



The allergic emergency – management of severe allergic reactions

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Summary

Anaphylaxis is characterized by the sudden onset of acute allergic symptoms involving two or more organ systems. An acute allergic emergency is a challenge for physicians due to its life-threatening potential. The incidence of anaphylactic reactions has increased in recent years. Most frequent elicitors of mast cell and primarily histamine dependent anaphylactic reactions are food, insect venom or drugs. Allergic reactions are graded into four groups according to the classification by Ring and Messmer; grade I is defined by the onset of cutaneous symptoms only whereas grade IV is characterized by cardiovascular shock as well as cardiac and/or respiratory arrest.

The treatment of allergic reactions should be guided by the severity of the reaction. Initially an intramuscular epinephrine injection into the lateral thigh should be given if cutaneous, mucosal and cardiovascular/respiratory symptoms occur. Additionally, the patient should receive intravenous antihistamines and corticosteroids. For self-treatment in the case of an allergic emergency, oral antihistamines and corticosteroids should be prescribed to the patient.

Introduction

Anaphylaxis was first described by Richet and Portier in 1902 [1]. The lifetime prevalence of anaphylaxis is estimated at 0.05–2 % and appears to be on the rise [2]. More accurate epidemiologic data is not available, in part due to the lack of uniformly implemented ICD coding for anaphylaxis and the fact that not every allergic emergency is actually treated by a physician [3].

Pathophysiology and classification of severity

Anaphylaxis is defined as a mast cell-dependent reaction with acute onset and potentially fatal outcome.

Anaphylaxis is defined as a mast cell-dependent reaction with acute onset and potentially fatal outcome [4]. An allergic emergency or anaphylaxis is usually triggered via direct or indirect mast cell activation, resulting in the release of numerous mediators. IgE-mediated triggering of anaphylaxis is caused by various allergens through activation of Fc-ε-RI with subsequent mast cell degranulation following cross-linkage of two adjacent IgE molecules. Anaphylaxis may also be triggered by non-IgE-dependent direct mast cell activation. However, the exact molecular mechanism has not yet been elucidated. It is currently being debated to what extent IgG antibodies may also be involved in triggering such reactions.

Table 1 Classification of anaphylaxis according to Ring and Messmer [5].

Stage	Symptoms
I	Skin lesions and/or slight increase in body temperature
II	Detectable, but not life-threatening cardiovascular reactions (tachycardia, hypotension)
III	Shock, life-threatening smooth muscle spasms (uterus, bronchi etc.)
IV	Cardiac arrest

According to Sampson, anaphylaxis is characterized by the onset of symptoms within a few minutes to hours affecting more than two organ systems [4]. In 1977, Ring und Messmer reported on allergic reactions to volume replacement products [5]. In German-speaking countries, the severity of anaphylaxis has since then been classified in four stages as per the definition proposed by Ring and Messmer (Table 1).

Common triggers of anaphylaxis

Depending on age and geographic region, the most common triggers of anaphylaxis may vary.

Depending on age and geographic region, the most common triggers of anaphylaxis may vary. In children under the age of six, the most common specific allergens are egg and milk protein, whereas children over the age of six more frequently react to food proteins like tree nuts and peanuts [6]. In adults, insect venoms are also frequent triggers of anaphylaxis, especially bee and wasp venom [3]. Drugs are important triggers of severe allergic reactions in any age group, particularly in seniors. The respective agents vary, however: in children, these are predominantly analgetics and antibiotics, primarily beta lactam antibiotics. In addition, nonsteroidal anti-inflammatory drugs (NSAIDs) are common triggers in adults [3].

Apart from the above-mentioned domestic factors for allergic reactions, anaphylaxes may also occur during medical procedures or may otherwise be iatrogenically induced in doctors' offices and hospitals.

Based on where the reaction occurs, certain triggers may be more common. Domestic anaphylaxes are above all caused by foods or insect venoms, whereas the spectrum of inpatient or iatrogenic reactions primarily covers drugs or allergens themselves, e.g. in the context of specific immunotherapies (Table 2).

Risk factors for an allergic emergency

The occurrence as well as the severity of anaphylaxis may be co-determined by risk factors.

The occurrence as well as the severity of anaphylaxis may be co-determined by risk factors. Certain drugs may aggravate the severity of anaphylaxis, among them cardiovascular drugs like ACE inhibitors or beta blockers, but also nonsteroidal anti-inflammatory drugs or acetyl salicylic acid. Concomitant conditions such as mastocytosis may also have an effect on the likelihood of allergic reactions [3] and their severity. With respect to elevated serum tryptase levels, it has been shown that patients suffering from insect venom allergy display significantly more severe reactions following a sting [7].

The prevalence and severity of anaphylaxis also vary depending on the allergen involved. For example, especially in childhood, peanuts are a risk factor for severe allergic reactions and even tiniest amounts suffice to result in severe organ manifestations [8].

Table 2 Potential triggers of allergic emergencies inside and outside the hospital.

Domestic environment	Hospital / iatrogenic
Anaphylaxis (foods, insect venoms)	▶ Specific immunotherapy (SIT/SCIT) ▶ Provocation testing ▶ Diagnostic work-up (e. g. contrast medium) ▶ Surgery ▶ Drugs

Table 3 Risk factors for anaphylaxis.

Drugs	▶ Antihypertensive drugs (ACE inhibitors, beta blockers) ▶ Analgetics (ASS, COX inhibitors)
Concomitant diseases	▶ Mastocytosis ▶ Allergic asthma ▶ Elevated serum tryptase
Life circumstances	▶ Exercise ▶ Alcohol ▶ Illegal drug abuse ▶ Infections ▶ Male gender

Life circumstances or demographic aspects may also represent risk factors for allergic reactions. Since men are more frequently affected, it has been postulated that sex hormones may play a role, as they have an effect on the immune system and can also directly activate mast cells [3].

Clinical manifestations and differential diagnoses of an allergic emergency

The diagnosis of anaphylaxis or an allergic emergency is primarily made clinically.

The diagnosis of anaphylaxis or an allergic emergency is primarily made clinically and symptoms predominantly depend on the organ system involved. The sudden onset of symptoms in more than two organ systems is a hallmark [4]. In this context, affected organ systems are defined as the cardiovascular system, the gastrointestinal tract, skin and mucosa as well as the respiratory tract. The most commonly affected organ systems are skin and mucosa. More than 80 % of patients suffering an allergic emergency exhibit cutaneous reactions [9], most commonly urticaria, angioedema, and itching [9]. Patients with cardiovascular symptoms may show dizziness, drop in blood pressure, syncope, or tachycardia. With respect to the respiratory tract, afflicted patients generally display symptoms like dyspnea, stridor, and coughing. The gastrointestinal tract is less frequently impacted. Here, typical symptoms are nausea, vomiting, and difficulty swallowing [9].

The differential diagnoses to be considered vary depending on the affected organ system. In patients with wheals or swelling of the skin and/or mucosa, the

Table 4 Primary differential diagnoses of anaphylaxis by organ systems [10].

Skin/mucosa	▶ Chronic urticaria ▶ Hereditary angioedema
Respiratory tract/ lung	▶ Upper respiratory infection ▶ Foreign-body aspiration ▶ Asthma attack ▶ Pulmonary embolism
Cardiovascular system	▶ Vasovagal syncope ▶ Myocardial infarction ▶ Cardiac arrhythmia ▶ Hypertensive crisis
Neuropsychiatric	▶ Anxiety disorder / panic attack ▶ Somatoform disorder ▶ Stroke ▶ Intoxication with opiates/thanol
Endocrinologic system	▶ Hypoglycemia ▶ Thyrotoxic crisis ▶ Pheochromocytoma ▶ Carcinoids

history may be indicative of chronic spontaneous urticaria or hereditary angioedema. In patients with respiratory tract dysfunction, infections, pulmonary embolism, and, especially in children, foreign body aspiration have to be ruled out.

In the event of sudden blood pressure and cardiovascular problems, one of the major differential diagnoses is acute myocardial infarction. The most important differential diagnoses are listed by organ systems in table 4.

Above all, it is the acute onset of symptoms that points to an anaphylactic reaction. Specific details in the history may corroborate the diagnosis. In most cases, symptoms develop immediately (minutes to few hours) after exposure to a specific allergen. Data on the interval between allergen exposure and cardiac arrest shows that some allergens may induce particularly dramatic anaphylactic reactions. On average, only 5 minutes pass between drug administration and anaphylactic cardiac arrest, whereas the interval between an insect sting and cardiac arrest is 10–15 minutes. Food products primarily cause asthmatic respiratory arrest after an average of 25–35 minutes [11].

A fundamental reason for these different intervals lies in the various routes of entry into the organism. Accordingly, intravenously administered drugs exhibit the shortest interval between exposure and onset of symptoms. Orally ingested foods may show a delayed onset of usually two hours. However, longer intervals have been reported, most recently for alpha-GAL sensitizations relevant in meat allergy [12].

Diagnostic work-up

In the acute setting of an allergic emergency, the most important diagnostic tools are the history and the patient's clinical symptoms. Although measuring serum

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tryptase levels may be helpful at the acute stage, for various reasons, it is not always feasible.

In the aftermath of a reaction (2–4 weeks), an allergy work-up should always be performed. In this context, screening for type 1 sensitizations by prick testing is paramount. The most common triggers of allergic reactions vary in different age groups. In children under the age of six, the most important allergens are egg and milk protein, in older children peanuts and tree nuts, and in adults besides wheat, soy, and celery, most notably also insect venoms and drugs [7]. This diversity should therefore be factored in accordingly when selecting test series. Severe allergic reactions in the past have to be taken into account during the work-up, i.e. skin and provocation tests have to be conducted in an appropriate environment offering monitoring and emergency treatment facilities.

Even miniscule amounts of the triggering allergen may induce another anaphylactic reaction in predisposed patients, which is why an IV and an emergency medical team on standby has to be ensured during testing.

Measuring serum tryptase levels is of particular significance. It was first shown in 2009 that elevated serum tryptase levels in patients with insect venom allergy resulted in more frequent anaphylactic reactions following a sting [7]. For this to happen, mastocytosis is not a *sine qua non*. Even an isolated serum tryptase elevation increases the risk for a severe allergic reaction.

Further *in vitro* tests include measuring IgE. Total serum IgE may point to an atopic diathesis and help interpret specific IgE values. Testing for specific IgE for individual allergens may help identify defined allergy triggers, which may be helpful in patients with indeterminate anaphylaxis.

Finally, provocation testing may be performed, if, at the end of the diagnostic work-up, there is clinical suspicion, possibly backed up by lab and skin test results, that a specific allergen is a trigger of anaphylaxis [13]. Here, the patient is given defined amounts of e. g. foods or drugs in a double-blind, placebo-controlled setting. Provocation testing should always be done as an inpatient with an IV in place and an emergency medical team on standby. The allergens have to be administered in titrated doses, ergo provocation testing should, for example, not be started with the highest dose of the drug in question.

If thus an allergen can be established as trigger or if there is strong suspicion, an allergy ID card has to be issued to be carried by the patient at all times. Moreover, patients should be educated about the prevalence of the respective allergen and potential alternatives (Table 5).

Acute therapy of an allergic emergency

The early, preferably intramuscular, administration of epinephrine has been recommended by European and German guidelines as first-line therapy.

Once the diagnosis of anaphylaxis is made, stage-oriented treatment has to be initiated immediately. The early, preferably intramuscular, administration of epinephrine has been recommended by European and German guidelines as first-line therapy [9], as soon as symptoms such as hypotension, syncope, stridor, dyspnea, or cardiac arrest set in. The expected pharmacologic effects outweigh the potential risks in patients with known cardiovascular disorders. If administered intramuscularly, the initial dose should be 0.01 ml/kg body weight up to a maximum dose of 0.5 mg. Should repeated intramuscular administration not lead to cardiovascular stabilization, intravenous epinephrine administration may be considered. This, however, should only be done by personnel experienced in the use of catecholamines such as emergency physicians or anesthesiologists. Supportive measures such as oxygen, fluid replacement, and, as far as practicable, allergen removal should also be implemented. It is imperative that patients with anaphylactic

Table 5 Diagnostic work-up following an allergic emergency.

Work-up in the acute setting	Follow-up work-up
▶ Serum tryptase ▶ Rule out life-threatening differential diagnoses (e.g. EKG) ▶ History	▶ Prick testing ▶ Total serum IgE and possibly specific serum IgE ▶ Provocation testing ▶ Food diary

reactions necessitating such intensive treatment be admitted as inpatients and closely monitored.

If dyspnea and stridor are the predominant symptoms, short-acting β -2 agonists should be used to treat the respiratory obstruction.

Although the administration of H1 and H2 antihistamines as well as corticosteroids is very common in routine clinical practice, there is only limited or no data from controlled clinical trials regarding their benefit in severe allergic reactions. Antihistamines and corticosteroids may be given after epinephrine (e. g. 4 mg dimetindene maleate and 250 mg prednisolone IV). Antihistamines likely primarily lessen the cutaneous symptoms of an allergic reaction, while corticosteroids are supposed to have a beneficial effect on potential late manifestations.

Besides the pharmacologic treatment, patients should be positioned according to their chief symptoms. In case of respiratory distress, an upright position is recommended to enable use of the auxiliary respiratory muscles, while patients with circulatory problems should lie with legs elevated to facilitate blood circulation. Pregnant patients should be positioned on the left side with legs elevated, unconscious patients in the lateral recumbent position.

For less severe allergic reactions such as e. g. acute urticaria, oral administration of antihistamines and corticosteroids is an option (Figure 1).

Technical prerequisites

Apart from the technical equipment, e.g. cardiac monitoring and CPR facilities, the physicians and nurses involved have to be trained in allergic emergency procedures.

Adequate therapy of an allergic emergency requires numerous infrastructural prerequisites. Apart from the technical equipment, e. g. cardiac monitoring and CPR facilities, the physicians and nurses involved have to be trained in allergic emergency procedures. Patients developing respiratory distress during an allergic reaction should be monitored for at least 6–8 hours, patients requiring treatment for a drop in blood pressure for 12–24 hours. Since such long intervals are usually not feasible in a private office setting, inpatient monitoring frequently becomes necessary.

Prevention

Apart from the acute intervention, preventive measures should be established for patients following a severe allergic reaction. Subcutaneous specific immunotherapy (SCIT) with bee and wasp venom is recommended for children as well as adults with severe reactions and evidence of sensitization. In case of food allergy as trigger of anaphylaxis, the patient has to be thoroughly informed about dietary measures, with particular consideration towards potential cross allergies.

Patients with drug-induced allergic reactions receive an allergy ID card to be carried with them at all times. For extensive intolerances, inpatient provocation

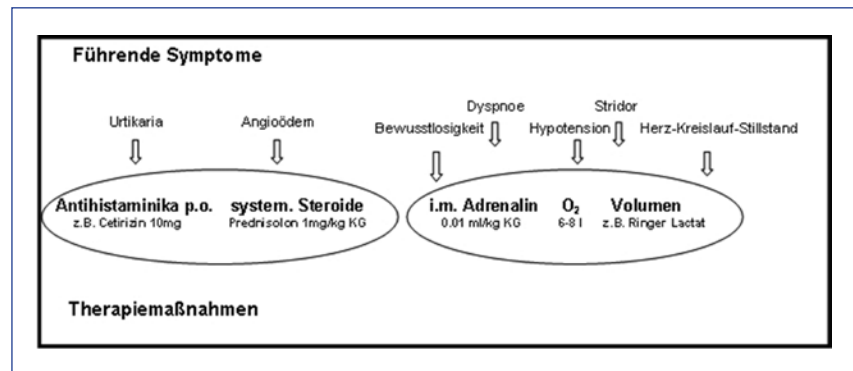


Figure 1 First-line medication in an allergic emergency [9].

testing for alternative drugs may have to be conducted. There are numerous information platforms and education programs for patients on the internet, e.g. AGATE (registered association) (Work Group Anaphylaxis – Training and Education). Patients or parents of affected children should be educated how to avoid allergens at home and when traveling and to recognize early warning signs and clinical symptoms.

Emergency allergy kit

All patients having suffered a severe allergic reaction to foods or insect venoms have to receive an emergency allergy kit.

All patients having suffered a severe allergic reaction to foods or insect venoms have to receive an emergency allergy kit. The kit comprises an epinephrine autoinjector (children under 30 kg 0.15 mg and adults 0.3 mg), a corticosteroid (e.g. two tablets of prednisolone 50 mg) and an antihistamine (e.g. two tablets of cetirizine). Depending on respective symptoms or history, the emergency kit may also include a β -2 receptor agonist inhaler (e. g. salbutamol).

The epinephrine autoinjector is not only crucial in patients with mastocytosis, elevated serum tryptase levels or those with severe reactions in the past. Concomitant unstable asthma, exercise-induced anaphylaxis or anaphylaxis to foods, latex, and airborne allergens also represent absolute indications for prescribing an emergency allergy kit (Table 6).

Conclusion

Anaphylaxis represents a common allergic emergency. According to Sampson, the likelihood of an anaphylactic reaction is high, if there is an acute onset of allergic symptoms such as skin lesions, oral swelling, or itching in conjunction with systemic symptoms like dyspnea, hypotension, syncope, or incontinence. Once the diagnosis of anaphylaxis is made, stage-oriented treatment has to be implemented. After ruling out cardiovascular contraindications, the intramuscular injection of epinephrine (initially 0.01 ml/kg body weight) is the foremost therapeutic measure in severe allergic shock situations. Moreover, fluids should be replaced and, in case of respiratory distress, short-acting β -2 agonists inhaled. Less severe reactions are commonly treated with corticosteroids such as prednisolone and antihistamines like cetirizine and dimetindene maleate, which, depending on the severity of the reaction, should be administered intravenously or orally.

During the subsequent allergy work-up, prick testing, measuring total IgE and possibly specific IgE as well as serum tryptase levels are of particular significance.

Table 6 Indications for prescribing an epinephrine autoinjector (modified after [10]).

Indications	Evidence level
Status post anaphylaxis caused by foods, latex, or airborne allergens	IV
Exercise-induced anaphylaxis	IV
Idiopathic anaphylaxis	IV
Concomitant unstable or moderate to severe asthma and food allergy	IV
Insect venom allergy in adults with systemic reactions (without SIT) and in children with more than skin/mucosa reactions	IV
Underlying mast cell disorder or elevated basal serum tryptase levels in conjunction with any previous systemic allergic reaction to insect stings (even under SIT)	IV

Inpatient provocation testing should be considered. Following an anaphylaxis or in case of increased risk for anaphylactic reactions such as elevated serum tryptase, the patient has to receive an emergency allergy kit. It comprises oral prednisolone and antihistamines, an epinephrine autoinjector, and possibly a short-acting β -2 agonist inhaler. Finally, the patient should be issued an allergy ID card.

Case examples

Case 1

A 15-year old boy presents to your office with his mother for evaluation of recurrent spontaneous urticaria. He complains about a tingling sensation of the lips and tongue. Upon questioning, he admits to eating a fruit salad 30 minutes earlier. During the consultation he additionally notices a progressive itching rash that changes in shape and size.

You make the diagnosis of an oral allergy syndrome with acute urticaria. As there are no notable cardiovascular or respiratory symptoms, you decide on immediately administering oral antihistamines (e. g. cetirizine 10 mg). A follow-up appointment is arranged for further allergy work-up with prick testing for foods and airborne allergens. For the time being, you recommend to avoid crude stone fruits.

Case 2

A 24-year old female student with known wasp venom allergy (severity grade III according to Müller) has been receiving subcutaneous specific immunotherapy (SCIT) at your office for the past 8 months. Until now, she has always tolerated the specific immunotherapy well. Few minutes after administration of the booster injection, she complains about a progressive tightness in her chest, dizziness, and an itching rash. You suspect an incipient anaphylaxis and immediately administer intramuscular epinephrine according to guidelines and apply oxygen via nasal cannula. You put in an IV and have the patient emergently admitted to a hospital for inpatient monitoring.

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