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Position paper

The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology

Anaphylaxis is a growing paediatric clinical emergency that is difficult to diagnose because a consensus definition was lacking until recently. Many European countries have no specific guidelines for anaphylaxis. This position paper prepared by the EAACI Taskforce on Anaphylaxis in Children aims to provide practical guidelines for managing anaphylaxis in childhood based on the limited evidence available. Intramuscular adrenaline is the acknowledged first-line therapy for anaphylaxis, in hospital and in the community, and should be given as soon as the condition is recognized. Additional therapies such as volume support, nebulized bronchodilators, antihistamines or corticosteroids are supplementary to adrenaline. There are no absolute contraindications to administering adrenaline in children. Allergy assessment is mandatory in all children with a history of anaphylaxis because it is essential to identify and avoid the allergen to prevent its recurrence. A tailored anaphylaxis management plan is needed, based on an individual risk assessment, which is influenced by the child's previous allergic reactions, other medical conditions and social circumstances. Collaborative partnerships should be established, involving school staff, healthcare professionals and patients' organizations. Absolute indications for prescribing self-injectable adrenaline are prior cardiorespiratory reactions, exercise-induced anaphylaxis, idiopathic anaphylaxis and persistent asthma with food allergy. Relative indications include peanut or tree nut allergy, reactions to small quantities of a given food, food allergy in teenagers and living far away from a medical facility. The creation of national and European databases is expected to generate better-quality data and help develop a stepwise approach for a better management of paediatric anaphylaxis.

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Introduction

Anaphylaxis is a clinical emergency and all physicians caring for children should be familiar with its management. This position paper has been prepared by the EAACI Taskforce on Anaphylaxis in Children. It aims to provide evidence-based guidelines for managing anaphylaxis in childhood. Particular emphasis has been placed on how to tackle the practical issues associated with managing children at risk of anaphylaxis.

An extensive literature search was undertaken using appropriate search terms in Medline and EMBASE (e.g. anaphylaxis, hypersensitivity, immediate, food hypersensitivity, drug hypersensitivity, latex hypersensitivity, respiratory hypersensitivity, insect hypersensitivity, epidemiological, aetiology, pathophysiology, prevention, drug therapy, diet therapy, therapy). Although a systematic review of the evidence was undertaken, only the highest available evidence for each issue is presented here. The recommendations in this document are labelled to indicate the strength of evidence (1).

Definitions

Anaphylaxis has been defined as a 'severe, life-threatening generalized or systemic hypersensitivity reaction' (2) (D).

Box 1. Clinical criteria for the diagnosis of anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria are 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:
   a. Respiratory compromise (e.g. dyspnoea, bronchospasm, stridor, hypoxia).
   b. Cardiovascular compromise (e.g. hypotension, collapse).
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 or mucosal tissue (e.g. generalized hives, itch, flushing, swelling).
   b. Respiratory compromise (e.g. dyspnoea, bronchospasm, stridor, hypoxia).
   c. Cardiovascular compromise (e.g. hypotension, collapse).
   d. Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting).
3. Hypotension after exposure to known allergen for that patient (minutes to several hours):
   Hypotension for children is defined as systolic blood pressure <70 mmHg from 1 month to 1 year [<70 mmHg + (2 × age)] from 1 to 10 years, and <90 mmHg from 11 to 17 years.

Adapted from Sampson [5] (D).

The World Allergy Organisation (WAO) has suggested that the term allergic anaphylaxis is used to describe immunological reactions involving IgE, IgG or immune complexes. In IgE-mediated allergic anaphylaxis there is a systemic release of mediators by mast cells and basophils. Where nonimmunological mechanisms are involved, the WAO paper suggests that the term nonallergic anaphylaxis is used (2) (D). As nonallergic anaphylaxis is a relatively uncommon condition in children, this will not be discussed further. The term 'anaphylactoid' should be avoided. The lack of specific clinical criteria for defining anaphylaxis has made it difficult for physicians to promptly diagnose an anaphylactic reaction and has resulted in its incidence being underestimated (3, 4). An international task force on anaphylaxis has recently recommended a new working clinical definition that should assist clinicians in making the diagnosis and help lay people to recognize anaphylaxis (see adapted version in Box 1) (5).

Epidemiology

Our understanding of the epidemiology of anaphylaxis is challenged by inconsistencies in the definitions used by different investigators. It has been suggested that the incidence of anaphylaxis in adults is 30 per 100 000 person years (6). The prevalence of life-threatening anaphylaxis has been estimated at 5–15 per 100 000 (7). United Kingdom (UK) studies based on routine hospital admission data have recorded a sevenfold increase in anaphylaxis from 1990/91 to 2003/04 (8, 9) with the highest rate in school-age children.

The risk of anaphylaxis in childhood cannot be assessed accurately because there is minimal paediatric data. The available data suffer from methodological shortcomings because of the use of substantially different definitions of anaphylaxis. For example, some reports claim that the annual incidence of childhood anaphylaxis is the same as in adulthood (10, 11) while others place it at only 0.19 in 100 000 (12). This latter figure is probably an underestimation because of methodological problems (13). Other approaches have been used to explore the epidemiology of anaphylaxis. In a survey of all French schoolchildren, it was estimated that one in 1000 have personalized anaphylaxis management plans (14). Additionally, prescriptions of adrenaline have increased reflecting the growing perception of the allergic risk. For example, in the UK they increased sevenfold for children born 1990–1992 compared with those born between 1981 and 1983(15). In Canada, the prescription rate for adrenaline is now 1% of the population, with a peak of 5% in males aged 12–17 months (16).

Food allergy is the most common cause of anaphylaxis in children (17–19). For example, a 3-year retrospective Australian emergency department chart review revealed that food (56%), drugs (5%) and insects (5%) were the principal agents responsible for anaphylaxis in children; in the remainder, the cause was not identified (11). Antibiotics, particularly β-lactams and penicillins, are the most commonly incriminated drugs reported to the Allergy Vigilance Network (7). Muscle relaxants remain the commonest cause of severe anaphylaxis during anaesthesia (20, 21). Children with an atopic background, spina bifida or multiple operations are particularly at risk of anaphylaxis to latex (22–24). Anaphylaxis has also been reported with specific immunotherapy (25). The last category of anaphylactic reactions is idiopathic. This is a diagnosis of exclusion and its incidence in the paediatric population is unclear (26).

The outcome of severe anaphylaxis is fatal in 0.65–2% of cases (27, 28) causing an estimated 1–3 deaths per million people annually. A series of 32 cases of lethal food-allergy induced anaphylaxis from 1994 to 1999 was evaluated in the USA (18). Age of death was between 2 and 33 years, with acute severe bronchospasm occurring in most cases (96%). This is similar to the UK experience (29). Peanuts and tree nuts accounted for 63% and 31%, respectively of the American fatal cases, while other allergens were milk and fish. The estimated frequency of deaths because of food anaphylaxis in the USA is 150 deaths per year (18).

Clinical presentation

Clinical manifestations of anaphylaxis

Clinically anaphylaxis is a severe, systemic syndrome involving respiratory and/or cardiovascular symptoms and/or signs, such as stridor, wheezing or hypotension. In absence of treatment, the reaction may rapidly progress with increasingly severe manifestations with a potentially fatal outcome. With IgE mediated allergy,

symptoms occur within 2 h of exposure to the allergen. With food allergens symptoms often occur within 30 min, even faster with parenteral medications and insect stings. Cutaneous symptoms or signs occur with most cases of anaphylaxis, particularly in childhood (10, 11, 30). Pruritus, particularly on the palms, feet and head, may be an early sign of impending anaphylaxis but it is important to note that progression to anaphylaxis can occur in the absence of cutaneous manifestations.

The most worrying manifestation of anaphylaxis in children is bronchospasm (10, 11, 31, 32) (D). Upper airway symptoms because of laryngeal oedema, presenting with stridor, dysphonia, aphonia or respiratory distress, should alert clinicians to the severity of a reaction. Hypotension and shock are less common as early manifestations of anaphylaxis in childhood (11, 32). Hypotension is often accompanied by a sensation of light-headedness and a feeling of impending doom, or loss of consciousness. Acute, severe abdominal cramps, possibly associated with severe vomiting and/or diarrhoea, can herald a severe anaphylactic reaction (30) (D). Other early manifestations of anaphylaxis include acute rhinorrhoea and sudden-onset itching of the eyes and nose. A severity score can be helpful in the diagnosis and ensuring the timely administration of adrenaline (see Table 1) (33). An overall incidence of 6% was reported for recurrent or biphasic anaphylaxis (32) with 3% severe reaction, in a retrospective study of a US pediatric inpatient service. Ninety per cent of the recurrent reaction occurred within 4–12 h of the first signs. Delay in giving adrenaline injection increases the incidence of biphasic reactions (34–37). Some subjects may also have persistent anaphylaxis lasting many hours. Exercise-induced anaphylaxis (EIA) is a syndrome characterized by urticaria, symptoms of upper airway obstruction and vascular collapse after exercise (38, 39). It mainly affects teenagers and is often associated with food (Food Dependent EIA).

Risk factors for anaphylaxis

Patients who have had an anaphylactic reaction have a strong likelihood of having another one (B) (40–42). Comparing the severity of past reactions, the characteristics of the last reaction seem to be important in estimating the risk of anaphylaxis (43) (C). However, there are data demonstrating that children with only mild reactions may suffer more severe ones (44).

A history of asthma appears to be a major risk factor for life-threatening anaphylactic reactions to food (33, 35, 41, 42) (B). Almost all fatal cases of anaphylaxis occur in patients with asthma (29, 31, 45) (C). While asthma would seem to be a sensitive marker, it is not particularly specific as about a third of food allergic patients have asthma. Moreover, life-threatening anaphylaxis is experienced by children without asthma. In summary, a history of previous anaphylactic reactions or coexistent asthma can identify sub-groups of food-allergic children at higher

Table 1. Grading the severity of anaphylactic reactions

Grade	Skin	GI tract	Respiratory	Cardiovascular	Neurological
1 Mild	Sudden itching of eyes and nose, generalized pruritus, flushing, urticaria, angioedema,	Oral pruritus, oral 'tingling', mild lip swelling, nausea or emesis, mild abdominal pain	Nasal congestion and/or sneezing, rhinorrhoea, throat pruritis, throat tightness, mild wheezing	Tachycardia (increase >15 beats/min)	Change in activity level plus anxiety
2 Moderate	Any of the above	Any of the above, crampy abdominal pain, diarrhoea, recurrent vomiting	Any of above, **hoarseness, 'barky' cough, difficulty swallowing, stridor, dyspnoea, moderate wheezing**	As above	'Light headedness' feeling of 'pending doom'
3 Severe	Any of the above,	Any of the above loss of bowel control	Any of the above, **cyanosis** or Saturation <92%, **respiratory arrest**	**Hypotension* and/or collapse, dysrhythmia, severe bradycardia and/or cardiac arrest**	Confusion, loss of consciousness

The severity score should be based on the organ system most affected. Bold face symptoms and signs are mandatory indication for the use of adrenaline (epinephrine) (33).
* Hypotension defined as systolic blood pressure: 1 month to 1 year <70 mmHg; 1–10 years< [70 mmHg + (2 × age)]; 11–17 years <90 mmHg. Modified from Sampson (33).

risk of anaphylaxis but it is impossible to identify a very low risk group. Additional risk factors are linked to the amount and type of allergen (e.g. peanut), physical location and age group (e.g. adolescence). High levels of atopy has been reported as being associated with more severe reactions (31, 43, 45) (C). A full risk assessment should be performed for each child encompassing all these factors.

Managing anaphylaxis

The management of anaphylaxis includes both the treatment of acute episodes and the implementation of community strategies to avoid recurrences.

Treating the acute episode

Rapid treatment is crucial. Adrenaline (epinephrine) is the medication of choice for anaphylactic episodes (A); other medications should be regarded as adjuvants (46) (D). The α-adrenergic effects of adrenaline increase peripheral vascular resistance, blood pressure and coronary artery perfusion, while reducing angioedema and urticaria. Whilst its β1-adrenergic effects increase heart rate and contraction, the β2-adrenergic effects mediate bronchodilation and inhibit the release of inflammatory mediators (47). Adrenaline has a relatively narrow therapeutic window (benefit/risk ratio) which must be considered when planning treatment (B). Its early use has been associated with a better outcome (48) (C) but adrenaline autoinjectors are infrequently prescribed and used in paediatric practice (48–50).

Indications for adrenaline administration

Physicians. Adrenaline should be administered to a child with an anaphylactic reaction involving any respiratory and/or cardiovascular symptoms or signs; otherwise it is usually not recommended. However, specific management should be tailored to the individual. For example, if a child has recurrent episodes of anaphylaxis commencing with severe abdominal pain, the earlier use of adrenaline would be justified if they developed severe abdominal pain with contact with the same allergen (D). Also an earlier use of adrenaline is justified in children with a history of asthma, particularly for those needing regular asthma medication (D).

Parents or patients. In general, the same indications apply as for physicians. Families find it difficult to identify which symptoms and signs should prompt the use of adrenaline. They should be told to administer adrenaline if in doubt, without waiting for severe symptoms to develop as delayed treatment has been associated with fatality (29, 31, 51) (C). Unfortunately many parents and relatives do not use adrenaline even when their child is experiencing a life-threatening anaphylactic reaction because they do not know when to use the device or are anxious about its use (48, 52, 53). Indications for prescribing a self-injectable adrenaline device are reviewed in the section 'Self-injectable adrenaline device and indication for their prescription in the community'.

Contraindications

In childhood, there are no absolute contraindications for the use of adrenaline as children do not usually suffer from any significant co-morbidities, such as coronary heart diseases or cardiac arrhythmias. In few situations however, advice to families may need to be modified. An example is a food allergic child at higher risk of tachyarrhythmias because of hypertrophic obstructive cardiomyopathy; in this situation, the paediatrician must weigh the risks and benefits remembering that adrenaline can be life saving in anaphylaxis.

Route of administration

Intramuscular route. The intramuscular route is preferred for both families and professionals because intramuscular adrenaline is rapidly bioavailable, with peak concentrations occurring within 10 min of administration (47, 54), and has a much better safety profile and longer-lasting action (B) than intravenous adrenaline (29). The vastus lateralis muscle (lateral side of the thigh) has been recommended as the best site for injection (46, 54) (B). Self-injection devices are marketed and are a more effective option than the cheaper ampoules and syringes which are difficult to use outside hospital (55) (C).

Intravenous route. In children with severe anaphylaxis refractory to intramuscular adrenaline or in cardiovascular collapse, intravenous adrenaline should be given with blood pressure (ideally invasive) and continuous cardiac monitoring because of the danger of inducing a hypertensive crisis or ventricular arrhythmia. (57–59) (B).

Respiratory route. Inhaled adrenaline is not effective as a result of its inadequate systemic bioavailability at doses available from an inhaler or nebulizer (60) (C). Oral swelling or oedema may benefit from inhaled adrenaline from metered dose inhalers or nebulizers (D).

Miscellaneous routes. If it is impossible to place an intravenous line, the intraosseous route can be used (61) (B). Formulations for sublingual administration are under investigation (62). In a rabbit model, the systemic bioavailability of sublingual adrenaline is slightly slower than intramuscular adrenaline. Patients may use sublingual adrenaline earlier making it a potentially useful adjunct in future for community treatment.

Doses

For the intramuscular route, 1 : 1000 adrenaline (1 mg/ml) should be used at a dose of 0.01 ml/kg body weight (maximum single dose 0.5 mg). This equates to 10 μg adrenaline per kg body weight. This dosage can be repeated at short intervals (every 5–10 min) until the patient's condition stabilizes. If intravenous adrenaline is used, a dose of 0.1 μg /kg/min has been recommended (36, 57) (D). The dose of adrenaline recommended in cardiac arrest protocols has recently been reduced in the light of paediatric evidence suggesting that high-dose adrenaline is less effective than lower doses, particularly in cases of arrest precipitated by asphyxia (63) (B). Unfortunately, there are no similar data focusing specifically on anaphylaxis.

Fluid support

Severe episodes of anaphylaxis often involve the cardiovascular system and result in tachycardia and decreased arterial blood pressure. They should be treated with both adrenaline and volume support. A crystalloid solution or a colloid expander can be used, starting with a volume of 20 ml/kg over 10–20 min. This can be repeated. If more than 40 ml/kg is required, inotropic support with a dopamine or adrenaline infusion should be started, ideally with invasive blood pressure monitoring. Ventilation support is also likely to be required at this stage (58, 59) (B).

Inhaled beta-2-agonists

An inhaled beta-2-agonist via a spacer device or nebulizer is a useful adjuvant in treating bronchospasm associated with anaphylaxis. However, their delivery may be impaired by acute bronchospasm and systemic adrenaline must still be considered the first line therapy.

Oxygen

High-flow oxygen, preferably via a nonrebreathing mask, is essential. It should be administered to any patient experiencing respiratory symptoms or hypotension associated with anaphylaxis (58, 59).

H_1 antagonists

H_1 antagonists should be given promptly if a child has been exposed to an allergen or develops clinical symptoms or signs of an allergic reaction. However, there is no evidence of their efficacy in anaphylaxis (64) (B). Their use is based mainly on clinical observation (D) and should never delay the administration of adrenaline. The ideal antihistamine should be in liquid form, rapid-in-onset, nonsedating and long-lasting (Table 2). Diphenhydramine or chlorpheniramine are the only antihistamines available for the intravenous route.

Corticosteroids

Corticosteroids should not be considered as a first-line treatment for anaphylaxis. They do not act fast enough and their efficacy in reducing the risk of late-phase reactions has not been fully proven (D). Hydrocortisone or methylprednisolone succinate are generally used for the intravenous route.

Other treatment options

Other treatment options proposed for adults, such as intravenous H_2 antagonists and glucagon, have not been adequately tested in children (65–68).

Protocol for initial anaphylaxis management in the emergency department

Assessment should start with a rapid assessment of the child's airway, breathing and circulation (A). If the child is in cardio-respiratory arrest, they should be managed using a standard arrest protocol (59). Patients must be regularly reassessed; repeated doses of adrenaline are indicated until clinical improvement is achieved. Children showing respiratory symptoms or signs should be closely monitored for at least 6–8 h (34, 36, 37) (C) Children presenting with hypotension or collapse should be admitted to a high-dependency or intensive care facility for at least 24 h (C). Prior to discharge, the families of children presenting with anaphylaxis should receive

Table 2. Examples of antihistamines used in the management of anaphylaxis (British National Formulary)

Medication	Antihistamine type	Dose
Chlorpheniramine	H_1	Intravenous or intramuscular: up to 1 year chlorpheniramine 250 mcg/kg (maximum 2.5 mg); 1–6 years 2.5–5 mg; 7–12 years 5–10 mg; 12–18 years 10–20 mg; oral: 1 month–1 year 1 mg; 1–6 years 2 mg; 12 years 4 mg; 12–18 years 8 mg 6–12 years 4 mg; 12–18 years 8 mg.
Cetirizine	H_1	Oral: 2–6 years 5 mg; 6–18 years 10 mg
Levocetirizine	H_1	Oral: 6–18 years 5 mg
Loratadine	H_1	Oral: <30 kg: 5 mg; >30 kg: 10 mg
Desloratadine	H_1	Oral: >12 years: 5 mg
Fexofenadine	H_1	Oral: >12 years: 120–180 mg
Oxatomide	H_1	Oral: 0.5 mg/kg twice a day

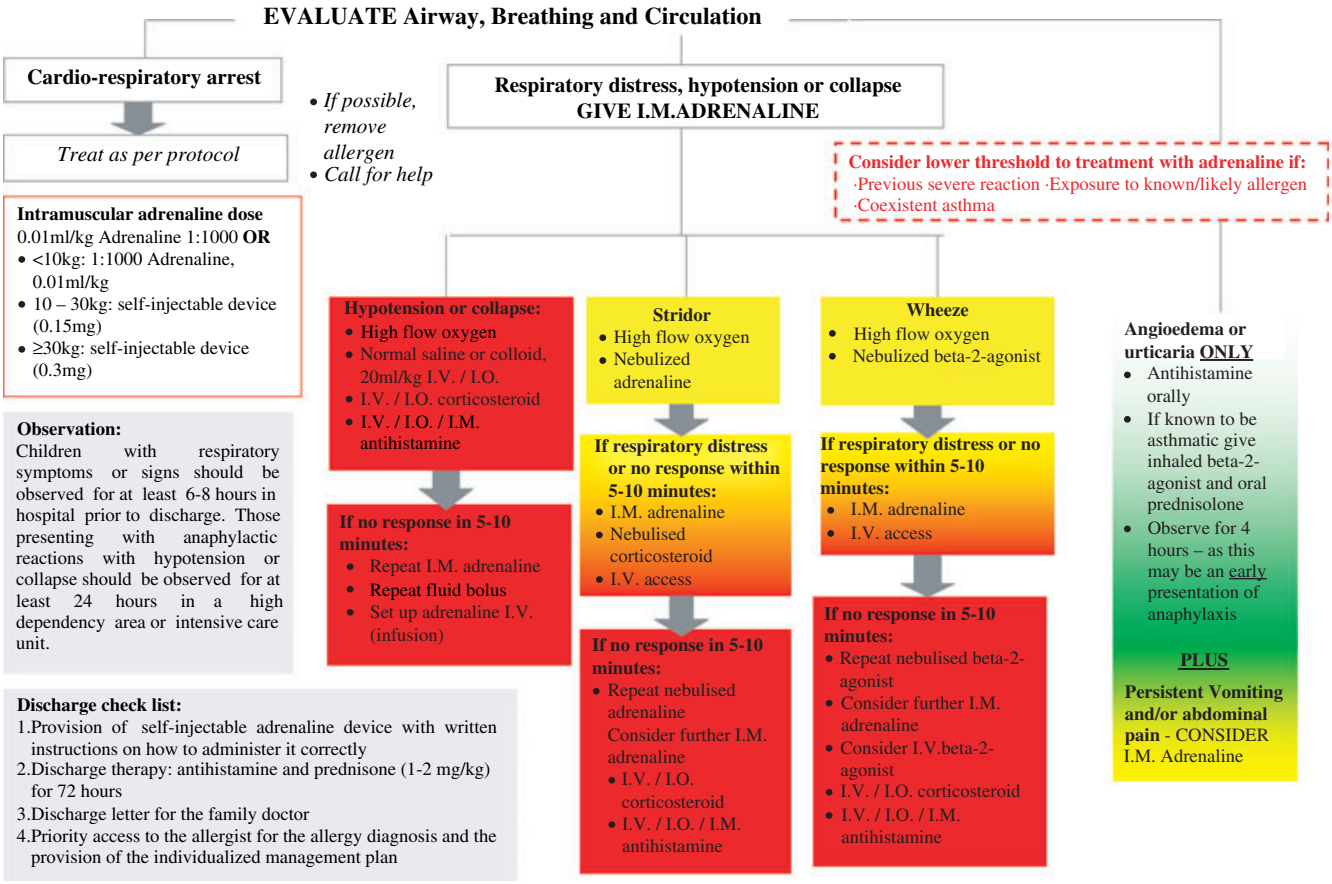

Figure 1. An example of a protocol for the initial management of anaphylaxis in the emergency department.

training on how to use the self-injectable devices and avoid contact with the precipitant (C). They should also be informed of the risk of a late-phase reaction. An example of a protocol for initially managing anaphylaxis in hospital is shown in Fig. 1.

Management of anaphylaxis in the community

Most episodes of anaphylaxis occur in the community. Children and their care givers must know how to prevent further reactions and promptly recognize and appropriately manage any anaphylactic reactions that occur outside the hospital.

Assessing the child to identify the allergen

Children and teenagers with a history suggestive of an anaphylactic reaction need urgent referral to a paediatric allergy clinic for a diagnostic assessment to identify the allergen (D). Knowing the allergen involved in a previous anaphylactic reaction is crucial to the management of the child so that the family can take the necessary steps to prevent further exposures.

History

The clinical history is key part of the diagnostic work-up. It is important to analyse the labels from any food ingested in the 2 h preceding the reaction. A comprehensive history is required to identify hidden allergens. Apart from foods, particular focus should be placed on identifying any prior stings, contact with latex or associated exercise. The history should also explore the differential diagnosis of anaphylaxis. This includes vasovagal syncope (the child is usually relatively bradycardic with no cutaneous or respiratory signs of anaphylaxis), panic attacks, vocal cord dysfunction, hereditary angioedema, systemic mastocytosis and other causes of acute respiratory or cardiovascular impairment. It is also important to identify risk factors for recurrence (31, 56) (C).

Investigations

There is no diagnostic test for anaphylaxis. Serum tryptase, selectively produced by mast cells, may be elevated in some children in the early hours after the onset of anaphylaxis (69) (C). The degree of elevation is correlated

with the degree of hypotension but normal results do not exclude the diagnosis especially in food anaphylaxis (35). Tryptase levels may also be elevated in systemic mastocytosis.

Most anaphylactic reactions are IgE-mediated and tests to demonstrate specific IgE antibodies should be performed (71). A positive skin prick test or specific IgE in the context of a convincing history will confirm the diagnosis (C). Unfortunately, anaphylaxis is occasionally seen in children with no detectable cutaneous or serum specific IgE while positive skin test and specific IgE antibodies may be found in asymptomatic individuals (45).

Identifying the food allergen implicated in the anaphylactic reaction is important in preventing inappropriate restrictions on the growing child's diet and lifestyle (70) (C). The serum specific IgE and skin prick test cut-off levels for true IgE-mediated allergy have been studied (72–77) but no values have been established so far to identify subjects at risk of anaphylaxis (B). The evaluation of the number and diversity of allergenic epitopes bound by patients' IgE antibodies, enabled by the development of protein and peptide microarrays, may be more useful for predicting the clinical severity of food allergic reactions (78). Patients with a history of life-threatening anaphylaxis should be challenged only when the causative antigen cannot be conclusively determined by history and laboratory testing or if the patient is believed to have outgrown the food allergy. Oral food challenges should include exercise testing if exercise is considered an amplifying factor (38).

Avoidance to prevent recurrence

Strategies to avoid the precipitants should be customized considering factors such as, age, occupation, activity, hobbies, living conditions and access to medical care.

General principles of food avoidance including cross-reactivity, contamination, indirect exposure

Patients or parents should be informed of the possibility of an allergic reaction after ingestion, contact or inhalation of food allergens. Patients should be carefully instructed about hidden allergens (79–82), cross-reactions to other allergens (83) and situations that constitute a special hazard for children with food allergy, such as exposure to foods at school, day-care, the homes of friends or relatives and restaurants. In addition, information should be provided about unforeseen risks during medical procedures. Physicians should teach patients about the risks of future anaphylaxis, as well as the benefits of avoidance measures. Several training sessions may be needed before families are competent to manage the condition (84). Additional information can be provided by patient association web sites (e.g. www.foodallergyalliance.org; accessed 14 May 2007) or other sources (e.g. www.foodallergens.info; accessed 14 May 2007).

Strategies for avoiding further anaphylactic reactions

Insect sting hypersensitivity. Patients should be advised to avoid wearing bright clothes or consuming sweet foods or drinks out of doors as these attract bees and wasps (D). Allergen immunotherapy with the appropriate insect venom is recommended for patients with anaphylactic reactions (85, 86) (A).

Allergen immunotherapy. Anaphylaxis is a known adverse event with allergen immunotherapy. Only physicians trained to recognize and treat anaphylaxis should administer immunotherapy. Poorly-controlled asthma is a contraindication to immunotherapy. Patients should be monitored for at least 30 min after allergen immunotherapy (25) (C). If severe allergic reactions occur with allergen immunotherapy, it is best to consider stopping the therapy (87).

Medications. The drug-allergic child must avoid the specific medication and similar compounds (e.g. penicillins). Desensitization to medications known to have caused anaphylaxis may be effective (88) (B). In most cases, the effect is temporary and the desensitization process must be repeated if the medication is required again.

Latex. Precautions should be taken when a latex-sensitive patient undergoes surgery or dental treatment (89). The operating room or dental surgery should be latex-free. No latex gloves should be used and the patient should be the first case of the day. It is important to recognize the risk of cross-reactivity between latex and foods. Commonly-reported cross-reactive foods include banana, avocado, kiwi and chestnut.

Exercise induced anaphylaxis. Where a particular food or group of foods has been identified by association in so-called food-dependent exercise-induced anaphylaxis (FDEIA), the specific foods should be avoided for at least 4 h prior to exercise (38, 39). An empty stomach or fasting before exercise is of utmost importance when no precise food has been correlated with the clinical manifestations. Patients should also be instructed to avoid cross-reactive foods (e.g. rye or barley in subjects with wheat-dependent EIA).

Protocol for managing anaphylaxis in the community

There is a limited evidence base that has resulted in the suboptimal management of anaphylaxis in the community (83, 90–93). Some recommendations can be made (see Box 2)

Box 2. Recommended actions for the management of children at risk of anaphylaxis in the community

- Prescription of adrenaline.
- Education of families and care givers.
  - Instructions on allergen avoidance measures.
  - Instructions on prompt recognition of symptoms of anaphylaxis.
  - Regular training on the use of the self-injectable adrenaline.
  - Reinforcement with revision at yearly intervals.
- Provision of emergency kit with tailored medications for self-treatment.
- Provision of individualized management plan.
- Implementation of the management plan to the community.

Box 3. Indications for prescribing self-injectable adrenaline

Absolute indications:
- Previous cardiovascular or respiratory reaction to a food, insect sting or latex.
- Exercise induced anaphylaxis.
- Idiopathic anaphylaxis.
- Child with food allergy and co-existent persistent asthma*.

Relative indications:
- Any reaction to small amounts of a food (e.g. airborne food allergen or contact only via skin).
- History of only a previous mild reaction to peanut or a tree nut.
- Remoteness of home from medical facilities.
- Food allergic reaction in a teenager.

*This is an opinion-based indication extrapolated from data emerging from retrospective studies.

Table 3. Self-injectable adrenaline devices

Device	Adrenaline content	Indications
Anapen®	0.3 mg	>30 kg
Anapen junior®	0.15 mg	15–30 kg
*EpiPen®	0.3 mg	>30 kg
*EpiPen junior®	0.15 mg	15–30 kg
†Twinject®	0.3 mg	>30 kg
†Twinject junior$_1$	0.15 mg	15–30 kg

*The EpiPen is also marketed as Fastjekt®.
†The Twinject carries two doses of adrenaline and is currently marketed only in the US.

Self-injectable adrenaline devices and indications for their prescription in the community (Box 3)

Several self-injectable adrenaline devices are available in many countries (Table 3), each containing a fixed dose. Although adrenaline degrades rapidly, these devices keep well if stored at room temperature, away from heat sources and direct sunlight (94). There is no self-injectable adrenaline device for infants under 15 kg body weight. Mild overdosing of a child with a self-injectable adrenaline device does not seem to represent a major risk in otherwise healthy children (95) (C). The alternative is to provide parents of young children with an ampoule of adrenaline and a syringe. However, parents take a long time to prepare the injection and the dosage actually administered varies widely (55). It is probably more practical to provide otherwise healthy infants over 7.5 kg body weight with a 150 μg self-injectable adrenaline device giving an arbitrary maximum dose of 20 μg /kg (C).

There are four absolute indications for a self-injectable adrenaline device (Box 3): a prior cardiovascular or respiratory reaction to a food, insect sting or latex (B); EIA; idiopathic anaphylaxis and coexistent persistent asthma in children with food allergy (D). This last indication is extrapolated from data emerging from retrospective studies. Prospective studies are needed to better define the severity and control (96) of asthma associated with increased risk of anaphylaxis in food allergic children. Relative indications are a history of even a mild reaction to peanut or a tree nut; any reaction to small amounts of a food including airborne food allergen and cutaneous contact (97, 98); living far from medical facilities and food allergic reactions in teenagers (18, 45) (D). Isolated food-induced atopic dermatitis and oral allergy syndrome do not warrant the prescription of a self-injectable adrenaline device.

The current inconsistency in the prescription of self-injection devices (49, 99–101) is mainly because of conflicting data from studies. For example, for children with previous mild reaction to nut, a USA study (44) has reported a 5% annual rate of anaphylaxis whereas a UK study reported only a 1% annual risk (102). A possible explanation is that the USA study focused on the first reaction while the UK one focused on the most severe reaction. Moreover, the UK patients were all reviewed at yearly intervals to reinforce avoidance training and prescribe self-injectable adrenaline if a subject developed asthma.

While a self-injectable adrenaline device can be life saving, over-prescription is potentially disadvantageous. It is easy to speculate that if every child with food allergy were prescribed one, less attention would be focused on the children with the highest risk of anaphylaxis. Care givers, teachers and families could also face the additional burden of carrying medical equipment wherever the child goes (103). Additionally, the availability of a self-injectable adrenaline device may encourage children to be less compliant with avoidance measures.

The number of self-injectable adrenaline devices that should be prescribed depends on the careful evaluation of the individual situation of the family and the child, as well as on any national practice parameters. The reasons for prescribing two self-injection adrenaline devices include the possibility of misfiring (104), remote location without rapid access to medical support, a large child (e.g. >45 kg) or concern about the failure to respond to the first dose. There are community and emergency department data (98, 105–107) suggesting that 20% of patients suffering from an anaphylactic event who used a self-injectable adrenaline device received a second dose and case-series data demonstrates that a single self-injectable adrenaline device may be insufficient to prevent a fatal outcome in some patients (29). Additionally, many

schools and nurseries insist that they keep self-injection devices for each child with a severe allergy. An alternative approach would be for self-injectable adrenaline devices to become a standard part of a readily accessible school emergency medical kit. In this case, each child's personalized management plan would then direct the care givers to use the appropriate device from this kit.

Use of other medications to manage allergic reactions in the community

The provision of an inhaled beta-2-agonist, oral antihistamines and oral steroids for treating early symptoms of anaphylaxis in the community is highly controversial as it is argued that this can potentially delay the timely administration of adrenaline in absence of an evidence base for their efficacy. However, there is general agreement that an oral fast acting H_1 antagonist should be carried with the child at all times and administered at the beginning of an allergic reaction regardless of its predicted severity. An antihistamine syrup is ideal as it is more easily ingested and rapidly absorbed.

Training the family and other care givers

The task of identifying in a timely manner the symptoms related to the onset of anaphylaxis and administering lifesaving medication is usually the responsibility of nonmedical care givers (e.g. school teachers). Appropriate training of care givers in allergen avoidance and administration of emergency medication is therefore crucial. Education is an ongoing process and regular reinforcement with revisions is also necessitated by possible changes in the child's clinical condition and in the allergen content and labelling of foods (108) (C). Families and care givers need to be able to recognize an allergic reaction and know how to react according to the different levels of clinical severity. In addition families are frequently poorly trained in the use of the self-injectable adrenaline devices and may forget vital parts of the procedure even after a full training session (109) (C). This is not helped by the different techniques of the available devices. Regular refresher training sessions are required aiming to ensure that parents react appropriately, even when in panic.

There is also a need to educate physicians in the management of anaphylaxis (49, 105, 110). Only a quarter of professionals are able to demonstrate the three critical steps required to administer a self-injectable adrenaline device correctly (50, 110–112).

Individualized management plan for treating anaphylactic reactions

In this section we have covered all the components of a complete management package for children at risk of anaphylaxis. This constitutes a model of good practice as it has been shown to reduce the frequency and severity of

Box 4. Individualized anaphylaxis management plan: specific issues

- Personal identification data: name and address; contact details of the parents, allergist, the family doctor and the local ambulance service; and preferably a photograph.
- Clear identification of the allergens to be avoided; further information may be included on alternative names for allergens (e.g. lecithin for soya or arachis for peanut).
- Copy of plan to be kept by the child, his/her relatives, preschool care givers, school nurse, school staff, family doctor and be stored with the emergency medication.
- Individualized instructions:
  Written clearly in simple, nonmedical language
  Stepwise approach with simple instructions for each step, e.g.:

1. At the beginning of an allergic reaction (e.g. 'any swelling or redness of the face, itching of the mouth or nausea') immediately administer a liquid antihistamine.
2. Monitor closely the child for signs of breathing problems or collapse.
3. Call emergency numbers.
4. Keep the child lying down on his/her side unless he/she has severe breathing problems.

  Clear description of symptoms of bronchospasm and laryngeal oedema in nonmedical language (e.g. If there is wheezing or whistling from the chest, tightness in the throat or difficulty in breathing) so can rapidly administer adrenaline and call emergency medical services.

  Detailed instructions, possibly with photographs, on how to correctly administer the child's particular self-injectable adrenaline device.

  Recommendation to inject a second dose of adrenaline if there is no apparent improvement after 5–10 min.

- Ensure that self-injectable adrenaline is readily accessible to every care-giver.

Table 4. Suggested tailored treatment plan for individual management of children with food allergy at risk of suffering anaphylactic reactions

Patient factors			Components of anaphylaxis management plan		
Previous severe reaction	Co-existent persistent asthma	Other risk factor*	Self-injectable adrenaline	Antihistamine	Inhaled bronchodilator
Yes	No	Yes/no	Yes	Yes	No
Yes	Yes	Yes/no	Yes	Yes	Yes
No	Yes	Yes/no	Yes	Yes	Yes
No	Yes	No	Yes	Yes	Yes
No	No	Yes	Consider	Yes	No

*Other risk factors are a history of only a previous mild reaction to peanut or a tree nut; any reaction to small amounts of a food, including cutaneous contact (97) and airborne food allergen (96); remoteness of home from medical facilities; or a food allergic reaction in a teenager (18, 45) (D). It should be noted that the evidence base in this area is weak (D) (see section 'Self-injectable adrenaline devices and indications for their prescription in the community').

Box 5. Individualized management plan in the community: healthcare professionals

- Plan of communication with written information among the allergy clinic, the emergency department and the family doctors.
- Family doctors should be prompt in detecting signs and symptoms of food allergy in children.
- Physicians should participate actively in the educational programmes for anaphylaxis.
- Other health professionals should be involved in the network e.g. nurses and pharmacists.

Box 6. Individualized management plan in the community: schools

- Establishment of collaborative partnership among school staff, medical professionals and community health organizations.
- School staff must be notified about a child at risk of anaphylaxis.
- School staff members should be trained with regular refresher courses, possibly with audio-visual support.
- The emergency kit and management plan location should be known to each member of the staff.
- Periodic checks on adrenaline availability and expiration dates should be agreed upon; stocking a supply of self-injectable adrenaline devices should be considered.

further food reactions (93, 102, 108, 113–114) (C). This process is reinforced with the provision of an individualized management plan that encompasses the key management issues (see Box 4). A suggested approach to deciding which medications should be provided to a child at risk of anaphylaxis is presented in Table 4. A summary of the role of healthcare professionals in managing children at risk of anaphylaxis is presented in Box 5.

Special issues in the school

Additional recommendations should be put in place for the school to ensure the safety of children at risk of anaphylaxis at school (Box 6) (92, 115–118). National guidelines for responding to allergic emergencies at school should be established in each country (119–121).

Conclusions

Most of the treatments for anaphylaxis currently in use are based on consensus (grade D recommendation) rather than on higher levels of evidence. Due in part to the difficulty in implementing well designed randomized control trials in a disease characterized by unpredictable, acute manifestations and potentially life-threatening symptoms, few good quality studies have so far been published. Some conclusions can be drawn though from the available literature (Box 7).

Box 7. Recommendations from the EAACI Taskforce for Anaphylaxis in Children

- Adrenaline is the cornerstone of therapy (A) both in the hospital and in the community (C).
- Each child with a history of a previous allergic reaction to a food or other allergen should have a risk assessment to identify whether they are at high risk of anaphylaxis (C).
- Previous anaphylactic reactions (B) and co-existent persistent asthma (D) are indicators of higher risk of severe reaction.
- Other risk factors to consider are a reaction to small amounts of allergen including airborne allergen and cutaneous contact, previous mild reaction to peanut or tree nut, a long distance from emergency medical care and being a teenager (D).
- Prescription of self-injectable adrenaline is mandatory for high-risk subjects (B).
- An individualized management plan and education of all the child's care givers are essential in the prevention of recurrences (C).

• Adrenaline remains the cornerstone of therapy and its administration is strongly recommended in all cases as soon as the first symptoms of anaphylaxis are recognized. The use of intramuscular adrenaline in anaphylaxis is associated with relatively few side-effects and is acknowledged as the first line of therapy both in the hospital and in the community.

• Food allergy in childhood should be diagnosed early to prevent further reactions. For each child, a risk assessment must be undertaken to identify subjects at high risk of anaphylaxis.

• Previous anaphylactic reactions and co-existent persistent asthma are indicators of higher risk of severe reaction. The following circumstances may also indicate that a child is at an increased risk of anaphylaxis: reaction to trace amounts of allergen including aerosolized allergen and cutaneous contact, previous mild reaction to peanut or tree nut and being a teenager. In addition, distance from emergency medical care should be considered when developing a personalized management plan. The risk assessment should encompass all these aspects.

• The prescription of self-injectable adrenaline is part of a larger, comprehensive approach to the management of anaphylaxis. It is mandatory for high-risk subjects. For other subjects, an evaluation of all risk factors should be made on a case-by-case basis. There are no absolute contraindications to the administration of adrenaline to children. The number of devices to be prescribed to each subject is still being debated in an attempt to balance the cost of the device with the actual cost in case of mishap or failure to respond with the first dose.

• The specific anaphylaxis management plan decisions must be tailored towards the individual child. It will be influenced by the child's previous allergic reactions, co-existing medical conditions and social circumstances.

• Education is essential in the prevention of recurrences. Patients need individualized management plans and regular training programmes are required for families, care givers and school staff. Physicians need to be active participants in the entire educational process to fully contribute to its success. Empowerment through education of other health professionals [e.g. nurses (122) and pharmacists (123)] should be undertaken.

Future perspectives

The ongoing effort to provide a universally accepted definition of anaphylaxis will hopefully allow its earlier identification and the development of a stepwise approach for the better management of anaphylaxis in the near future. The central issue is the creation of a system that improves transmission of good quality data between the emergency room, the allergist and the family doctor. The creation of databases and registries on a national and European scale will provide better data about the prevalence of anaphylaxis and clarify the causative

relationship between trigger agents and diverse clinical patterns. The implementation of a plan, which combines regularly scheduled visits to the allergists along with the education of family doctors dealing with anaphylaxis, will facilitate an ongoing comprehensive care of the patient outside of the hospital.

Educational programmes should be targeted to the specific groups, starting in the emergency room, and efforts should be made to evaluate adequate training materials aimed at empowering families, healthcare professionals, patients and school staff. Partnerships with patients' organizations will promote skills and better dissemination of information to the community at large.

There is an urgent need that each country institutes regulations to define school responsibilities for administering medication and includes anaphylaxis in emergency response programmes for school staff. This will ultimately ensure a network of emergency response to anaphylaxis and the creation of an anaphylaxis surveillance system in schools (117).

Many questions about therapy are still unresolved. Studies are needed on the pharmacokinetics of adrenaline in infants and small children as well as on the most appropriate dose of adrenaline and alternative routes of administering it. The development of user-friendly, premeasured adrenaline doses suitable for infants is eagerly anticipated. At this stage the role of steroids in the management of anaphylaxis is questionable. Further studies are required to ascertain their efficacy and ultimately to clarify the role of the different drugs currently included in the therapeutic armamentarium for anaphylaxis.

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Levels of evidence according to SIGN[1] are indicated in a bracket () after each relevant reference.

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Appendix

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