

R E V I E W

What is new in anaphylaxis?

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Abstract. 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 adrenaline. After successful treatment of an anaphylactic episode, attention must be paid to the prevention of early recurrences (biphasic anaphylaxis) and assessment of causes. Children should not be discharged before prescribing self-injectable adrenaline and explain how and under what circumstances it must be injected, An action plan must be communicated to their communities. Inform the school about potential reactions, how to prevent them and avoidance measures. (www.actabiomedica.it)

Key words: anaphylaxis, food allergy, drug allergy, IgE, adrenaline

Introduction

Anaphylaxis is a systemic, allergic reaction with rapid onset and potentially life-threatening and because of this, it is the quintessence of emergency medicine. It occurs unexpectedly, often in young and otherwise healthy subjects, may progress rapidly from its apparently innocuous presentation. It is potentially fatal, particularly if inadequately treated, has no bedside valuable diagnostic test and requires pure clinical recognition. It responds dramatically to treatment (intramuscularly injected adrenaline), and usually allows discharge within 18-24 h unless a recurrence occurs (biphasic response). However, patients who experience an episode of anaphylaxis are at risk of new episodes.

Mimickers of anaphylaxis include infectious, autoimmune, malignant, autoinflammatory and pseudo-allergic causes. Because of this, Pediatricians must recognize anaphylaxis and emergency doctors must be prepared to cope with it.

Epidemiology

In childhood, the following factors can cause anaphylaxis: food, drugs, hymenoptera venom and latex. There are also other forms, which include idiopathic and exercise-induced anaphylaxis, with and without food intake. It is not easy to exactly quantify anaphylaxis cases. In fact, the diagnoses can be modified by

the different classifications used in various countries. In addition, some diagnoses may be overestimated or underestimated. The most robust datasets currently available are based largely on hospital admissions, which are limited by inherent issues of misdiagnosis, misclassification and generalizability. Despite this, there is convincing evidence of a global increase of all cause-anaphylaxis, driven largely by food-related anaphylaxis and medication (1). Many episodes occur in the community without presentation to healthcare facilities, and most regions have not yet developed reliable systems to monitor severe allergic events. The most common serious condition in children presenting to US emergency departments (EDs) is severe respiratory disease. Anaphylaxis is the fastest-increasing severe condition (2). Anaphylaxis accounts for up to 0.26% of overall hospital admissions. In general, the literature reports global (UK, Europe, USA, Australia, New Zealand) increases in hospitalizations for anaphylaxis, both all-cause anaphylaxis and trigger-induced anaphylaxis (1). The incidence of food anaphylaxis is higher in Australia and Europe although incidence rates differ among surveys. The incidence of anaphylaxis in European observational studies, ranges from 1.4 to 76.6 per 100,000 persons/year and in Australia it ranges from 10.3 to 16.2 per 100,000 persons/year (3). In infants presenting with their first food anaphylaxis, in a setting with a high rate of infant formula use, the most predominant trigger was cow milk (4). The most severe shock-provoking reactions are generally due to the ingestion of the offending allergen (peanut, cow milk, and egg are involved most frequently). Some episodes of food-induced anaphylaxis by inhalation have been considered “severe” inasmuch as they required adrenaline, but rarely such episodes have been so severe as to make cardiopulmonary resuscitation necessary. In very severe cases, anaphylaxis by inhaling vapors from cow’s milk can also cause death (5). Although the most common causes of anaphylaxis globally are food, medications, and hymenoptera venom and it occurs primarily in a home setting, internists are most likely to encounter drug-induced anaphylaxis in the hospital (6,7). The antibiotics that can more frequently induce anaphylaxis are amoxicillin and ampicillin (8). However, many drugs can be nonspecific mast cell activators, often causing acute onset urticaria

with or without associated angioedema and not mediated by any underlying allergy (e.g., specific IgE leading to anaphylactic mast cell degranulation).

Laboratory diagnosis and molecular diagnosis with IgE

Diagnosis of anaphylaxis is primarily clinical, based on history and symptoms, but it can sometimes be supplemented by laboratory tests. Biomarkers in anaphylaxis may be useful to improve diagnosis, to allow endotyping of patients, and to predict risk. In IgE-mediated anaphylaxis, the presence of positive specific IgE antibodies to the relevant allergen is necessary to confirm the diagnosis, can partially predict a severe reaction, and facilitate the identification of cross-reactive foods in food allergy. IgEs are specific because they are directed against well-defined proteins (9). Some proteins are more resistant than others to metabolic processes, due to their robust chemical structures: e.g. storage proteins from peanut (Ara h 1, Ara h 2, Ara h 3 and Ara h 6) or ovomucoid from chicken egg (Gal d 1) (10). As these allergens have higher resistance to digestion, their allergenic potential is also higher as their epitope structures stay intact longer. As a result, these proteins cause more systemic symptoms than unstable proteins. The main families of proteins and the risk of systemic reactions are shown in table 1. The proteins with higher resistance are also a model for studying new therapeutic approaches. It has recently been proposed that a single monoclonal antibody specific for Ara h 2 can improve local and systemic allergic symptoms induced by the entire allergen mixture (11). High serum basal tryptase levels may help to identify children at increased risk of more severe anaphylaxis, prompting physicians to initiate immediate therapy to avoid further acute episodes (12). Serum basal tryptase, which is released during mast cell degranulation, peaks at the second hour of the anaphylactic reaction and can remain high for 6 h, especially during food induced or insect-sting-induced anaphylaxis. Basal serum tryptase is not a risk factor for immediate-type drug hypersensitivity during childhood (13). Ideally, the measurement should be obtained between 1 and 2 h after the onset of

Table 1. Protein families and risk for systemic reactions

Protein family	Risk for anaphylaxis
Storage Proteins and Lipid transfer protein	High. These proteins are heat and digestion stable which explains their ability to more often cause systemic reaction in addition to oral allergy syndrome (OAS)
PR-10	Low. These proteins occur in a wide variety of plants. They often cause local symptoms only such as OAS due to their sensitivity to heat and digestion, but a few cases with systemic reactions have been reported
Profilin	Low. Several studies have shown that only 10–20% of children with pollen allergy are sensitized to profilins, but they react to a broad range of inhalant and food allergens. They often have little clinical relevance in allergic diseases. However, profilins may cause local reactions in some patients allergic to plant foods including citrus fruits, banana and tomato, and a few cases with systemic reactions have been reported especially with the ingestion of large quantities of food
Cross-reactive carbohydrate determinants (CCDs)	No risk. CCDs play a role in the context of allergy diagnosis. Usually non associated with clinical reactions but may induce IgE antibody responses in some children

symptoms. As it is stable at room temperature, it can be measured in biological samples even postmortem. In food-induced anaphylaxis, however, serum basal tryptase is seldom elevated because in this condition basophiles and monocyte macrophages are involved more than mastocytes.

Clinical diagnosis

The presentation of an anaphylactic reaction in ED can vary widely. It can affect several target organs: the skin (urticaria, angioedema), respiratory tract (rhinitis, asthma), gastrointestinal tract (oral allergy syndrome, nausea, vomiting, pain, flatulence, emesis, and diarrhea), and/or the cardiovascular system (anaphylactic shock). 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. Other symptoms include tingling sensations, itchy and flushed skin, throbbing in the ears, coughing, sneezing, hives and swelling (angioedema). Breathing may

become difficult, and wheezing may occur because of constriction or swelling of the upper airway.

In prehospital emergency care, and in the emergency care unit, the involvement of skin is often the first signs of the clinical manifestations (14). Respiratory symptoms are more frequent in food anaphylaxis, while they are less frequent in anaphylaxis induced by medication and iatrogenic causes and by hymenoptera venom (15). An anaphylactic reaction may progress so rapidly as to lead to collapse, cessation of breathing, seizures and loss of consciousness within 1–2 min. The reaction may be fatal unless treatment is given immediately. Tree nuts, compared to other foods and with equal dose of ingested proteins, are much more dangerous in inducing mortality (16). A clinical history of asthma and chronic/relapsing gastrointestinal symptoms, probably linked to food allergy, may predict the development of respiratory and gastrointestinal symptoms and the severity of anaphylaxis (17).

Therapy

As an anaphylactic episode is potentially life-threatening, prompt treatment should be given even

when diagnosis is not fully established. The intervention to be rapidly started, 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 hypovolemic shock with cerebral underperfusion or respiratory insufficiency due to bronchial asthma). The child must be kept supine, with raised legs, to promote the perfusion of vital organs. In the absence of dyspnea, the Trendelenburg position is recommended to avoid cardiac arrest. Adrenaline should be given intramuscularly. Subcutaneous administration is not recommended, as local vasoconstriction can reduce absorption. The injection should be given intramuscularly in the outer top part of the thigh that provides a quicker and higher absorption than either subcutaneous or intramuscular administration in the deltoid in children. A needle gauge of at least 2.5 cm must be used in obese children to prevent subcutaneous administration. The dose is 0.01 ml/kg of aqueous adrenaline 1 : 1000 (up to 0.5 ml), can be repeated – if necessary – after 5–15 min (18). In about 25% of cases there is a need to administer a second adrenaline injection after a few minutes from the first (19). If the patient's weight is unknown, an approximate dosage is 50 microg (0.05 ml) for infants less than 6 months; 120 microg (0.12 ml) for children between 6 months and 6 years; 250microg (0.25 ml) from 6 to 12 years old; 500 microg (0.5 ml) for children older than 12 years. During the administration of adrenaline, 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 insect sting (20), drug injection, or immunotherapy subcutaneous injection, a tourniquet must be placed above the injection point to reduce absorption of the causative agent.

Several mistakes are usually made in the hospital during the preparation of adrenaline (21). In descending order of frequency:

- 1) Administration site not specified (29.4%)
- 2) Incorrect dose prepared (16.5%)
- 3) Incorrect dose ordered (14.1%)
- 4) Incorrect concentration ordered (12.9%)

- 5) Incorrect concentration prepared (12.9 %)
- 6) Intravenous route ordered (10.6%)
- 7) Route not specified (3.5%)

Finally, the treatment of anaphylaxis involves the prompt administration of intramuscular adrenaline in the vastus lateralis, with adjuncts of intravenous fluids, supplemental oxygen, and anti-H1 antihistamines. There may be a limited role for corticosteroids.

Why aren't adrenaline auto-injectors used when needed?

There can be many causes for the non-use of adrenaline autoinjectors. They include: failure to recognize anaphylaxis; uncertainty about administration technique; uncertainty about the indication for use; fear of side effects (22). In a survey on 1385 cases, failure to use adrenaline autoinjectors was due to administration of oral antihistamine instead of adrenaline (38%), lack of a prescription for an adrenaline autoinjector (28%). Patients thought their symptoms were mild and would resolve over time (13%). Patients were afraid (6%), they could not afford an adrenaline autoinjector (1%) (23).

In the hospital, the use of an adrenaline vial allows a more precise dosage with respect to the child's body weight. The preparation and administration of the correct amount of adrenaline usually takes three times longer compared to the use of an adrenaline autoinjector.

Family education programs should consider these data in order to direct the specific interventions to avoid the most common mistakes. The most important message for families is that adrenaline should be administered in all doubtful cases. The main effect of adrenaline is to determine a rapid and marked increase in blood pressure. In a elastic cardiovascular system such as that of a child, the adrenaline effect on blood pressure can only be beneficial.

Biphasic anaphylaxis

A biphasic reaction is a "two phase" anaphylactic event. This means that after anaphylaxis is treated and

symptoms resolve, they return without the patient being re-exposed to the allergen. The second reaction can be less severe, equal to or more severe than the first reaction. This makes them dangerous as some people may think that they are fully recovered and they may not have their adrenaline auto-injector as they will have used it to treat their first reaction. A second reaction can occur as little as 2 hours and as much as 48 hours after the first reaction. The average length between reactions is 6-10 hours. Biphasic reactions seem to be associated with the severity of the initial anaphylactic reactions. The arterial hypotension at the onset is the most important clinical predictor of biphasic anaphylaxis that could ultimately be used to identify patients who would benefit from prolonged ED monitoring and enable better utilization of ED resources (24).

Action plan

The action plan (AP) emphasizes the important role of epinephrine and de-emphasizes the role of steroids. It lists symptoms and clearly tells the caregiver or child when to use the epinephrine auto-injector. Allergy and anaphylaxis emergency plans are especially important to provide to schools and child care facilities. Anaphylaxis emergency care plan overview. It includes simple criteria to identify potential allergic emergencies for use by patients, families, school staff, and all caregivers; it is accessible and understandable to anyone caring for a child; given to school, child care, after-school programs, or any place where others care for child; others to use child's specific ECP should be trained. When creating an AP, it is also important to customize it to the specific needs of the child, allergies, family, and your state and local regulations. Engaging children and parents in the design and contents of a written anaphylaxis action plan is an innovative approach to produce a useful document for the end-users (25). The AP has to be updated and commented at least twice a year and it has to become a true guide for any upcoming anaphylaxis. Each stage must be explained and commented not only to parents, but, if possible, also to other family members. Even babysitters and schoolteachers should be involved in this communication. It is also useful to place a summary sheet at the

end of the AP, which can simply list the various steps, because patients and their parents need to review the practical steps. It is important for children with drug anaphylaxis, once the diagnosis has been confirmed, to provide them with an updated list of new commercial drugs. They have to be made aware that they always have to bring with them the list of dangerous drugs, in case of access to the emergency room and to new medical assessments. The children with severe reaction to wasp sting, should be encouraged to start and complete specific immunotherapy for hymenoptera venom. The rush protocol is useful too; it has a proven effect both in preventing severe reactions and in improving the quality of life (26). A correct prevention of anaphylaxis must be multifaceted and should also target school staff. In a recent intervention carried out in Italian schools, the personnel reported low self-efficacy in anaphylaxis management, especially in recognizing anaphylaxis symptoms and administering proper drugs. After the specific multidisciplinary training course, all scores improved. Results highlighted the effectiveness of specific multidisciplinary training courses in improving teachers and school caretakers' self-efficacy in managing food allergy and anaphylaxis (27). Training kits containing empty syringes are available for family and patient education. Family members and children caregivers should be trained to inject adrenaline. After injecting adrenaline, the caregiver should call the local emergency phone number to get medical help. The child must also take an antihistamine at the onset of symptoms.

Teenagers

Teenagers are more exposed to severe and fatal anaphylaxis episodes for many reasons (28). Teenagers are certainly characterized by restlessness, sense of agitation and rebellion and this life stage determines a need for autonomy which may result in poor adherence to prevention and treatment programs. During this period, young people express their own identity and, that's why, teenagers are more at risk of severe reactions of anaphylaxis, because they underestimate the danger, forget to bring the kit with adrenaline, and may be ashamed of their situation. For teenagers is

useful a practical education health care that, in case of food allergy, has to be extended to paying attention to commercial product labels, and avoid taking away food that has not been checked. Periodical medical checks are indispensable in order to repeat to them the clinical characteristics for the early recognition of anaphylaxis and the modalities for self-injection techniques.

Conclusions

Prevention of future episodes of anaphylaxis is vital. This requires identification of the anaphylactic trigger, which is often difficult. The physician's primary tool is a detailed history of recent exposure to food, medications, latex, and insects known to cause anaphylaxis. Previous tolerance of a substance does not rule it out as the trigger. Despite a detailed history, the triggering cause can remain elusive in some children. In cases of suspected anaphylaxis, the consultation with an allergist is important to confirm the diagnosis of anaphylaxis and to identify the anaphylactic trigger through history, skin testing and/or the serum assay of specific IgE. The whole family must be made aware of the risk factors that may be involved in severe reactions and know the main strategies to prevent them. The family must be educated about prevention and the initial treatment of future episodes and, sometimes, be helped in desensitization and pretreatment, when indicated. When there is no choice but to re-expose the child to the anaphylactic trigger, desensitization or pretreatment may be attempted. Desensitization carries a risk of anaphylaxis and should be performed by experienced persons in a well-equipped location also for foods (29). Immunotherapy is recommended for insect sting anaphylaxis, because it is 97% effective at preventing recurrent severe reactions (30). Protocols are available for oral and parenteral desensitization to penicillin, as well as to several other antibiotics and medications (31). Desensitization must be repeated if treatment with the agent is interrupted.

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