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Anaphylactic shock

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1 Shock

1.1 Brief overview of the pathophysiology of shock

Shock is characterized by decreased oxygen delivery and/or increased oxygen consumption or inadequate oxygen utilization leading to cellular and tissue hypoxia. It is a life-threatening condition of circulatory failure and most commonly manifested as hypotension (systolic blood pressure less than 90 mm Hg or MAP less than 65 mmHg) and elevated lactate levels (more than 2 mmol/L). Shock is the final manifestation of a complex list of etiologies and could be fatal without timely management.

1.1.1 Distributive Shock

Characterized by peripheral vasodilatation.

Causes: septic shock, systemic inflammatory response syndrome (various infections, pancreatitis, burns, fat embolism, air embolism, and amniotic fluid embolism), anaphylactic shock, neurogenic shock (disruption of the autonomic pathway resulting in decreased vascular resistance and changes in vagal tone due to spinal cord injury)

1.1.2 Hypovolemic Shock

Hypovolemic shock is characterized by decreased intravascular volume and increased systemic venous resistance (compensatory the mechanism to maintain perfusion in the early stages of shock). In the later stages of shock due to progressive volume depletion, cardiac output also decreases and manifest as hypotension.

Causes: gastrointestinal bleed, trauma, vascular etiologies, spontaneous bleeding in the setting of anticoagulant use, GI losses, renal losses, skin losses/insensible losses (burns, Stevens-Johnson syndrome, toxic epidermal necrolysis, heatstroke, pyrexia), third-space loss (pancreatitis, cirrhosis, intestinal obstruction, trauma).

1.1.3 Cardiogenic Shock

Due to intracardiac causes leading to decreased cardiac output and systemic hypoperfusion.

Causes: cardiomyopathies (acute myocardial infarction, fulminant dilated cardiomyopathy, cardiac arrest, myocarditis), arrhythmias (both tachy- and bradyarrhythmias), mechanical (severe aortic insufficiency, severe mitral insufficiency, rupture of papillary muscles or chordae tendinae, traumatic rupture of ventricular free wall aneurysm).

1.1.4 Obstructive Shock

Mostly due to extracardiac causes leading to a decrease in the left ventricular cardiac output

Causes: Pulmonary vascular - due to impaired blood flow from the right heart to the left heart (pulmonary embolism, severe pulmonary hypertension) or mechanical - impaired filling of right heart or due to decreased venous return to the right heart due to extrinsic compression (tension pneumothorax, pericardial tamponade, restrictive cardiomyopathy, constrictive pericarditis).

1.2 Epidemiology and signs of shock

Distributive shock is the most common type of shock, followed by hypovolemic and cardiogenic shock. Obstructive shock is relatively less common. The most common type of distributive shock is septic shock and has a mortality rate between 40 to 50 %.

Hypoxia at the cellular level causes a series of physiologic and biochemical changes, resulting in lactic acidosis and a decrease in regional blood flow, which further worsens the tissue hypoxia. In

hypovolemic, obstructive, and cardiogenic shock, there is a decrease in cardiac output and decreased oxygen transport. In distributive shock, there is decreased peripheral vascular resistance and abnormal oxygen extraction. Shock is a spectrum of physiologic changes, ranging from early stages, which are reversible to the final stages, which are irreversible with multiorgan failure and death. Generally, shock has the following three stages:

1. Pre-shock or compensated shock - As the name suggests, this stage is characterized by compensatory mechanisms to counter the decrease in tissue perfusion, including tachycardia, peripheral vasoconstriction, and changes in systemic blood pressure
2. Shock - During this stage, most of the classic signs and symptoms of shock appear due to early organ dysfunction, resulting from the progression of the pre-shock stage as the compensatory mechanisms become insufficient.
3. End-organ dysfunction - This is the final stage, leading to irreversible organ dysfunction, multiorgan failure, and death

1.3 Treatment

The initial approach to management is the stabilization of the airway and breathing with oxygen and oral mechanical ventilation when needed. Peripheral IV or intraosseous infusion (IO) access should be obtained. Immediate treatment with intravenous (IV) fluid should be initiated, followed by vasopressor therapy, if needed, to maintain tissue perfusion; the first choice of a vasopressor is norepinephrine, with the addition of vasopressin if refractory. Depending on the underlying etiology of shock, specific therapies might also be needed:

- Septic shock - empiric antibiotic therapy within one hour followed by microbiologic examination and tailored antibiotic therapy.
- Anaphylactic shock - stop the offending agent, intramuscular epinephrine, fluid resuscitation, antihistamines, corticosteroids, nebulized albuterol.
- Hypovolemic shock - obtain two large-bore IVs or central line. Place the patient in the Trendelenburg position. IV fluid resuscitation, PRBC (pure red blood cells) transfusion if ongoing bleeding. Appropriate medical or interventional strategies to treat the underlying aetiology.
- Obstructive shock - the judicious use of IV crystalloids, early initiation of vasopressors. In acute massive pulmonary embolism - thrombolysis. In tension pneumothorax - needle thoracotomy followed by tube thoracotomy. In cardiac tamponade - pericardiocentesis, significant clinical improvement is possible, even with minimal fluid removal.
- Cardiogenic shock - if unstable tachyarrhythmia or bradyarrhythmias, follow ERC guidelines (cardioversion, pacing, antiarrhythmic drugs). Consider inotropes (dobutamine is the most commonly used agent) or intra-aortic balloon pump (IABP), if refractory shock. If STEMI - consider coronary revascularization procedures or thrombolysis.

1.4 Important points to remember

- Shock is a clinical manifestation of circulatory failure and is associated with high morbidity and mortality.
- There are broadly four types of shock: distributive, cardiogenic, hypovolemic, and obstructive.
- An accurate diagnosis requires a good understanding of underlying pathophysiology, clinical, biochemical, and hemodynamic manifestations of the different types of shock.
- Serum lactate level is a useful risk stratification tool in managing undifferentiated shock.

- Timely diagnosis and initiation of appropriate therapy are of paramount importance as it can prevent progression to the reversible shock, multiorgan failure, and death.
- Treatment includes oxygenotherapy, hemodynamic stabilization and correction of underlying etiology of shock.

2 Anaphylaxis

2.1 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, chlorhexidine, opioids...) and insect bites (Hymenopthera species).

2.1.1 IgE-mediated anaphylaxis

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.

2.1.2 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 several biological effects, some overlapping with those of histamine. For example, it can inactivate a vasoactive intestinal peptide with a bronchodilation 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 can release arachidonic acid from membrane phospholipids, a precursor in the synthesis of prostaglandins and leukotrienes. Both 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.

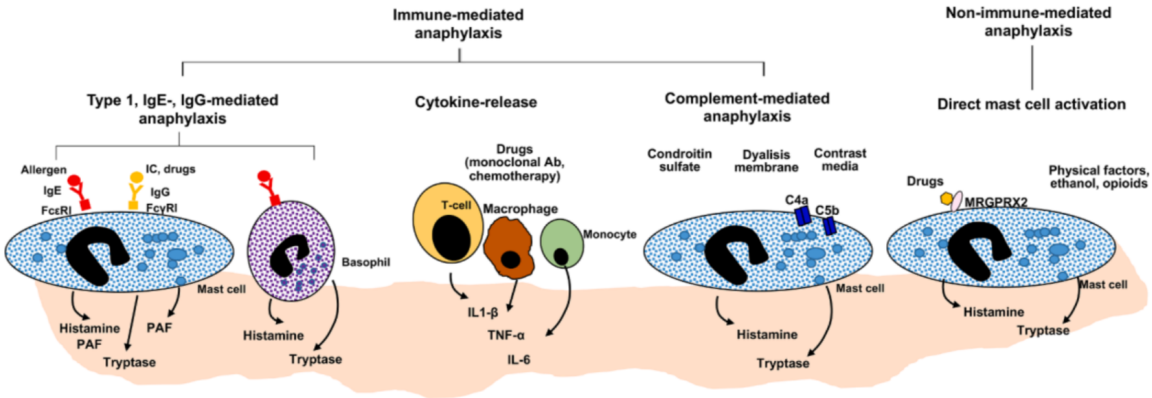
2.1.3 Non-IgE mediated anaphylaxis

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 **IgG-mediated anaphylaxis**, where IgG-containing immunocomplexes bind to neutrophils and macrophages, but also mast cells and platelets, through Fcγ receptors, and induce the release of mediators, including lipid-derived ones, such as PAF [16]. Chimeric IgG monoclonal antibodies, such as rituximab, and neuromuscular-blocking agents (NMBA), such as atracurium and rocuronium, protamine-containing drugs, such as insulins, have been shown to induce anaphylaxis, even in the absence of IgE, possibly through this mechanism [17]. Symptoms may be indistinguishable from those of IgE-mediated anaphylaxis.

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.

The **cytokine storm-like reaction** is determined by the release of proinflammatory mediators, such as tumor necrosis factor (TNF) α, interferon (IFN) γ, interleukin (IL) 1β and IL6, from other cellular types than mast cells, such as monocytes, macrophages, mast cells, and other immune cells. These mediators induce vascular leakage, by increasing capillary permeability, and activation of the extrinsic coagulation pathway. Preferentially involved triggers are monoclonal antibodies and chemotherapeutic agents, such as oxaliplatin. In this type of anaphylaxis, specific inflammatory symptoms such as chills, fever, and generalized malaise are usually observed. Another frequent and typical symptom is pain.



2.2 Signs and symptoms of anaphylaxis in an acute context

Anaphylaxis can be life-threatening, but majority of reactions do not result in severe outcomes. Many reactions are not treated appropriately, yet fatal anaphylaxis is (fortunately) a rare event, with a case fatality rate under 0.001%. Severe anaphylaxis, however, is unpredictable, and severe reactions may mimic more mild anaphylaxis reactions in the first instance. Delay in appropriate treatment almost certainly contributes to fatalities. Therefore, **all anaphylaxis reactions must be treated as a medical emergency**. Foods (especially in children), drugs and insect bites are the commonest triggers.

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 (wheezing). 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 abnormal breath sounds.

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.

2.3 Diagnosis of anaphylaxis in an acute context

Anaphylaxis is a clinical emergency, so the diagnosis needs to be made rapidly. Anaphylaxis causes **life-threatening** airway (swollen lips, tongue, uvula), breathing (dyspnoea, wheeze, bronchospasm, stridor, reduced peak flow, hypoxaemia) and circulation problems (hypotension, cardiac arrest) with or without skin or mucosal changes (generalised urticaria, flushing or itching) as part of an allergic reaction. Skin and mucosal changes are not always present or obvious to the rescuer and severe bronchospasm, hypotension, or rarely **sudden cardiac arrest** can be the first features. Knowledge of the patient's allergy history and triggers can help make the diagnosis, but this will not always be known.

Healthcare professionals require training in how to recognize anaphylaxis (see Box 1) and differentiate it from other diagnoses:

Skin or mucosal (chronic remittent or physical urticaria and angioedema, pollen food allergy syndrome)

Respiratory diseases (acute laryngotracheitis, foreign body airway obstruction, status asthmaticus)

Cardiovascular diseases (vasovagal syncope, pulmonary embolism, myocardial infarction, arrhythmias)

Pharmacological or toxic reactions (ethanol, histamine-scombroid fish poisoning, opiates)

Psychiatric diseases (hyperventilation syndrome, anxiety and panic disorder, dissociative disorder…)

Neurologic diseases (epilepsy, cerebrovascular event)

Endocrinological diseases (hypoglycemia, thyrotoxic crisis, carcinoid syndrome, vasointestinal polypeptide tumours, pheochromocytoma)

BOX 1 Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

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
   a. Respiratory compromise (eg dyspnoea, wheeze–bronchospasm, stridor, reduced PEF and hypoxemia)
   b. Reduced BP 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):
   a. Involvement of the skin–mucosal tissue (eg generalized hives, itch-flush, swollen lips–tongue–uvula
   b. Respiratory compromise (eg dyspnoea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or >30% decrease in systolic BP*
   b. Adults: systolic BP of <90 mmHg or >30% decrease from that person's baseline

2.4 Emergency management

Remove or stop the trigger if possible

Based on expert consensus, stop any drug suspected of causing anaphylaxis. Remove the stinger after a bee sting - early removal is more important than the method of removal. Do not delay definitive treatment if removing the trigger is not feasible.

Give intramuscular adrenaline early and repeat after 5 min if necessary

Adrenaline is the most important drug for the treatment of anaphylaxis and is the first line treatment according to all current guidelines for anaphylaxis based on both its alpha- (vasoconstrictor) and beta-

(bronchodilator, inotropic, mast cell stabilisation) agonist properties. Intramuscular (IM) adrenaline works within minutes and adverse effects are extremely rare with the correct doses. The best site for IM injection is the anterolateral aspect of the middle third of the thigh. 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. Intravenous adrenaline should be used only by those experienced in the use and titration of vasopressors in their normal clinical practice (based on expert opinion and exiting guidelines) Patients who are given IV adrenaline must be monitored continuous ECG and pulse oximetry and frequent non-invasive blood pressure measurements as a minimum. Titrate IV adrenaline using a 20-50 mcg bolus according to response. If repeated adrenaline doses are needed, start an IV adrenaline infusion.

For intramuscular administration use undiluted solution. 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; for children under 6 years, only 0.15 mg of adrenaline. If the condition does not improve, repeat the dose after 5 minutes.

Ensure the patient is lying and do not suddenly sit or stand the patient up

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. Patients who are breathing and unconscious should be placed on their side (recovery position). Pregnant patients should lie on their left side to prevent aortocaval compression. Sudden changes in position of patient might lead to cardiac arrest.

Give intravenous fluids

Anaphylaxis can cause hypotension due to vasodilation, redistribution of blood between vascular compartments, and fluid extravasation. ERC guidelines suggest the use of either balanced crystalloids or 0.9% sodium chloride bolus doses and further doses based on haemodynamic response.The first resuscitation fluid bolus should be about 500 ml over 5 -10 min.

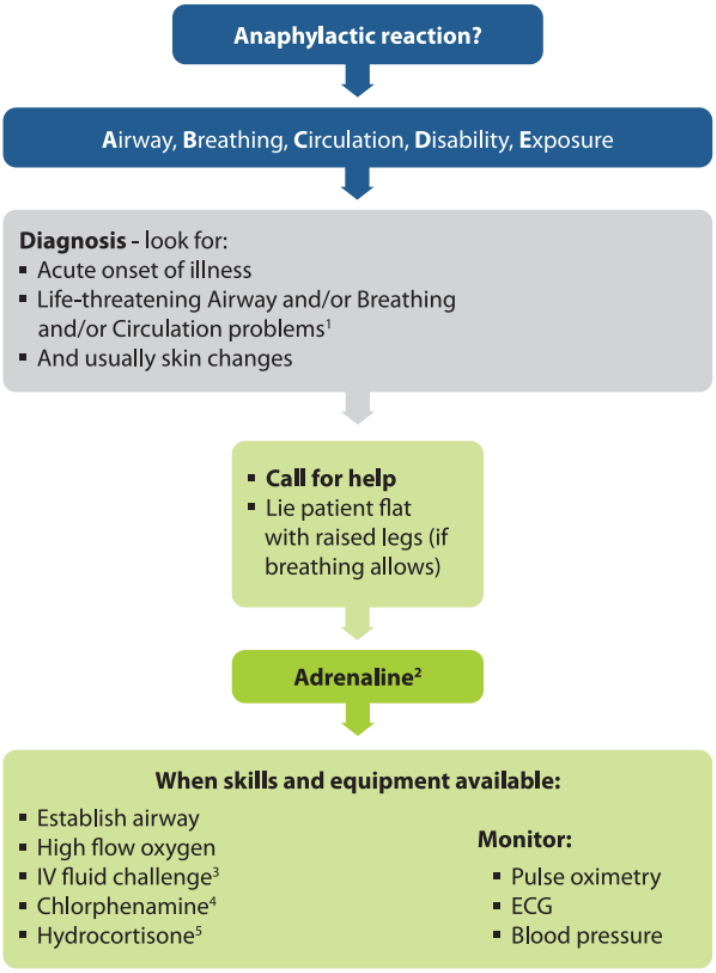
Give oxygen

Oxygen therapy to correct hypoxaemia is a standard part of critical care.

Role of steroids and antihistamines in the immediate management of anaphylaxis

No evidence supports the routine use of either steroids or antihistamines in the initial resuscitation of a patient with anaphylaxis. They do not appear to alter the progress of anaphylaxis or prevent biphasic reactions. Steroids should be considered if there are ongoing asthma-like symptoms or in the setting of refractory shock following guidelines for asthma and shock states. The effect of corticosteroids occurs after 4-6 hours and consists of a decrease in plasma exsudation, 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).

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

[1] **Life-threatening problems:**
Airway: swelling, hoarseness, stridor
Breathing: rapid breathing, wheeze, fatigue, cyanosis, SpO_2 < 92%, confusion
Circulation: pale, clammy, low blood pressure, faintness, drowsy/coma

[2] **Adrenaline** *(give IM unless experienced with IV adrenaline)*
IM doses of 1:1000 adrenaline (repeat after 5 min if no better)

Adult	500 microgram IM (0.5 mL)
Child more than 12 years	500 microgram IM (0.5 mL)
Child 6-12 years	300 microgram IM (0.3 mL)
Child less than 6 years	150 microgram IM (0.15 mL)

Adrenaline IV to be given **only by experienced specialists**
Titrate: Adults 50 mcg; Children 1 mcg kg^{-1}

[3] **IV fluid challenge (crystalloid):**
Adult 500 - 1000 mL
Child 20 mL kg^{-1}
Stop IV colloid if this might be the cause of anaphylaxis

	[4] Chlorphenamine (IM or slow IV)	[5] Hydrocortisone (IM or slow IV)
Adult or child more than 12 years	10 mg	200 mg
Child 6 - 12 years	5 mg	100 mg
Child 6 months to 6 years	2.5 mg	50 mg
Child less than 6 months	250 mcg kg^{-1}	25 mg

2.5 Long term management

Mast cell tryptase measurement can help diagnose anaphylaxis.

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. The consensus on optimal timing for measurement is that ideally three timed samples should be taken: First sample as soon as feasible after resuscitation has started, do not delay resuscitation to take sample. Second sample at 12 h after the start of symptoms. Third sample either after 24 h or in convalescence. This provides baseline tryptase levels some individuals have an elevated baseline level.

Monitoring of the patient

Patient after anaphylaxis should be monitored continuously and under constant medical supervision, which means placing the patient in an intensive care unit (ICU) or an emergency department (ED). Patients with anaphylaxis are at risk of protracted reactions and of developing biphasic reactions although the likelihood is low. The EAACI guideline suggests that they are monitored for 6–8 h with respiratory compromise and at least 12–24 h with hypotension. Early use of adrenaline appears to reduce the risk of biphasic reactions.

Before discharge

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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