УДК 612.017.3–053.2

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Food anaphylaxis: analysis of protocol standards, literary data and own clinical experience

Identification of preventive measures in the development of anaphylaxis – one of the primary medical tasks of western countries.
World Allergy Organization, 2013

Key words: *anaphylaxis, food allergy, cofactor, alcohol, children.*

Anaphylaxis is a severe life-threatening form of a generalized or systemic reaction of hypersensitivity characterized by a rapid onset of hazardous functional failures of respiratory and circulatory systems and is usually associated with clinical manifestations on the skin and mucous membranes [4].

Anaphylaxis has been seen to develop in 0,5–2,0% of people during their lifespan [1, 8, 11]. The main triggers in the development of anaphylaxis are foods, medicines, deceptive insects and latex [1, 9]. Among the leading products that can cause anaphylaxis in children are milk, eggs, soy and wheat, and in adults – nuts and seafood [3, 6, 8]. One of the most common causes of lethal effects of food allergens in the general population are peanuts [3, 5, 8].

The currently existing literary data allows us to determine the group affiliation regarding the degree of the risk of developing anaphylaxis, beginning with the highest:

Storage proteins: temperature-proof, associated with severe and systemic reactions: allergens of nuts and seeds. Ara h 1, Ara h 2, Ara h 3 – Peanut; Cor a 9, Cor a 14 – hazelnut; Jug r 1, Jug r 2 – Walnut; Gly m5, Gly m 6 – soybean; Tri a 19 – wheat.

Lipid transfer proteins (LTP): temperature-proof, associated with severe and systemic reactions: allergens of fruits, vegetables, nuts, and pollen. Pru P 3 – peach; Mal d 3 – apple; Cor a 8 – hazelnut; Jug r 3 – walnut; Ara h 9 – peanut; Tri a 14 – wheat; Gly m 1 – soybean.

Tropomyosins: temperature-proof, associated with severe and systemic reactions. There is a high affinity and the risk of cross-reactions in the middle of the family: allergens of marine products, ticks, cockroaches, nematodes – Pen a 1 – brown shrimp, Pen m 1 – tiger shrimp.

Lipocalins: allergic components of animals. Can f 1 – canine.

Parvalbumin: temperature-proof, associated with severe and systemic reactions. High risk of cross-reactions: allergens of fish and amphibians. Gad c 1 – codfish, Cyp c 1 – carp.

Serum albumins – heat-labile: allergenic components of animals – cow milk, blood, meat, epithelium. Fel d 2 – cat.

PR-10 protein, homologs Bet v 1: heat-labile, associated with the appearance of the oral allergic syndrome: allergenic components of pollen, fruits, vegetables, and nuts. Gly m 4 – soybean; Ara h 8 – peanut; Cor a 1 – walnut; Mal d 1 – apple; Cuc m 1 – melon; Dau c 1 – carrot.

Calcium-binding proteins: weed allergens, grass pollen and trees. Bet v 4 – birch.

Profilins – allergens of plant-based foods, latex, pollen of herbs, trees, weeds. Sensitive to heat treatment, have high risks of cross reactions: Cor a 2 – hazelnut; Pru p 4 – peach; Mal d 4 – apple; Cuc m 2 – melon; Dau c 4 – carrot; Gly m 3 – soybean; Ara h 5 – peanuts.

ISSN 2307-3373

Cross-reactive Carbohydrate Determinants – found in pollen, plant-based foods, and insects. Have a high risk of cross-reactions and could be considered as the marker of sensitization to CCD [1, 6].

Thus it could be assumed that labile allergens are associated with local reactions, while stable allergens – with systemic (scheme 1) [1].

A step-by-step algorithm for the diagnosis and treatment of anaphylaxis could be found in the unified clinical protocol of emergency, primary, secondary (specialized) and tertiary (highly specialized) medical aid for medical allergy, including anaphylaxis in the decree of the Ministry of Health of Ukraine № 916 from 30.12.2015 [4].

Symptoms and signs of anaphylaxis usually develop from a few minutes to two hours after contact with the allergen. When talking about food allergy, it should be mentioned that the symptoms of IgE-dependent allergic reactions develop predominantly after 30 minutes after consuming the product. At the same time, skin symptoms are more common, especially in younger children (rashes, pruritus). Itching is present more often on palms, feet, head, although it also might be prone to generalization. Early acute symptoms often include mucous discharge from the nose, pruritus of the eyes, lips, ears, and edema of the face. Severe reactions are associated with the development of bronchospasm and laryngospasm. The development of abdominal symptoms (acute abdominal pain, vomiting, diarrhea) and hypotension (more common in older children) are also possible. [4, 6, 11].

The classification of the severity of an anaphylactic reaction is given in Table 1 [6].

Medical indications to epinephrine administration could be found in Table 2 [6].

When administering adrenaline, it is necessary to take into account the patient's history of the disease. For example, the child's previous experience of severe allergic reactions is a medical indicator of immediate adrenaline administration. Exacerbation of bronchial asthma is a major criterion, which requires special vigilance in determining the need for adrenaline injection. [4, 14].

Indications for the purchase of an auto-injector (epipene) are given in Table 3 [6].

The administration of adrenaline is the first line in the treatment of anaphylaxis. The effect of adrenaline administration is the increase the vascular resistance, blood pressure, coronary perfusion, and the decrease oedema due to the α-adrenergic effect. Simultaneously, the β1-adrenergic effect increases the heart rate, the heart's ejection fraction, while the β2-adrenergic effect leads to bronchodilation and suppresses the release of inflammatory mediators [4, 7].

Adrenaline (1 mg/ml) should be administered intramuscularly in the middle of the outer thigh in a dose of 0.01 ml/kg of body weight to a maximum total dose of 0.5 ml. According to the literature data, more than 20% of patients with anaphylaxis require a second dose of adrenaline. The second dose can be repeated in 5–10 minutes after the first one [6].

For patients who can not be stabilised by the intramuscular injection of adrenaline, an intravenous injection of adrenaline should be administered. The procedure should be carried out in the intensive care unit under the control of ECG and pulse oximetry. Intravenous adrenaline administration

Table 1

The classification of the severity of an anaphylactic reaction

Degree	*Degree of severity*	*Skin*	*Gastrointestinal tract*	*Respiratory tract*	*Cardiovascular tract*	*Neurological changes*
1	Mild	Sudden onset of pruritus of the eyes and nose, generalized pruritus, redness, urticaria or angioedema	Pruritus of the oral cavity, sensation of tingling in the mouth, nausea or vomiting, mild abdominal pain	Nasal congestion and/or sneezing, rhinorrhea, itching in the throat, or light wheezing	Tachycardia (growth in >15/min)	Change in activity, flaccidity
2	Moderate	Any of the listed	Any of the listed, spastic abdominal pain, diarrhea, repetitive vomiting	Any of the listed, hoarseness, cough, difficulty swallowing, dyspnea, wheezing of moderate intensity	Any of the listed	Delirium, fear of death
3	Severe	Any of the listed	Any of the listed, loss of control over the symptoms of the intestinal tract	Any of the listed, cyanosis, saturation ≤ 92%, respiratory arrest	Hypotension * and / or collapse, disturbance of cardiac rhythm, severe bradycardia and / or cardiac arrest	Confused consciousness, loss of consciousness

* Hypotension is determined if the indexes of systolic blood pressure are the following: 1 month – 1 year old < 70 mm Hb.; 1–10 years < [70 mm Hb. + (2 x age)]; 11–17 years < 90 mm Hb. The degree of severity is idenified from the position of the system that was affected the most.

ISSN 2307-3373

Table 2

Indications to epinephrine administration

Required in the case of…	*Adrenalin administration should be considered…*
Respiratory distress	Mild skin and gastrointestinal symptoms are present: bronchial asthma; severe reactions in the history of the disease; previous exposure to a known allergen.
Hypotension	
Colaps	

Table 3

Indications for the purchase of an auto-injector (epipene)

Invariable indications	*Comparative indications*
Previous cardiovascular or respiratory reactions to food or insect bites	Any kinds of reactions to small amounts of a particular products, including inhalation and topical contact
Anaphylaxis caused by physical activity	The history of the disease includes allergic reaction to nuts, even in small amounts
Idiopathic reactions	Distant residence rom the medical institution
Children with food allergies and bronchial asthma	Food allergic reactions in teenagers

to a patient with normal arterial pressure can lead to dangerous conditions – hypertension, ischemia, arrhythmias [15].

Various countries have registered different variations of autoinjectors with epinephrine – epipenes.Two main variations are used most commonly: 0.15 mg (Junior) for children weighing 15–25 kg and devices with 0.3 mg of adrenaline for patients weighing more than 25 kg. For patients weighing up to 15 kg, there is currently no separate auto-injector with adrenaline. Although it has been established in the literature findings that the excess dose of the medication does not create a risk to the child's health from 7.5 kg of body weight (maximum dose of 20 μg/kg) [6, 11].

EpiPen should be stored at room temperature, separately from sources of heat and direct sunlight. The expiration date of EpiPen is 1–2 years, therefore, it is necessary to remember about its timely replacement. The administration of epinephrine has a decent safety profile, though patients may experience temporary pallor, palpitation and headaches [6]. Patient that are at risk of developing anaphylaxis should have not one, but two EpiPens, as it has been registered that anaphylaxis could undergo in different courses.Simultaneously, it is necessary to put the patient on the back with the raised lower limbs, remove the trigger of the reaction and administer glucocorticosteroids intravenous [4, 6].

H1-histamine receptor blockers are administered in the cases of development of mild clinical symptoms of anaphylaxis (eg, skin reactions). If necessary oxygen is provided through a mask and infusion therapy is performed. Short-acting inhaled β-2 agonists are used in cases of bronchospasm development and are delivered through a spacer or a nebulizer. [4].

It is necessary to keep the packaging of all medicines administered until the end of the patient's treatment. In children who have experienced anaphylaxis, it is essential to identify the reasons for the reaction and provide further individual training on health risks and medical care [5, 15]. The patient also should exclude the use of the group of drugs or a single drug that caused anaphylaxis (for these particular situations the physician needs to create a list of prohibited drugs in a written form and a list of alternative medicines) and become capable of predicting cross-reactions and eliminate co-factors.

The physician together with the patient should decide whether there is a need for a constant carriage of an automatic syringe pen with adrenaline (EpiPen) and for conducting a practical training. It is necessary to visualise information on anaphylaxis (a bracelet, a passport of a patient with anaphylaxis risk) and to provide information to the family physician, caretaker, teacher, or caregivers.

Clinical case

Patient M. Born from first pregnancy, first childbirth. The course of the pregnancy and the neonatal period passed without any complications.

During the first year of life the boy experienced a periodical body rash, which the mother associated with the introduction of new products in the diet (citrus, fish). From 2 to 15 years of age, the boy did not experience any allergic reactions. The child experienced no age deviations in development, had no serious illnesses (except for acute respiratory viral infections with frequency 1–2 times a year). Relatively clear family medical history.

At the age of 15, the boy experienced his first episode of anaphylaxis and 5 life threatening conditions were registered during last year. Therapeutic care in a medical facility was provided twice, and three episodes were managed by the patient independently (twice he used the EpiPen in the same doses and once he administered glucocorticosteroids and antihistamines intramuscularly).

A detailed medical history collection made it possible to link all of the episodes with the use of alcoholic beverages (beer and vermouth). The symptoms began to develop in 12–24 hours after drinking alcohol.

The results of the skin allergic examination conducted by the prick-test (using allergen extracts of the brands Diater,

ISSN 2307-3373

Spain and Immunolog, Ukraine): histamine 10x12 mm, control 2x2 mm, spring trees 7x7 mm, 12–16 mm grain, wheat 14x16 mm.

Total IgE – 640 kU / L (norm 0–60).

In order to detect the species-specific components of the allergens, ImmunoCAP Immunofluorescence method (Phadia AB, Sweden) was used. The results of the patient's examination are presented in Table 4.

Thus, the results of the multi-component diagnostic approach allowed to detect that the patient has a very high level of sensitisation to Tri a 14 (wheat flour, omega-5-gliadin) and a high level of sensitisation to Art v3 (wormwood). Both of the allergens belong to the class of lipid transporting proteins (LTP), which are stable under heat treatment and under the effects of hydrochloric acid and are associated with severe and systemic reactions. Without the presence of the stimulating factors (cofactors), the patient has not developed any pathological reactions. The pathophysiological mechanism of anaphylaxis started after alcohol intake: white beer (containing wheat) and vermouth (contains wormwood). Cofactors could be considered as allergen-independent factors that increase the clinical manifestations of allergic reactions, including those associated with food intake [2, 5]. In the context of the analysis of this case, it is necessary to keep in mind the Cofactor-Enhanced Food Allergy (CEFA) and the Wheat-Dependent Exercise-Induced Anaphylaxis (WDEIA) [1, 5, 6].

Literary data analysis allowed us to provide examples of the risks of cofactors of anaphylaxis:

I. Lifestyle factors: physical activity, alcohol, drugs, non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, β-blockers.

II. Individual factors of the patient: adolescent age, sex, infection, menstrual cycle, psychogenic stress.

III. Preliminary health status: bronchial asthma and other IgE-related diseases, cardiovascular disease, mastocytosis, increased basal concentration of tryptase [4].

In order to conduct a comprehensive evaluation of anaphylaxis, it is important to know the patterns of sensitisation, the proportions of immunoglobulin classes, the avidity and affinity of the immunoglobulins that bind with the allergen, the characteristics of the allergens, the route of administration of the allergen, and the presence of the cofactor [1, 2, 6, 14].

Based on the existing literary data and our own experience, we managed to formulate recommendations for the patient:

Acknowledge the life-threatening risks, associated with the development of a new episode of anaphylaxis.

Complete exclusion of alcoholic beverages.

Not to utilise non-steroidal anti-inflammatory drugs without the physician's supervision.

In case of emergency enable the possibility of urgent administration of adrenaline.

Conclusions

Patients with idiopathic anaphylaxis should be thoroughly examined in order to actively detect possible causes of a life-threatening condition.

The main allergens involved in the development of anaphylaxis are the spare proteins and lipid transporting proteins.

When collecting the anamnesis, it is necessary to pay attention to the possible influence of additional factors in the development of anaphylaxis – cofactors (physical activity, alcohol, medicines, concomitant infectious diseases, psychogenic stress, and hormonal particularities).

Patients with a high risk of anaphylaxis development should be provided with the first line drug – adrenaline in the form of an autoinjector (EpiPen) and clearly master the indications and skills of proper use of the drug.

Table 4

Results of the patient's examination (ImmunoCAP method, Phadia AB, Sweden)

Examination Title	*Result, kUA/L*	*Class*	*Interpretation*
	Spring trees		
Specific IgE to rBet v1 (birch)	*0,02*	0	No sensibilisation
Specific IgE to rBet v2, rBet v4 (birch)	0,02	0	No sensibilisation
	Herbs and weeds		
Specific IgE to rPhl p1, rPhl p5 (Timothy Meadow)	0,01	0	No sensibilisation
Specific IgE до rPhl p7, rPhl p12 (Timothy Meadow)	0,03	0	No sensibilisation
Specific IgE to nArt v1 (wormwood)	0,05	0	No sensibilisation
Specific IgE to nArt v3 (wormwood)	**11,5**	**3**	**High level of sensibilisation**
Specific IgE to nAmb a1 (ambrosia)	0,01	0	No sensibilisation
	Wheat flour		
Specific IgE to f416 r Tri a 19 (*wheat flour*, omega-5-gliadin)	<0,10	0	No sensibilisation
Specific IgE to f433 r Tri a 14 (*wheat flour*, omega-5-gliadin)	**19,10**	**4**	**Very high level of sensibilisation**

ISSN 2307-3373

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Theoretical and practical J. «Asthma and Allergy», 2017, 4
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