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REVIEW ARTICLE

Current management of anaphylaxis

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The term anaphylaxis is used to describe both IgE, immune-mediated reactions and non-allergic, non-immunologically triggered events. Co-morbities such as asthma or infection, exercise, alcohol or stress and concurrent medications such as beta-blockers, angiotensin converting-enzyme inhibitors (ACEI) and aspirin increase the risk of anaphylaxis occurring. The pathophysiology involves activated mast cells and basophils releasing preformed, granule-associated mediators, and newly formed lipid mediators, as well as generating cytokines and chemokines. These cause vasodilatation, increased capillary permeability and smooth muscle contraction, and attract new cells to the area. Positive feedback mechanisms amplify the reaction, although conversely reactions can self-limit. Parenteral penicillin, hymenopteran stings and foods are the most common causes of IgE, immune-mediated fatalities, with radiocontrast media, aspirin and other non-steroidal anti-inflammatory drugs most commonly responsible for non-allergic fatalities. Deaths are rare but do occur by hypoxia from upper airway asphyxia or severe bronchospasm, or by profound shock from vasodilatation and extravascular fluid shift. Oxygen, adrenaline (epinephrine) and fluids are first-line treatment. Adrenaline (epinephrine) 0.01 mg/kg to a maximum of 0.5 mg (0.5 mL of 1:1000 adrenaline) i.m. in the upper lateral thigh acts to reverse all the features of anaphylaxis, as well as inhibiting further mediator release. Crystalloids such as normal saline or Hartmann's solution at 10-20 mL/kg are essential in shock. The role of H_1 and H_2 antihistamines, steroids and glucagon is unclear. They should only be considered once cardiovascular stability has been achieved with first-line agents. Discharge may follow observation from four to six hours after full recovery. A clear discharge plan, and referral to an allergist for all significant, recurrent, unavoidable or unknown stimulus reactions are essential. Patient education is important to successful, long-term care. [Emergencias 2009;21:213-223]

Key words: Anaphylasis. Shock. Antihistamines.

Introduction

The term anaphylaxis literally meaning "against protection" was introduced by Richet and Portier in 1902[1]. It represents the most catastrophic of the immediate-type generalized hypersensitivity reactions. Anaphylaxis following exposure to a trigger presents in a dynamic continuum from mild to severe, gradual in onset to fulminant, and may involve multiple organ systems or cause isolated shock or wheeze. It presents unheralded in otherwise healthy people, and mandates prompt clinical diagnosis based on pattern recognition and probability, in the absence of any immediate confirmatory test. It remains the quintessential medical emergency, that clinicians and other health care workers both pre- and in-hospital must be familiar with this, as urgent treatment averts death from hypoxia or hypotension.

Method

A Medline™ and Embase™ search was performed from 1966-June 2008 using the search terms 'anaphylaxis', 'anaphylactic shock', 'anaphylactoid reaction', 'generalised allergic reaction', 'angioedema' and truncated versions of these words. Only English language papers were included. The highest levels of research data, where they existed, were used. Books and book chapters were selected from common emergency medicine large textbooks from America, Australasia and the UK.

Table 1. Definition of anaphylaxis. Clinical Criteria for Diagnosis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula).
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxaemia).
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula).
   b. Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxaemia).
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*.
   b. Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline.

PEF, Peak expiratory flow; BP, blood pressure. *Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year; less than (70 mmHg + [2 x age]) from 1 to 10 years; and less than 90 mmHg from 11 to 17 years. Reproduced with permission from Journal of Allergy and Clinical Immunology[5].

Definitions

Surprisingly, there is no international agreement on the classification, diagnosis or severity grading of anaphylaxis[2]. Recent guidelines from the Working Group of the Resuscitation Council (UK) used the European Academy of Allergology and Clinical Immunology Nomenclature Committee broad definition that "Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction", characterized by rapidly developing life-threatening airway and, or breathing and, or circulation problems usually associated with skin and mucosal changes[3].

The National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) in the USA, after convening international meetings in 2004 and 2005, had meanwhile recommended a brief, broad definition as "Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death"[4,5]. Their full definition aimed at capturing more than 95% clinical cases within three diagnostic criteria was more complex (see Table 1). Criterion 1 was to identify at least 80% of anaphylaxis cases, even if the allergic status of the patient and potential cause of the reaction was unknown, as the majority of anaphylactic reactions include skin symptoms. Criterion 2 was anaphylaxis in the absence of cutaneous features such as in children with food allergy, or insect sting allergy, but required a known allergic history and possible exposure. Gastrointestinal symptoms were included. Criterion 3 was proposed to capture the rare patient with an acute hypotensive episode after exposure to a known allergen[4,5]. This inclusive definition for anaphylaxis should be used by researchers until refined by future prospective data.

Severity grading

Not only is there no international agreement on the precise definition of anaphylaxis, there is also no prospectively validated grading system to link the clinical features of anaphylaxis with its severity, urgency, treatment or outcome. One system based on retrospective multivariate analysis of over 1000 clinically diagnosed generalized hypersensitivity reactions defined three grades (see Table 2)[6]. 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 represented true anaphylaxis according to the NIAID / FAAN criteria[7]. Again, this grading system should be used as a starting point by researchers for descriptive purposes, until future prospective data refine the criteria.

Aetiology and epidemiology

IgE-dependent activation of mast cells and basophils is the key trigger for the majority of cases of antigen-induced, immune-mediated allergic anaphylaxis. An identical clinical syndrome known as non-allergic anaphylaxis follows non-immunological mechanisms, with the release of identical inflammatory mediators. The term non-allergic anaphylaxis is preferred to the older one of anaphylactoid reaction[8]. Clearly non-allergic anaphylaxis may occur on first exposure to an agent, and does not require a period of sensitization.

Important general categories of anaphylaxis include anaphylaxis related to drugs, biologics including vaccines, as well as insect stings, food,

Table 2. Severity grading system for generalized hypersensitivity reactions

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 neurologic compromise).	Cyanosis or $SaO_2 \leq 92\%$ at any stage, hypotension (SBP < 90 mmHg in adults), confusion, collapse, LOC, or incontinence.

SBP, Systolic blood pressure; LOC, loss of consciousness. * = Mild reactions can be further sub-classified into those with and without angioedema. ‡ = Grades 2 and 3 constitute true anaphylaxis. Reproduced with permission from *Journal of Allergy and Clinical Immunology*[6].

peri-anaesthesia, latex exposure, exercise and idiopathic anaphylaxis (see Table 3)[9].

Drug-induced anaphylaxis

Penicillin is the most common cause of drug-induced anaphylaxis. Around 1:500 patient courses have an apparent allergic reaction, mostly urticaria alone[10]. True allergic cross-reactivity to cephalosporins occurs in under 4%, and is largely with the first-generation cephalosporins. Aspirin and nonsteroidal anti-inflammatory drugs (NSAID) 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 unrelated NSAIDs. Valid tests for IgE-mediated reactions are unavailable for most drugs or biologics, with the exception of penicillins.

Insect sting (hymenoptera) anaphylaxis

Reactions to stings from bees, wasps and ants of the order Hymenoptera are second only to drug-induced anaphylaxis and occur in up to 3% of the population. Reactions are often rapid and may be fatal within 30 minutes mandating the early use of adrenaline, including by self-administration. Non-anaphylactic toxic, large local or late serum sickness-like reactions also occur following a sting[11].

Food-induced anaphylaxis

Self-reported prevalence of food allergy varies greatly from 1.2-17% for milk, 0.2-7% for egg, 0-2.0% for peanuts and fish, to 3-35% for any food[12]. Food anaphylaxis is most common in the young, particularly following peanuts, tree nuts such as walnuts and pecans, shellfish, fin fish, milk and egg. Cross-reactivity with other foods is unpredictable, or reactions may occur to additives such as carmine, metabisulphite and tartrazine. Mislabeling and contamination during manufacturing or at home cause inadvertent exposure, and associated factors such as exercise after food must be recognized. Although fatalities are rare and usually associated with pre-existing asthma, biphasic reactions are seen as symptoms subside then recur several hours later. Patient and carer education is paramount, with schools in particular prepared to respond with adrenaline in an emergency.

Anaesthesia-related anaphylaxis

Neuromuscular blocking drugs (muscle relaxants), latex, antibiotics and induction agents cause most anaphylaxis cases, but opioids, col-

Table 3. Causes of anaphylaxis

1. IgE-dependent Mechanisms:
- Drugs, chemicals and biologic agents:
  - penicillins, cephalosporins, sulphonamides, muscle relaxants, vaccines, insulin, thiamine, protamine, gamma globulin, antivenoms, formaldehyde, ethylene oxide, chlorhexidine, semen.
- Foods:
  - peanuts, tree nuts, shellfish, fin fish, milk, egg, fruits, vegetables, flour.
- Hymenopteran sting venom, insect saliva, other venoms:
  - bees, wasps, ants, hornets, ticks, triatomid bugs, snakes, scorpions, jelly fish.
- Latex.
- Environmental:
  - pollen, horse dander, hydatid cyst rupture.

2. Non-IgE dependent Mechanisms:
- Physical factors:
  - exercise, cold, heat.
- Medications and biologic agents:
  - opiates, aspirin and NSAIDs, ACEI, vancomycin, radiocontrast media, N-acetylcysteine, fluorescein.
- Food additives:
  - metabisulphite, tartrazine.

3. Idiopathic

NSAIDs = nonsteroidal, anti-inflammatory drugs. ACEI = angiotensin converting-enzyme inhibitors.
Note: – Cross-reactivity occurs, and both IgE-dependent and non-IgE dependent reactions may happen with the same agent. – Several mechanisms may co-exist such as exercise-induced following food. – Non-IgE dependent mechanisms include complement activation, kinin production or potentiation, and direct mediator release.

loids, blood products, radiocontrast dye, isosulphan or methylene blue, methylmethacrylate, chlorhexidine and protamine may be responsible. The incidence ranges from 1:3,500 to 1:20,000 cases, with up to 4% of reactions fatal[13]. Muscle relaxants lead to 60% of general anaesthesia reactions, with suxamethonium in the highest-risk group. Reactions to suxamethonium and other relaxants occur in the absence of prior use suggesting cross-reactivity, and rendering large-scale preoperative testing untenable.

Latex-induced anaphylaxis

The highest-risk group for latex allergy includes health care workers, children with spina bifida and genitourinary abnormalities, and occupational exposure. Reactions follow direct contact, parenteral contamination or aerosol transmission[9]. Patients at known risk must be treated in a latex-free environment with glass syringes and non-latex containing gloves, stethoscope, breathing-system, BP cuff, intravenous tubing and administration ports.

Exercise-induced anaphylaxis

Anaphylaxis occurs with a variety of physical activities. Up to 50% cases are associated with the prior ingestion of a food, or follow aspirin or NSAID use. Prophylactic medication is not useful, unlike with exercise-induced asthma[9].

Idiopathic anaphylaxis

This is defined as prednisone-responsive anaphylaxis in which no discernible causative allergen or inciting physical factor can be identified. The majority of cases occur in adults, but it is seen in children. The diagnosis is by exclusion, but it can co-exist with food, drug or exercise-induced anaphylaxis[14].

Summation anaphylaxis

'Summation anaphylaxis' is the term given to the various co-morbidities and concurrent medications that increase the risk of anaphylaxis[15]. These include asthma, intercurrent infection, psychological stress, exercise, alcohol and drugs such as β-adrenergic blockers, angiotensin-converting enzyme inhibitors (ACEI), NSAIDs, and to a lesser extent angiotensin II blockers and α-adrenergic blockers. Summation anaphylaxis may also explain the unpredictable response in an individual to recurrent antigen exposure.

Incidence of anaphylaxis

The true incidence of anaphylaxis is unknown. Data are unreliable with lack of a standard definition, and are almost exclusively diverse, retrospective case collections from the emergency department, peri-operative or the allergist-immunologist's office. Under-reporting is common from missed diagnoses, or following spontaneous recovery, prehospital treatment or fatality. However, all anaphylaxis data from Western countries show the incidence is increasing[16].

Emergency department anaphylaxis

Emergency department (ED) anaphylaxis presentations in adults have an annual incidence from 1:439 to 1:1,100 ED cases. This represents about one adult presentation per 3,400 population per year[17]. The annual incidence of paediatric anaphylaxis is around 1:1,000 ED presentations, although generalised allergic reactions in children (without multisystem involvement) are almost ten times more common than this[18].

A causative agent, recognized from a prior reaction or by close temporal association with the onset of symptoms is found in 75% ED anaphylaxis cases. The most frequent in childhood are food-induced or drug-related, whereas in adults drug-related and hymenopteran stings predominate. Respiratory features appear more common in paediatric anaphylaxis, and cardiovascular features in adult[18].

Fatal anaphylaxis

Anaphylactic deaths result from hypoxia in upper airway swelling with asphyxia, or from bronchospasm and mucus plugging; and or from shock related to vasodilatation, extravascular fluid shift and direct myocardial depression. Tachycardia is usual in shock, but bradycardia related to a neurocardiogenic, vagally-mediated mechanism (Bezold-Jarisch reflex) has occasionally been observed. This may respond to atropine 0.6 mg intravenously up to 0.02 mg/kg if adrenaline fails[19].

Fatalities are rare at less than one per million population per year, but when they do happen, fatal reactions are rapid with a median time to cardiorespiratory arrest of just 5 minutes if iatrogenic, 15 minutes for venom and 30 minutes following foods. Adrenaline may only have been given in 14% cases prior to arrest, and not at all in 38% fatalities[20]. A more recent review of fatal food-induced anaphylaxis in the UK showed that

43 of 48 cases had associated asthma usually with suboptimal daily inhaled steroid use, and over half had only ever had mild previous food reactions, which suggested that the severity of subsequent reactions can not be predicted from the reaction history, and that sound professional advice was often inadequate or absent[21].

Pathophysiology

Mast cells and basophils release inflammatory mediators following binding of multivalent allergen that cross-links surface, high-affinity IgE Fc receptors (FcERI), or from cell membrane perturbation. This coupled with mobilisation of Ca^{++} in the endoplasmic reticulum leads to the release of preformed granule-associated mediators by exocytosis, or the de novo synthesis of lipid mediators based on arachidonic acid metabolism, and the activation of genes for various cytokines and chemokines[22].

Mast cell and basophil inflammatory mediators

The preformed mediators include histamine, proteases such as tryptase, chymase and carboxypeptidase A, and proteoglycans such as heparin and chondroitin sulphate E. Newly synthesized lipid mediators include prostaglandin D_2 and thromboxane A_2 via the cyclo-oxygenase pathway, and the leucotrienes LTC_4, LTD_4 and LTE^4 via the lipoxygenase pathway. Cytokines released include TNF-α, various interleukins such as IL-3, IL-4, IL-5, IL-6, IL-8, IL-13 and IL-16 and GM-CSF. Finally important chemokines include platelet activating factor (PAF), neutrophil chemotactic factor and eosinophil chemotactic factor, plus macrophage inflammatory protein Iα[23]. PAF actually has many pro-inflammatory properties that can lead to bronchoconstriction, vascular permeability and hypotension, and its concentration may relate to the severity of some anaphylactic reactions[24].

Mediator actions

The above mediators induce vasodilatation, increase capillary permeability and glandular secretion, cause smooth muscle spasm particularly bronchoconstriction and attract new cells to the area such as eosinophils, leucocytes and platelets. Positive feedback mechanisms amplify and perpetuate the reaction recruiting further effector cells to release increasing amounts of mediators in a "mast cell – leucocyte cytokine cascade" effect[25]. Conversely, other anaphylactic reactions can self-limit, with spontaneous recovery related to endogenous compensatory mechanisms including increased adrenaline, angiotensin II and PAF acetylhydrolase secretion[24,26].

Clinical features

Anaphylaxis is characteristically a disease of fit patients, and is rarely seen or described in critically ill or shocked patients, other than asthmatics. 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 symptoms can be delayed for some hours following oral or topical exposure.

Cutaneous and Generalised Allergic Reactions

A premonitory aura, tingling or warm sensation, anxiety and feeling of impending doom precede generalized erythema, urticaria with pruritus, and angioedema of the neck, face, lips and tongue. Rhinorrhoea, conjunctival injection and tearing are seen.

Eighty to ninety five percent of patients with anaphylaxis have cutaneous features, which assist the prompt, early diagnosis[17,18]. 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 systemic complications such as laryngeal oedema or shock may precede them[17].

Systemic Reactions

The hallmark of anaphylaxis is the precipitate-onset of multisystem dysfunction with respiratory, cardiovascular, gastrointestinal and or neurological system involvement (see Table 4).

Respiratory manifestations

Throat tightness and cough can precede mild to critical respiratory distress due to oropharyngeal or laryngeal oedema with dyspnoea, hoarseness, stridor even aphonia; or related to bronchospasm with tachypnoea and wheeze. Hypoxia with an oxygen saturation less than 92% on pulse oximetry and central cyanosis indicate severe anaphylaxis and the need for immediate treatment (see severity grading Table 2).

Cardiovascular and neurological manifestations

Light-headedness, sweating, incontinence, syncope or coma may precede or accompany cardiovascular collapse with tachycardia, hypotension and cardiac arrhythmias, again heralding severe anaphylaxis. These arrhythmias can appear as benign supraventricular rhythms, particularly in children, but may progress to an impalpable pulse requiring external cardiac massage (see Table 2).

Gastrointestinal manifestations

Difficult or painful swallowing, nausea, vomiting, diarrhoea and abdominal cramps may be associated with a severe reaction, although they are frequently overshadowed by more immediately life-threatening features.

Table 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, $SaO_2 \leq 92\%$ *, cyanosis*.

Cardiovascular and Neurological
- Tachycardia (rarely bradycardia), hypotension*, arrhythmias, cardiac arrest*.
- Light-headedness, sweating, incontinence*, syncope*, confusion*, coma*.

Gastointestinal
- Odynophagia (difficult or painful swallowing), abdominal cramps, nausea, vomiting, diarrhoea.

Non-specific
- Premonitory aura, anxiety, feeling of impending doom.
- Pelvic cramps.

SaO_2 = Oxygen saturation on pulse oximetry. * = indicates a severe reaction (See Table 2).

Diferential diagnosis

Respiratory and neurological

The protean manifestations of anaphylaxis have a potentially vast differential diagnosis, although the rapidity of onset, accompanying cutaneous features, and the relationship to a likely or known potential trigger suggest the true diagnosis in most cases. Differential diagnoses to be considered in the wheezy or short of breath patient include bronchial asthma, cardiogenic pulmonary oedema, foreign body inhalation, irritant chemical exposure and tension pneumothorax, which are distinguished by their history, co-morbidity and associated presenting features. In patients presenting with light-headedness and syncope, consider an anxiety or vasovagal reaction from a history of exaggerated fear of an impending reaction; or in the context of a painful procedure such as an injection or local anaesthetic infiltration with collapse. Bradycardia, sweating and pallor without urticaria, erythema or itch, associated with a brief prodrome and rapid response to the recumbent position favour the vasovagal reaction over anaphylactic shock.

Shock and or flushing

Other types of distributive shock such as septicaemia, spinal denervation, epidural or spinal block, hypovolaemic shock from haemorrhage or fluid loss, cardiogenic shock from primary myocardial dysfunction and obstructive shock from cardiac tamponade or tension pneumothorax should all be apparent from the history and examination. Cutaneous and respiratory features other than tachypnoea are absent in these non-anaphylactic causes of shock. In patients with flushing consider scombroid poisoning following spoiled-fish ingestion, carcinoid syndrome, alcohol and systemic mastocytosis that require a careful history and investigation to differentiate.

Facial oedema

Finally bacterial or viral infections usually have fever and or pain, and traumatic or anticoagulant-related bleeding cause recognisable bruising. Angioedema in the absence of urticaria can be caused by actual or functional C_1 esterase inhibitor deficiency. This may be hereditary autosomal dominant, with a positive family history, an absence of pruritus, prominent abdominal symptoms and a history of recurrent attacks related to minor stress[27]. Alternatively, C_1 esterase inhibitor deficiency may be acquired in lymphoproliferative and some connective tissue disorders. A rapid, inexpensive screening test for serum C4 should be performed, and if low, be followed by the more specific C_1 esterase inhibitor assay to confirm the diagnosis. Management is with C_1 esterase inhibitor concentrate in a serious attack, or with fresh frozen plasma in its absence.

Laboratory investigation

The diagnosis of anaphylaxis is clinical, and no immediate laboratory or radiological test confirms

the process, or should be allowed to delay the immediate management. While disease progress is monitored at the bedside by non-invasive monitoring with pulse oximetry, oxygen saturations and blood pressure, arterial blood gases may show a respiratory or metabolic acidosis. The measurement of a haematocrit level to show a rise with fluid extravasation, and electrolytes and renal function, blood glucose, chest x-ray and ECG are indicated if there is a slow response to treatment, or when there is doubt about the diagnosis.

Mast cell tryptase, and histamine

Mast cell tryptase in blood taken from one to six hours after a suspected episode, despite initial promise, can not be solely relied upon to diagnose anaphylaxis as it is not elevated consistently, particularly following food allergy. Conversely tryptase may be elevated *post mortem* in non-anaphylactic deaths, therefore is not diagnostic in establishing anaphylaxis as the cause. However, measuring serial levels, or specific allelic subtypes such as mature β tryptase may improve the value of the test[9,28]. Ideally take three samples, one immediately following resuscitation, the next 1-2 hours after symptom onset, and the last at 24 hours or during convalescence, for the patient's baseline tryptase level[3].

Histamine levels are impractical to measure as they are unstable and evanescent, only remaining elevated for 30 to 60 minutes maximum. Biomarker assay panels including histamine, tryptase, chymase, PAF and mast-cell carboxypeptidase A3 may become of value in the future[24].

IgE skin testing, in-vitro testing and challenge testing

Skin or blood tests for specific IgE antibodies are not emergency department tests, and must be done by those trained in their performance and interpretation. Skin prick testing is the more sensitive and when possible, standardized extracts should be used with correct technique. In addition, an experienced physician should supervise as occasional severe reactions occur[16]. *In-vitro* testing for allergen-specific IgE is less sensitive, and depends on clinical correlation and the availability of specific assays, of which there are over 500 different allergens available for testing with the ImmunoCAP™ system (Phadia AB, Uppsala, Sweden), or clinicians may use a radio-allergosobent (RAST) technique.

Table 5. Initial treatment of anaphylaxis

- Stop delivery of any potential causative agent.
- Call for help.
- Give adrenaline 0.01 mg/kg i.m. into lateral thigh, to maximum 0.5 mg (0.5 mL of 1:1000 adrenaline).
- May be repeated every 5-15 minutes.
- Or use patient's own EpiPen™ if readily available – may be given through clothing.
- Lay supine (or elevate legs) for shock.
- Give high-flow oxygen.
- Insert large-bore i.v. cannula (14-g or 16-g) and give crystalloid fluid bolus of 10-20 mL/kg.

Finally, challenge testing may help diagnose non-allergic anaphylaxis in particular. False positive and false negative reactions do occur but are much less likely than with skin prick or *in-vitro* testing, but again experienced physician supervision is essential[26].

Treatment

A patient with anaphylaxis may have the reaction in hospital on a ward, in the operating theatre, the radiology department, even in outpatients. More commonly the patient presents directly to his or her family doctor or to the emergency department. Make certain an ambulance is called early for all out-of-hospital anaphylactic reactions.

Initially stop any potential causative agent such as an intravenous drug or infusion and manage the patient in a monitored resuscitation area in the emergency department, or bring equipment including at least a pulse oximeter, non-invasive blood pressure device and 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 including vital signs, and looking particularly for upper airway swelling, bronchospasm or circulatory shock.

Administer oxygen, adrenaline and fluids with the patient supine as the mainstay of treatment to stabilize the cardiorespiratory status. Antihistamines and steroids play no role until this has been achieved, and even then their value is debatable (see Table 5)[5,9].

Oxygen and airway patency

Give oxygen by face mask to all patients aiming for an oxygen saturation above 92%. 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 for urgent experienced anaes-

Table 6. Failure to respond, or deteriorating rapidly

- Start adrenaline infusion 1 mL (1 mg) of 1:1000 adrenaline in 100 mL normal saline at 30-100 mL/hr (5-15 µg/min) titrated to response.
- Must be on ECG monitor.
- Give faster in cardiopulmonary collapse/arrest.
- Consider assisted ventilation and endotracheal intubation by skilled doctor, which may be extremely difficult.
- If the patient is in extremis and endotracheal intubation is impossible, perform a surgical airway via a cricothyroidotomy.

thetic assistance, if there are signs of impending airway obstruction such as worsening stridor or hoarseness, or rapidly progressive respiratory failure with tachypnoea and wheeze.

Cyanosis and exhaustion indicate imminent respiratory arrest, but sedative or muscle relaxant drugs should never be given unless the physician is trained in the management of the difficult airway. Endotracheal intubation and mechanical ventilation are extremely challenging. Perform a surgical airway via the cricothyroid membrane as a last resort, before hypoxic cardiac arrest occurs (See Table 6).

Adrenaline Dose and Route

Adrenaline is the drug of choice for acute anaphylaxis, whether allergic IgE-mediated or non-allergic. Give adrenaline in all but the most trivial cases, certainly if there is progressive airway swelling, bronchospasm or hypotension. It has beneficial α-, β_1- and β_2-adrenergic effects that counteract the profound vasodilatation, mucosal oedema and bronchospasm[3]. Another crucial role of adrenaline is via β_2-adrenergic receptors triggering a rise in intracellular cyclic AMP that inhibits further mast cell and basophil mediator release, thereby attenuating the severity of the reaction when given early.

Intramuscular adrenaline

Intramuscular adrenaline is recommended when anaphylaxis is treated early, progressing slowly, if venous access is difficult or delayed or in the unmonitored patient[29,30]. The dose of adrenaline is 0.01 mg/kg up to a maximum of 0.5 mg intramuscularly, repeated every 5 to 15 minutes as necessary. Give this as 0.01 mL/kg of 1:1000 aqueous adrenaline up to a maximum of 0.5 mL into the upper outer thigh (see Table 5). Adrenaline may be injected through clothing in an emergency, including when self-administered prehospital. Intramuscular adrenaline is superior to subcutaneous, and should be given into the vastus lateralis muscle in the thigh rather than the arm deltoid muscle[31].

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, 0.15 mg (0.15 mL of 1:1000 aqueous adrenaline) for ages 6 months to 6 years, and 0.1 mg (0.1 mL of 1:1000 aqueous adrenaline) for children aged less than 6 months[3].

Intravenous adrenaline

Intravenous adrenaline is indicated only when there is rapidly progressive vascular collapse with shock, imminent airway obstruction or critical bronchospasm, and should be given by practitioners with regular experience in its use. Administer the intravenous adrenaline slowly to the patient on an ECG monitor with extreme care, suitably diluted and titrated to response to avoid potentially lethal complications such as cardiac arrhythmias, myocardial ischaemia and cerebrovascular accident[19,20,32].

The initial dose of adrenaline intravenously is just 0.75-1.5 µg/kg (ie. 50-100 µg) over up to 5 minutes depending on the rapidity and severity of the patient's decline. This dose may be repeated according to response (see Table 6). Intravenous adrenaline is best delivered as an infusion of adrenaline 1 mg in 100 mL normal saline (10 µg/mL) started at 30-100 mL/hr, that is 5-15 µg/min titrated to response. Continue the infusion for anything up to 60 minutes after the resolution of all symptoms and signs of anaphylaxis, then wean over the next 30 minutes and stop, watching closely for any recurrence[25].

Although 1:10 000 adrenaline containing 100 µg/mL is readily available as a pre-diluted Min-I-JetTM preparation, it is difficult to give slowly at 10 µg/min, in small enough initial quantities of 0.75-1.5 µg/kg or around 50-100 µg (0.5-1.0 mL). Reserve the use of the 1:10 000 adrenaline Min-I-JetTM preparation for the patient in cardiac arrest. It is also reasonable to give patients with upper airway oedema and bronchospasm nebulized adrenaline 5 mg, or 5 mL of undiluted 1:1000 adrenaline, whilst parenteral adrenaline is being prepared as above.

Fluid replacement

Insert a large-bore intravenous cannula as soon as possible in patients showing signs of shock. Administer an initial fluid bolus of 10-20 mL/kg normal saline, up to 50 mL/kg total to counter the

massive intravascular fluid shifts and peripheral vasodilatation that occurs in minutes with anaphylactic shock. There are no outcome data favouring colloids over crystalloids[3,25,32].

Second-line Agents

Once oxygen, adrenaline and fluids have been given to optimize the cardio-respiratory status and tissue oxygenation, other second-line drugs may be given in a support role.

Vasopressors

Vasopressors such as noradrenaline, metaraminol, phenylephrine and vasopressin have anecdotally treated hypotension resistant to initial adrenaline and fluid therapy. Similar to intravenous adrenaline, only give these alternatives when experienced in their use[33].

H_1-antihistamines and H_2-antihistamines

Antihistamines are second line agents with only weak evidence to support their use.34 Reserve antihistamines predominantly for symptomatic relief of skin symptoms such as urticaria, mild angioedema and pruritus. They should never be relied upon as sole therapy in significant anaphylaxis, and side effects of sedation, confusion and vasodilatation can be troublesome, particularly if given parenterally[34]. The latest Resuscitation Council UK guideline still recommends chlorphenamine 10-20 mg intramuscularly or slowly intravenously after initial resuscitation to counter histamine-mediated vasodilation and bronchoconstriction[3].

The combination of an H_2-antihistamine with an H_1-antihistamine is better at attenuating the cutaneous manifestations of a generalized allergic reaction than an H_1-antagonist given alone[9,35]. However, there are no data in severe anaphylaxis and their combined use remains controversial. In addition, a non-sedating H_1-antihistamine should be selected especially on discharge, if the patient wishes to continue working, or driving a vehicle (see Discharge Oral Medication).

Corticosteroids

As with the antihistamines, despite their many theoretical benefits on mediator release and tissue responsiveness, there are no placebo-controlled trials to confirm the effectiveness of steroids in anaphylaxis. Most clinicians however give prednisone 1 mg/kg up to 50 mg orally or hydrocortisone 1.5-3 mg/kg IV particularly in patients with airway involvement and bronchospasm, based empirically on their important role in asthma[3].

It is unclear if steroids prevent a biphasic reaction with recrudescence of symptoms following recovery, as supporting data are unconvincing[36]. Steroids are of course fundamental to the management of recurrent idiopathic anaphylaxis[14,15].

Glucagon

Patients taking β-blockers have more severe or treatment-refractory anaphylaxis, and anecdotally glucagon is reported to have been successful when other more well-recognised treatments have failed[37]. Glucagon raises cyclic AMP via a non-adrenergic mechanism, given as 1-5 mg intravenously, followed by an infusion at 5-15 µg/min titrated to response. Note that it may cause nausea and vomiting.

Disposition

The vast majority of patients are discharged following observation, having considered the need for take-home medication, self-injectable adrenaline, and allergist-immunologist referral.

Observation

Patients with systemic anaphylactic reactions, including all those who received adrenaline, should be kept under observation. However, it is not known how long a patient should be observed for after recovering from an episode of anaphylaxis, as there is no evidence or consensus on factors that may predict a late phase recurrence, or biphasic anaphylaxis (see below)[38]. Expert opinion varies from at least four to six hours after apparent full recovery, up to 10 hours or longer[5,30,38]. Keep patients with reactive airways disease a little longer, because most deaths from anaphylaxis occur in this group[4]. Observation is safely performed in the Emergency Department if a suitable holding area exists, and does not mandate ECG monitoring[17,18].

Biphasic anaphylaxis

Most anaphylactic reactions are uniphasic and will respond rapidly and completely to treatment. Some patients develop protracted reactions with an incomplete response to adrenaline, or deterio-

rate on attempted adrenaline weaning. Keep these patients with unstable vital signs monitored and admit to an intensive care area.

Other patients relapse after an apparent complete resolution of all their initial symptoms and signs, known as biphasic anaphylaxis, which is reported in 1-5% of cases. It is unknown if more severe presenting features, delayed or inadequate doses of adrenaline, or the non-use of steroids predispose to, or predict the biphasic response[36,38].

Discharge oral medication

There are no data to support or refute the common practice of prescribing a two- or three-day discharge supply of combined H1- and H2-antihistamines plus oral steroids to prevent early relapse. However, consider the non-sedating H1-antihistamine cetirizine 10 mg once daily or loratadine 10 mg once daily, plus an H_2-antihistamine ranitidine 150 mg 12-hourly with prednisolone 50 mg once daily in adults with predominant cutaneous features following a generalised allergic reaction, or with bronchospasm[29].

Self-injectable adrenaline (epinephrine)

Attitudes vary as to whether the emergency physician or general practitioner should initiate self-injected adrenaline (epinephrine) use such as the EpiPen™, rather than waiting for specialist allergist – immunologist review, with formulation at that time of an individualised Anaphylaxis Action Plan. This quandary of who to prescribe self-injected adrenaline (epinephrine) to and what to write in the Anaphylaxis Action Plan is well described[39]. As a guide, consider self-injectable adrenaline (epinephrine) for the patient with anaphylaxis after exposure to venom sting, patients with food allergy particularly to nuts or peanuts, and for those in whom the reaction was severe and or the cause unknown[3].

It is absolutely essential to explain and demonstrate exactly how to use a self-injected adrenaline device such as the EpiPen™ with 0.3 mg (300 µg) of adrenaline (epinephrine) or the EpiPen Jr™ containing 0.15 mg (150 µg) of adrenaline, and to educate both the patient and another care-giver, particularly with children, if dispensed in the emergency department. Teach the patient and carer to recognize the symptoms and signs of anaphylaxis, and encourage the actual use the device particularly if distant from a health care facility. Tell recipients self-injectable adrenaline has a relatively short shelf-life of around one year, and how to look after it[40].

Drug and allergen avoidance

Patients with hypertension or ischaemic heart disease at risk of recurrent anaphylaxis should ideally be taken off β-blockers, and care taken not to substitute an ACE inhibitor. Discuss this with the patient's other specialists to be certain the overall risk-benefit favours medication change[30].

Advise patients to reduce allergen exposure risk by destroying nearby wasp nests and removing allergenic foods in the house, plus to prevent insect sting with appropriate clothing and avoid certain foods by checking the manufacturer's label.

Allergy/immunology referral

Disappointingly few patients who suffer an episode of anaphylaxis are referred from the emergency department for specialist allergist – immunologist follow up[17,18]. Refer anyone prescribed a self-injectable adrenaline (epinephrine) device, patients following a wasp or bee sting suitable for immunotherapy, suspected food-, drug-induced or exercise-induced anaphylaxis, and patients with severe reactions without an obvious trigger[41].

Remember to give every patient a discharge letter to take home detailing the nature and circumstances of the anaphylactic reaction, the treatment given, and the suspected causative agent(s). Ask the patient also to write a brief diary of the events in the six to twelve hours preceding the reaction, particularly when the cause is unclear, that should include all foods ingested, drugs taken including non-proprietary, cosmetics used and activities performed outside as well as indoors[3]. The patient's later recall of events at specialist allergist – immunologist review will be flawed unless documented contemporaneously. Skin or blood tests for specific IgE antibodies, skin prick tests or challenge testing will be guided by the history of the suspected exposure[16,26].

Conclusions

Anaphylaxis is a common challenge for emergency physicians, necessitating prompt clinical recognition and treatment with oxygen, adrenaline (epinephrine) and fluids to restore cardiorespiratory stability. Careful discharge planning, including allergy referral where appropriate, protects against further, often unheralded, attacks of anaphylaxis.

Progress in anaphylaxis research is hampered by the lack of a universally accepted definition, or an agreed severity grading system. Prospective data collection preferably in multiple sites is essential to validate assessment, treatment and follow-up protocols, whilst the current evidence-base to anaphylaxis care is systematically evaluated and published using Cochrane Collaboration reviews[42].

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Manejo actual de la anafilaxia

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El término anafilaxia se emplea para describir tanto las reacciones inmunes mediadas por IgE como las no alérgicas ni inmunológicas. El riesgo de producirse aumenta con la comorbilidad, como el asma, infección, ejercicio, alcohol o el estrés, así como por medicamentos como los betabloqueantes, los inhibidores de la enzima convertidora de angiotensina (IECAS) y la aspirina. La fisiopatología involucra los mastocitos activados y los basófilos que liberan mediadores preformados asociados a los gránulos, mediadores lípidos de nueva formación, además de generar citoquinas y quinoquinas. Éstas provocan vasodilatación, incremento de la permeabilidad capilar y contracción del músculo liso, y atraen a la zona nuevas células. Los mecanismos de retroalimentación positiva amplifican la reacción, aunque ésta también puede autolimitarse. Las causas más frecuentes de muerte relacionada con reacciones inmunes IgE son la penicilina parenteral, las picaduras de himenópteros y los alimentos, mientras que las sustancias empleadas para estudios de radiocontraste, la aspirina y otros medicamentos no esteroideos o los antiinflamatorios constituyen las causas más frecuentes de muerte por reacción no alérgica. La muerte por anafilaxia, muy infrecuente, es producida por hipoxia tras la afectación de la vía aérea alta, broncoespasmo grave o por *shock* profundo tras vasodilatación y extravasación de líquido. La primera línea de tratamiento es la administración de oxígeno, adrenalina (epinefrina) y fluidos. La adrenalina (epinefrina) 0,01 mg/Kg hasta un máximo de 0,5 mg i.m. (0,5 ml de 1:1.000 adrenalina) inyectada en el muslo lateral superior revierte todas las características de la anafilaxia, así como inhibe la liberación de más mediadores. Los cristaloides, como el suero normal o la solución de Hartmann a 10-20 ml/Kg, son preceptivos en los casos de *shock.* El papel de los antihistamínicos H_1 y H_2, los esteroides y el glucagón no está claro. Sólo deben considerarse una vez lograda la estabilidad cardiovascular con agentes de primera línea. El alta hospitalaria puede darse después de la recuperación completa y 4-6 horas de observación. Es esencial tener un plan de alta hospitalario claro y remitir al alergólogo los casos con una reacción importante o recurrente producida por estímulos inevitables o desconocidos, para su estudio. La educación del paciente es importante para asegurar el éxito del cuidado a largo plazo. [Emergencias 2009;21:213-223]

Palabras clave: Anafilaxia.Shock. Antihistamínicos.