

Anaphylaxis in the emergency department: a paediatric perspective

Alberto Martelli, Daniele Ghiglion, Teresita Sarratud, Elena Calcinai, Suzanne Veehof, Luigi Terracciano and Alessandro Fiocchi

Melloni Paediatrica, University of Milan Medical School at the Fatebenefratelli/Melloni Hospital, Milan, Italy

Correspondence to Alessandro Fiocchi, MD, Director of Paediatrics, Melloni Paediatrica, Department of Child & Maternal Medicine, University of Milan Medical School at the Fatebenefratelli/Melloni Hospital in Milan, 52 Via Melloni, 20129 Milan, Italy
Tel: +39 02 6363 3285; fax: +39 02 6363 3322; e-mail: allerg@tin.it

Current Opinion in Allergy and Clinical Immunology 2008, 8:321–329

Purpose of review

Correct management of anaphylactic manifestations in the emergency department is crucial to prevent mortality and future episodes, in particular for paediatric patients. We make here recommendations based on a critical review of the evidence for the management of anaphylaxis in emergency department with particular emphasis on children.

Recent findings

Available information suggests that anaphylaxis must be promptly recognized keeping in mind the airway patency, breathing (ventilation and respiration), circulation and mental status and treated. The first treatment is epinephrine. After successful treatment of an anaphylactic episode, attention must be paid at prevention of early recurrences (biphasic anaphylaxis) and assessment of causes. Patients should not be discharged before prescribing self-injectable epinephrine and explain how and in under what circumstances it must be injected; giving an action plan to be communicated to their communities; inform the school about the possible occurrence of reactions and the appropriate avoidance and rescue measures; and consider the necessity of a Medic-Alert identification.

Summary

As gross differences have been described in the awareness of the disease and its management between allergists and nonallergists, allergists should interact with emergency doctors to improve education in this area.

Keywords

anaphylaxis, emergency department, epinephrine, food allergy, paediatrics

Curr Opin Allergy Clin Immunol 8:321–329
© 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins
1528-4050

Introduction

Anaphylaxis is the quintessence of emergency medicine. It occurs unexpectedly, often in the young and otherwise healthy, may progress rapidly from an innocuous presentation, is potentially fatal, particularly if mistreated, has no bedside diagnostic test of value and demands pure clinical recognition. It responds dramatically to treatment (intramuscularly injected epinephrine), and usually allows discharge within 6–8 h unless there is a recurrence (biphasic response). However, patients who experience an episode of anaphylaxis are at risk of new episodes [1]. For these reasons, allergists and emergency doctors must be prepared for this eventuality.

For a number of obvious reasons, it is difficult or impossible to conduct prospective, randomized, double-blind, placebo-controlled trials of anaphylaxis treatment and

epidemiological evaluations are based mainly on case reports from emergency departments (EDs) [2]. Although most cases of anaphylaxis occur unpredictably in community settings, they also continue to occur in healthcare settings despite vigilant preventive efforts. Thus, correct management of anaphylactic manifestations in the ED, including the identification of the cause of single episodes, is crucial not only in treating a severe, life-threatening condition but also in preventing future episodes in children who have had an anaphylactic reaction [3].

Epidemiology of anaphylaxis in emergency departments

Different definitions, differing interpretation of symptoms and different attitudes towards anaphylaxis plague the

current definition of this condition. Anaphylaxis is a life-threatening condition resulting from mast cell degranulation. It is characterized by an acute-onset illness (from minutes to several hours after exposure to the offending agent) 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:

- (1) respiratory compromise (e.g. dyspnoea, wheeze–bronchospasm, stridor, reduced peak expiratory flow, hypoxemia);
- (2) reduced blood pressure or associated symptoms of end-organ dysfunction [e.g. hypotonia (collapse), syncope, incontinence] [4].

On the basis of this or similar definitions, its incidence has been estimated at 30 cases per 100 000 per year [5], but there are few studies in the general population; most epidemiological studies have been done on the prevalence of anaphylaxis among ED patients, in which the prevalence ranges from 0.09% in a single-centre study [6] to 1% in a large national database [7^{••}], the latter figure greatly exceeding the estimated prevalence in the literature prior to 2005 (Table 1) [6,8–13].

Another important piece of epidemiological information relevant for management is the incidence of anaphylactic reactions that are fatal. Again the estimates are widely divergent, but 48 deaths meeting the criteria for anaphylactic shock were reported in the UK between 1999 and 2006 [14^{••}]. The ages ranged from 5 months to 85 years, median 21 years, emphasizing that anaphylactic shocks in young people are more likely to be fatal.

On the basis of figures for the prescription of epinephrine, the incidence of anaphylaxis has been estimated as 1–5 children per 1000 (Table 2) [15–17]. Interestingly, the prescription of adrenaline in the UK increased seven-fold between the 1980s and 1990s, which suggests that the phenomenon is increasing. Other reports confirm this trend: in the UK, the admission rates for anaphylaxis

Table 1 Epidemiology of anaphylaxis in emergency departments

Reference	Country	Method	Incidence per 100 000
Sorenson <i>et al.</i> [9]	Denmark	Retrospective	3.2
Amornmarn <i>et al.</i> [10]	Germany	Retrospective	36 ^a
Stewart and Ewan [11]	UK	Retrospective	46 ^a
Klein and Yocum [6]	USA	Retrospective	90 ^a
Kaufman [12]	International	Retrospective	154 ^b
Pastorello <i>et al.</i> [13]	Italy	Retrospective	40 ^a

^a Cases per emergency admissions.

^b Cases per hospital admissions.

Table 2 'Epidemiology' of prescription of epinephrine

Reference	Country	Outcome	Incidence
Moneret-Vautrin <i>et al.</i> [15]	France	Personalized management plans	1 : 1000
Morritt and Aszkenasy [16]	UK	Prescriptions of adrenaline: born in 1980 vs. born in 1992	×7
Simons <i>et al.</i> [17]	Canada	Prescriptions of adrenaline	1 : 100 (5 : 100 for age 12–17 months)

increased from 5 to 36 per million of population between 1990 and 2004 [18^{••}], and in Australia, hospitalization rates for anaphylaxis increased by 8.8% per year between 1994 and 2004 [19]. These reports are based on International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes, which have been shown to be relatively insensitive to the specific diagnosis (they can miss almost half the patients with food allergy and 13% of patients with insect sting allergy) [20]; this increase has not been reported in the USA, where between 1993 and 2004 the number of ED visits for allergic reactions remained stable at 3.8 : 1000 people [7^{••}]. It has been estimated that in the USA, food allergy is responsible for 30 000 anaphylaxis episodes per year [21], leading to 2000 hospitalizations and 200 deaths. For children at risk of anaphylaxis, the possibility of recurrences from foods is one every 2 years [22], with a mortality of 0.6–5% of episodes [5,9]. Most episodes develop in children with an established diagnosis of food allergy, and are thus preventable. Fatalities due to food anaphylaxis happen predominantly away from home [23], which indicates the need to promote public awareness of the problem. In that study, although 63% of visits had been registered as 'urgent', only 4% were eventually admitted to hospital. A low hospitalization tax has also been described for patients with acute insect sting reaction [24]. EDs in developed countries may need to be prepared for an increase of this condition in the next few years.

Clinical diagnosis

The presentation of an anaphylactic reaction in ED can vary widely. Whatever the symptom, the patient usually presents with a reaction that has occurred within 1–15 min of exposure to the allergen. Rarely, reactions begin after 30 min or even after 1 h. The patient may feel uneasy and become agitated with tachycardia and tachypnoea. Blood pressure may fall, causing fainting (Table 3). Other symptoms include tingling sensations

Table 3 Blood systolic pressure values indicating hypotension

Age	Systolic blood pressure (mmHg)
1–28 days	<60
1–12 months	<70
1–10 years	<70 + 2 × age in years
Over 10 years	<90

('pins and needles'), itchy and flushed skin, throbbing in the ears, coughing, sneezing, hives and swelling (angio-oedema). Breathing may become difficult, and wheezing may occur because of constriction or swelling of the upper airway. An anaphylactic reaction may progress so rapidly that it leads to collapse, cessation of breathing, seizures and loss of consciousness within 1–2 min. The reaction may be fatal unless treatment is given immediately. At presentation in emergency room, anaphylaxis may not be recognized if it is triggered by a novel agent, if it is an individual's first episode or if it occurs in an infant or young child or in an aphonic, dyspnoeic or unconscious individual [25,26**].

The diagnosis of anaphylaxis is based primarily on the clinical history, and clinical criteria for accurate early identification of anaphylaxis have recently been published [27**]. According to the many classifications of anaphylaxis appearing in the last few years [4,28,29], an anaphylactic episode is defined not only by the simultaneous involvement of two or more organs or systems but mainly by the involvement of vital systems (circulatory and respiratory). This must be kept in mind in EDs, in which the patient often presents without a clinical history. In some countries, children may come with warning bracelets [28] or identification cards that are recommended for the prevention of the recurrences of anaphylaxis, in particular in drug-allergic patients [29]. These cards may have been put in wallets, so that, in particular when the patient is unconscious, inspection of the patient's belt and belongings can give useful diagnostic information.

Anaphylaxis can present in various ways. In 60% of cases, the first symptom has to do with the skin – hives and flushing – but there can also be serious respiratory or cardiovascular insufficiency, difficulty in breathing, swollen or tingling lips, or a fall in blood pressure leading to dizziness or nausea and pallor. Table 4 shows the dynamics of involvement of different organs and systems in paediatric anaphylaxis [30].

Table 4 Temporal involvement of various organs during acute anaphylactic episodes in paediatrics

System	Percentage
Initial presenting signs and symptoms	
Dermatological	60
Respiratory	25
Gastrointestinal	5
Neurological	4
Cardiovascular	2
Other	4
Overall signs and symptoms	
Dermatological	93
Respiratory	93
Gastrointestinal	26
Neurological	26
Cardiovascular	13

As clinical manifestations can change during a single episode, an accurate record of symptoms at onset and careful observation of the patient are necessary to gain experience of clinical variations [31]. The clinical presentation of anaphylaxis is very varied, even in the same patient from one episode to another: the time between exposure to the trigger and the onset of symptoms can vary from minutes to hours, and the severity of symptoms from mild and self-limiting to fatal within minutes [2].

Differential diagnosis

When there is a history of recent exposure to a known allergen, anaphylaxis diagnosis is easy – particularly when urticaria and pruritus are present. When gastrointestinal and cardiovascular manifestations predominate, diagnosis is more difficult. Hives, anxiety, asthma, panic and fainting are the commonest differential diagnoses to be considered in the ED [27**].

Respiratory, neurological and gastrointestinal pathologies

Almost all acute conditions can be confused with anaphylaxis. The following should first be excluded by appropriate evaluation: respiratory distress syndromes, recent inhalation of foreign bodies, and epileptic syndromes with predominant hypotonia and loss of consciousness.

Vasovagal reactions

These are the most frequent conditions mimicking anaphylaxis. Vasovagal reactions are a reflex of the involuntary nervous system causing bradycardia, vasodilatation and hypotension. The resultant fainting is synonymous with situational syncope, vasovagal syncope and vasodepression. Characterized by hypotension, pallor, asthenia, nausea, vomiting and profuse sweating, vasovagal reactions are generally caused by physical or emotional stress. Bradycardia is present rather than tachycardia. As these clinical manifestations can be present also in anaphylactic reactions [32], the absence of bronchospasm and especially of flushing and other cutaneous manifestations is of particular importance in differential diagnosis.

Flushing syndromes

Various agents have been implicated in causing flushing, including histamine, calcicrein, neuropeptides, nicotine and angiotensin-converting enzyme inhibitors. Flushing is also observed in carcinoid syndrome [33], in which patients present with flushing, diarrhoea, colic and wheezing. Another important condition to be differentiated is medullary carcinoma of the thyroid (persistent flushing of face, hands and feet, and telangiectasia; often familial). Flushing syndromes have been divided into 'wet' and 'dry' forms. In the wet form, sweating accompanies the flushing because of sympathetic cholinergic

stimulation of the sweat glands, and can be caused by the postmenopausal state or spicy foods. In dry flushing, for example in carcinoid syndrome, sweat glands are not activated. Flushing can also be due to alcohol ingestion, especially among Asian people who lack the enzyme aldehyde dehydrogenase 2. Alcohol can also lead to flushing in patients with Hodgkin's disease, hypereosinophilic syndrome and splenectomy. All these conditions should be considered in the history of a patient presenting with a possible anaphylactic reaction. Autonomic epilepsy can also be characterized by hypotensive and hypertensive crises, flushing, tachycardia and syncope.

Restaurant syndromes

Scombroid-fish poisoning due to histamine has been described in adults and children. With faulty storage and conservation measures, fish colonized by enterobacteria (*Klebsiella oxytoca* and *Morganella morganii* in particular) can contain large amounts of histamine derived from histidine through bacterial action. Histamine poisoning should therefore be considered in the differential diagnosis of children presenting after a meal with acute urticaria with headache, nausea and/or vomiting [34]. Patients taking isoniazide seem particularly vulnerable [35]. Differential diagnosis is simplified if a number of people taking the same fish appear in the ED. One peculiarity is that in scombroid syndrome, blood histamine is elevated but serum tryptase levels are not.

Monosodium glutamate in foods may also provoke flushing, headache and abdominal symptoms (the Chinese restaurant syndrome). Symptoms are thoracic pain, facial swelling, flushing, paraesthesia, sweating, headache, palpitations, nausea and/or vomiting [35]. Sulphites are used as preservatives in gelatines, sauces, wine, fruit juices, molluscs, and can cause the same symptoms as monosodium glutamate 1–14 h after ingestion.

Other causes of shock

In hypovolaemic shock, diarrhoea and colic can be present, but – as in all hypotensive shocks – there is no cutaneous involvement. In general, differential diagnosis of septic and cardiogenic shocks is not difficult because they occur in the wake of infectious, febrile or cardiovascular conditions [36].

Excess of endogenous histamine production

Rare conditions including systemic mastocytosis can determine anaphylactic acute events. Even rarer are acute promyelocytic leukaemia and basophilic leukaemia: in these patients treatment with tretinoin can cause anaphylactic reactions [37]. Histamine released by echinococcal cysts is another possible cause of anaphylactic episodes [38]. The vancomycin-induced 'red man syndrome' can be mediated by histamine release. Vancomycin when rapidly administered intravenous can act

directly on mastocytes in the absence of sensitization [39].

Nonorganic diseases

Some psychogenic conditions can mimic anaphylactic reactions. These include Munchausen's stridor (intentionally made sounds but not anaphylaxis, remitting after cough [40]), globus hystericus and panic attacks. Vocal cord dysfunction is typical of adolescents and may mimic an acute anaphylactic reaction [41].

Miscellaneous

Hereditary angioedema, during episodes of subcutaneous and submucosal oedema involving respiratory and gastrointestinal systems, can mimic anaphylactic attacks [42]. At presentation in the ED, these patients have usually had episodes triggered by trivial traumas such as oral or dental manipulations. The prevalence in the general population is 1 : 50 000. Prompt recognition of these attacks may be critical, as oedema of the tongue and upper airways is the cause of death in 15–30% of these patients. They are generally well known, however, and differential diagnosis is easy.

A severe, sometimes fatal, idiopathic condition presenting with acute episodes of generalized angioedema, malaise, irritability, oliguria or anuria is the Systemic Capillary Leak Syndrome [43]. Massive release of IL-2 has sometimes been reported. Gleich syndrome is characterized by hyper-eosinophilia (up to 60 000–70 000/ μ l blood) with a large increase in serum IgA and IgE. The symptoms are in proportion to the number of peripheral eosinophils, whose degranulation is the cause of angioedema [44].

Laboratory diagnosis

Diagnosis in ED is primarily clinical, on the basis of history and symptoms, but it can sometimes be supplemented by laboratory tests. In IgE-mediated anaphylaxis, the presence of a specific IgE is necessary but the test is of limited use in the ED. More valuable is the measurement of metabolites such as serum tryptase and plasma and urinary histamines [45].

β -Tryptase, which is released during mast cell degranulation, peaks in the first hour of the anaphylactic reaction and can remain high for 12 h, in particular during drug-induced or insect-sting-induced anaphylaxis. Ideally, the measurement should be obtained between 1 and 2 h after the start of symptoms [45]. As it is stable at room temperature, it can be measured in biological samples even postmortem [46]. In food-induced anaphylaxis, however, β -tryptase is seldom elevated because in this condition basophiles and monocyte macrophages are involved more than mastocytes. High levels of α -tryptase (immature tryptase) indicate the presence of mastocytosis.

Plasma histamine levels begin to increase within 5–10 min of the onset of symptoms of anaphylaxis and remain high for 30–60 min [46,47], whereas methylhistamine can be detected in urine up to 24 h after the start of symptoms [48]. In the measurement of histamine, the blood sample requires special handling and this makes its use impractical in the ED. The lack of availability of rapid laboratory tests to confirm the clinical diagnosis of anaphylaxis contributes to underrecognition and undertreatment of the condition [27^{••}]. A test for mature (β) tryptase, which is a more specific mast cell activation marker for anaphylaxis than total tryptase, is sorely needed. Measurement of chymase, mast cell carboxypeptidase A3, platelet-activating factor and other mast cell products in serum or plasma might prove useful, and consideration should be given to measuring a panel of mediators from mast cells and basophils [27^{••}].

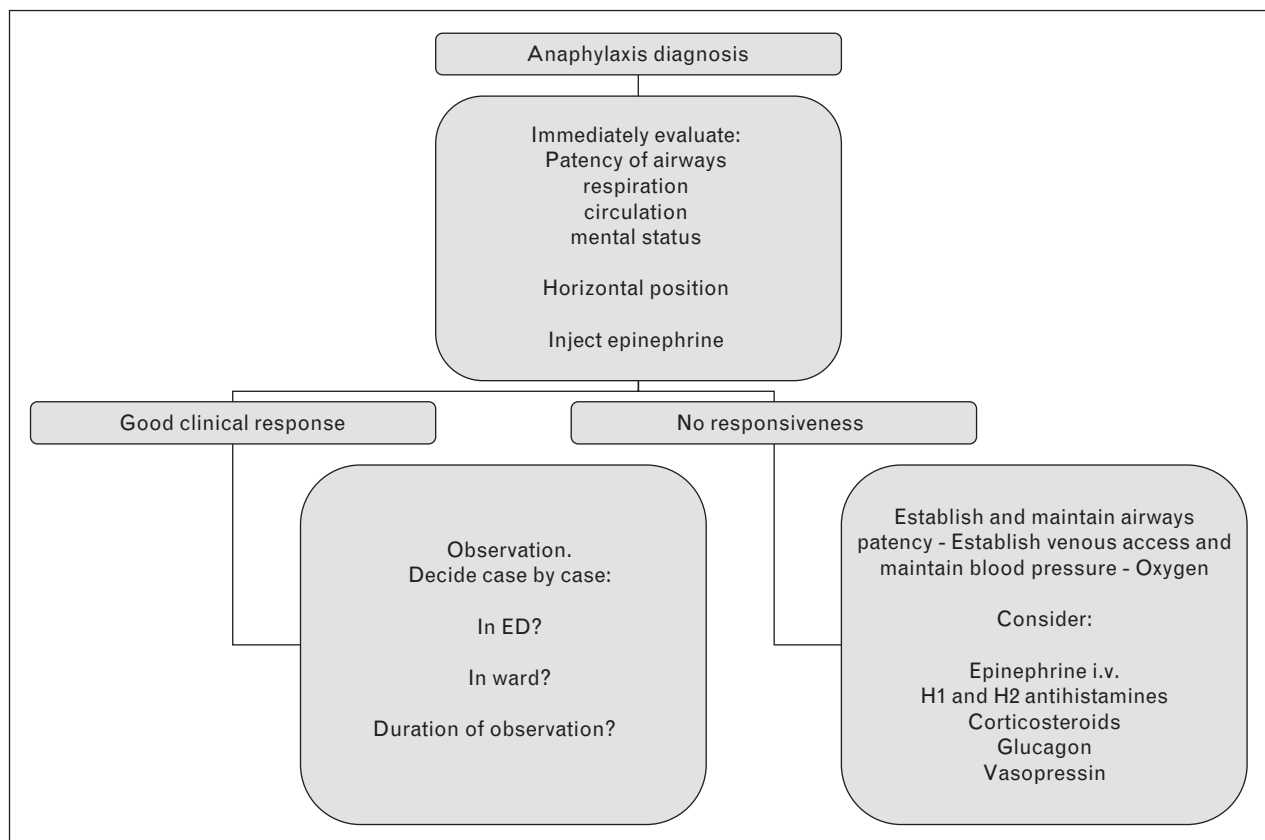
Emergency treatment of anaphylaxis

As an anaphylactic episode is potentially life-threatening, prompt treatment should be given even when diagnostic is incomplete. Despite this, only 18% of patients in one study were found to be brought to the ED by ambulance

[49]. In such acute conditions, the treatment must be individualized, and the different algorithms that have been proposed must be used with appropriate variation in the timing and drug dosage [50,51]. Figure 1 shows a synthetic algorithm for the recognition and treatment of anaphylaxis in ED. The elements of the intervention to be rapidly activated can be summarized in the mnemonic airway patency, breathing (ventilation and respiration), circulation, and finally mental status assessment (ABCM) (an alteration in mental status suggests hypoxia from either hypovolaemic shock with cerebral underperfusion or respiratory insufficiency due to bronchial asthma).

The patient, whether adult or child, must be kept horizontal, with raised legs, to promote the perfusion of vital organs. In the absence of dyspnoea, the Trendelenburg position is recommended to avoid cardiac arrest [4]. Inject epinephrine intramuscularly; subcutaneous administration is not recommended, as local vasoconstriction can reduce absorption. Pharmacological studies show that in children the time to reach the peak of plasma adrenaline ($t_{\max}$) is 8 ± 2 min after intramuscular injection and 34 ± 14 min after subcutaneous administration [52]. The

Figure 1 Anaphylaxis in the emergency room: what to do when



ED, emergency department; i.v., intravenous.

injection should be done intramuscularly in the thigh: the lateral part of the quadriceps provides the most efficient pathway in young adults, with a shorter $t_{\max}$ than for either subcutaneous or intramuscular administration in the deltoid [53]. A needle gauge of at least 2.5 cm must be used in obese children to prevent inadvertent subcutaneous administration [54]. The dose is 0.01 ml/kg of aqueous epinephrine 1:1000 (up to 0.5 ml), to be repeated – if necessary – after 5–30 min [55]. If the patient's weight is unknown, an approximate dosage is 50 µg (0.05 ml) for infants less than 6 months; 120 µg (0.12 ml) for children between 6 months and 6 years; 250 µg (0.25 ml) from 6 to 12 years old; 500 µg (0.5 ml) older than 12 years [56].

During the administration of epinephrine, vital signs (cardiac activity, respiratory function and blood pressure) should be continuously monitored and airways patency should be continuously maintained to prevent rapid worsening of the condition towards airway obstruction and cardiorespiratory arrest. In cases of anaphylaxis due to an insect sting or drug or immunotherapy injection, a tourniquet must be placed above the injection point to reduce the absorption of the causative agent.

If symptoms do not decrease, or there is progression to severe hypotension, bradycardia and/or severe bronchospasm, the following actions must be taken [57]:

- (1) repeat epinephrine administration after 5 min;
- (2) establish a venous access and – in the case of hypotension – rapidly administer isotonic saline solution at 20–30 ml/kg in the first hour;
- (3) if hypotension persists, rapid infusion of volume expanders (colloid-containing solutions) may be necessary [51];
- (4) administer oxygen, 6–8 l/min, depending on the oxygen saturation value;
- (5) administer support drugs such as
 - (a) antihistamine (e.g. chlorpheniramine maleate);
 - (b) bronchodilators, for example salbutamol;
 - (c) corticosteroids, for example hydrocortisone or prednisone;
 - (d) glucagons;
 - (e) dopamine.

Antihistamines are indicated for treatment of pruritus and urticaria, but they cannot prevent the onset of anaphylaxis [58]. Intended as an adjunctive pharmacological intervention because of their inferior rapidity over epinephrine, H1 antihistamines are commonly used as an adjuvant therapy in the treatment of anaphylaxis. Recently, a Cochrane systematic review assessed the benefits and harmfulness of H1 antihistamines in the treatment of anaphylaxis. On the basis of this

review, we are unable to make any recommendations for clinical practice [59]. If deemed necessary, chlorpheniramine maleate 1 mg/kg intramuscular or intravenous is indicated in children even if less than 1 year of age. Other antihistamines include levocetirizine and desloratadine [50]. Another option is to use H2 antihistamines [60] or a combination of H1 and H2 antihistamines [61].

Salbutamol can be used for relief of bronchospasm, up to high doses if necessary, and corticosteroids can play a complementary role, as they are long acting. However, corticosteroids can have an additive effect on respiratory manifestations of bronchial asthma [50] and could have a role in prevention of biphasic and protracted anaphylactic crises. Methylprednisolone 1–2 mg/kg per day intravenous is the preferred option [34].

Biphasic anaphylaxis

Treatment of an acute anaphylactic episode must keep in view the possibility of biphasic anaphylaxis, which can develop after as many as 20% of anaphylactic reactions. The biphasic reaction can be less severe than, equally severe as, or more severe than the initial reaction, ranging from mild symptoms to a fatality.

Biphasic reactions happen in up to one-third of patients who have had fatal or near-fatal reactions. These patients seem to have fully recovered when severe bronchospasm suddenly recurs; the recurrence is typically more refractory to standard therapy and often requires intubation and mechanical ventilation [62]. Predicting such recurrences is not easy. The more severe the anaphylactic reaction, the more probable is a recurrence: although the absolute number of patients requiring more than one epinephrine injection is similar for each degree of severity, the number of patients requiring several epinephrine injections increases significantly with increased symptom severity [63]. The interval between the first anaphylactic reaction and the subsequent fatal or near-fatal anaphylactic episode can be between 2 and 72 h (mean 6–10 h), and no specific symptom is predictive of recurrence. Systemic corticosteroids are unable to prevent recurrence [64]. Even though up to 20% anaphylactic reactions are followed by a biphasic reaction, 97% of patients are discharged from the ED after an acute episode of anaphylaxis, particularly when they are of lower social level [50]. This may reflect economic and social considerations, but it seems too high a proportion of the episodes. No specific protocols have been established, but a 24-h admission after an anaphylactic attack would seem reasonable [65]. A recent article [66] reviews retrospective and prospective studies on the incidence of biphasic reactions, the clinical characteristics that may suggest that a reaction will develop into a biphasic

reaction, and the recommendations for observation periods after an anaphylactic reaction.

Discharging patients from the emergency department

Several pieces of information should be given at discharge if a recurrence of anaphylaxis is to be prevented. When a diagnosis of potentially fatal anaphylaxis has been made, the following four actions should be taken:

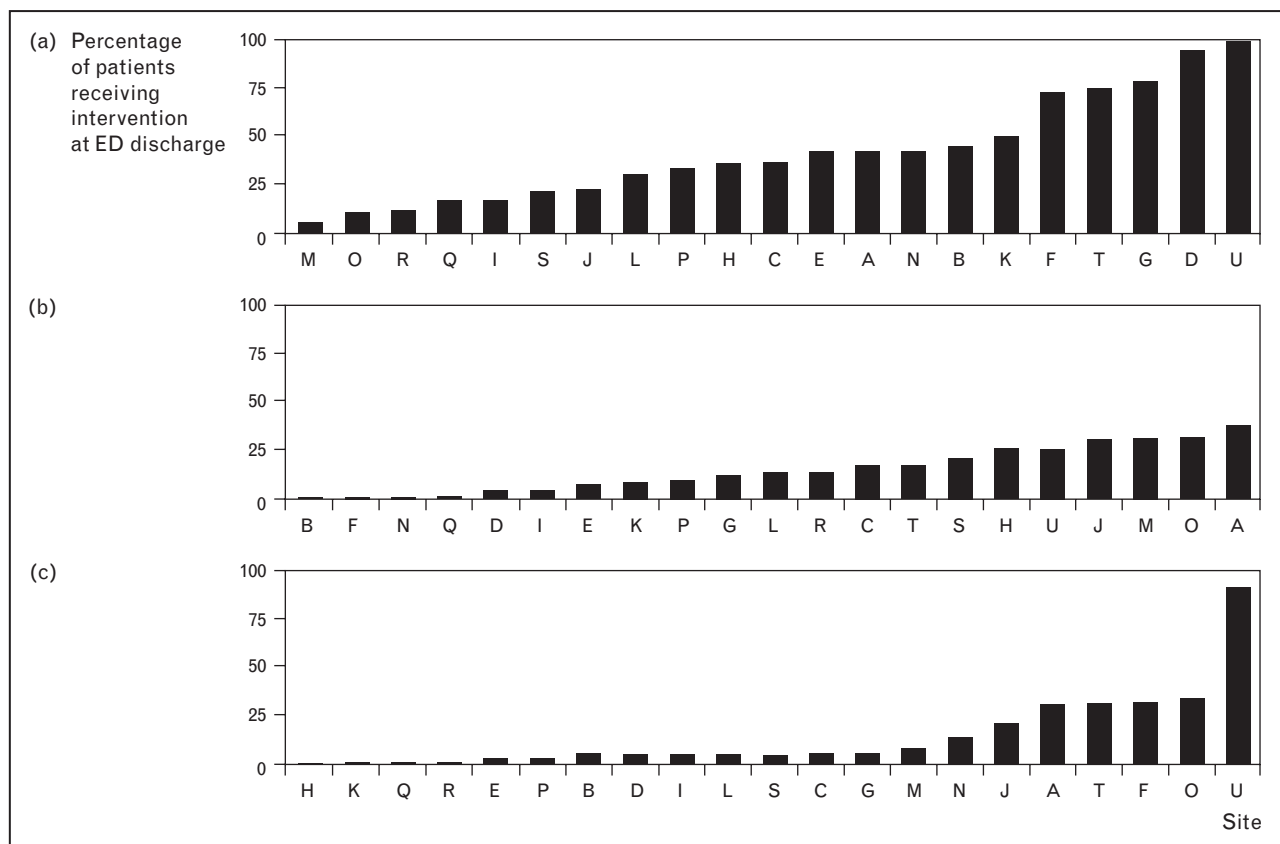
- (1) prescribe self-injectable epinephrine and explain how and in under what circumstances it must be injected;
- (2) give the patient an action plan to be communicated to the child's communities (school, sports organisers, church, etc.);
- (3) inform the school about the possible occurrence of reactions and the appropriate avoidance and rescue measures;
- (4) consider the necessity of a Medic-Alert identification [67].

Education of teachers and health personnel is also necessary [68] to avoid under use or errors in the use of epinephrine [69].

Information on allergen avoidance, prescription of self-injectable epinephrine, and indications for allergists' follow-up are important actions to be taken at discharge. Only a minority of patients currently receive such advice (Fig. 2) [7^{••}]. That only 12% of the patients are referred to an allergist for consultation is particularly worrying; the American Academy of Allergy Asthma and Immunology recommends doing so in all cases [70].

When used appropriately, devices for self-administering epinephrine appear to reduce subsequent morbidity from anaphylaxis [69]. Despite this, they are infrequently used in children with recurrent episodes of anaphylaxis. The reasons for this require further research, but include reluctance by parents and children to use autoinjectors. It is likely that parents and other carers will require continuing education and support in first-aid anaphylaxis management. Other routes of administration, such as

Figure 2 Patients receiving advice at emergency department discharge



(a) Instructed to avoid offending allergen, 40% (95% CI, 36–43). (b) Prescribed self-injectable epinephrine, 16% (95% CI, 14–20). (c) Referred to an allergist, 12% (95% CI, 9–15). CI, confidence interval; ED, emergency department. Reprinted from Clark S, Bock SA, Gaeta TJ, Brenner BE, Cydulka RK, Camargo CA; Multicenter Airway Research Collaboration-8 Investigators. Multicenter study of emergency department visits for food allergies. *J Allergy Clin Immunol.* 2004;113(2):347–52, with permission from Elsevier.

Table 5 Perception of the frequency of anaphylaxis by allergists vs. nonallergists

Anaphylaxis	Allergists	Nonallergists
Common	44.3	16.4
Rare	55.4	82.2
No evidence	0.2	1.4

Reprinted from Simons FE, Frew AJ, Ansotegui IJ, Bochner BS, Golden DB, Finkelman FD, Leung DY, Lotvall J, Marone G, Metcalfe DD, Müller U, Rosenwasser LJ, Sampson HA, Schwartz LB, van Hage M, Walls AF. Risk assessment in anaphylaxis: current and future approaches. *J Allergy Clin Immunol*. 2007 Jul;120(1 Suppl):S2–24, with permission from Elsevier.

sublingual tablets [71], could contribute to better compliance with recommendations.

Conclusion

The emergency department is a crucial site for anaphylaxis treatment and the prevention of subsequent recurrences. Anaphylactic shock happens unexpectedly, often in young and healthy patients, and if not adequately diagnosed and treated may progress rapidly to a fatal or near-fatal situation. ED paediatricians in particular must be prepared to deal with it. A thorough knowledge of the relatively simple protocols for anaphylaxis diagnosis and treatment is necessary to decide what strategy to adopt in specific cases. However, much more work is needed on devising and implementing effective ways to prevent recurrence after an anaphylactic episode. Recently, gross differences have been described in the very awareness of the disease between allergists and nonallergists (Table 5), which highlights the need to improve education in this area [72]. Even when correctly managed, therefore, anaphylaxis remains a problematic condition [73].

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 364).

- 1 Mullins RJ. Anaphylaxis: risk factors for recurrence. *Clin Exp Allergy* 2003; 33:1033–1040.
- 2 Simons FE, Sheikh A. Evidence-based management of anaphylaxis. *Allergy* 2007; 62:827–829.
- 3 Webb LM, Lieberman P. Anaphylaxis: a review of 601 cases. *Ann Allergy Asthma Immunol* 2006; 97:39–43.
- 4 Sampson HA, Muñoz-Furlong A, Campbell RL, *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. *J Allergy Clin Immunol* 2006; 117:391–397.
- 5 Yocum MW, Butterfield JH, Klein JS, *et al.* Epidemiology of anaphylaxis in Olmsted County: a population-based study. *J Allergy Clin Immunol* 1999; 104:452–456.
- 6 Klein JS, Yocum MW. Underreporting of anaphylaxis in a community emergency room. *J Allergy Clin Immunol* 1995; 95:637–638.
- 7 Gaeta TJ, Clark S, Pelletier AJ, Camargo CA. National study of US emergency department visits for acute allergic reactions, 1993 to 2004. *Ann Allergy Asthma Immunol* 2007; 98:360–365.
- This is the most comprehensive study on clinical epidemiology of acute allergic reactions in the emergency department in the USA. On the basis of the National Hospital Ambulatory Medical Care Survey, it uses ICD-9 codes to conclude that anaphylaxis accounts for 1% of all ED visits (or 1 030 000 visits) per year.
- 8 Lieberman P. Epidemiology of anaphylaxis: findings of the American College of Allergy. *Asthma and Immunology Epidemiology of Anaphylaxis Working Group*. *Ann Allergy Asthma Immunol* 2006; 97:596–602.
- 9 Sorenson HT, Nielsen B, Nielsen-Ostergaard J. Anaphylactic shock occurring outside hospitals. *Allergy* 1989; 44:288–290.
- 10 Amornmarn L, Bernard L, Kumar N, *et al.* Anaphylaxis admissions to a university hospital [abstract]. *J Allergy Clin Immunol* 1992; 89 (Suppl): 349.
- 11 Stewart AG, Ewan PW. The incidence, aetiology and management of anaphylaxis presenting to an accident and emergency department. *Q J Med* 1996; 89:859–864.
- 12 Kaufman DW. An epidemiologic study of severe anaphylactic and anaphylactoid reactions among hospital patients: methods and overall risks: abstract from report from the International Collaborative Study of Severe Anaphylaxis. *Epidemiology* 1998; 9:141–146.
- 13 Pastorello EA, Rivolta F, Bianchi M, *et al.* Incidence of anaphylaxis in the emergency department of a general hospital in Milan. *J Chromatogr B Biomed Sci Appl* 2001; 756:11–17.
- 14 Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999–2006. *J Allergy Clin Immunol* 2007; 119:1018–1019.
- A precise review of deaths associated with anaphylaxis indicating that about 50% were and 50% could not be attributed to asphyxia. Peak age was 17–27 with a female and atopic predominance for food anaphylaxis, 45–70 with male and nonatopic predominance for stinging insect stinging anaphylaxis and 60–75 for drug anaphylaxis. The review underlines the danger of epinephrine overdose and its limitations in reversing anaphylaxis.
- 15 Moneret-Vautrin DA, Romano MC, Kanny G, *et al.* The individual reception project (IRP) for anaphylactic emergencies. The situation in France and French overseas territories in 2002. *Presse Med* 2003; 32:61–66.
- 16 Morritt J, Aszkenasy M. The anaphylaxis problem in children: community management in a UK National Health Service District. *Public Health* 2000; 114:456–459.
- 17 Simons FE, Peterson S, Black CD. Epinephrine dispensing patterns for an out-of-hospital population: a novel approach to studying the epidemiology of anaphylaxis. *J Allergy Clin Immunol* 2002; 110:647–651.
- 18 Gupta R, Sheikh A, Strachan DP, Anderson HR. Time trends in allergic disorders in the UK. *Thorax* 2007; 62:91–96.
- Food allergy and anaphylaxis are increasing in the developed world. In UK, since 1990 admissions for anaphylaxis have increased by 700%, for food allergy by 500% and for angioedema by 40%.
- 19 Poulos LM, Waters AM, Correll PK, *et al.* Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993–1994 to 2004–2005. *J Allergy Clin Immunol* 2007; 120:878–884.
- 20 Clark S, Gaeta TJ, Kamarthi GS, Camargo CA. ICD-9-CM coding of emergency department visits for food and insect sting allergy. *Ann Epidemiol* 2006; 16:696–700.
- 21 Sampson HA. Clinical practice. Peanut allergy. *N Engl J Med* 2002; 346:1294–1299.
- 22 Gold MS. EpiPen epidemic or good practice? *J Paediatr Child Health* 2003; 39:376–377.
- 23 Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000; 30:1144–1150.
- 24 Clark S, Long AA, Gaeta TJ, Camargo CA Jr. Multicenter study of emergency department visits for insect sting allergies. *J Allergy Clin Immunol* 2005; 116:643–649.
- 25 Simons FE, Frew AJ, Ansotegui IJ, *et al.* Risk assessment in anaphylaxis: current and future approaches. *J Allergy Clin Immunol* 2007; 120 (Suppl):S2–S24.
- 26 Muraro A, Roberts G, Clark A, *et al.*, EAACI Task Force on Anaphylaxis in Children. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. *Allergy* 2007; 62:857–871.
- A European practical guideline for managing anaphylaxis in childhood acknowledging the importance of intramuscular adrenaline as first-line therapy for anaphylaxis, volume support, nebulized bronchodilators, antihistamines and corticosteroids.

- 27 Simons FE, Frew AJ, Ansoategui IJ, *et al.* Practical allergy (PRACTALL) report: risk assessment in anaphylaxis. *Allergy* 2008; 63:35–37. This practical guideline is endorsed by European and North American Allergy Societies and aims at a common approach in terms of definitions, clinical approach and risk assessment.
- 28 Brown SG, Mullins RJ, Gold MS. Anaphylaxis: diagnosis and management. *Med J Aust* 2006; 185:283–289.
- 29 Drain KL, Volcheck GW. Preventing and managing drug-induced anaphylaxis. *Drug Saf* 2001; 24:843–853.
- 30 Dibs SD. Anaphylaxis in children: a 5-year experience. *Pediatrics* 1997; 99:E7.
- 31 Walker S, Sheikh A. Managing anaphylaxis: effective emergency and long-term care are necessary. *Clin Exp Allergy* 2003; 33:1015–1018.
- 32 Brown SGA, Blackman KE, Stenlake V, Heddle RJ. Insect sting anaphylaxis: prospective evaluation of treatment with intravenous adrenaline and volume resuscitation. *Emerg Med* 2004; 21:149–154.
- 33 Aldrich LB, Moattari R, Vinik AL. Distinguishing features of idiopathic flushing and carcinoid syndromes. *Arch Intern Med* 1988; 148:2614–2618.
- 34 Lieberman P. Anaphylaxis. *Med Clin N Am* 2006; 90:77–95.
- 35 Settiple GA. The restaurant syndromes. *Arch Intern Med* 1986; 146:2614–2618.
- 36 Lieberman P. Anaphylaxis and anaphylactoid reactions. In: Middleton E Jr, editor. *Allergy: principles and practice*. 5th ed. St. Louis: Mosby; 1998. pp. 1079–1092.
- 37 Koike T, Tatewaki W, Aoki A. Brief report: severe symptoms of hyperhistaminemia after the treatment of acute promyelocytic leukemia with tretinoin. *N Engl J Med* 1992; 327:385–387.
- 38 Wellhoener P, Weitz G, Bechstein W, *et al.* Severe anaphylactic shock in a patient with a cystic liver lesion. *Intensive Care Med* 2000; 26:1578.
- 39 Sivagnanam S, Deleu D. Red man syndrome. *Crit Care* 2003; 7:119–120.
- 40 Patterson R, Schatz M. Factitious allergic emergencies: anaphylaxis and laryngeal edema. *J Allergy Clin Immunol* 1975; 56:152–159.
- 41 Goodman DL, O'Connell MA, Sklarew PR. Vocal cord dysfunction presenting as anaphylaxis. *J Allergy Clin Immunol* 1991; 87:278.
- 42 Gompels MM, Lock RJ, Abinun M, *et al.* C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; 139:379–394.
- 43 Sahnoun I, Harmouche H, Aouni M, *et al.* Systemic Capillary Leak Syndrome: two case reports. *Rev Int Med* 2005; 26:409–414.
- 44 Gleich GJ. Episodic angioedema associated with eosinophilia. *N Engl J Med* 1984; 310:1621–1626.
- 45 Lin RY, Schwartz LB, Curry A, *et al.* Histamine and tryptase levels in patients with acute allergic reactions: an emergency department-based study. *J Allergy Clin Immunol* 2000; 106:65–71.
- 46 Schwartz LB, Yunginger JW, Miller J, *et al.* The time course of appearance and disappearance of human mast cell tryptase in the circulation after anaphylaxis. *J Clin Invest* 1989; 83:1551–1555.
- 47 Laroche D, Vergnaud MC, Sillard B, *et al.* Biochemical markers of anaphylactoid reactions to drugs. Comparison of plasma histamine and tryptase. *Anesthesiology* 1991; 75:945–949.
- 48 Kaliner M, Dyer J, Merlin S, *et al.* Increased urine histamine and in contrast media reactions. *Invest Radiol* 1984; 19:116–118.
- 49 Clark S. Multicenter study of emergency department visits for food allergies. *J Allergy Clin Immunol* 2004; 113:347–352.
- 50 Sampson HA. Anaphylaxis and emergency treatment. *Pediatrics* 2003; 111:1601–1608.
- 51 Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 2005; 115:S483–S523.
- 52 Simons FER, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol* 1998; 101:33–37.
- 53 Simons FER, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *J Allergy Clin Immunol* 2001; 108:871–873.
- 54 Chowdhury BA, Meyer RJ. Intramuscular versus subcutaneous injection of epinephrine in the treatment of anaphylaxis. *J Allergy Clin Immunol* 2002; 109:720.
- 55 McLean-Tooke APC, Bethune CA, Fay AC, Spickett GP. Epinephrine in the treatment of anaphylaxis: what is the evidence? *BMJ* 2003; 327:1332–1335.
- 56 Project Team of The Resuscitation Council (UK). Update on the emergency medical treatment of anaphylactic reactions for first medical responders and for community nurses. *Resuscitation* 2001; 48:241–243.
- 57 van der Klauw MM, Wilson JH, Stricker BH. Drug-associated anaphylaxis: 20 years of reporting in The Netherlands (1974–1994) and review of the literature. *Clin Exp Allergy* 1996; 26:1355–1363.
- 58 Fan HW, Marcopito LF, Cardoso JL, *et al.* Sequential randomised and double blind trial of promethazine prophylaxis against early anaphylactic reactions to antivenom for bothrops snake bites. *BMJ* 1999; 318:1451–1452.
- 59 Sheikh A, Ten Broek V, Brown SG, Simons FE. H1-antihistamines for the treatment of anaphylaxis: Cochrane systematic review. *Allergy* 2007; 62:830–837.
- 60 Lin RY, Curry A, Pesola GR, *et al.* Improved outcomes in patients with acute allergic syndromes who are treated with combined H1 and H2 antagonists. *Ann Emerg Med* 2000; 36:462–468.
- 61 Runge JW, Martinez JC, Caravati EM, *et al.* Histamine antagonists in the treatment of acute allergic reactions. *Ann Emerg Med* 1992; 21:237–242.
- 62 Lee JM. Biphasic anaphylactic reactions in pediatrics. *Pediatrics* 2000; 106:762–766.
- 63 Korenblat P, Lundie MJ, Dankner R, Day JH. A retrospective study of the administration of epinephrine for anaphylaxis: how many doses are needed? *Allergy Asthma Proc* 1999; 20:383–386.
- 64 Stark BJ. Biphasic and protracted anaphylaxis. *J Allergy Clin Immunol* 1986; 78:76–83.
- 65 AAAI Board of Directors. The use of epinephrine in the treatment of anaphylaxis. *J Allergy Clin Immunol* 1994; 94:666–668.
- 66 Tole JW, Lieberman P. Biphasic anaphylaxis: review of incidence, clinical predictors, and observation recommendations. *Immunol Allergy Clin North Am* 2007; 27:309–326.
- 67 Simons FER, Chan ES, Gu X, Simons KJ. Epinephrine for out-of-hospital (first-aid) treatment of anaphylaxis in infants: is the ampule/syringe/needle method practical? *J Allergy Clin Immunol* 2001; 108:1040–1044.
- 68 Grouhi M, Alshehri M, Hummel D, Roifman CM. Anaphylaxis and epinephrine auto-injector training: who will teach the teachers? *J Allergy Clin Immunol* 1999; 103:190–193.
- 69 Gold MS, Sainsbury R. First aid anaphylaxis management in children who were prescribed an epinephrine autoinjector device (EpiPen). *J Allergy Clin Immunol* 2000; 106:171–176.
- 70 American Academy of Allergy, Asthma, & Immunology website. Available at: <http://www.aaaai.org/patients/publicedmat/tips/whatisanaphylaxis.stm>. [Accessed 14 March 2008]
- 71 Rawas-Qalaji MM, Simons FE, Simons KJ. Fast-disintegrating sublingual epinephrine tablets: effect of tablet dimensions on tablet characteristics. *Drug Dev Ind Pharm* 2007; 33:523–530.
- 72 Cruz NV, Wilson BG, Fiocchi A, Bahna SL, American College of Allergy, Asthma and Immunology Adverse Reactions to Food Committee. Survey of physicians' approach to food allergy. Part 1: prevalence and manifestations. *Ann Allergy Asthma Immunol* 2007; 99:325–333.
- 73 Sampson HA. Anaphylaxis: persistent enigma. *Emerg Med Australas* 2006; 18:101–102.