17.3 Anaphylaxis 3849 Anthony F.T. Brown

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ESSENTIALS The term anaphylaxis describes both IgE immune-mediated re- actions, plus non-IgE immune-mediated, and nonallergic, non- immunologically triggered events. Comorbidities such as asthma or infection, exercise, alcohol, or stress and concurrent medications such as β-blockers and aspirin increase the risk, a concept known as ‘summation anaphylaxis’. Aetiology and pathogenesis—activated mast cells and basophils re- lease preformed, granule-associated mediators and newly formed lipid mediators, and generate cytokines and chemokines. These cause vasodilatation, increased capillary permeability, and smooth muscle contraction, as well as attracting new cells to the area. Positive feedback enhancing mechanisms amplify the reaction in a ‘mast cell—leucocyte cytokine cascade’, although conversely reactions can be self-limiting. Parenteral penicillins, hymenopteran stings, and food are the most common causes of IgE immune-mediated fatal- ities, with radiocontrast media, aspirin, and other nonsteroidal anti- inflammatory drugs most commonly responsible for non-IgE and nonallergic fatalities. Diagnosis—anaphylaxis is a clinical diagnosis and is highly likely when any one of the following three criteria is fulfilled: (1) acute onset (minutes to hours) of an illness with involvement of the skin, mucosal tissues, or both, together with (a) respiratory compromise, or (b) hypotension/syncope/collapse; (2) two or more of the fol- lowing that occur rapidly after exposure to a likely allergen for that patient: (a) involvement of the skin, mucosal tissues, or both, (b) re- spiratory compromise,
(c) hypotension/syncope/collapse, or (d) per- sistent abdominal symptoms; (3) reduced blood pressure after exposure (minutes to hours) to a known allergen for that patient. Clinical features—80–95% of patients with anaphylaxis have cu- taneous manifestations, which assist prompt early diagnosis. These cutaneous or mucosal features alone do not constitute anaphylaxis, which requires multisystem involvement. Deaths occur by hypoxia from upper airway obstruction or severe bronchospasm or by pro- found shock from vasodilatation and extravascular fluid shift. Management—if anaphylaxis is suspected, any potential causative agent (e.g. intravenous drug/infusion) should be stopped immedi- ately. First-line treatment is with (1) adrenaline—0.01 mg/kg to a max- imum of 0.5 mg (0.5 ml of 1:1000 adrenaline) given intramuscularly into the lateral thigh which acts to reverse all the features of anaphyl- axis, as well as inhibiting further mediator release; (2) oxygen—high flow or to maintain adequate oxygen saturations; (3)

intravenous fluid—crystalloids (0.9% saline) at 10 to 20 ml/kg are essential in shock. Other issues relating to immediate management—(1) If skilled as- sistance is available, intravenous adrenaline should be given for se- vere hypotension or critical bronchospasm. If intravenous access is not immediately available, intramuscular adrenaline should be given while intravenous access is obtained. Intravenous adrenaline should be given as a dilute solution (1 mg in 100 ml 0.9% saline, i.e. 10 µg/ ml), slowly (0.5–1.5 ml/min), and titrated against clinical response. Nebulized adrenaline (5 mg, i.e. 5 ml of undiluted 1:1000 adrenaline) can be given while parenteral adrenaline is being prepared, particu- larly for upper airway oedema and bronchospasm. (2) The roles of H1 and H2 antihistamines, steroids, salbutamol, and glucagon are unclear: they should only be considered once cardiovascular sta- bility has been achieved with first-line agents. (3) Patients must be observed for at least 4–6 h after full recovery before discharge from immediate medical care, when a clear plan for further management is essential. Further management—(1) Referral to an immunologist is needed for all those who have had significant, recurrent, unavoidable, or unknown reactions. (2) Patient education is important for successful long-term care. (3) An adrenaline autoinjector should be given to patients with anaphylaxis after known allergen exposure outside of a medical setting, patients with food allergy (particularly to nuts or peanuts), and those in whom the reaction was severe and/or the cause unknown, including idiopathic anaphylaxis. Whoever takes responsibility for prescribing must explain and demonstrate exactly how to use the device provided, educating both the patient and an- other caregiver, particularly in children with anaphylaxis. Introduction The term anaphylaxis, literally meaning ‘against protection’, was introduced by Richet and Portier in 1902 (Fig. 17.3.1). It repre- sents the most catastrophic of the immediate-type, generalized hypersensitivity reactions, and remains the quintessential medical 17.3 Anaphylaxis Anthony F.T. Brown

Section 17 Critical care medicine 3850 emergency. Anaphylaxis following exposure to a trigger can range from mild to severe, gradual in onset to fulminant, and may involve multiple organ systems or cause isolated shock or wheeze. It pre- sents unheralded in otherwise healthy people, and mandates prompt clinical diagnosis based on pattern recognition and probability in the absence of any immediate confirmatory test. All clinicians and other healthcare workers must be familiar with the condition: urgent treatment can prevent death from hypoxia or hypotension. Definition There is no absolute agreement on the classification, diagnosis, or severity grading of anaphylaxis, although published guidelines mostly differ on emphasis rather than content. After convening international consensus meetings in 2004 and 2005, the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) in the United States of America recommended a brief, broad definition as ‘Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death’, with the agreed full definition aimed at capturing more than 95% of clinical cases within three diagnostic criteria (see Box 17.3.1). Criterion 1 should identify at least 80% of anaphylaxis cases, even if the allergic status of the patient and potential cause of the reac- tion may be unknown, as most anaphylactic reactions include skin symptoms. Criterion 2 is anaphylaxis in the absence of cutaneous features such as in children with food allergy, or insect sting allergy, but requires a known allergic history and possible exposure: gastro- intestinal symptoms are included. Criterion 3 captures the rare pa- tient with an acute hypotensive episode after exposure to a known allergen. This inclusive definition for anaphylaxis underlies the up- dated guidelines (Practice Parameters) developed by the American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI), as well as the World Allergy Association (WAO) and European Academy of Allergy and Clinical Immunology

(EAACI) guidelines. These consensus criteria should be used by researchers, until refined by future prospective data. Most recently in 2014, the EAACI Taskforce on Anaphylaxis pro- posed the succinct definition that ‘Anaphylaxis is a severe, potentially life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with life-threatening airway, breathing, or cir- culatory problems and is usually, although not always, associated with skin and mucosal changes’. Severity grading There is no prospectively validated grading system linking the clinical features of anaphylaxis with its severity, urgency, treat- ment, or outcome. One system based on retrospective multi- variate analysis of over 1000 clinically diagnosed generalized hypersensitivity reactions defined three grades (Table 17.3.1). Mild cases were generalized allergic reactions confined to the skin and subcutaneous tissues, but moderate and severe grades with multisystem involvement correlated with the need for adrenaline and represent true anaphylaxis according to the NIAID/FAAN criteria. This grading system should again be used as a starting point by researchers for descriptive purposes, until future pro- spective data refine the criteria. Important clinical categories of anaphylaxis include anaphylaxis related to medications, biologicals, and vaccines, as well as insect Fig. 17.3.1 The discovery of anaphylaxis in 1901. Stamps showing Charles Richet, Paul Portier, and Prince Albert of Monaco. Box 17.3.1 Definition of anaphylaxis: clinical criteria for diagnosis Anaphylaxis is highly likely when any one of the following three criteria is fulfilled: 1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus, or flushing, swollen lips–tongue–uvula), and at least one of the following: • Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxaemia) • Reduced BP or associated symptoms of end organ dysfunction (e.g. hypotonia (collapse), syncope, incontinence) 2 Two or more of the following that occur rapidly (minutes to several hours) after exposure to a likely allergen for that patient: • Involvement of the skin–mucosal tissue (e.g. generalized hives, itch-flush, swollen lips–tongue–uvula) • Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxaemia) • Reduced BP or associated symptoms (e.g. hypotonia (collapse), syn- cope, incontinence) • Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting) 3 Reduced BP after exposure (minutes to several hours) to known allergen for that patient: • Infants and children: low systolic BP (age-specific) or more than 30% decrease in systolic BPa • Adults: systolic BP of less than 90 mm Hg or more than 30% decrease from that person’s baseline BP, blood pressure; PEF, peak expiratory flow. a Low systolic blood pressure for children is defined as less than 70 mm Hg from one month to one year; less than 70 mm Hg + (2 × age) from 1 to 10 years; and less than 90 mm Hg from 11 to 17 years. Reproduced from Journal of Allergy and Clinical Immunology, 117, Hugh A. Sampson et al., Second Symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium, 391–397, 2006 with permission from Elsevier.

 stings, food, anaesthesia, latex exposure, exercise, and idiopathic anaphylaxis (see Table 17.3.2). Aetiology IgE-dependent activation of mast cells and basophils is the key trigger for most cases of antigen-induced, immune-mediated allergic anaphylaxis. An identical clinical syndrome due to non-IgE-mediated, and nonimmunologic mechanisms leads to release of the exact same inflammatory mediators. Non-IgE- mediated and nonimmunologic anaphylaxis (terms preferred by the WAO and EAACI to ‘anaphylactoid’, whose use is dis-couraged) may occur on first exposure to an agent and do not require a period of sensitization. However, immune-mediated anaphylaxis may also occur on first exposure from prior aller- genic

cross-sensitization, as for instance with the neuromus- cular blocking drugs (see later). Drug-induced anaphylaxis Penicillin is the most common cause of drug-induced anaphylaxis, with around 1:500 patient courses having an apparent allergic reac- tion, mostly urticaria alone. True allergic cross-reactivity to ceph- alosporins occurs in around 1–2% of cases and is largely with the first-generation cephalosporins. Aspirin and nonsteroidal anti- inflammatory drugs (NSAIDs) are the next most common cause of drug-induced anaphylaxis. Reactions appear to be medication- specific, as there is no clinical cross-reactivity with structurally un- related NSAIDs. Reactions to chemotherapy drugs including cis-/carboplatinum and doxorubicin are becoming increasingly common as their use increases, as well as reactions to monoclonal antibodies such as omalizumab, cetuximab, and rituximab. In the case of cetuximab this may relate to IgE directed against galactose-α-1,3-galactose (α-gal), an oligosaccharide also responsible for red meat allergy following tick-bite. Skin or serum tests for IgE-mediated reactions are unreliable for most drugs or biological agents, with the exception of penicillins. Short-term desensitization may be possible, supervised by an al- lergy/immunology specialist. Insect sting anaphylaxis Reactions to stings from bees, wasps, and ants of the order Hymenoptera are second only to drug-induced anaphylaxis in adults and occur in up to 3% of the population (<1% of children). Reactions are often rapid and may be fatal within 30 min, mandating the early use of adrenaline, including by self-administration. Insect stings are the most common cause of severe anaphylaxis in patients with indolent systemic mastocytosis. Nonanaphylactic toxic, large local, or late serum sickness-like reactions also occur following a sting (see Chapter 10.4.2). Food-induced anaphylaxis This cause of anaphylaxis is most common in the young, particu- larly following the ingestion of peanuts, tree nuts such as walnuts and pecans, fish, shellfish, milk, eggs, wheat, and soy—the eight most common ingredients that trigger 90% of food allergies, known as ‘The Big-8’, and included among food products that require mandatory labelling. Cross-reactivity with other foods is unpredictable, or re- actions may occur to additives such as carmine, metabisulphite, and tartrazine. Mislabelling and contamination during manufacturing or at home can lead to inadvertent exposure, and associated factors, such as exercise after food, must be recognized (see later). Although fatalities are rare and usually associated with pre- existing asthma, biphasic reactions are seen as symptoms sub- side then recur several hours later. Patient and carer education is Table 17.3.1 Severity grading system for generalized hypersensitivity reactions Grade Defined by

1. Milda (skin and subcutaneous tissues only) Generalized erythema, urticaria, periorbital oedema, or angioedema
2. Moderateb (features suggesting respiratory, cardiovascular, or gastrointestinal involvement) Dyspnoea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain
3. Severeb (hypoxia, hypotension, or neurological compromise) Cyanosis or SpO2 ≤92% at any stage, hypotension (systolic blood pressure <90 mm Hg in adults), confusion, collapse, loss of consciousness, or incontinence a Mild reactions can be further subclassified into those with and without angioedema. b Grades 2 and 3 constitute true anaphylaxis. Reproduced from Journal of Allergy and Clinical Immunology, 114, Simon G. A. Brown, Clinical features and severity grading of anaphylaxis, 371–376. 2004, with permission from Elsevier. Table 17.3.2 Causes of anaphylaxis IgE-dependent, immunologic mechanisms Drugs, chemicals, and biological agents: Penicillins, cephalosporins, sulphonamides, muscle relaxants, vaccines, insulin, thiamine, protamine, γ-globulin, cis-/carboplatinum and doxorubicin, monoclonal antibodies omalizumab/cetuximab/rituximab,

antivenoms, formaldehyde, ethylene oxide, chlorhexidine, semen Foods: Peanuts, tree nuts, shellfish, finfish, milk, eggs, wheat, soy, fruits, vegetables, sesame Hymenopteran sting venom, insect saliva, other venoms: Bees, wasps, ants, hornets, ticks, triatomid bugs, snakes, scorpions, jellyfish Natural rubber latex Environmental: Pollen, horse dander, hydatid cyst rupture Non-IgE-dependent, and nonimmunologic mechanisms Medications and biological agents: Opiates, aspirin, and NSAIDs, ACEI, vancomycin, radiocontrast media, N-acetylcysteine, fluorescein Food additives: Metabisulphite, tartrazine Physical factors: Exercise, cold, heat, sunlight Idiopathic No apparent trigger ACEI, angiotensin-converting enzyme inhibitors; NSAIDs, nonsteroidal, anti-inflammatory drugs. Note: Cross-reactivity occurs, and both IgE-dependent and nonimmunologic reactions may happen with the same agent. Several mechanisms may coexist such as exercise-induced following food. Non-IgE-dependent, and nonimmunologic mechanisms include complement activation, coagulation system activation, kinin production or potentiation, and direct mediator release.

Section 17 Critical care medicine 3852 paramount including carrying an adrenaline autoinjector at all times, with schools in particular prepared to respond with adren- aline in an emergency. Radiocontrast media anaphylaxis Nonimmunologic reactions requiring treatment occur in around 1% of patients receiving iodinated radiocontrast media, with se- vere reactions in less than 0.01%. Patients at greatest risk are those with asthma, cardiovascular disease particularly if on a β-blocker, a previous reaction, and those given ionic high-osmolality contrast. Seafood allergy is not relevant, and subsequent use of gadolinium- based contrast with MRI is safe. Pretreatment with prednisone 50 mg, for instance at 13 h, 7 h, and 1 h before, with or without anti- histamine reduces the frequency of symptoms, but does not prevent a life-threatening reaction. Perioperative anaphylaxis The incidence of perioperative anaphylaxis, both IgE-related and nonimmunologic, ranges from 1:4000 to 1:25 000 cases, with around 4% of reported reactions being fatal. Neuromuscular blocking drugs (muscle relaxants), antibiotics, latex, and induction agents cause most cases of anaphylaxis, but opioids, NSAIDs, colloids, blood products, radiocontrast dye, isosulphan, or methylene blue, methyl methacrylate, chlorhexidine, and protamine may be responsible. Muscle relaxants cause 60% of all reactions, with suxamethonium and rocuronium most commonly responsible. Reactions to suxa- methonium and other relaxants occur in the absence of prior use: this suggests cross-reactivity and renders large-scale preopera- tive testing untenable. Latex-induced anaphylaxis The highest risk group for natural rubber latex allergy includes healthcare workers, children with spina bifida and genitourinary ab- normalities, and occupational exposure. Atopy and cross-reacting fruit allergy are also associated with an increased risk. Reactions follow direct contact, parenteral contamination, or aerosol trans- mission. Patients at known risk must be treated in a latex-free en- vironment with glass syringes and non-latex-containing gloves, stethoscopes, breathing systems, blood pressure cuffs, intravenous tubing, and administration ports. Exercise-induced anaphylaxis Anaphylaxis can occur with a variety of physical activities. Up to 50% of cases are associated with the prior ingestion of a food—food dependent—in the preceding hours, or can follow aspirin/NSAID use, and high pollen level triggers. Prophylactic medication is in- consistently effective and unreliable, unlike with exercise-induced asthma, although reactive episodes themselves are occasional and unpredictable. Idiopathic anaphylaxis This is defined as anaphylaxis in which no discernible causative allergen or inciting physical factor can be identified: most cases occur in adults of whom 50% are atopic, but it is seen in children. Diagnosis is by exclusion including C1 esterase inhibitor deficiency, mastocytosis, and IgE to serum

galactose-α-1,3-galactose (α-gal) following red meat ingestion. Steroid and an H1 antihistamine prophylaxis is essential. Cofactors ‘summation anaphylaxis’ Various cofactors, comorbidities, and concurrent medications in- crease the risk of anaphylaxis, giving rise to the concept of ‘sum- mation anaphylaxis’. These include asthma, severe atopy, exercise, intercurrent infection, cardiac disease, premenstrual status, psycho- logical stress, alcohol, and drugs such as β-blockers, angiotensin- converting enzyme inhibitors, NSAIDs, and, to a lesser extent, angiotensin II blockers. Cofactors are reported in up to 30% of ana- phylactic episodes, and may explain an individual’s unpredictable response to recurrent antigen exposure (see Table 17.3.3). Pathophysiology Mast cells and basophils release inflammatory mediators following binding of multivalent allergen that cross-links surface, high-affinity IgE Fc receptors (FcεRI), or from cell membrane perturbation. This is coupled with mobilization of calcium in the endoplasmic re- ticulum and leads to the release of preformed, granule-associated mediators by exocytosis, or the de novo synthesis of eicosanoid lipid mediators based on arachidonic acid metabolism, and the activation of genes for various cytokines and chemokines. Mast cell and basophil inflammatory mediators The preformed mediators released by mast cells and basophils include histamine, proteases such as tryptase, chymase, and carboxypeptidase A, and proteoglycans such as heparin and chon- droitin sulphate E. Newly synthesized lipid mediators include pros- taglandin D2 and thromboxane A2 via the cyclo- oxygenase pathway, and the leukotrienes LTC4, LTD4, and LTE4 via the 5-lipoxygenase pathway. The cytokines released include TNFα, various interleu- kins such as IL-3, IL-4, IL-5, IL-6, IL-10, IL-13, and IL-16, and granulocyte-macrophage colony-stimulating factor (GM-CSF). The chemokines include platelet activating factor, neutrophil chemo- tactic factor (IL-8), and eosinophil chemotactic factor, plus macro- phage inflammatory protein-1α. Mediator actions Mediators act to induce systemic vasodilatation, coronary artery vasospasm, increased capillary permeability and glandular secretion, smooth muscle spasm—particularly bronchoconstriction—and to Table 17.3.3 Cofactors and risk factors in anaphylaxis Medical conditions Asthma Severe atopy Infection Cardiac disease Mastocytosis Patient dependent Exercise Psychological stress Premenstrual status Drugs / ingestions Alcohol Beta-blockers (β-blockers) ACEI NSAID ARB ACEI, angiotensin-converting enzyme inhibitor; NSAID, nonsteroidal anti-inflammatory drug; ARB, angiotensin II receptor blocker.

 attract new cells such as eosinophils, leucocytes, and platelets to the area. Positive feedback enhancing mechanisms amplify and per- petuate reactions to recruit further effector cells to release increasing amounts of mediators in a ‘mast cell–leucocyte cytokine cascade’ effect. In addition, it appears that severe and/or fatal reactions also re- late not only to the amount of mediators released, but also to the speed of their degradation, for instance in the case of reduced platelet activating factor (PAF) catabolism from lower levels of PAF acetylhydrolase. By contrast, other anaphylactic reactions self-limit, with spontaneous recovery related to endogenous compensatory mechanisms including increased secretion of adrenaline, angio- tensin II, and endothelin 1. Epidemiology The true incidence of anaphylaxis is unknown. Data—which are unreliable with lack of a standard definition—are almost exclu- sively in the form of diverse, retrospective case collections from the emergency department, anaesthetic department, or the allergist/ immunologist’s office. Under-reporting is common due to missed diagnoses, or following spontaneous recovery, prehospital treat- ment, or fatality. However, all the data from western countries show the incidence of anaphylaxis admissions is increasing; for instance, in England and Wales it went up sevenfold between 1992 and 2012. Emergency department anaphylaxis Between 1:439 and 1:1100 presentations of adults to the emergency department are with anaphylaxis, representing up to one adult pres- entation per 3400 population

per year. Anaphylaxis is the cause of about 1:1000 of paediatric emergency department presentations, although generalized allergic reactions in children (without multisystem involvement) are almost 10 times more common than this. A causative agent is found in over 75% of cases of anaphylaxis pre- senting to the emergency department, recognized from a prior re- action or by close temporal association with the onset of symptoms. The most frequent in childhood are food-induced or drug-related, whereas in adults drug-related and hymenopteran stings predom- inate. Respiratory features appear more common in paediatric ana- phylaxis and cardiovascular features in adults. Fatal anaphylaxis Fatalities are rare: less than one per million population per year, with the overall rate remaining stable despite an increase in anaphylaxis admissions, as well as in drug-induced anaphylactic deaths. When they do happen, fatal reactions are rapid, with a median time to car- diorespiratory arrest of just 5 min after parenteral medication (iatro- genic), 15 min for venom, and 30 min following foods. Deaths follow hypoxia in upper airway swelling with asphyxia, bronchospasm, and mucus plugging, and/or shock related to vasodilatation, extra- vascular fluid shift, and direct myocardial depression. Tachycardia is usual in shock, but bradycardia related to a neurocardiogenic, vagally mediated mechanism (Bezold–Jarisch reflex) has occasion- ally been observed. The most common causes include drugs, foods, and insect stings; patients may have had no prior or only a minor previous reaction to the agent. Risk factors for a severe and potentially fatal episode include asthma, cardiovascular disease, peanut or tree nut allergy, and a lack of early treatment. One study found adrenaline was given in only 14% cases prior to cardiopulmonary arrest, and not at all in 38% of fatalities. Clinical features Anaphylaxis characteristically affects fit people and is rarely seen or described in critically ill or shocked patients, other than asth- matics. The speed of onset relates to the mechanism of exposure and the severity of the reaction. Parenteral antigen exposure may cause life-threatening anaphylaxis within minutes, whereas symp- toms can be delayed for some hours following oral or topical exposure. Between 80 and 95% of patients with anaphylaxis have cuta- neous features, which assist prompt early diagnosis. However, alerting cutaneous features may be absent because of prehospital treatment or their spontaneous resolution, be subtle clinically and missed, or the onset of other life-threatening complications such as laryngeal oedema or shock may precede them. Cutaneous or mucosal changes alone do not constitute anaphylaxis, the hall- mark of anaphylaxis being the precipitate onset of respiratory, cardiovascular, gastrointestinal, and/or neurological dysfunction (see Table 17.3.4). Cutaneous and general reactions A premonitory aura, tingling or warm sensation, anxiety, and feeling of impending doom precede generalized erythema, urti- caria with pruritus, and angioedema of the neck, face, lips, and tongue (Fig. 17.3.2). Rhinorrhoea, conjunctival injection, and tearing are seen. Respiratory manifestations Throat tightness and cough precede mild to critical respiratory dis- tress due to oropharyngeal or laryngeal oedema with dyspnoea, hoarseness, stridor, and even aphonia; or related to bronchospasm Table 17.3.4 Clinical features of anaphylaxis Cutaneous Tingling or warmth, erythema (flushing), urticaria, pruritus (itch), angioedema Rhinorrhoea, conjunctival injection, lacrimation Respiratory Throat tightness, cough, dyspnoea, hoarseness, stridor, aphonia Tachypnoea, wheeze, Spo2 ≤92%a, cyanosisa Cardiovascular and neurological Tachycardia (rarely bradycardia), hypotensiona, chest pain, arrhythmias, cardiac arresta Light-headedness, sweating, incontinencea, syncopea, confusiona, comaa Gastrointestinal Odynophagia (difficult or painful swallowing), abdominal cramps, nausea, vomiting, diarrhoea Nonspecific Premonitory aura, anxiety, feeling of impending doom Pelvic cramps Sao2, oxygen saturation (on pulse oximetry). a Indicates severe reaction (see Table 17.3.1).

Section 17 Critical care medicine 3854 with tachypnoea and wheeze. Hypoxia with oxygen saturation less than 92% on pulse oximetry and central cyanosis indicate severe anaphylaxis and the need for immediate treatment (see severity grading in Table 17.3.1). Cardiovascular and neurological manifestations Light-headedness, sweating, syncope, incontinence, or coma may precede or accompany cardiovascular collapse with tachycardia, hypotension, and cardiac arrhythmias. These can appear benign supraventricular rhythms, particularly in children, but with an impalpable pulse. Chest pain may occur due to coronary artery vasospasm from cardiac mast cell release of histamine, leukotrienes and platelet activating factor even in the absence of coronary artery disease, or exacerbate this when it is present or subclinical in the older patient. Cardiovascular involvement during anaphylaxis plays a key nega- tive role in prognosis, irrespective of the additional, well-known side effects of adrenaline on the heart. Gastrointestinal manifestations Difficult or painful swallowing, nausea, vomiting, diarrhoea with soiling, and abdominal cramps may be associated with a severe reaction, but are usually overshadowed by more immediately life- threatening features. Differential diagnosis The protean manifestations of anaphylaxis have a potentially vast differential diagnosis, although the rapidity of onset, accompanying cutaneous features, and relationship to a likely or known potential trigger suggest the diagnosis in most cases, but the following may need to be considered. Wheeze and difficulty breathing—bronchial asthma, cardiogenic pulmonary oedema, foreign body inhalation, irritant chemical ex- posure, and tension pneumothorax are distinguished by the history, comorbidity, and associated presenting features. Light-headedness and syncope—an anxiety or vasovagal reaction need to be considered when there is a history of fearing an actual reaction, or in the context of a painful procedure such as an in- jection or local anaesthetic infiltration. Bradycardia, sweating and pallor without urticaria, erythema, or itch, associated with a brief prodrome and rapid response to the recumbent position favour the diagnosis of a vasovagal reaction. Facial swelling or angioedema—bacterial or viral infections usu- ally cause fever and/or pain, and traumatic or anticoagulant-related bleeding causes recognizable bruising. Angioedema in the absence of urticaria or pruritus can be bradykinin-related due to angiotensin- converting enzyme inhibitor (ACEI), or caused by actual or func- tional C1 esterase inhibitor deficiency. This may be hereditary (HAE), an autosomal dominant condition associated with prom- inent abdominal symptoms and recurrent attacks related to minor stress, or acquired (lymphoproliferative and some connective tissue disorders). Measurement of serum C4 is a rapid and inexpensive screening test, followed by the more specific C1 esterase inhibitor assays to confirm the diagnosis if the C4 is low. Management of a serious attack of HAE is with 20 units/kg C1 esterase inhibitor con- centrate intravenously, or with icatibant 30 mg subcutaneously, a bradykinin 2 receptor (BR-2) antagonist. Flushing—scombroid poisoning following ingestion of spoiled fish, carcinoid syndrome, alcohol-induced and systemic mastocytosis all produce flushing and require differentiation by a careful history and investigation. Other forms of shock—hypovolaemic, septic, cardiogenic, and other forms of shock should all be apparent from the history and examination. These are commonly associated with tachypnoea, but not with the other cutaneous and respiratory features of anaphylaxis. Clinical investigations The diagnosis of anaphylaxis is clinical: no immediate laboratory or radiological test confirms the process, and these must never delay immediate management. Disease progress may be monitored by pulse oximetry, haem- atocrit level (may rise with fluid extravasation), and arterial or venous blood gases (looking for respiratory or metabolic acidosis). Measurement of electrolytes and renal function, blood glucose, chest radiography, and electrocardiogram (ECG) are indicated if there is a slow response to treatment, or when there is doubt about the diagnosis. Mast cell tryptase, histamine, and platelet activating factor Despite

initial promise, mast cell tryptase (MCT) in blood taken from 1 to 6 h after a suspected episode cannot be totally relied upon to diagnose anaphylaxis. It is not elevated consistently above the reference range of 1–11.4 ng/ml, particularly following food allergy or in children, and conversely it may be elevated post-mortem in nonanaphylactic deaths including trauma. However, measuring serial levels, or specific allelic subtypes such as mature β tryptase im- prove diagnostic value. When possible, three MCT samples should be taken: one immediately following resuscitation; the next 1–2 h after symptom onset (but no later than 6 h); the last at 24 h or during convalescence to establish the patient's baseline tryptase level. Fig. 17.3.2 Massive facial and body oedema with cardiovascular collapse in rapid sequence induction-related anaphylaxis, within 2 min of intravenous drug bolus. Picture reproduced with permission.

17.3 Anaphylaxis 3855 Serum histamine levels are impractical to measure as they are unstable and evanescent, only remaining elevated for 30 to 60 min maximum. Urinary histamine metabolites remain raised for sev- eral hours, but their interpretation requires further standardization. Platelet activating factor, chymase, and mast cell carboxypeptidase A3 levels may offer alternative marker profiles in the future. IgE skin testing, in vitro testing, and challenge testing Skin or blood tests for specific IgE antibodies must be done by those trained in their performance and interpretation, ideally about four weeks after the acute episode. Skin prick testing is the more sensitive: standardized extracts should be used with correct technique, supervised by an experienced physician in case of the occasional se- vere reaction. In vitro testing for allergen-specific IgE is less sensitive and depends on clinical correlation and the availability of specific assays. Over 600 different allergens are available for testing with the ImmunoCAP® system, or clinicians may use a radioallergosorbent (RAST) test (see Chapter 5.3). Challenge testing may be particularly useful in the diagnosis of nonimmunologic anaphylaxis, or to verify the clinical rele- vance of positive skin or IgE tests. False positive and false nega- tive reactions do occur, but are much less likely than with skin prick or in vitro testing; supervision by an experienced physician is essential. Immediate treatment A patient with anaphylaxis may present directly to his or her family doctor, or the emergency department, or the reaction may happen in hospital on a ward, in the operating theatre, the radiology depart- ment, and even in the outpatient department. Make certain that an ambulance is called at an early stage for all out-of-hospital anaphyl- actic reactions. Stop any potential causative agent such as an intravenous drug or infusion immediately. Manage the patient in a monitored resuscita- tion area, or bring equipment including at least a pulse oximeter, a noninvasive blood pressure device, and an ECG monitor to them. Obtain a brief history of possible allergen exposure and perform a rapid assessment of the extent and severity of the reaction. Look particularly for signs of upper airway swelling, bronchospasm, or circulatory shock. The first priority is to achieve cardiorespiratory stability by giving adrenaline, oxygen, and fluids with the patient supine. Antihistamines and steroids play no role until this has been achieved, and even then their value is debatable (see Box 17.3.2). Adrenaline Adrenaline is the drug of choice for acute anaphylaxis, whether allergic IgE-mediated or nonallergic. This should be given in all but the most trivial cases, certainly if there is progressive airway swelling, bronchospasm, or hypotension. It has beneficial α-, β1- and β2-adrenergic effects that counteract the profound vasodila- tation, mucosal oedema, and bronchospasm. Equally important is that adrenaline, via β2-adrenergic receptors, triggers a rise in intra- cellular cAMP and thereby inhibits further mast cell and basophil mediator release, thus attenuating the severity of the reaction when given early. Intramuscular adrenaline Intramuscular adrenaline is recommended when anaphylaxis is treated early, is progressing slowly, in the unmonitored patient, or if venous access is difficult or delayed. The dose is 0.01 mg/kg up to

a maximum of 0.5 mg (1:1000 aqueous adrenaline up to a maximum of 0.5 ml), repeated every 5–15 min as necessary. This should be given into the upper outer thigh and may be injected through clothing in an emergency, including when self-administered prehospital using an EpiPen® or other autoinjector. Intramuscular adrenaline is su- perior to subcutaneous, and the vastus lateralis muscle in the thigh is preferred to the arm deltoid muscle. Safe and practical intramuscular adrenaline doses in children are 0.3 mg (0.3 ml of 1:1000 aqueous adrenaline) for children aged 6– 12 years and 0.15 mg (0.15 ml of 1:1000 aqueous adrenaline) for chil- dren aged less than six years (Working Group Resuscitation Council UK, 2008). Intravenous adrenaline Intravenous adrenaline is only ever needed if there is rapidly progressive vascular collapse with shock, imminent airway ob- struction, or critical bronchospasm. It should only be given by practitioners experienced in its use, with continuous ECG moni- toring. It must be given with extreme care, suitably diluted, slowly, and titrated to response to avoid potentially lethal complications such as cardiac arrhythmias, myocardial ischaemia, and cerebro- vascular accident. The initial intravenous dose is 0.75–1.5 µg/kg (i.e. 50–100 µg) given slowly over up to 5 minutes depending on the rapidity and severity of the patient's decline, with the dose repeated according to response. Although 1:10 000 adrenaline containing 100 µg/ml is readily available (e.g. as a Minijet preparation), it is difficult to give slowly enough (10 µg/min) for intravenous use. An infusion of adrenaline containing 1 mg in 100 ml 0.9% saline (10 µg/ml) can be delivered at 30–90 ml/h (5–15 µg/min) and titrated to response, con- tinuing for up to 60 min after the resolution of all symptoms and signs of anaphylaxis, then weaning over the next 30 min and stop- ping while watching closely for any recurrence. Box 17.3.2 Initial treatment of anaphylaxis • Stop delivery of any potential causative agent • Call for help • Give adrenaline 0.01 mg/kg intramuscularly into lateral thigh, to max- imum 0.5 mg (0.5 ml of 1:1000 adrenaline) — May be repeated every 5–15 minutes — Alternatively, use the patient's EpiPen® or other autoinjector if readily available—may be given through clothing • Lay supine (or elevate legs) for shock • Give high flow oxygen • Insert large-bore intravenous cannula (14 G or 16 G) and give crystal- loid fluid bolus of 10–20 ml/kg Failure to respond or rapid deterioration • Start adrenaline infusion 1 ml (1 mg) of 1:1000 adrenaline in 100 ml normal saline at 30–90 ml/h (5–15 µg/min) titrated to response — Institute continuous ECG monitoring — Give adrenaline faster in cardiopulmonary collapse/arrest. • Consider assisted ventilation and endotracheal intubation by a skilled doctor, which may be extremely difficult

Section 17 Critical care medicine 3856 Nebulized adrenaline (5 mg, which is 5 ml of undiluted 1:1000 adrenaline) can be given while parenteral adrenaline is being pre- pared as just described, particularly for upper airway oedema and bronchospasm. Oxygen and airway patency Give oxygen by face mask to all patients, aiming for an oxygen sat- uration above 93%. Place the patient supine, preferably with the legs elevated to optimize venous return in shock. Elevate the head and torso if respiratory distress is prominent or worsened. Call urgently for skilled airway assistance if there are signs of impending airway obstruction such as worsening stridor or hoarseness, or rapidly pro- gressive respiratory failure with tachypnoea and wheeze. Cyanosis and exhaustion indicate imminent respiratory arrest, but sedative or muscle relaxant drugs should never be given un- less the physician is trained in the management of the difficult airway. Endotracheal intubation and mechanical ventilation are extremely challenging. Create a surgical airway via the crico- thyroid membrane as a last resort, but before hypoxic cardiac ar- rest occurs. Fluid replacement A large-bore intravenous cannula should be inserted as soon as possible in patients showing signs of shock to give an initial fluid bolus of 10–20 ml/kg 0.9% saline, with up to 50 ml/kg needed in total to

counter the massive intravascular fluid shifts and peripheral vaso- dilatation that occur in minutes with anaphylactic shock. There are no outcome data favouring colloids over crystalloids. Second-line treatment Once oxygen, adrenaline, and fluids have been given to optimize the cardiorespiratory status and tissue oxygenation, the following drugs may be administered in a support role. Recommendations differ, and in the absence of any evidence base their use is largely extrapo- lated from success in other diseases. Their preparation or use must never delay the prompt administration of adrenaline. H1 and H2 antihistamines There is only weak evidence to support the use of antihista- mines, which should be reserved for the symptomatic relief of skin symptoms such as urticaria, mild angioedema, and prur- itus, although the Resuscitation Council (UK) recommends chlorphenamine 10 mg intramuscularly or (given slowly) intravenously to counter histamine-mediated vasodilation and bronchoconstriction. They must never be relied upon as sole therapy in significant anaphylaxis. Side effects of sedation, con- fusion, and vasodilatation can be troublesome, particularly when given parenterally. The combination of an H2 antihistamine with an H1 antihistamine is better at attenuating the cutaneous manifestations of a generalized allergic reaction than an H1 antagonist alone. However, there are no data in severe anaphylaxis and their combined use remains contro- versial. Choose a nonsedating H1-antihistamine on discharge (e.g. cetirizine 10 mg or loratadine 10 mg), both once daily, if the patient intends to continue working or driving a vehicle (see discharge oral medication). Corticosteroids As with the antihistamines, there are no placebo-controlled trials to confirm the effectiveness of steroids in anaphylaxis, despite their many theoretical benefits on mediator release and tissue responsive-ness. Most clinicians give prednisone 1 mg/kg (up to 50 mg) orally or hydrocortisone 1.5–3 mg/kg intravenously, particularly in pa- tients with airway involvement and bronchospasm, based on their important role in asthma. It is also thought that steroids prevent a biphasic reaction with recrudescence of symptoms following re- covery, but again supporting data are unconvincing, although they are essential in the management of recurrent idiopathic anaphylaxis. Salbutamol, glucagon, and atropine Nebulized salbutamol can be given in addition to adrenaline for re- sistant bronchospasm, which has the advantage of familiarity. Patients taking β-blockers are prone to very severe or treatment- refractory anaphylaxis. Glucagon should be given if adrenaline has been ineffective, 1–5 mg intravenously, followed by an infusion at 5–15 μg/min titrated to response. This raises cAMP by a nonadren- ergic mechanism, but may cause nausea and vomiting. Some patients with anaphylactic shock develop bradycardia re- sistant to adrenaline, possibly mediated by a neurocardiogenic vagal reflex. Atropine 0.6 mg intravenously up to 0.02 mg/kg has been suc-cessful in this situation. Vasopressors Vasopressors such as noradrenaline, metaraminol, phenylephrine, and vasopressin have anecdotally been reported as treatments for hypotension resistant to initial adrenaline and fluid therapy. As with intravenous adrenaline, these agents should only be given by those experienced in their use. Methylene blue Methylene blue, a competitive inhibitor of guanylate cyclase, at a dose of 1.5–2.0 mg/kg may counter resistant, nitric oxide-medi- ated vasodilatation particularly related to platelet activating factor. However, in turn it has occasionally caused anaphylaxis itself. Observation Most anaphylactic reactions are uniphasic and respond rapidly and completely to treatment. However, some patients develop pro- tracted reactions with an incomplete response to adrenaline, or deteriorate on attempted weaning from adrenaline. Such patients with unstable vital signs should be monitored and admitted to an intensive care facility. Biphasic anaphylaxis Patients who relapse after apparent complete resolution of all their initial symptoms and signs are described as having biphasic ana- phylaxis, which is reported in less than 1 to 20% of cases. It is un- known if this is predisposed to or caused by more severe presenting features, delayed or inadequate doses of adrenaline, or the failure to

give steroids. However, the risk of a biphasic response means that patients with systemic anaphylactic reactions, including all those who have received adrenaline, must be observed for at least 4–6 h after apparent full recovery. Those with a more prolonged reaction,

17.3 Anaphylaxis 3857 oral allergen exposure, reactive airways disease, or cardiac disease should be kept under close watch a little longer (8–10 h) because deaths from anaphylaxis occur in this group. Observation is safely performed in the emergency department, if a suitable holding area exists: ECG monitoring is not essential. Ongoing management All patients should be given a letter to take home detailing the nature and circumstances of the anaphylactic reaction, the treatment given, and the suspected causative agent(s). Before discharge, the need for take-home medication, an adrenaline autoinjector, and an allergy/ immunology referral must be considered (see Table 17.3.5). Oral medication Although there are no good data to support or refute their use, it is common practice to prescribe a two- or three-day discharge supply of combined H1 and H2 antihistamines plus oral steroids to pre- vent early relapse. Consider cetirizine 10 mg or loratadine 10 mg once daily, ranitidine 150 mg every 12 h, and prednisolone 50 mg once daily in adults with predominant cutaneous features such as urticaria following a generalized allergic reaction, or in those with bronchospasm. Adrenaline autoinjector The quandary of who to prescribe an adrenaline autoinjector to, and what to write in an action plan, is well described. As a guide, an adrenaline autoinjector should be given to a patient with ana- phylaxis after known allergen exposure outside of a medical setting, patients with food allergy (particularly to nuts or peanuts), and those in whom the reaction was severe and/or the cause unknown, including idiopathic anaphylaxis. Various autoinjectors are available in the United Kingdom and Europe including EpiPen®, Jext®, Emerade®, and Anapen® (latter under review in the United Kingdom). These autoinjector pens typically contain a single dose of 0.3 mg (300 µg) of adrenaline for adults, and 0.15 mg (150 µg) for children, with some manufacturers also producing a 0.5 mg (500 µg) adult device. They are approved for self-administered intramuscular use, although they are not interchangeable as their delivery technique differs, and inadequate needle length has caused concern particularly in the obese. The Auvi-Q® currently only available in the United States, was devel- oped as a ‘smart’, credit-card sized device with visual and audio prompts plus a retractable needle. Attitudes vary as to whether the emergency physician or general practitioner should initiate adrenaline autoinjector use, rather than waiting for specialist allergy/immunology review. However, who- ever takes responsibility must explain and demonstrate exactly how to use the device, and educate both the patient and another care- giver, particularly for children. Both need to be able to recognize the symptoms and signs of anaphylaxis and be prepared to actually use the autoinjector, particularly if distant from a healthcare facility. Recipients must be reminded that self-injectable adrenaline has a relatively short shelf life of between 18–24 months, and be shown how to look after it. Also as up to 30% patients will require more than one dose of adrenaline, this raises the need for two autoinjectors to be provided at a time. Allergy/immunology referral Disappointingly, few patients who suffer an episode of anaphyl- axis are referred for specialist allergy/immunology follow-up. Referral should be mandatory for anyone prescribed an adrenaline autoinjector device, and for patients following a wasp or bee sting suitable for immunotherapy, suspected food-induced, drug- in- duced, or exercise-induced anaphylaxis, and those with severe reac- tions without an obvious trigger. To assist the allergist/immunologist it is useful to ask the patient to write a brief diary of events in the 6–12 h preceding the reaction, particularly when the cause was un- clear. This should include all foods ingested, drugs taken (including nonproprietary), cosmetics used, and activities performed outside as well as indoors. Later recall of events will be flawed unless docu- mented

contemporaneously. Prevention Education A written anaphylaxis action plan suitable for the patient, carer, or school (in children) is essential, particularly for anyone given an adrenaline autoinjector. Patients must understand the nature and cause of the reaction, how to recognize anaphylaxis, and the importance of carrying an adrenaline autoinjector at all times. Individualized antigen elimination measures such as hymenopteran avoidance must be explained, with information on hidden or un- expected sources of antigen such as salicylate in over-the-counter preparations, trace food elements such as nuts, and possible cross- reactions to unrelated substances. Also, make certain patients are on optimal therapy for any coexistent asthma or severe atopy, and appropriate cardiovascular medication (see next). It is sensible to recommend that the patient wears an alert bracelet such as the MedicAlert® following a severe reaction that may recur with sufficient severity to prevent them from giving a history, par- ticularly highlighting drug or vaccine allergy to avoid inadvertent iatrogenic exposure. Table 17.3.5 Discharge checklist following anaphylaxis Adrenaline autoinjectora EpiPen®, Jext®, Emerade® Anapen® Auvi-Q® Oral medication 2–3 day supply Allergy/immunology referral Include comprehensive description of acute event Education+ Anaphylaxis Action Plan Allergen avoidance Optimize other management Coexistent asthma/atopy Appropriate cardiovascular therapy (avoid β-blocker / ACEI) Patient alert Discharge summary Printed allergy warning MedicAlert® bracelet a Available in 0.15 mg, 0.3 mg, or 0.5 mg (some) intramuscular dose; +, provide information in writing; ACEI, angiotensin-converting enzyme inhibitor.

Section 17 Critical care medicine 3858 A variety of web-based resource material is now available, including from the British Society for Allergy and Clinical Immunology (http://www. bsaci.org), the Anaphylaxis Campaign (http://www.anaphylaxis.org. uk), the European Academy of Anaphylaxis and Clinical Immunology (http://www.eaaci.org), the American Academy of Allergy, Asthma & Immunology (http://www.aaaai.org), and the American College of Allergy, Asthma & Immunology (http://www.acaai.org). Pretreatment There is no convincing justification for pretreatment. In particular, the practice of giving prophylactic corticosteroids and/or antihis- tamines to reduce the risk of a severe iodinated contrast media reaction during radiological procedures is neither reliable, nor sup- ported by the literature, and should be abandoned. Skin testing and short-term desensitization Skin testing should be considered in certain clinical circumstances, such as when penicillin is considered essential but there is a history of possible penicillin allergy. If positive, it can be followed by short- term desensitization over several hours, with increasing doses at 15 min intervals under strict medical control in a monitored area. There are well-tried desensitization regimes for other β-lactams and sulphonamides, and some that are empirically derived for a var- iety of other antimicrobials, chemotherapeutic drugs including the platins, and the monoclonal antibodies. Long-term desensitization (immunotherapy) Venom immunotherapy (VIT) hyposensitization is reserved for Hymenoptera venom in wasp and bee allergy because these reac- tions may become life-threatening and yet are preventable in over 90% of cases. Patients with asthma or on a β-blocker or angiotensin- converting-enzyme (ACE) inhibitor require careful risk–benefit evaluation. Therapy needs to be continued at increasing intervals for at least three to five years. Drug and allergen avoidance Wherever possible give drugs orally or, if intravenously, administer slowly. Avoid drugs known to predispose to reactions in allergic pa- tients, particularly aspirin, NSAIDs, and ACE inhibitors, as well as β-blockers. Patients at risk of recurrent anaphylaxis with hyperten- sion or ischaemic heart disease should ideally not take β-blockers. This may need discussion with the patient’s other specialists to be certain that the overall risk–benefit favours medication change if the patient is already taking a β-blocker, and care should be taken not to

substitute an ACE inhibitor. Patients should be advised to reduce the chance of allergen ex- posure risk by destroying nearby wasp nests and removing al- lergenic foods from the house, also to avoid insect sting with appropriate clothing and certain foods by always checking the manufacturer's label. Areas of uncertainty and future developments Progress in anaphylaxis research is hampered by the lack of a univer- sally accepted definition, or an agreed grading system for severity. Prospective data collection, preferably in multiple sites, is essential to improve the evidence base and allow validation of assessment, treatment, and follow-up protocols. Particular areas that need elucidating include which symptoms or signs most reliably pre- dict the risk of severe anaphylaxis; which laboratory test(s) could be employed to confirm and ideally quantify the severity of an ana- phylactic reaction; what predicts a biphasic reaction; the true role of steroids and antihistamines; and finally whether novel treatments such as anti-IgE therapy in peanut allergy, oral or sublingual im- munotherapy for other food allergy, or even sublingual adrenaline for self-medication will prove effective and acceptable. FURTHER READING Guidelines and practice parameters Campbell R, et al. (2014). Emergency department diagnosis and treat- ment of anaphylaxis: a practice parameter. Ann Allergy Asthma Immunol, 113, 599–608. Lieberman P, et al. (2015). Anaphylaxis - a practice parameter update 2015. Ann Allergy Asthma Immunol, 115, 341–84. Muraro A, et al. (2014). Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy, 69, 1026–45. Sampson HA, et al. (2005). Symposium on the definition and man- agement of anaphylaxis: summary report. J Allergy Clin Immunol, 115, 584–91. Sampson HA, et al. (2006). Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol, 117, 391–7. Scolaro R, et al. (2017). Australian and New Zealand anaesthetic al- lergy group perioperative anaphylaxis investigation guidelines. Anaesth Intensive Care, 45, 543–55. Simons FER, et al. (2011). International Consensus on (ICON) ana- phylaxis. World Allergy Organisation J, 7, 9. Simons FER, et al. (2011). World Allergy Organization guidelines for the assessment and management of anaphylaxis. J Allergy Clin Immunol, 127, 593.e1–e22. Simons FER, et al. (2015). World Allergy Organization anaphyl- axis guidelines: 2015 update of the evidence base. World Allergy Organization J, 8, 32. Truhlar A, et al. (2015). European Resuscitation Council Guidelines for Resuscitation 2015 Section 4. Cardiac arrest in special circum- stances. Resuscitation, 95, 148–201. Working Group of the Resuscitation Council (UK) (2008). Emergency treatment of anaphylactic reactions—guidelines for healthcare pro- viders. Resuscitation, 77, 157–69. Reviews and overviews Brown SG (2004). Clinical features and severity grading of anaphyl- axis. J Allergy Clin Immunol, 114, 371–6. Brown SG (2006). Anaphylaxis: clinical concepts and research prior- ities. Emerg Med Australas, 18, 155–69. Brown SG, Mullins RJ, Gold MS (2006). Anaphylaxis: diagnosis and management. Med J Aust, 185, 283–89. Dhami S, et al. (2014). Management of anaphylaxis: a systematic re- view. Allergy, 69, 168–75. Sicherer S, Sampson H (2018). Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention and manage- ment. J Allergy Clin Immunol, 141, 41–58. Simons FER, Sheikh A (2013). Anaphylaxis: the acute episode and be- yond. BMJ, 346, f602.

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