DE GRUYTER OPEN

REVIEWS

Anaphylactic shock: are we doing enough and with the right timing and order?

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Anaphylactic shock became, unfortunately, a common presence in Romanian mass-media, due to some fatal cases in the last months. The coincidence that in December 2014 the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy Asthma and Immunology released Practice parameters offers a good opportunity to renew for all practitioners what is now considered the "golden standard" of good practice.

Epinephrine must be considered the cornerstone and the most urgent measure to be applied in these cases, immediately after the diagnosis. A very important notice is to forget the administration of antihistamines or corticosteroids as first line therapy instead of epinephrine. Proper positioning of the subjects and quick fluid replacement (1-2 l of normal saline in a few minutes) are also mandatory.

Key words: anaphylaxis, epinephrine, proper positioning, biphasic/recurrent anaphylaxis, prophylactic measures.

The last six months offered unfortunately too frequently "breaking news" concerning deaths due to anaphylactic shock.

So, it became obviously necessary to review, but also to renew data concerning this pathology.

The most frequently used definition is: "Anaphylaxis is an acute, potentially fatal, multiorgan system reaction caused by the release of chemical mediators from mast cells and basophils" [1].

In this old problem Portier and Richet were the first to use the term **anaphylaxis** in 102 (when a second vaccinating dose of sea anemone toxin caused a dog's death) [2].

ESSENTIAL UPDATE: NEW PRACTICE PARAMETERS FOR ED MANAGEMENT OF ANAPHYLAXIS

In December 2014 the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy Asthma and Immunology released Practice parameters that recommend that **patients with signs of anaphylaxis should receive epinephrine in the antero-lateral thigh as first-line treatment in the emergency department** [3, 4].

Anaphylaxis is very likely if any of these three criteria are met:

- Acute onset of illness with involvement of skin and/or mucosa accompanied by either respiratory compromise, falling blood pressure, or end-organ dysfunction;
- Two or more of the following symptoms occurring rapidly after exposure to the likely allergen: involvement of skin and/or mucosa, signs of respiratory compromise, falling blood pressure or end-organ dysfunction, and persistent gastrointestinal symptoms;
- Falling blood pressure within minutes to several hours following exposure to a known allergen [4-8].

Before a quasi-exhaustive presentation of the signs and symptoms [6] that are considered criteria for the diagnosis of anaphylactic shock we must underline that for the diagnosis of anaphylaxis it is not necessary to consider mandatory the presence of shock [4].

The second very important measure to consider is to place patients in a supine position (or in lateral left decubitus if it's a pregnant woman or in a "position of comfort" if dyspneic or vomiting), legs elevated. A reliable analysis of the causes of fatal outcomes in those with anaphylactic shock revealed that 4/10 are due to an inappropriate position of the patients (upright or sitting) [9].

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The third measure considered mandatory, no matter the respiratory condition, is represented by oxygen administration for all cases [3, 4, 10-12].

A very important notice is to forget the administration of antihistamines or corticosteroids as first line therapy instead of epinephrine.

Epinephrine must be considered the cornerstone and the most urgent measure to be applied in these cases, immediately after the diagnosis [4-**8, 13-15].**

When epinephrine is administered promptly and symptoms seem to subside completely, the subject who was treated with epinephrine should always be taken to the emergency room for further evaluation and treatment.

If patients do not respond to intramuscular administration of epinephrine we must administer it either i.v. or intraosseous [14, 15].

Another very important step in the management of anaphylactic shock is to counteract the extra-vascular leakage of 35 to 50% of the intravascular volume, by administration of a large volume of normal saline (1-2 liters in the first minutes) i.v. or intraosseous through large-bore catheters [4-8, 12].

The most frequently encountered modality of beginning of the anaphylactic shock is represented by a combination of "impending doom, pruritus and flushing". In adults, urticaria, erythema or angioedema are the most frequent manifestations, but in children the respiratory symptoms can precede the cutaneous symptoms [16].

Signs and symptoms of the anaphylaxis:

- Dermatologic/ocular: **flushing, urticaria, angioedema**, cutaneous and/or conjunctival injection, pruritus, warmth, swelling;
- Respiratory: nasal congestion, coryza, rhinorrhea, sneezing, throat tightness, **wheezing**, shortness of breath, cough, **hoarseness, dyspnea**;
- Cardiovascular: **collapse**, dizziness, weakness, syncope, chest pain, palpitations;
- Gastrointestinal: dysphagia, nausea, vomiting, diarrhea, bloating, cramps;
- Neurologic: headache, dizziness, blurred vision, **seizures** (usually associated with significant hypotension);
- General: metallic taste, feeling of impending doom [4, 6, 13, 16, 17].

It is extremely important, due to the fact that the diagnosis of anaphylaxis is a clinical one, that the clinical examination must be quickly made: **anaphylactic shock is a medical emergency that requires immediate recognition and intervention**.

One very frequent accusation directed to doctors that administered a substance that provoked an anaphylactic shock is the lack of previous testing.

But the recent released statements about anaphylactic shock revealed: "**Laboratory studies are not usually required and are rarely helpful**".

– plasma/urinary histamine and serum triptase assessment may help to confirm the diagnosis of anaphylaxis [2];

– skin tests or *in vitro* immunoglobulin E (Ig E) tests or both may help to determine the causing agent of the anaphylactic shock: testing for food allergy; testing for medication allergy; testing for causes of Ig E-independent reaction;

– **skin testing has no role because there is no evidence suggesting that this kind of test can reliably identify those at risk for a systemic reaction** [18-20].

After epinephrine administration and a useful positioning (supine with elevated legs), the following measures must be taken:

1. Airway management (even with endotracheal intubation, if necessary);
2. High-flow oxygen (6 l/min., hyperbaric);
3. Cardiac monitoring and/or pulse oxymetry;
4. Intravenous access (large-bore catheter)
5. Fluid resuscitation with isotonic crystalloid solution [4-14, 17, 19-21].

In the recommended order of administration of the substances, therapeutic interventions are:

- Adrenergic agonists (epinephrine);
- Antihistamines;
- H_2-receptor antagonists;
- Bronchodilators (inhalatory);
- Corticosteroids (i.v.);
- Eventually: positive inotropic agents; vasopressors.

The World Organization recommends to use the following terminology [22]:

- Immunologic anaphylaxis (Ig E-mediated and non-Ig E-mediated: Ig G-mediated and immune complex complement-mediated);
- Non-immunologic anaphylaxis (due to sudden degranulation of mast cells and basophiles, in the absence of immunoglobulins).

The classic mechanism of Ig E-mediated anaphylaxis (the most frequent type of anaphylaxis) is represented by an Ig E antibody response generated, in a susceptible subject, by a senziting antigen. These Ig E antibodies (antigen-specific) then bind to mast cells and basophils and a subsequent exposure to the specific antigen will generate mast cells and basophiles degranulation [1, 23, 24].

The clinical manifestations are generated by the release of anaphylaxis mediators:

– smooth muscle spasm (in respiratory and gastro-intestinal tracts);

– vasodilation;

– increased vascular permeability;

– stimulation of sensory nerve endings.

The respiratory symptoms are generated by:

– increased mucous secretion;

– increased bronchial smooth muscle tone;

– airway edema (inflammatory swelling of the bronchial mucosa).

The cardiovascular effects: decreased vascular tone and capillary leakage are generating intra-vascular volume loss, vasodilation, myocardial dysfunction that are followed by hypotension, cardiac arrhythmias, syncope and shock.

Other mediators: neutral proteases, tryptase and chymase, proteoglycans (heparin and chondroitin sulfate), chemokines and cytokines that can activate the kallikrein-kinine contact system, the complement cascade and coagulation cascade [23, 25, 26].

Newly generated lipid-derived mediators: prostaglandin D2, leukotriene B4, platelet activating factor (PAF) [27] and cystenyl leukotrienes (LTC4, LTD4, LTE4) also augment the pro-inflammatory cascade of anaphylaxis. It is worth mentioning that the development and the severity of anaphylaxis depend also on the responsiveness of the cells targeted by these mediators, but **histamine infusion alone is sufficient to produce most of the symptoms of anaphylaxis** (through H_1 and H_2 receptors activation).

Their simultaneous activation is producing vasodilation, hypotension and flushing.

The H_1 receptor activation is producing: coronary artery vasoconstriction, tachycardia, vascular permeability, pruritus, bronchospasm and rhinorhea.

The H_2 receptor activation is producing: an increase of atrial and ventricular contractility, of atrial electric instability and of coronary artery vaso-dilation.

The initial response to hypovolemia is represented by a baroreceptor-mediated increase in overall cardiac sympathetic drive and a concomitant withdrawal of resting vagal drive, their allied action being represented by peripheral vaso-constriction and tachycardia.

The most frequent inciting agents are:

– foods: especially peanuts, tree nuts, fish and shellfish; in children: cow's milk, eggs, wheat, soy;

– hymenoptera stings;

– intra-venous contrast materials. [28-31]

But, at least one third of the cases are considered idiopathic [32].

- Hypersensitivity to food [28-35] is the most frequent etiological agent: in the United States 4 million Americans have well-substantiated food allergies and all over the world reactions to food are considered to be the commonest cause in outpatients and in the US it is the cause of about 125 deaths/year. The Rochester Epidemiology Project [30] demonstrated that food ingestion is the leading cause of anaphylaxis (1/3 of all cases) .
- [34] high-lighted that 62% of 32 fatalities food-induced were generated by peanuts (it is worth also mentioning that in peanut-sensitive patients [by placebo-controlled food challenges] can react to as little as 100 μg peanut protein.
- Hymenoptera stings – a common cause of anaphylaxis: 0.5-3% of the US population had anaphylactic experiences due to them [16, 36], generating less than 100 deaths/year. But the survivors must pursue a desensitization course and they must be instructed to always carry with them 2 epinephrine auto-injectors (due to biphasic forms) and a few tablets of oral antihistamines [36, 37].
- Most cases of Ig E-mediated drug anaphylaxis in the US are due to beta-lactam antibiotics [38-40] [penicillin is a hapten; the other beta-lactam antibiotics generate anaphylaxis either by cross-reactions with penicillin or by having structures that are acting like haptens]. In penicillin-allergic patients older cephalosporines (cephalotin, cephalexin, cefadroxil, cephazolin) can also generate reactions in penicillin-alergic patients, due to greater antigenic similarity of the side-chain [40-42]. But, being allergic to penicillin means that the subject is at higher risk (about three times more) of sub-sequent reaction to **any** drug and about eight times more to cephalosporines [14, 15]. It was also demonstrated that **about 85% of those allergic to penicillin have negative skin tests** [42].

But, when for a life-threatening emergency the drug of choice is penicillin or a cephalosporin, when the anamnestic elements are unclear, one can administer them under close observation, with all the necessary drugs/devices available. When the anamnestic elements about an allegic reaction are more reliable, either an alternative agent is used, or, if possible, a desensitization protocol is pursued [41].

- Regarding the risks of anaphylaxis during a surgical intervention, the high and dangerous pre-valence of latex allergy has significantly decreased due to the widespread use, nowadays, of latex-free materials [43, 44]. Volatile anesthetic agents

(associated with the risk of immune-mediated hepatic toxicity) have never been associated to anaphylactic reactions [45].

- Severe anaphylaxis due to subcutaneous immunotherapy [46-48] is associated with some risk factors: poorly controlled asthma, concomitant treatment with beta-blockers, a large dose of allergen, errors of administration (intravascular, not subcutaneous), lack of sufficient observation period following injection. Angiotensin-converting enzyme inhibitors (ACEI) are associated with angioedema (0.5-1%), but systemic anaphylaxis is rarely seen [49, 50]. Antihypertensive pharmacotherapy has been associated to an increased risk for organ system involvement: ACEI (2 fold increase), beta-blockers, diuretics, with severe reactions that are imposing inpatient admission [49, 50].
- Intra-venous administered radio-contrast media cause an anaphylactoid reaction (similar to anaphylaxis and having the same treatment), the risk for a fatal reaction being estimated to 0.9 cases for 100.000 exposures. A useful precaution is considered pretreatment with antihistamines /cortico-steroids and to use low-molecular-weight (LMW) contrast agents. It is mandatory, also, after these precautions, to have nearly all the necessary agents/devices and to obtain an informed consent before administration [51, 52].
- "Idiopathic anaphylaxis is a syndrome of recurrent anaphylaxis for which no consistent triggers can be determined despite an exhaustive search" [28-32]. Most of the subjects are female and a significant proportion of them have a coincidental occurrence of anaphylaxis with their menstrual cycle: *catamenial anaphylaxis.* [53]. The diagnosis of this particular type is confirmed by the appearance of an anaphylactic event after the administration of low doses of progesterone.

BIPHASIC ANAPHYLAXIS

The incidence of biphasic (recurrent) varies from 1 to 23% (the time of onset being from 1 to 72 hours, but the vast majority between 8 and 10 hours). Some factors are considered associated with this kind of reactivity:

- increased sensitivity of the initial phase;
- delayed administration or suboptimal doses of epinephrine;
- laryngeal edema during the initial phase;
- delayed onset of symptoms after the exposure to the antigen;
- prior history of biphasic anaphylaxis [54, 55].

Due to the existence of this possible biphasic it is very important to monitor patients for 24-32 hours after recovery from the initial phase (that means also that every subject that experienced an anaphylactic shock should have 2 injectors with him all the time).

Regarding risk factors for anaphylaxis:

– Rochester Epidemiology Project [30] demonstrated that 53% had a history of atopic disease (allergic rhinitis, asthma, atopic dermatitis);

But, one must underline that an atopic back-ground does nor appear as a risk factor for important reactivity to penicillin or insect stings.

CONSIDERATIONS REGARDING THE ROUTE OF ADMINISTRATION AND TIMING

Oral administration is less likely to cause a reaction, the possible reaction being less severe (but, we must not forget that lethal reactions to food can occur).

INCIDENCE OF ANAPHYLAXIS

The true incidence of anaphylaxis is unknown, mainly because clinicians use the same denomi-nation for cases of different severity.

It is considered [31] that the lifetime prevalence of anaphylaxis is 1-2% of the population.

[56] consider that 1-15% of the US population is at risk for an anaphylactic or an anaphylactoid reaction: 0.0004% due to food; 0.7-10% due to penicillin; 0.22-1% to radiocontrast media; 0.5-5% to insect stings.

A Rochester population-based study [30] highlighted that: the average annual incidence is 58.9 cases/100.000 person-years: 33% secondary to a specific food; 18.5% due to insect stings; 13.7% due to medications; 25% of cases were considered to be idiopathic.

A study in Memphis, Tennesee (10) offered the following distribution of anaphylactic reactions: 34% due to food, 20% due to medications, 7% due to exercise and 59% were considered idiopathic.

An estimation of 20.000-47.000 of idiopathic anaphylaxis, that means 8-19 episodes per 100.000 person-years is made for the USA [30, 56].

In Denmark: 3.2 cases/100.000 person-years; in Munich, Germany: 9.8 cases out-of-hospital anaphylaxis per 100.000 person-years and in Europe 1-3 cases/10.000 (91), the trend being augmentative [57].

FATAL ANAPHYLAXIS

This condition is infrequent, but not rare: 500-1.000 fatal cases per year are estimated to occur in the US, the estimated mortality rates range from 0.65 to 2% [58]; in the United Kingdom, around 50% of fatal anaphylaxis reactions are of iatrogenic origin (anesthesics, antibiotics, radio-contrast media).

The common causes of death in fatal cases are:

– cardiovascular collapse;

– respiratory compromise.

The acute bronchospasm as cause of death was associated only in those **preexisting (and poor controlled) asthma**.

Delayed administration of epinephrine is also a risk factor for fatal outcome [3-5, 7, 10].

Four of ten of fatal cases [9] in the United Kingdom were associated with an unproper position assumption during anaphylaxis: upright or sitting position.

THE IMPORTANCE OF EDUCATION

Avoidance education is mandatory in cases of food anaphylaxis.

Important and very useful advice can be found in: The Food Allergy & Anaphylaxis Network and Food Allergy Research & Education (FARE) sites, for families and physicians [59].

In 2011, the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology and the Joint Council of Allergy, Asthma and Immunology issued an updated practice parameter [36] on insect sting hypersensitivity, teaching those with this kind of hypersensitivity to be referred to an allergist/ immunologist to receive the necessary preventive education: about the risk for another reaction, the benefits of wearing permanently a medical identification necklace or bracelet, to avoid insect stings, how to use the epinephrine auto-injection, to avoid the exposure of the device to extreme temperatures (epinephrine is sensitive to light and extreme temperatures) and to verify its validity (around 1 year).

For patients and practitioners, it is extremely important to know that an important risk factor for a fatal outcome of anaphylaxis is represented by the delayed administration of epinephrine. The main causes of this fact are represented by underprescription of epinephrine by physicians and the latency of the patients/parents [59, 60]. Those who are allergic to certain avoidable allergens (as insect stings) may benefit from long-term allergen immunotherapy (desensitization).

Epinephrine is the only medication that can reverse the symptoms of anaphylaxis. We must underline that it is a safe drug, the risks of anaphylaxis outweight any risk of epinephrine administration (rare exceptions are considered elderly patients with defined heart diseases).

The unpredictability of anaphylaxis is one of the most difficult aspects of living with a food allergy: someone with previously only mild reactions can have the next time a life-threatening reaction.

And, more important than all: "An anaphylactic reaction may progress so rapidly that people collapse, stop breathing, have seizures, and lose consciousness within 1 to 2 minutes. The reaction may be fatal unless emergency treatment is given immediately".

Anaphylactic reactions can be caused by any allergen.

An anaphylactic reaction does not usually occur after the first exposure to an allergen, but may occur after a subsequent exposure. But, usually, most people do not recall a first exposure.

OTHER PHARMACOTHERAPIES

Antihistamines – are prescribed to relieve mild allergy reactions [49].

Steroids – although they do not act fast enough for emergency treatment, the reason of their administration is to help prevention of a recurrence after the initial reaction (they prevent mast cells and basophiles degranulation, besides their anti-inflammatory reaction) [55].

Sympatomimetics – may be used to help relieve breathing problems **(but all mentioned in this last section are to be administered after epinephrine injection).**

Remember also to visit:

ACAAI Web site;

Food Allergy Research & Education (FARE) at www.foodallergy.org

And for those with a previous allergic episode: always have in mind: be S.A.F.E. Action Guide:

S – Seek immediate help;

A – Identify the allergen;

F – Follow-up with a specialist;

E – Carry epinephrine for emergencies.

Şocul anafilactic a devenit, din nefericire, o prezență frecventă în mass-media românească, datorită câtorva cazuri fatale, în ultimele luni. Coincidența că în decembrie 2014 American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, şi the Joint Council of Allergy, Asthma and Immunology au dat publicității o actualizare a datelor care se constituie actualmente în "standardul de aur" al regulilor de bună practică în abordarea şocului anafilactic ne oferă o bună oportunitate de actualizare sub multiple aspecte a acestei urgențe majore.

Epinefrina trebuie să fie considerată „piatra unghiulară" şi cea mai urgentă măsură ce trebuie aplicată în aceste cazuri, imediat după stabilirea diagnosticului. Este foarte important a nu mai considera antihistaminicele şi corticosteroizii ca medicație de primă intenție, în locul epinefrinei. Poziționarea corectă a subiecților şi rapida reumplere a patului vascular (1-2 l ser fiziologic din primele minute) sunt măsuri obligatorii, salvatoare.

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