found that confusion, collapse, unconsciousness and incontinence were strongly associated with hypotension and hypoxia whereas diaphoresis, vomiting, presyncope, dyspnoea, stridor, wheeze, chest/throat tightness, nausea, vomiting and abdominal pain had weaker although significant associations. A three-tiered grading system constructed using these data correlated well with adrenaline usage (Table 2). It should be noted that this is a grading system for allergic reactions in general, with only the moderate and severe grades representing anaphylaxis as defined above.⁵

Causation

Aetiologies are grouped as either *allergic* or *non-allergic*, with use of the term 'anaphylactoid' now discouraged.⁹ Most reactions are to foods, medications and insect venoms, and are *immunoglobulin E (IgE)-mediated allergic anaphylaxis*. Triggering mechanisms other than IgE have been proposed; however, many of these remain poorly defined, often with conflicting evidence as to whether specific antibodies play a role.^{21–25} A list of common causes, derived from a recent Tasmanian study, is presented in Table 3. Causes will vary according to differing allergens in the community. For example, in southern mainland Australia and Tasmania, ant of the genus *Myrmecia* (bulldog ants and jumper ants) are common causes of anaphylaxis,^{14,26} but in north-eastern mainland Australia, greenhead ants (*Rhytidoponera metallica*) and paper wasps (*Polistes* and *Ropalidia* spp.) become more important.²⁷

In most studies, roughly equal proportions of reactions are due to insect venoms, medications, foods and unidentified causes. We now recognize that exposure to

Table 2. Grading system for generalized hypersensitivity reactions (from Brown 2004⁵)

Grade	Defined by
1 Mild (skin and subcutaneous tissues only)†	Generalized erythema, urticaria, periorbital oedema or angioedema
2 Moderate (features suggesting respiratory, cardiovascular or gastrointestinal involvement)	Dyspnoea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain
3 Severe (hypoxia, hypotension or neurological compromise)	Cyanosis or SpO ₂ ≤92%, hypotension (SBP <90 mmHg in adults), confusion, collapse, LOC or incontinence

†The 'mild' grade does not represent anaphylaxis according to the National Institute of Allergy and Infectious Disease-Food Allergy and Anaphylaxis Network (NIAID-FAAN) definition (Box 2). LOC, loss of consciousness; SBP, systolic blood pressure.

Table 3. Suspected causes of 1149 generalized hypersensitivity reactions presenting to a Tasmanian ED (The Royal Hobart Hospital)⁵

Venomous stings and bites	Ant (mainly the Jack Jumper Ant, <i>Myrmecia pilosula</i>)	165
342 (30%)	Bees (71) and Vespids (16)	87
	Others (11) and unidentified (79)	90
Iatrogenic	Antibiotics, administered orally in	145
250 (22%)	139 (96%), and including penicillins (73), cephalosporins (27) and cotrimoxazole (18)	
	Non-steroidal anti-inflammatory drugs	32
	Narcotics	11
	Radiological contrast	7
	ACE inhibitor†	4
	Vaccine	4
	Others or uncertain	47
Food	Sea food	47
205 (18%)	Nut	46
	Egg	14
	Monosodium glutamate	7
	Kiwi fruit	4
	Others or uncertain	87
Other	Topical or inhaled (not associated	57
61 (5%)	with severe reactions)	
	Exercise-induced anaphylaxis	4
Unidentified		291
291 (25%)		

†Simple angioedema (no other skin or systemic features) due to angiotensin-converting enzyme (ACE) inhibitor was not included; the reactions here included other features of anaphylaxis.

a combination of allergen, infection, physical exercise, psychological stress and/or concomitant medication (particularly α -blockers, β -blockers, angiotensin-converting enzyme inhibitors and non-steroidal anti-inflammatory drugs) might be necessary to provoke a reaction. This concept of *summation anaphylaxis* might explain many 'idiopathic' reactions, as well as many episodes of exercise-induced anaphylaxis.²⁵

Pathophysiology

Effector cells and mediators

A detailed discussion of effector cells and mediators is beyond the scope of the present paper, and can be found elsewhere.^{16,28,29} In the early 20th century, histamine was thought to be the principal mediator of anaphylaxis.³⁰ Since then, a huge range of inflammatory mediators have been implicated in anaphylaxis, including

preformed mediators (histamine, heparin, tryptase, chymase and tumour necrosis factor alpha), mediators newly generated over minutes (platelet-activating factor, prostaglandin D₂, and the sulphidoleukotrienes; leukotriene [LT]-B₄, LT-C₃, LT-D₄ and LT-E₄) and mediators generated over hours (interleukin [IL]-4, IL-5, IL-13 and granulocyte macrophage colony stimulating factor). Activation of the contact system, fibrinolytic and complement cascades has also been described. Although tissue mast cells and circulating basophils play a pivotal role, other cells including eosinophils, platelets, monocytes/macrophages, endothelial cells and antigen-presenting cells have also been implicated. The large numbers of mediators provide for significant redundancy and positive feedback mechanisms by which other effector cells are recruited to release more mediators. This has led to the concept of a 'mast cell-leucocyte cytokine cascade' that initiates, amplifies and perpetuates the allergic response.²⁹

Analysing the roles of these mediators in humans is difficult because of the opportunistic nature of anaphylaxis research, because much of the 'action' occurs locally in the tissue where the reaction is initiated, because the presence of some mediators in serum such as histamine is transient³⁰ and because of technical difficulties assessing the concentrations of some mediators. Variability in mediator release patterns and target organ sensitivities might also complicate interpretation. A single reliable diagnostic serum marker of anaphylaxis has yet to be identified.

Vasodilation, fluid extravasation and smooth muscle contraction

Inflammatory mediators released during anaphylaxis cause a variety of minor but characteristic general, skin and mucosal symptoms as outlined in Table 1. Most pathophysiological effects can be ascribed to vasodilation, fluid extravasation and smooth muscle contraction, leading to major clinical manifestations as summarized in Figure 1. Fluid extravasation causes upper airway obstruction and, in combination with vasodilation, causes a mixed distributive-hypovolaemic shock pattern; circulating blood volume might decrease by as much as 35% within 10 min as a result of extravasation,³ and severe vasodilation resistant to adrenaline has been described in both human case reports³¹⁻³⁴ and animal studies.³⁵ As with severe asthma, lower airway obstruction in anaphylaxis can result from fluid extravasation (mucosal oedema) and mucous plugging as well as smooth muscle contraction (bronchospasm).⁸

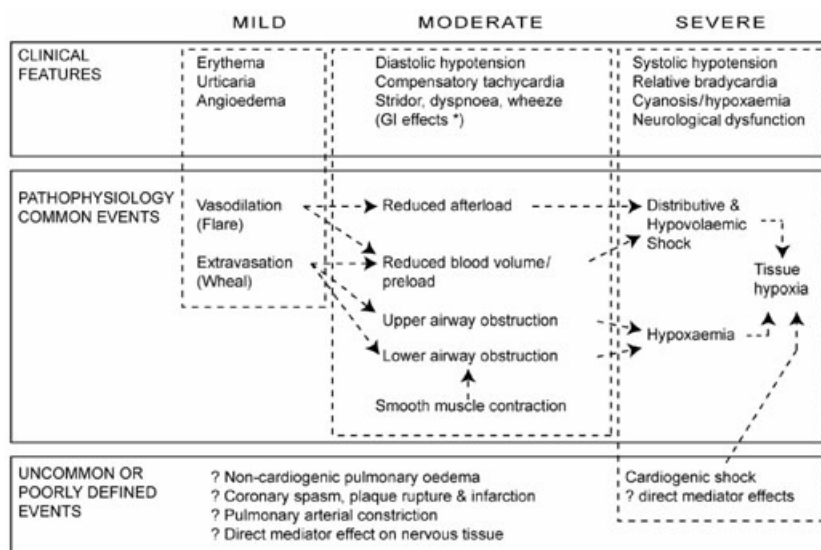


Figure 1. Pathophysiology of anaphylaxis. *Gastrointestinal (GI) effects may be due to mediators acting on nociceptors, smooth muscle contraction, oedema and/or tissue hypoxia.

Smooth muscle contraction also affects gastrointestinal and uterine muscles, sometime resulting in severe abdominal and pelvic pain.

Relative bradycardia

While performing a randomized controlled trial of venom immunotherapy, we observed eight hypotensive reactions, two of which were associated with severe bradycardia and treated with intravenous (i.v.) atropine.³⁶ In every case the sting itself induced tachycardia, but the onset of hypotension was accompanied by a *relative* bradycardia with the heart rate falling as the blood pressure fell. We postulated this to be a neurocardiogenic reflex, triggered by cardiac mechanoreceptors and enhanced by increased levels of mediators known to potentiate this reflex that are also elevated by anaphylaxis.⁶ Bradycardia might also be a non-specific reflex feature of distributive-hypovolaemic shock, with a slower heart rate permitting the heart to fill between contractions; studies of awake mammals have found severe hypovolaemia to be characterized by bradycardia and reduced vascular tone.³⁷

Myocardial dysfunction

As well as being exposed to circulating anaphylactic mediators, the human heart contains a large number of mast cells around cardiac blood vessels and between

myocardial fibres.³⁸ The ability of anaphylactic mediators to depress cardiac contractility in humans has been demonstrated.³⁹ Severe reversible cardiac dysfunction associated with non-specific electrocardiogram changes and normal coronary arteries has been described during human anaphylaxis,^{30,40,41} and pulmonary oedema described as non-cardiogenic has been reported in one large series of reactions in anaesthesia.² We have also observed global ST segment changes in a patient without any cardiovascular instability, suggesting a direct mediator effect.⁶ However, under emergency conditions it can be difficult to determine the cause of pulmonary oedema (cardiogenic *vs* non-cardiogenic), and to quantify the effects of primary cardiac dysfunction as opposed to the effects of poor venous return, pulmonary vasoconstriction and myocardial ischaemia due to low diastolic blood pressure and hypoxaemia. Furthermore, high catecholamine levels might have an adverse effect in the myocardium in susceptible individuals, including significant reductions in cardiac output, ischaemic chest pain and electrocardiogram changes in the absence of coronary artery disease.⁴² Therefore, the contribution of severe 'cardiac anaphylaxis' to morbidity and mortality remains to be defined.

Other effects

Neurological dysfunction is generally regarded to be secondary to hypotension; however, direct mediator

effects cannot be excluded because unconsciousness, stroke and visual loss have been observed without, or preceding the onset of hypotension.^{6,43,44} An allergic acute coronary syndrome has also been proposed based on case reports of acute myocardial infarction beginning within 48 h of an allergic event and proposed as due to mediator-induced vasospasm and plaque ulceration.^{45,46} However, such case reports are inherently selective and might represent chance occurrences.

Therapeutic considerations

Adrenaline

The mast cell-leucocyte cytokine cascade with its redundant and amplifying effects and multiple mediators means that mediator antagonists are unlikely to be therapeutic. This underlies the current emphasis on *physiological* antagonism with adrenaline. Published guidelines emphasize the intramuscular (i.m.) route for adrenaline at a dose of 0.01 mg/kg up to 0.5 mg,^{10,47–49} because anecdotally this seems to work, because it can be given without delay and because it avoids the potentially lethal effects of large i.v. bolus injections.¹² Studies in human volunteers without anaphylaxis indicate that injection should be into the lateral thigh because absorption here appears more reliable than deltoid muscle or subcutaneous injections.^{50,51}

No human studies have been performed to evaluate the bioavailability and optimal dose of i.m. adrenaline during anaphylaxis, and only the i.v. route was used in the two studies that indicate a beneficial treatment effect in reactions characterized by cardiovascular collapse; therefore, i.v. infusion of adrenaline should be considered in this situation.^{3,6} Intravenous infusions might be safer and more efficacious than bolus administration; a study of severe anaphylactic shock in dogs found that the i.m. route is ineffective with a dose of 0.01 mg/kg, whereas noticeable haemodynamic improvements are seen transiently with an i.v. bolus of 0.01 mg/kg and are sustained with an i.v. infusion at 0.19–0.45 µg/kg/min.^{35,52} However, the therapeutic effect in this model was from positive inotropy, with no increases in either systemic vascular resistance or pulmonary arterial wedge pressure. Thus, for severe reactions at the generally recommended doses, adrenaline on its own might not adequately counteract the effects of vasodilation and distributive-hypovolaemic shock.

Posture

It is often forgotten that a blood volume shift to the central compartment can be achieved by the supine position with legs elevated. Conversely, the upright or even sitting position, by enhancing blood pooling in the lower extremities, can be lethal.⁵³

Fluids

Rapid fluid extravasation, combined with maldistribution of blood due to vasodilation, suggests that as much as 50 mL/kg of isotonic crystalloid might be required during initial resuscitation. Indeed, successful management of hypotensive anaphylaxis has been described using volume resuscitation and antihistamines without the use of adrenaline.⁵⁴

Atropine and vasopressors

Although i.v. atropine and potent vasopressors should not be given prominence above fluid resuscitation and adrenaline, they should be considered for severe bradycardia and persistent hypotension, respectively. The absence of a detectable vascular effect of adrenaline in the canine model noted above might represent concentration-dependant difference in α_1 -receptor versus β_1 -receptor activation; higher (but transient) adrenaline concentrations in the i.v. bolus group appeared to have α_1 effects temporarily reversing vasodilation. In more severe reactions, very high infusion rates of adrenaline and/or other vasopressors such as noradrenaline might be required to reverse peripheral vasodilation. Case reports suggest that the α_1 -agonists phenylephrine,³³ metaraminol³² and the pituitary hormone vasopressin can be effective.^{31,34}

Other treatments, comorbidities and concurrent medications

In some cases, severe myocardial depression might be resistant to standard treatment. This might be from underlying cardiac failure, β -blocker treatment⁴⁹ or in some cases due to anaphylactic mediators alone.⁴¹ β -Blockers might also exacerbate bronchospasm. α -Blockers (as well as other vasodilators) can exacerbate anaphylactic vasodilation.^{55,56}

It can be difficult to attribute the relative contributions of profound vasodilation and cardiac dysfunction to circulatory collapse. Therefore, it seems sensible to

use vasopressors in the first instance to treat hypotension that is resistant to adrenaline and fluids, and add glucagon and/or a phosphodiesterase inhibitor if blood pressure does not improve sufficiently or if skin perfusion is poor despite an adequate blood pressure.^{57,58} Urgent bedside echocardiography and invasive monitoring should be considered to guide ongoing management. Mechanical circulatory support (intra-aortic balloon pump) might be required.⁴¹

Antihistamines

H₁ blockade appears to be useful for mild allergic reactions confined to the skin.^{59,60} However, there are no published trials that systematically examine utility during anaphylaxis. Histamine levels peak early then return rapidly to normal despite the persistence of severe physiological compromise,³⁰ suggesting there would be little benefit from antihistamines. One study has found a small benefit of combined H₁ + H₂ blockade over H₁ blockade alone for mild allergic reactions; however, the results are difficult to interpret because a confounder was that adrenaline was administered more frequently in the H₁ + H₂ group.⁶¹ In a canine model, treatment with antihistamines appears to be ineffective in the treatment of anaphylactic shock.⁶² In a rat model, pretreatment with H₁-receptor blockade with or without concurrent H₂-receptor blockade worsens hypotension and decreases survival time,⁶³ whereas combined blockade of histamine, serotonin and nitric oxide slows reductions in blood pressure but does not improve survival.⁶³ These findings are of concern, because they suggest the potential for antihistamines to be harmful in severe reactions, more so because the only parenteral formulation available in Australia (promethazine, Phenergan) is a vasodilator. Until human research clarifies the potential risks and benefits of antihistamines, it would seem prudent in Australia to use restrict antihistamine use to oral, selective non-sedating agents for the symptomatic relief of skin symptoms.

Steroids

Although often used, there are no clinical trials of steroids in the treatment of anaphylaxis, and they do not appear to prevent anaphylactic reactions to antivenom.^{64,65} Current recommendations to consider steroids for patients with bronchospasm are based on an extrapolation from their known utility for the treatment of asthma.⁴⁷

Practical application – assessment and management

Assessment

Anaphylaxis is a dynamic process, so periodic reassessments are important. A severe reaction might not require treatment if improvement occurs by the time of initial assessment. Conversely, life-threatening features might be delayed for an hour or more after the onset of symptoms.¹³ As outlined above, anaphylaxis must be a differential diagnosis for any episode of upper airway obstruction, bronchospasm or hypotension; a careful assessment for erythema (flushing) and other mucocutaneous features might help confirm the diagnosis (Table 1).

Once a diagnosis of anaphylaxis is entertained, an assessment of physiological compromise should be made and recorded. Observations should include heart rate, blood pressure, perfusion/capillary return, SpO₂ breathing air, presence or absence of stridor and/or wheeze, and evidence of increased work of breathing (indrawing and accessory muscle use). This will facilitate an objective assessment of reaction severity. Peak flow measurements and spirometry are generally not performed because they can be unreliable and difficult to interpret as a result of general patient compromise and lack of prior training.

After life-threatening effects have been addressed, a careful assessment is required of possible triggers (especially foods, drugs, stings, physical activity and occupational exposures such as latex), times of exposure, time of reaction onset, and all symptoms and signs. This information, recorded when the memory is fresh, can be invaluable later on. The potential for summation anaphylaxis should be considered. In the case of sting anaphylaxis, be wary of statements as to the species responsible; record a description of the appearance of the offending insect including size and coloration, whether a sting sac was left in the skin (pathognomic for honey bee sting) and circumstances of the sting, for example, brushing against a nest hanging from the eave of a house (paper wasps) or being stung in or near native bushland where bulldog and jumper ants are common.

Management

A variety of consensus treatment guidelines are available.^{10,47–49} A one-page guideline derived from these documents and also the above considerations is presented

in Figure 2. As noted above, a single dose of i.m. adrenaline might not work in some severe reactions. Therefore, Figure 2 encourages rapid progression to an i.v. infusion where there is an immediate life threat. Figure 3 presents an i.v. adrenaline infusion guideline based on our prospectively validated protocol,⁶ with the following changes: (i) the infusion duration has been extended to 90 min after reaction resolution including a 30 min weaning phase, because 7 of 11 people in our study with severe reactions had a recurrence after stopping the infusion at 30 min;⁶ and (ii) a recommendation to reduce the rate after a good response has been obtained because of our unpublished observations that initial infusion rates of 50–100 mL/h (8–17 µg/min) produced a rapid response but, as reaction features resolved, slower rates of 20–50 mL/h (3–8 µg/min) were optimal, with higher rates causing side-effects and lower rates leading to a recurrence of reaction features.

Confirming the diagnosis of anaphylaxis

Not all episodes of anaphylaxis are typical, so the use of serum mast cell tryptase (MCT) assay has been recommended to confirm the diagnosis of anaphylaxis and thus assist long-term management.⁴⁷ However, MCT might increase significantly during anaphylaxis without exceeding the stated upper limit of normal and repeated measurements will increase sensitivity and specificity.⁶⁶ Even using this approach, MCT has a sensitivity of only 70% in the setting of sting anaphylaxis,⁶⁶ and little is known of diagnostic sensitivity in other types of reactions. Thus, a positive result is more useful than a negative one. The degree of elevation of MCT is correlated with the degree of hypotension,⁶⁷ and sensitivity might be poor in predominantly respiratory reactions.

Observation

The time-course of anaphylaxis can be classified as uniphasic, protracted or biphasic.⁶⁸ An observation period is recommended for all patients because the reaction might fail to improve or worsen as the effect of adrenaline wears off (protracted anaphylaxis), and because of the risk of a biphasic reaction. Six retrospective studies report biphasic reaction rates of 4–20%; 18–20% which were often severe in studies of patients admitted to hospital,^{68,69} but only 3–6% and mostly mild in studies that included patients discharged from the ED.^{70–73} Reported intervals from initial treatment to

recurrence ranged from 1 to 72 h.^{68–73} No clinical feature consistently identified patients at risk of a biphasic reaction across all studies; however, risk factors in different studies included an initially severe reaction,^{13,68} initial treatment with larger doses of adrenaline⁶⁹ and the precipitating agent having been ingested.⁶⁸ Expert consensus is that a reasonable length of observation following reaction resolution is 4–6 h in most patients, with more prolonged observation in those with severe or refractory symptoms and in those with reactive airway disease as most fatalities associated with anaphylaxis occur in these patients.¹⁰

Discharge planning

Risk assessment and follow up

Prior to discharge, the risks of repeated allergen exposure and of a severe/life-threatening reaction should be considered. In insect sting allergy, subsequent reactions tend to follow the pattern of previous reactions and are of similar or lesser severity.^{14,17} However, a few people proceed to have more severe reactions when diagnostic stings are administered under controlled conditions.^{36,74} In food allergy, prior reaction severity is less predictive of subsequent severity but asthma appears to be a significant risk factor for lethal and life-threatening reactions.^{11–13}

Overall, this risk of repeated exposure is substantial – one Australian allergy clinic recently reported a risk for repeated reactions during follow up of 57 reactions per 100 patient years, including 10 severe reactions per 100 patient years.⁷⁵ The risks of subsequent exposure can be reduced by careful avoidance (Table 4), but insect stings and highly allergenic foods such as peanuts can be difficult to avoid. It must be remembered that confirmatory diagnostic testing for allergen-specific IgE and allergist follow up are usually required to be certain of the precipitant.

Ideally all patients who have experienced anaphylaxis should be referred to a specialist clinical immunologist/allergist; however, the practical reality is that because of workforce shortages this is difficult in many areas. Allergist review provides the opportunity to:

- Carefully assess risk and the need for adrenaline for self-administration
- Review and re-enforce action plans
- Educate the patient and relatives on how to use and care for adrenaline self-injection devices

EMERGENCY MANAGEMENT OF ANAPHYLAXIS			
1	Stop administration of precipitant, assess reaction severity and treat accordingly: Call for assistance Adrenaline i.m. (lateral thigh) 0.01mg/kg up to 0.5 mg i.v. access Lie flat/elevate legs if tolerated High flow oxygen, airway/ventilation support if needed IF HYPOTENSIVE ALSO: Additional wide bore i.v. access (i.e. 14G or 16G in adults) for normal saline infusion i.v. normal saline bolus 20 mL/kg over 1–2 min under pressure		
2	If there is inadequate response, an immediate life threat, or deterioration: Start an i.v. adrenaline infusion as per hospital guidelines/protocol OR Repeat i.m. adrenaline every 3–5 min as needed <i>And consider also:</i> <table border="0"> <tr> <td style="vertical-align: top;"> Hypotension - Repeat normal saline boluses 10–20mL/kg as needed, up to 50 mL/kg total over the first 30 min - i.v. atropine 0.02 mg/kg if severe bradycardia (minimum dose 0.1 mg). - i.v. vasopressors to overcome vasodilation (vasopressin 10–40 units in adults, or metaraminol 2–10 mg in adults)*. For anaphylactic cardiac arrest, rapid escalation to high dose adrenaline (3–5 mg every 2–3 min) might be effective - i.v. glucagon/phosphodiesterase inhibitors/balloon pump if β-blocked or heart failure: Glucagon dose in adults: load with 1–5 mg over 5 min, followed by 5–15 μg/min* * In children, hypotensive anaphylaxis is very rare, with inadequate experience to provide dosing recommendations </td> <td style="vertical-align: top;"> Bronchospasm - Continuous salbutamol nebulizers or continuous actuations of metered dose inhaler into ventilation circuit if intubated) - i.v. hydrocortisone 5mg/kg 6 hourly followed by oral prednisone 1 mg/kg (max. 50 mg) for 4 days Upper airway obstruction - Nebulized adrenaline (5 mg in 5 mL, i.e. 5 mL of 1:1000) may provide some relief - Prepare for surgical airway </td> </tr> </table>	Hypotension - Repeat normal saline boluses 10–20mL/kg as needed, up to 50 mL/kg total over the first 30 min - i.v. atropine 0.02 mg/kg if severe bradycardia (minimum dose 0.1 mg). - i.v. vasopressors to overcome vasodilation (vasopressin 10–40 units in adults, or metaraminol 2–10 mg in adults)*. For anaphylactic cardiac arrest, rapid escalation to high dose adrenaline (3–5 mg every 2–3 min) might be effective - i.v. glucagon/phosphodiesterase inhibitors/balloon pump if β-blocked or heart failure: Glucagon dose in adults: load with 1–5 mg over 5 min, followed by 5–15 μg/min* * In children, hypotensive anaphylaxis is very rare, with inadequate experience to provide dosing recommendations	Bronchospasm - Continuous salbutamol nebulizers or continuous actuations of metered dose inhaler into ventilation circuit if intubated) - i.v. hydrocortisone 5mg/kg 6 hourly followed by oral prednisone 1 mg/kg (max. 50 mg) for 4 days Upper airway obstruction - Nebulized adrenaline (5 mg in 5 mL, i.e. 5 mL of 1:1000) may provide some relief - Prepare for surgical airway
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3	Observe for an adequate period and arrange appropriate follow up: (i) Observe for a minimum of 4 h after the resolution of all symptoms and signs Take blood for serum mast cell tryptase on arrival, 1 h after arrival and prior to discharge Admit longer (overnight) those with severe reactions, a history of life-threatening reactions or poorly controlled asthma, and those who present late in the evening (ii) Outpatient follow up by a specialist allergist is recommended for all those with moderate–severe reactions, and with mild reactions to food if the patient also has asthma Prior to discharge, discuss allergen avoidance measures (including Medic Alert). ensure that an alert is placed in hospital/practice records/computer system, and ensure that your referral letter/summary contains a detailed record of reaction features & timing, possible precipitants and times of exposure (ii) Arrange for an EpiPen, demonstrate correct use with an EpiPen Trainer and provide a written action plan (http://www.allergy.org.au) if there is a significant risk of re-exposure and outpatient follow up will be delayed		

Figure 2. Guidelines for immediate management of anaphylaxis. i.m., intramuscular; i.v., intravenous.

ADRENALINE INFUSION GUIDELINE FOR ANAPHYLAXIS	
1 PREPARATION	
- Requires continuous physiological monitoring (ECG, SpO₂, BP 3–5 minutely) - Give via an infusion pump through a dedicated line, or piggybacked with anti-reflux valves on all other lines to prevent the adrenaline going back up into another fluid bag instead of into the patient - BEWARE infusions on the same side as a BP cuff; frequent BP measurements may interfere with the infusion - FIRST BAG: 1 mg adrenaline in 100 mL saline = 0.01 mg/mL (1:100 000) i.e. 1 mL/kg/h gives the equivalent of a 0.01 mg/kg dose over 1 h (0.17 µg/kg/min)	
2 INITIATION & ADJUSTMENT	
- Start at 0.5–1 mL/kg/h (30–100 mL/h in adults) depending on reaction severity: Moderate severity: 0.5 mL/kg/h Severe (hypotensive or hypoxic): 1 mL/kg/h - Titrate up or down according to response, aiming for the lowest effective infusion rate Allow for a short elimination half-life; steady state is reached 5–10 min after a change in the infusion rate - Tachycardia, tremor and pallor with a normal or raised blood pressure are signs of adrenaline toxicity: Reduce the infusion rate (if toxicity is severe, stop the infusion briefly before recommencing at a lower rate) - The safe maximum rate of adrenaline infusion is unknown, but is probably <1 µg/kg/min (6 mL/kg/h of the above solution of 1 mg in 100 mL).	
3 DE-ESCALATION AND CESSATION	
- As the reaction resolves, an infusion that was previously therapeutic can start to have toxic effects: Therefore, when features resolve, begin reducing the infusion, aiming for around half the starting rate if possible - 60 min after the resolution of all symptoms and signs, wean the infusion over another 30 min and stop; watch closely for reaction recurrence	

Figure 3. An adrenaline infusion guideline. BP, blood pressure; ECG, electrocardiogram.

Table 4. Allergen avoidance

Likely allergen	Advice
Insect sting	<i>All insects:</i> Wear closed footwear and thick socks when outside <i>Flying insects:</i> Drive with windows closed, full face helmet/neck cover (motorcyclists). Drink from clear glass and watch for bees in drink; honeybees seek any fluid in hot weather, European wasps (yellow jackets) seek the sugar in sweet drinks <i>Paper wasps:</i> Avoid nests hanging from tree branches and eaves of houses <i>Ants (jack jumper, bull dog ant):</i> Have nests around the home and/or school destroyed by a pest exterminator, be careful when sitting down outside (e.g. use a spreadsheet on the ground at picnics) and when passing overhanging bushes on which ants might be foraging
Food	Careful attention to food labelling. Beware takeaway and restaurant foods. Allergic preschool children: remove allergenic foods from the home and preschool environments
Medications	Record alert in medical record and patient information system. Provide a Medic Alert bracelet

- Determine the causative agent by allergen-specific serum IgE testing, skin testing and deliberate food, drug or sting challenge
- Assess allergenic cross-reactivities (important for food and drug allergy)
- Provide allergen avoidance strategies
- Provide venom immunotherapy (desensitization) for insect venom allergic patients.

Venom immunotherapy is highly efficacious for preventing future reactions and improving quality of life.^{36,76–78} For food allergic patients, anti-IgE treatment offers promise.⁷⁹ Referral to an allergist can provide the opportunity for patients to access these and other novel

therapeutic approaches through involvement in clinical trials.

Medical alerts

Entering an alert into computerized clinical information systems and a Medic Alert bracelet are advisable for any patient with drug allergy, to alert health-care workers in the future when the patient is unable to recall or communicate their allergy details. Medic Alert bracelets might have additional benefit for all types of anaphylaxis by encouraging the administration of adrenaline

in future reactions when health-care staff are uncertain of the diagnosis.¹²

Providing self-administered adrenaline

Prescription of an adrenaline self-injection devices (e.g. EpiPen) should be considered after any episode of anaphylaxis as defined in Box 2. Patients experiencing milder reactions might also benefit if they have other risk factors such as asthma and suspected nut allergy, or are living and/or working in remote areas with limited access to emergency care. The complexities and ethical dilemmas of prescribing self-injectable adrenaline have been discussed in detail elsewhere.^{80,81}

Because of the complexities of prescription and education, it is appropriate to defer the prescription of self-injectable adrenaline until review by a specialist allergist. However, where there is limited access to specialty allergist services, ED prescription might be warranted. The prescribing clinician must provide clear instructions on when and how to use, and how to care for the device, and the patient must be educated using a training device (e.g. EpiPen Trainer) to reduce the risk of accidental discharge into the thumb. Adrenaline should be kept at room temperature and not stored in domestic refrigerators (which can freeze) nor kept in a car or other potentially hot place.

A written action plan/instructions *must* accompany self-injectable adrenaline because verbal advice given in the ED is usually forgotten or misinterpreted. See <http://www.allergy.org.au/anaphylaxis/index.htm> for prescription guidelines and to download a written plan developed by the Anaphylaxis Working Party of the Australasian Society of Clinical Immunology and Allergy (ASCIA).

Future research priorities

A number of research priorities were proposed by the Second NIAID-FAAN Symposium.¹⁰ These included prospective human studies of diagnostic criteria, biomarkers of disease, immunopathological features, clinical features, treatment outcomes and natural history of the disease. The symposium recognized the lack of evidence base for virtually all currently recommended treatments. Put simply, we need to conduct prospective human research and clinical trials to move from opinion to evidence-based practice.

From an emergency medicine perspective, the first step will be to validate a definition, disease subclassifi-

cation system and a severity-grading system, so that baseline characteristics can be compared between treatment groups in clinical trials. We also require clinically relevant severity scales for measuring response to treatment, and a better understanding of dichotomous treatment outcomes such as when to check for complete symptom resolution, and the real incidences of protracted and/or biphasic anaphylaxis and adverse events due to treatment. With these pieces of information, a systematic approach will be possible using a combination of prospective assessments of treatment protocols and randomized controlled trials of specific interventions. Because of the relative infrequency and heterogeneous nature of anaphylaxis, a large multicentre collaboration will be required.

Summary

Adrenaline and volume resuscitation remain the cornerstones of management for anaphylaxis; however, our treatment guidelines continue to be opinion- and consensus-based. An effective multicentre collaboration is required to improve our understanding and management of this disease.

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Competing interests

Simon Brown is a section editor for the journal.

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