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Food poisoning, anaphylactic shock

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1 Anaphylaxis

1.1 Brief overview of the pathophysiology of anaphylaxis

Anaphylaxis is a severe, life-threatening generalized or systemic hypersensitivity reaction with rapid onset of clinical manifestations that can cause death. Its most severe form is anaphylactic shock. From the pathophysiological point of view, anaphylaxis can be divided into IgE-mediated and non-IgE-mediated, but in the acute state, the therapeutic approaches are completely identical. The most common triggers of an anaphylactic reaction are foods (nuts, milk, seafood...), drugs (neuromuscular blocking agents, local anesthetics, disinfectants, latex...) and insect bites.

Mast cells and basophils play a key role in IgE-mediated anaphylaxis. Both cell types carry a receptor on their surface for the Fc fragment of immunoglobulin molecules (abbreviated Fcε-RI), to which circulating IgE immunoglobulin binds. Activation and degranulation of mast cells then occurs when the appropriate antigen binds to IgE, which is already bound to the cell surface via the Fcε-RI receptor. Here it is evident that individuals with atopy have a higher risk of IgE mediated anaphylaxis. This is defined as a predisposition of the organism to respond preferentially to new antigens by the production of IgE class antibodies, which subsequently occupy free Fcε-RI receptors. In addition, elevated IgE levels cause upregulation of the synthesis of Fcε-RI receptors themselves.

Once the antigen binds to the IgE - Fcε-RI complex, a signal is transmitted to the cell, which causes an increase in the intracellular calcium concentration. The released calcium is responsible for two events: degranulation and simultaneous activation of transcription factors in the cell nucleus, which leads to the production of late mediators of anaphylaxis.

The granules of cells contain mainly histamine, a biogenic amine acting through histamine receptors. It can induce bronchoconstriction, both directly via receptors on smooth muscle and indirectly via stimulation of receptors at afferent vagal synapses. In the arteries, however, it exerts a vasodilatory effect, mainly through its vascular receptors, by which it induces increased nitric oxide synthesis (a potent vasodilatory agent). However, it is also able to induce vasodilation via its receptors at sympathetic synapses, thereby reducing vascular tone. Further, among its effects, it is claimed to increase the permeability of the walls of the venules and to increase mucus secretion in the airways.

Other important preformed mediators of anaphylaxis in granules are a group of proteases, of which tryptase and kininogenase are important. There are 2 forms of tryptase, α and β, of which α-tryptase is secreted constitutively and β-tryptase only during mast cell degranulation. During anaphylaxis, serum β-tryptase levels peak within 60-90 minutes and persist for 6-12 hours after the episode, which is used in diagnostics. Tryptase has a number of biological effects, some overlapping with those of histamine. For example, it is able to inactivate a vasoactive intestinal peptide that has a bronchodilator effect. Kininogenase in turn facilitates the production of bradykinin, a peptide with significant vasodilatory and vascular permeability-enhancing effects.

Binding of the antigen to the IgE - Fcε-RI complex also activates phospholipase A2 in mast cells and basophils, which concentrates on the nuclear membrane and is able to release arachidonic acid from membrane phospholipids, a precursor in the synthesis of prostaglandins and leukotrienes. Both of these groups of substances subsequently cause bronchoconstriction, vasodilation, increased vascular permeability, and chemotaxis of eosinophils and neutrophils to tissues.

Mast cells and basophils also produce a variety of cytokines involved in the anaphylactic reaction. Examples are interleukins 4 and 13, which promote the production of IgE antibodies. In addition, TNFα,

for example, increases the expression of adhesion molecules on the endothelium, allowing eosinophils and neutrophils to travel outside the vascular system.

Non-IgE mediated anaphylactic reaction represents a group of several pathophysiologically different mechanisms, but with identical clinical picture and treatment. Again, the release of the above described mediators of anaphylaxis from mast cells and basophils plays a key role. However, the release is not linked to the interaction between the antigen and the IgE - Fcε-RI complex. The first mechanism is the direct effect of some therapeutic and diagnostic agents (such as X-ray contrast agents, opiates, myorelaxants, dextran and other plasma expanders) on mast cells and basophils, by which their immediate degranulation occurs. The exact mechanism is not yet known. Another mechanism is complement activation, which produces the so-called anaphylatoxins C3a and C5a. A typical clinical example is replacement therapy with intravenous immunoglobulins in patients with the presence of IgG antibodies to IgA. Another complement trigger may be the action of the dialysis membrane, which directly releases C3a and C5a.

However, do not confuse a non-IgE mediated anaphylactic reaction with a non-IgE mediated allergic reaction to food, which is most commonly encountered in childhood. The basis of this allergic reaction is in no way related to the degranulation of mast cells and basophils, but is based on the activation of mucosal and cutaneous T lymphocytes. Therefore, the spectrum of symptoms is skin and mucosal related. Patients therefore experience gastrointestinal (diarrhoea, vomiting, reflux), cutaneous (urticaria) and respiratory (recurrent pneumonia) symptoms when exposed to the allergen. The onset of clinical manifestations is slower (hours to days) compared to the anaphylactic reactions described above (either IgE or non-IgE mediated). Hypotension may occur in such patients only secondarily, from dehydration following diarrhoea. Skin tests for allergy cannot be used in this case. The most common forms of this food allergy include food protein-induced enterocolitis syndrome and eosinophilic oesophagitis.

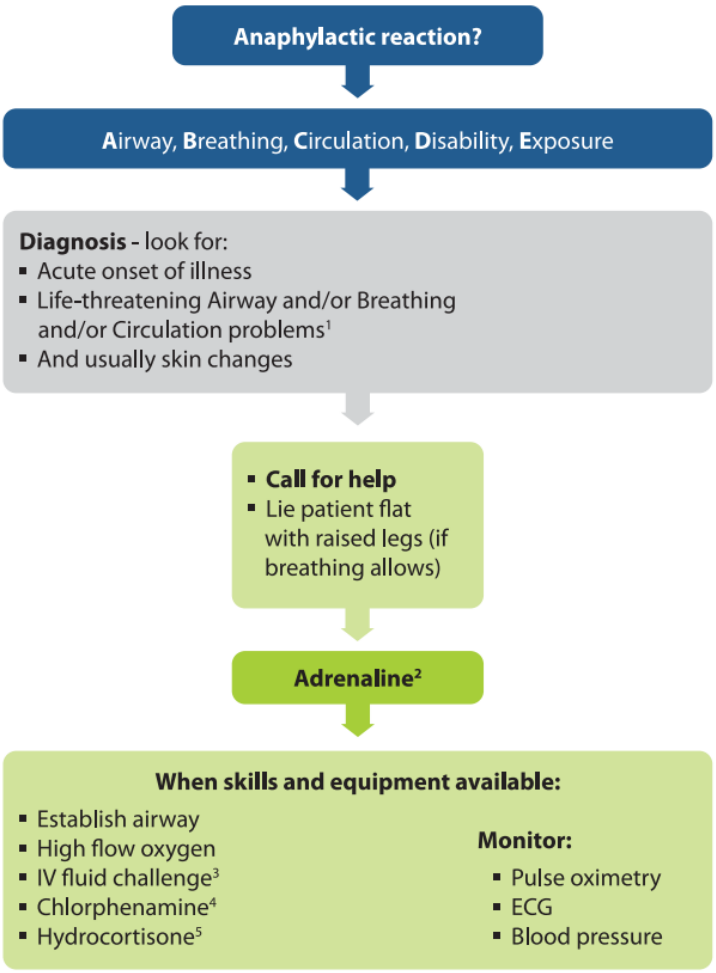
1.2 Symptoms, diagnosis, and treatment

Symptoms of anaphylaxis develop within seconds to minutes. However, some reactions occur after a delay of 30 min or more. The clinical picture of anaphylaxis is based on the action of the described mediators. The three key phenomena induced by mediators are vasodilation, smooth muscle spasm and increased vascular permeability. If we follow the ABCDE algorithm in the first contact with the patient, we find clinical manifestations of these phenomena in each organ system. If we take the airways (A; Airway), the upper airways are particularly at risk of swelling, which is due to increased permeability of the vessels. Swelling affects the tongue and the mucous membranes of the nasal, oropharyngeal and laryngeal mucosae. Its formation leads to narrowing of the upper airways, resulting in inspiratory stridor. Inspiratory because the narrowing of the upper airways is exacerbated by the negative pressure that builds up inside the airways relative to the surroundings during inspiration. The lower airways are at risk of bronchospasm because of the ability of anaphylaxis mediators to induce smooth muscle spasm. As the lower airways are located intrathoracically, their bronchospastic constriction is accentuated in expiration due to increased intrathoracic pressure. Therefore, bronchospasm accompanies expiratory stridor. At the level of respiration (B; Breathing), a disturbance in gas exchange is manifested as a result of alveolar oedema resulting from increased vascular permeability. The combination of impaired airway patency and gas exchange leads to desaturation, dyspnea, rapid breathing, signs of an obstructed airway (e.g., jugular retraction), and the development of an auditory finding. The circulation (C; Circulation) is compromised by vasodilation and increased vascular permeability, leading to hypotension. As the bloodstream volume increases, anaphylactic shock is called distributive shock. We generally recognize a shock state by tachycardia, prolonged capillary return, weak pulses on the periphery and hypotension. In distributive shock, the capillary return may initially be rapid and the skin flushed until its development slows down the capillary return and the skin becomes pale to marbled. If hypotension progresses, myocardial ischaemia may occur with the development of malignant

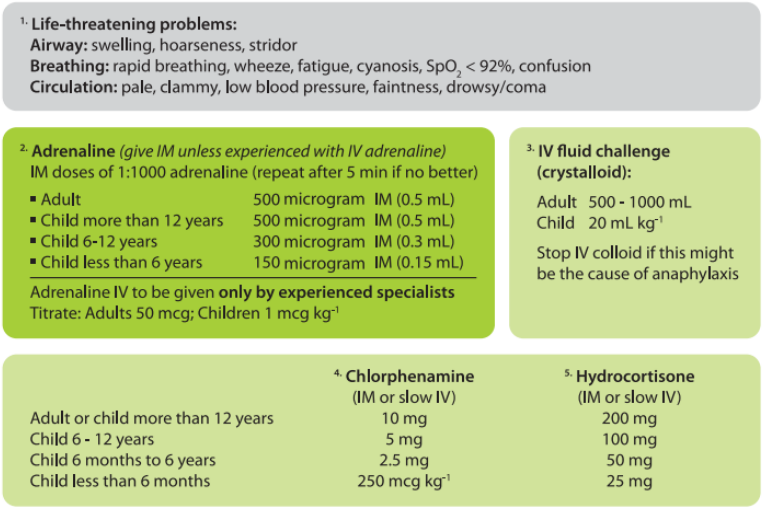
arrhythmia and subsequent circulatory arrest. Neurological status (D; Disability) is also affected by the resulting hypotension. The patient complains of headache, fainting and may become unconscious. Other symptoms (E; Exposure) include urticaria and crampy abdominal pain accompanied by vomiting or diarrhoea as a result of smooth muscle spasm and increased vascular permeability in the gastrointestinal tract.

If anaphylaxis is suspected (symptoms are acute and life-threatening - see A, B and C), adrenaline (or epinephrine) is the first choice (picture 1). By its action via α1 receptors, it induces peripheral vasoconstriction, thereby limiting the development of hypotension and reducing mucosal oedema. Adrenaline also increases blood pressure by direct action on the myocardium via β1 receptors (positive inotropic and chronotropic effect). An important effect of adrenaline via action on β2 receptors is smooth muscle dilation, which is particularly beneficial for inducing bronchodilation. Adrenaline also reduces the release of inflammatory mediators. The recommended route of administration is intramuscular administration. Compared with intravenous administration, no reduced clinical effect was observed with the first dose. In contrast, intravenous administration is associated with a higher incidence of cardiovascular complications. In particular, hypertension, which can be fatal, especially in hypertonic patients, myocardial ischemia caused by β-mimetic-induced increase in oxygen consumption, and the development of malignant arrhythmias. We use undiluted epinephrine for intramuscular administration. In adults and children over 12 years of age, we administer 0.5 mg of epinephrine (half of a standard vial containing 1 mg). In children between 6 and 12 years of age, we administer 0.3 mg of adrenaline. And for children under 6 years, only 0.15 mg of adrenaline. If the condition does not improve, repeat the dose after 5 minutes.

Pic. 1 Poster of guideline in case of anaphylaxis according to European Resuscitation Council 2015



Pic. 2 Comments on guideline in pic. 1, ERC guideline 2015



The next step in the treatment is the administration of bolus fluids, antihistamines (most commonly bisulepin) and corticosteroids. The effect of corticosteroids occurs after 4-6 hours and consists of a

decrease in plasma exudation, mucus secretion, leukocyte infiltration of tissues, increase in β-receptor susceptibility and blocking of phospholipase A2, which leads to a decrease in the synthesis of mediators of anaphylaxis. Detailed drug dosages can be found in the attached recommendations (picture 1, 2).

As part of the initial approach, the patient should be placed in a horizontal position (with the lower limbs elevated) and examined by the ABCDE procedure, have a patent airway, be connected to continuous monitoring and be under constant medical supervision, which means placing the patient in an intensive care unit (ICU) or an emergency department (ED). As up to 20% of cases describe delayed reactions with symptoms occurring 8-12 hours after the initial attack, a patient with a severe anaphylactic reaction should spend at least 12 hours in a monitored bed. Subsequent symptoms with a longer time interval of 24-72 hours cannot be excluded. The serum tryptase level is used to confirm that the patient has had an anaphylactic reaction due to mediators released from mast cells and basophils. This is the only laboratory evidence of an anaphylactic reaction and should be performed whenever an anaphylactic reaction is suspected. We must always instruct the patient properly before discharge. During the interview, four basic things should be said: 1) Inform him that an anaphylactic reaction has taken place in his body and that the symptoms may recur in the next three days as part of the late phase of anaphylaxis. 2) Avoid the triggering factor. If the allergen is unknown, the patient should see an allergist where skin prick tests will be performed to identify the allergen. 3) Report the fact to their GP and 4) Equip the patient with an EpiPen and teach them how to use it.

References & recommended further reading

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2 ACUTE INFECTIOUS DIARRHOEA

2.1 Definition, pathophysiology

Acute diarrhea is characterized by the occurrence of three or more loose, unformed or watery stools in the preceding 24 hours. Persistent diarrhea is defined as diarrhea that is acute in onset and lasts for more than 14 days. At the same time, the stool volume exceeds 250 ml or 200 g per day.

In terms of etiology, diarrhea is divided into infectious and non-infectious. In the case of infectious etiology, the causative agent may be a virus, bacteria or protozoa. From the point of view of pathophysiology, there are 3 possible mechanisms of infectious diarrhea:

1. The pharmacological effect of toxins released by bacteria, which cause disruption of the normal fluid and electrolyte balance in enterocytes, is manifested by malabsorptive or secretory diarrhea. A combination of the two is also possible, as in the case of cholera (the cholera toxin CTA1 causes a chain of events culminating in phosphorylation of the CFTR protein, which secretes chloride and sodium ions into the intestinal lumen, thereby eliminating water).
2. Inflammatory response to infection - a response to damage caused by infection with invading pathogens. The degree of inflammation is influenced by the site and degree of invasion, which is balanced by host immune response mechanisms on the mucosal surface and in the relevant lymphoid tissue. In response to a superficial invasion (e.g. Campylobacter jejuni or Shigella dysenteriae), local inflammation will normally occur. When the mucosal barrier is breached as a result of tissue damage and local bleeding, blood sometimes appears in the stool (as in the case of dysentery, the typical symptom of which is blood and pus in the stool). C. jejuni causes local inflammation, and in severe cases there is an admixture of blood in the stool. C. jejuni releases a cytotoxin that damages enterocytes, causing diarrhea. Some pathogens produce deep abscesses with perforations and mucosal ulcers leading to peritonitis and intra-abdominal abscesses (e.g. Entamoeba histolytica - amoeba dysentery). Blood in the stool is therefore consistent with this type of damage.
3. Some viruses directly kill enterocytes, which leads to the collapse of the villous structure (villous atrophy), and thus water absorption is prevented (hence the increased amount of fluid in the stool - diarrhea). Reparative mechanisms result in hypertrophy of the Lieberkühn crypts manifested by a temporary increase in fluid secretion until normal villous architecture is restored (about three days). Common intestinal viral infections are caused by noroviruses (winter vomiting disease) and rotaviruses (especially in young children). Both genera cause diarrhea.

A brief overview of the causes of non-infectious diarrhea is also included:

- side effect of some drugs (e.g., antibiotics, antihypertensives, overdose of hypothyroidism replacement), in some poisonings (egg, with mushrooms),
- ingestion of osmotically active substances (e.g. laxatives, artificial sweeteners),
- enzyme deficiency (e.g. lactase),
- reduction of the absorptive surface (e.g. intestinal resection),
- disruption of enterocyte transport mechanisms (e.g. Crohn's disease, bile acid malabsorption, pancreatic steatorrhea),
- bowel wall disorders (e.g. colitis, ischemia, diverticulitis),
- pathological processes in the small pelvis (sudden abdominal episodes, perirectal abscess, extrauterine pregnancy),
- increased motility (e.g. irritable bowel, diabetes mellitus, thyrotoxicosis).

Diarrhea can also be the first manifestation of a serious infection localized outside the intestinal tract (sepsis, pneumonia, urinary infection in the elderly, viral hepatitis).

2.2 Diagnosis and treatment

The following text discusses the diagnosis and treatment of diarrhea in a GP's outpatient clinic. It is difficult to determine the incidence of acute diarrheal diseases; for the most part, it is a hidden incidence. In most cases, spontaneous recovery occurs and only about 25 % of patients consult a physician.

When taking a history, we should focus on the following points to help us confirm our suspicion that this is infectious diarrhea and to help us answer three critical therapeutic questions: 1) whether to do a stool culture, 2) whether to give antibiotics, and 3) whether to hospitalize the patient in the infectious disease unit.

- What does the stool look like? We are particularly interested in the presence of mucus or blood.
- Is the patient suffering from fevers?
- Is he being chronically treated for something serious?
- What diet preceded the onset of diarrhea and was there anything risky in this respect?
- Does the patient's environment have similar symptoms?
- Where does the patient work and live? Workers in the food industry, health care or nursing homes are at risk in this respect. At the same time, if the patient stays in social facilities, he or she may also pose a risk of spreading the disease.
- Did the patient travel?

2.3.1 Stool culture examination

If we have the patient's answers to these points, we may decide to perform a stool culture. According to the recommendations, this applies to the following patients:

- ✓ who repeatedly seek medical attention for failure of symptomatic therapy,
- ✓ with a severe clinical course of diarrhea (then preferably repeatedly),
- ✓ with blood and mucus in the stool,
- ✓ weakened (elderly, immunosuppressed patients),
- ✓ with an increased risk of spreading the disease to the surrounding area (e.g. in collective facilities, hospitals or shelters),
- ✓ who carry out activities of epidemiological significance (in particular food and health care work) and their family members.

2.3.2 Therapy

Another issue is the deployment of antibiotic therapy. It is recommended to administer antibiotics in case of bacterial or protozoal diarrhea in immunocompromised, polymorbid and severe patients. Bacterial or protozoal diarrhea can be suspected if the patient answers positively to questions about the presence of blood or mucus in the stool and fever. The administration of antibiotics before the result of stool culture must be based on the current epidemiological situation. Salmonella and Campylobacter are the most commonly identified causative organisms. Therefore, we choose antibiotics from groups such as cotrimoxazole, fluorinated quinolines or macrolides.

Cholera *	Doxycycline 300 mg once,
	Azithromycin 1g once
	Ciprofloxacin 2 x 500 mg for 3 days
Salmonellosis (only if diarrhea is accompanied high fever)	
	Cotrimoxazole 2x 960 mg for 3 days
	Ciprofloxacin 2x 500 mg for 3 days
Shigellosis**	Ciprofloxacin 2x 500 mg 3 days
	Ceftriaxone 2-4 g once
Amoebiasis**	Metronidazole, 3x 750 mg 5 days
Giardiasis	Metronidazole, 3x 250 mg 5 days
Campylobacteriosis***	Azithromycin 500 mg daily for 3 days
	Clarithromycin 2x 500 mg 3-5 days

* If a patient with cholera were to appear in the Czech Republic, he would have to be hospitalized in the infectious disease department by law.

** In the case of shigellosis and amebiasis, patient isolation in the infectious disease department is mandatory

*** More than 50% of campylobacter strains in the Czech Republic are resistant to fluoroquinolones

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However, let us always keep in mind that in most cases causal (i.e. antibiotic therapy) is not necessary. If stool culture reveals another pathogen that is not covered by the antibiotic therapy already administered, treatment should be adjusted according to the antibiotic sensitivity results of the pathogen detected.

To alleviate subjective discomfort and in situations where diarrhea is undesirable for practical reasons (urgent work, travel), patients may be recommended antimotility drugs (loperamide, possibly loperamide combined with simeticon). The duration of administration should not exceed 48 hours. Loperamide is contraindicated in young children and with signs of invasive inflammatory diarrhea; with fever, stools with admixture of blood and with severe abdominal pain. It is not recommended for breastfeeding and only with caution can it be given in pregnancy. Of other antimotility drugs, diphenoxylate may be prescribed. For the symptomatic treatment of acute diarrhea or as an adjunct to causal treatment, a drug that reduces intestinal secretion in infectious diarrhea, racecadotril, may be recommended. Treatment should not exceed 7 days. The drug can also be recommended for children. No dosage adjustment is needed in elderly patients. In cases of presumed bacterial etiology of diarrhea (e.g., traveler's diarrhea, diarrhea after ingestion of contaminated water, food) or in dysenteric form of diarrhea (febrile state with blood and mucus, pieces of mucous in stool), intestinal desinfectant (nifuroxazide, cloroxinum) is the drug of choice. Short-term combination of antimotility drugs, antisecretory drugs and intestinal desinfectants (nifuroxazide) is possible. Of the adsorbents, smectite can be used. The main disadvantage of carbo adsorbens, is the limitation of the possibility of objectively evaluating the stool. Spasmolytics can be used exceptionally in case of colic pain.

2.3.3 Hospitalization

The last question is the indication for hospitalization in the infectious disease ward. We are considering this for the following patients:

- diarrhea lasting more than 3 days, accompanied by symptoms such as blood and/or mucus in the stool, flatulence and abdominal pain, tenesmus and repeated vomiting, febrile condition,
- severe dehydration and hypotension, malaise, confusion, deep and slow (Kussmaul) breathing,
- diarrhea complicating a serious chronic disease,
- failure to provide adequate home care,
- unsuccessful rehydration at home,
- staying in epidemiologically serious areas,
- compulsorily hospitalized diseases such as bacillary and amoebic dysenteria, cholera, paratyphoid, typhoid, anthrax and salmonellosis accompanied by high fever.

Before leaving the GP's surgery, a patient with uncomplicated acute diarrhea should be given the following instructions:

- adequate fluid intake (4 liters per day, sweet tea, mineral water, even with vomiting and diarrhea, some of the fluid intake is absorbed) or commercially produced oral rehydration solutions,
- temporary discontinuation of diuretic therapy,
- limiting fats and laxative, bloating or irritating foods is advisable,
- food intake according to individual tolerance, in smaller doses more often, probiotics are suitable,
- compliance with hygiene principles is required,
- risk of decreased drug resorption, including oral contraceptives, change in extracellular fluid distribution volume for drugs (antihypertensives),
- educating the patient about possible medications for diarrhea,
- a follow-up visit to a patient with uncomplicated acute diarrhea is not necessary.

Finally, it should be added that reporting on the "Infectious Disease Reporting" form is mandatory for all acute diarrhea of infectious etiology. In the event of a risk of further spread of an infectious disease, the report is made immediately by telephone or fax to the public health authority (the relevant health station) and subsequently confirmed by means of the form.

References & recommended further reading

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