Czyż Rafał, Leśkiewicz Marcin, Czyż Izabela. Anaphylaxis: the current state of knowledge. Journal of Education, Health and Sport. 2018;8(9):605-615 eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.1412111
http://ojs.ukw.edu.pl/index.php/johs/article/view/5953

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part b item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eissn 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 02.08.2018. Revised: 18.08.2018. Accepted: 09.09.2018.

Anaphylaxis: the current state of knowledge

Rafał Czyż[1], Marcin Leśkiewicz[2], Izabela Czyż[3]

[1]Department of Emergency Medicine, Wroclaw Medical University

[2]Department of Emergency Medical Services, Wroclaw Medical University

[3]Graduate of Wroclaw Medical University

Rafał Czyż - orcid - http://orcid.org/0000-0001-5504-4543

Marcin Leśkiewicz - orcid - http://orcid.org/0000-0003-0167-1618

Izabela Czyż - orcid - http://orcid.org/0000-0002-7838-1670

Address for correspondence:

Rafał Czyż, Department of Emergency Medicine Wroclaw Medical University, Wrocław. Poland; e-mail: rafalczyz1990@o2.pl

Abstract

Anaphylaxis is a severe, life threatening, generalised or systemic hypersensitivity reaction. In the last decade there has been a significant increase in the frequency of anaphylactic reactions in all age groups and all regions of the world. It is estimated that about 0.3% of the European population experience anaphylaxis at some point in their lives.

In connection with the above, this article summarizes current information about anaphylaxis. The following aspects were discussed: definition, epidemiology of disease,

pathomechanism, triggers, signs and symptoms, clinical criteria for the diagnosis, treatment and preventive activities.

Key words: anaphylaxis, adrenaline, anaphylactic reaction, anaphylactic shock

Introduction and aim of work

Despite the fact that the pathomechanism of the anaphylactic reaction over the years has been thoroughly examined, the rapid and rather drastic course of the anaphylactic reaction often surprises not only the patient himself, but also the medical staff. Delay in the introduction of therapeutic measures can have disastrous effects on the health and even life of the patient. The source of detailed recommendations, guidelines and algorithms for dealing with the victim of anaphylaxis is the systematically updated reports of the World Allergy Organization (WAO), expert reports from American Academy of Allergy, Asthma & Immunology (AAAAI) and American College of Allergy, Asthma & Immunology (ACAAI), and in the pediatric European Academia from Allergology and Clinical Immunology (EAACI).

The aim of this study is to draw attention to still present problems of anaphylactic reaction by presenting current definition, epidemiology of disease, pathomechanism, triggers, signs and symptoms, clinical criteria for the diagnosis, treatment and preventive activities.

Description of knowledge

Definition

In the literature, the concept of anaphylaxis was first used by Paul Portier and Charles Richet in 1902 [1]. The word comes from Greek: “a*na”* - means "opposite", and “*phyl”* - "protection". The European Academy of Allergy and Clinical Immunology Nomenclature Committee proposed the following broad definition [2]: anaphylaxis is a severe, life threatening, generalised or systemic hypersensitivity reaction. This is characterized by rapidly developing life-threatening airway and/or breathing and/or circulation problems usually associated with skin and mucosal changes.

Epidemiology

The results of research conducted by Panesar et. al. indicate that an estimated 0.3% of the European population experience anaphylaxis at some point in their lives [3]. What is more,

in the last decade there has been a significant increase in the frequency of anaphylactic reactions in all age groups and all regions of the world [4]. The overall prognosis of anaphylaxis is good, with a case fatality ratio of less than 1% reported in most population-based studies. The European Anaphylaxis Registry reported that only 2% of 3333 cases were associated with cardiac arrest [5]. Every year in Great Britain for a reason of anaphylaxis die approximately 20 people [6]. The overall mortality caused by the severe course of anaphylactic shock in the USA ranged from 0.63 - 0.76 / million population (186-225 deaths per year) and appeared stable in the decade studied [7].

Patomechanism

The development of allergic symptoms and even anaphylactic shock may occur in the mechanism of anaphylactic and pseudoanaphylactic reactions. In the first of these, IgE is involved, and at the beginning, it must have exposure to antigen and they have to product a specific IgE in plasma cells. The next step in this reaction is to join it to mast cells and basophils. Complications in this type of reaction may occur only in the case of subsequent contact of the antigen with IgE. This allergen must quickly enter the circulatory system and penetrate to the described mast cells and basophils, which will already contain the specific allergen-specific immunoglobulin class E. As a result of the collision of these substances, the histamine and other mediators are intensively released - this causes a turbulent anaphylactic reaction [8]. These mediators may lead to: dilation of the vascular, which leads to reduction of venous return to the heart, drop in cardiac output and lowering of blood pressure. There may also be an increase in vascular permeability and, as a result, the movement of plasma into the extravascular space [9]. The pseudoanaphylactic reaction occurs and proceeds through various mechanisms, but always different than the action of the class E immunoglobulin. The release of mediators and histamine is most often directly due to the reaction of pseudoallergen with mast cells and basophils. The further course of the reaction is identical to the one previously described [8].

Factors causing anaphylaxis

The most common triggers of the anaphylactic reaction are [3]:

- stinging insects (wasps, bees, hornets, bumblebees)
- food (peanuts and nuts, fish, crustacea, eggs, milk, grain sesame, soy, wheat)
- medications (antibiotics, local anesthesia, muscle relaxants, proton pump inhibitors, radiological contrast)
- other important factors (latex, cold, effort, effort + food).

The most common factor causing a strong and intense anaphylactic reaction was medication. They were also the most common cause of death in the course of anaphylaxis [3].

Signs and symptoms of anaphylaxis

Clinical symptoms occur after about a few to several minutes after exposure to a potential triggering factor. The symptoms of anaphylaxis most often concern five systems: the circulatory system, the digestive system, the respiratory system, the nervous system as well as the skin and mucous membrane. Pediatric patients are dominated by clinical symptoms from the respiratory system, whereas in adults - by the circulatory system [10]. Quite a frequent form of the course of the anaphylactic reaction is a biphasic form (7-20% of all anaphylactic reactions). It consists in the occurrence of the late phase of symptoms even after a few to several hours after contact with the developing agent [10]. This type of reaction is most often associated with such triggers as drugs and foods.

Table 1. Signs and symptoms of anaphylaxis from other systems.

1.	Disorders of the respiratory system	• Dyspnoea • Shortness of breath • Wheeze • Stridor • Tachypnoea • Cyanosis • Hoarseness • Laryngeal oedema • increased breathing ef fort • Accessory respiratory muscle use • cough
2.	Disorders of the circulatory system	• Hypotension • Capillary refill >2 seconds • Moist and pale skin • Tachycardia • Ischemia of the myocardium • Cardiac arrest
3.	Disorders of the digestive system	• Nausea, • Vomiting, • Diarrhea, • Abdominal pain
4.	Disorders of the nervous system	• Entanglement • Stimulation • Loss of consciousness
5.	Changes on the skin and mucous membranes	• Pruritus • Rhinitis/conjunctivitis • Erythema • Urticaria • Angioneurotic edema ➢ swollen eyelids and lips ➢ swelling of the throat and larynx

(Source: own elaboration based on: Braganza S.C, Acworth J.P, Mckinnon D.R.L. et al.: Paediatric emergency department anaphylaxis; different patterns from adults. Arch. Dis. Child. 2006; 91: 159-63.)

Clinical criteria for the diagnosis of anaphylaxis

The European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on Anaphylaxis state that anaphylaxis is highly likely when any one of the following three criteria is fulfilled [11,12]:

Table 2. Clinical criteria for the diagnosis of anaphylaxis.

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg. generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
• **Respiratory compromise** (eg. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
• **Reduced blood pressure or associated symptoms of end-organ dysfunction** (eg. hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
• **Involvement of the skin-mucosal tissue** (eg. generalized hives, itch-flush, swollen lips-tongue-uvula)
• **Respiratory compromise** (eg. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
• **Reduced blood pressure or associated symptoms** (eg. hypotonia [collapse], syncope, incontinence)
• **Persistent gastrointestinal symptoms** (eg. crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
• **Infants and children:** low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure*
• **Adults:** systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline
** Low systolic blood pressure for children is age specific and defined as: < 70 mmHg for age 1 month to 1 year; < 70mmHg + [2 x age] for age 1 to 10 years; < 90mmHg for age 11 to 17 years.*

(Source: Sampson H.A, Muñoz-Furlong A, Campbell R.L. et. al.: Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006; 117 (2): 391-7.)

Treatment

The basis for treatment of a patient with symptoms of developing anaphylactic reaction should be a systematic examination according to the ABCDE scheme (A-Airway, B-Breathing, C-Circulation, D-Disability, E-Exposure). Life-threatening problems should be treated when they are determined. The basic principles of treatment are the same for all age

groups. Monitor all patients who have suspected anaphylaxis as soon as possible. Minimum monitoring includes: pulse oximetry (SpO_2), non-invasive blood pressure (NIBP) and a 3-lead electrocardiogram. In the aspect of patient placement, it is important to remember that all patients will adopt a body position that is comfortable for them. Patients with airway and breathing problems may prefer to sit up, as this will make breathing easier. Lying flat with or without leg elevation is helpful for patients with a low blood pressure [13]. Another very important aspect of helping a person with symptoms of anaphylaxis is to remove the trigger if it is possible. Stop any drug suspected of causing anaphylaxis. Remove the stinger after a bee/wasp sting. Do not delay definitive treatment if removing the trigger is not feasible [13].

Pharmacologic treatment

Adrenaline is first line and the most important drug for the treatment of anaphylaxis [14, 15]. Although there are no randomised controlled trials, adrenaline is a logical treatment and there is consistent anecdotal evidence supporting its use to ease bronchospasm and circulatory collapse [13]. Adrenaline is most effective when given early after the onset of the reaction, and adverse effects are extremely rare with correct intramuscular doses. Give adrenaline to all patients with life-threatening features [13].

The intramuscular route has several benefits:

- There is a greater margin of safety.
- It does not require intravenous access.
- The intramuscular route is easier to learn.
- Patients with known allergies can self-administer intramuscular adrenaline.

The best site for intramuscular injection is the anterolateral aspect of the middle third of the thigh. The needle for injection needs to be long enough to ensure that the adrenaline is injected into muscle [16].

The evidence for the recommended intramuscular doses is limited. The European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on Anaphylaxis suggests intramuscular adrenaline (1 mg ml^{-1}) should be given a dose of 10 mcg kg^{-1} of body weight to a maximum total dose of 0.5 mg [11]. The table below gives the recommended dosage of adrenaline intramuscularly according to the 2015 guidelines of the European Resuscitation Council [13]:

Table 3. The recommended dosage of adrenaline with intramuscular supply.

Age group	Dose of intramuscular adrenaline	Equivalent volume of 1:1000 adrenaline
>12 years and adults	500 microgram	(0.5 ml)
>6–12 years	300 microgram	(0.3 ml)
>6 months–6 years	150 microgram	(0.15 ml)
<6 months	150 microgram	(0.15 ml)

(Source: Truhlář A, Deakin C.D, Soar J. et. al.: European Resuscitation Council Guidelines for Resuscitation 2015: Section 4. Cardiac arrest in special circumstances. Resuscitation. 2015; 95: 148-201.)

The intravenous dose of adrenaline in the case of anaphylaxis is reserved and recommended for use only by specialists who are experienced in its use in this way of administration. The recommended dosage according to the 2015 European Resuscitation Council guidelines is given below [13]:

- Adults: Titrate intravenous adrenaline using 50 microgram boluses according to response. If repeated adrenaline doses are needed, start an intravenous adrenaline infusion.
- Children: intramuscular adrenaline is the preferred route for children having anaphylaxis. Child may respond to a dose as small as 1 mcg kg^{-1}. This requires very careful dilution and checking to prevent dose errors.

Oxygen is another important drug that should be given to the patient as soon as possible. The most effective way is to give oxygen to the patient through a face mask with a reservoir, paying special attention to the proper oxygen flow, so that the reservoir bag does not collapse (oxygen flow> 10 liters per minute).

Another very important element of patient therapy during anaphylaxis is the supply of fluids infusion. This should be done as soon as possible and available. This is important due to the fact that during anaphylaxis there may be enough to lose large volumes of fluids from the circulatory system and blood vessels dilate. If only an intravenous approach is obtained, a 20 ml/kg^{-1} fluid bolus for child or an intense infusion of 500-1000ml should be given to an adult [13]. There is no evidence to support the use of colloids over crystalloids in this setting [13]. However, due to the fact that colloids may be a factor that causes or intensifies the anaphylactic reaction, it is recommended to use crystalloids. Additionally, it should be remembered that achieving an intravenous route should not delay the intramuscular dose of adrenaline. If repeated attempts at intravenous administration fail, consider using a ready-to-use intraosseous access device.

The second line of treatment during anaphylaxis will be the supply of antihistamine drugs. Despite the fact that scientific evidence of their effectiveness in this clinical situation is

limited there are logical reasons for their use. H1-antihistamines help counter histamine-mediated vasodilation, bronchoconstriction, and particularly cutaneous symptoms. There is little evidence to support the routine use of an H2-antihistamine for the initial treatment of anaphylaxis [13].

Another second-line treatment is glucocorticoids, which prevent and shorten prolonged reactions, although precise and reliable evidence is unfortunately limited. Accurate and recommended by the European Resuscitation Council, the dosage of Hydrocortisone is given in the table below.

Table 4. The recommended dosage of Hydrocortisone with intramuscular or intravenous supply.

Age group	Hydrocortisone (intramuscular or slow intravenous)
> 12 years and adults	200 mg
> 6–12 years	100 mg
> 6 months–6 years	50 mg
< 6 months	25 mg

(Source: Truhlář A, Deakin C.D, Soar J. et. al.: European Resuscitation Council Guidelines for Resuscitation 2015: Section 4. Cardiac arrest in special circumstances. Resuscitation. 2015; 95: 148-201.)

Other drugs that may be helpful in combating the associated symptoms of anaphylaxis are bronchodilators. Consider expanding therapy for use salbutamol (inhaled or intravenous), ipratropium (inhaled), aminophylline (intravenous) or magnesium (intravenous). It is very important that magnesium-intravenous administration may cause a fall in blood pressure due to vasodilating effects [13].

Prevention of severe anaphylactic reaction

Activities that may reduce the risk of a severe anaphylactic reaction include:

1. Identification of the triggering factor,
2. Avoid exposure to the triggering factor,
3. Allergen immunotherapy, e.g. on hymenoptera venom,
4. Education of the exposed person and his relatives in the field of recognizing the early symptoms of reaction and giving first aid - including the use of a pre-filled syringe with adrenaline,
5. Assumption by the exposed person to anaphylaxis of a medical identifier - a wrist bracelet.

Unfortunately, these recommendations are often neglected by vulnerable people, which create a real threat to their health and life. The most common mistakes are:

- Disbelief that such a situation may surprise such a person
- Lack of proper equipment, including a pre-filled syringe with adrenaline
- Lack of systematic equipment control and checking, for example, adrenalin expiry date
- Delayed introduction of intensive treatment
- Lack of proper education of the patient and people from his immediate environment
- Lack of information about the possibility of such a situation occurring in the workplace of the exposed person
- Fear of adrenaline administration
- Lack of detailed diagnosis after anaphylaxis episode

Summary

Increasing the emphasis on patient education can significantly reduce the incidence of severe anaphylactic reactions and reduce patient mortality. What is more, it seems necessary to organize trainings aimed at increasing the awareness among people about the disturbing symptoms that accompany the developing anaphylactic reaction as well as systematic training in providing basic life-saving treatments for anaphylaxis patients. Due to the fact that anaphylaxis is quite common among people, it seems advisable to increase financial expenditures both for prevention and organizing various types of social and information campaigns in order to promote a proper social response in the situation of anaphylactic reaction in humans.

References:

[1] - Richet G.: The discovery of anaphylaxis, a brief but triumphant encounter of two physiologists (1902). Hist Sci Med. 2003; 37 (4): 463-9.

Indexed in Pubmed: 14989211.

[2] - Johansson S.G, Bieber T, Dahl R, et al.: Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization 2003. J Allergy Clin Immunol. 2004; 113: 832-6.

DOI: 10.1016/j.jaci.2003.12.591, indexed in Pubmed: 15131563.

[3] - Panesar S.S, Javad S, de Silva D. et al.: The epidemiology of anaphylaxis in Europe: a systematic review. Allergy. 2013, 68: 1353-61.

DOI: 10.1111/all.12272, indexed in Pubmed: 24117770.

[4] - Tang M.L, Osborne N, Allen K.: Epidemiology of anaphylaxis. Curr Opin Allergy Clin Immunol. 2009; 9 (4): 351-6.

DOI: 10.1097/ACI.0b013e32832db95a, indexed in Pubmed: 19506470.

[5] - Worm M, Moneret-Vautrin A, Scherer K, et al.: First European data from the network of severe allergic reactions (NORA). Allergy. 2014; 69: 1397-404.

DOI: 10.1111/all.12475, indexed in Pubmed: 24989080.

[6] - Gibbison B, Sheikh A, McShane P, et. al.: Anaphylaxis admissions to UK critical care units between 2005 and 2009. Anaesthesia. 2012; 67 (8): 833-9.

DOI: 10.1111/j.1365-2044.2012.07159.x, indexed in Pubmed: 22607557.

[7] - Ma L, Danoff T.M, Borish L.: Case fatality and population mortality associated with anaphylaxis in the United States. J Allergy Clin Immunol. 2014; 133 (4): 1075-83. DOI: 10.1016/j.jaci.2013.10.029, indexed in Pubmed: 24332862.

[8] - Reber L.L, Hernandez J.D, Galli S.J.: The pathophysiology of anaphylaxis. J Allergy Clin Immunol. 2017; 140 (2): 335-48.

DOI: 10.1016/j.jaci.2017.06.003, indexed in Pubmed: 28780941.

[9] - Rutkowski K, Dua S, Nasser S.: Anaphylaxis: current state of knowledge for the modern physician. Postgrad Med J. 2012; 88 (1042): 458-64.

DOI: 10.1136/postgradmedj-2011-130634, indexed in Pubmed: 22467837.

[10] - Braganza S.C, Acworth J.P, Mckinnon D.R.L. et al.: Paediatric emergency department anaphylaxis; different patterns from adults. Arch. Dis. Child. 2006; 91: 159-63.

DOI: 10.1136/adc.2004.069914, indexed in Pubmed: 16308410.

[11] - Muraro A, Roberts G, Worm M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy. 2014; 69: 1026–45.

DOI: https://doi.org/10.1111/all.12437, indexed in Pubmed: 24909803.

[12] - Sampson H.A, Muñoz-Furlong A, Campbell R.L. et. al.: Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006; 117 (2): 391-7.

DOI: 10.1016/j.jaci.2005.12.1303, indexed in Pubmed: 16461139.

[13] - Truhlář A, Deakin C.D, Soar J. et. al.: European Resuscitation Council Guidelines for Resuscitation 2015: Section 4. Cardiac arrest in special circumstances. Resuscitation. 2015; 95: 148-201.

DOI: 10.1016/j.resuscitation.2015.07.017, indexed in Pubmed: 26477412.

[14] - Simpson C.R, Sheikh A.: Adrenaline is first line treatment for the emergency treatment of anaphylaxis. Resuscitation. 2010; 81: 641-2.

DOI: https://doi.org/10.1016/j.resuscitation.2010.04.002, indexed in Pubmed: 20413204.

[15] - Kemp S.F, Lockey R.F, Simons F.E.: Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy. 2008; 63: 1061-70.

DOI: 10.1111/j.1398-9995.2008.01733.x, indexed in Pubmed: 8691308.

[16] - Song T.T, Nelson M.R, Chang J.H. et. al.: Adequacy of the epinephrine autoinjector needle length in delivering epinephrine to the intramuscular tissues. Ann Allergy Asthma Immunol. 2005; 94: 539-42.

DOI: 10.1016/S1081-1206(10)61130-1, indexed in Pubmed: 15945556.