

Guideline for acute therapy and management of anaphylaxis

S2 Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Association of German Allergologists (AeDA), the Society of Pediatric Allergy and Environmental Medicine (GPA), the German Academy of Allergology and Environmental Medicine (DAAU), the German Professional Association of Pediatricians (BVKJ), the Austrian Society for Allergology and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Anaesthesiology and Intensive Care Medicine (DGAI), the German Society of Pharmacology (DGP), the German Society for Psychosomatic Medicine (DGPM), the German Working Group of Anaphylaxis Training and Education (AGATE) and the patient organization German Allergy and Asthma Association (DAAB)

JOHANNES RING¹, KIRSTEN BEYER², TILO BIEDERMANN³, ANDREAS BIRCHER⁴, DOROTHEA DUDA⁵, JÖRG FISCHER³, FRANK FRIEDRICHS⁶, THOMAS FUCHS⁷, UWE GIELER⁸, THILO JAKOB⁹, LUDGER KLIMEK¹⁰, LARS LANGE¹¹, HANS F. MERK¹², BODO NIGGEMANN¹³, OLIVER PFAAR¹⁰, BERNHARD PRZYBILLA¹⁴, FRANZISKA RUEFF¹⁴, ERNST RIETSCHEL¹⁵, SABINE SCHNADT¹⁶, ROLAND SEIFERT¹⁷, HELMUT SITTER¹⁸, EVA-MARIA VARGA¹⁹, MARGITTA WORM²⁰, KNUT BROCKOW¹

¹Dept. Dermatology and Allergology Biederstein, Technical University Munich; ²Department of Pediatrics, Division of Pneumology and Immunology, Charité University Medical Centre, Berlin; ³University Department of Dermatology, Tübingen; ⁴Department of Dermatology, University Hospital of Basel, Switzerland; ⁵Department of Anesthesiology and Critical Care Medicine, University Mainz; ⁶Pediatric practice Laurensberg, Aachen; ⁷Department of Dermatology, University Hospital Göttingen; ⁸Dept. of Psychosomatic Medicine and Psychotherapy, University of Gießen; ⁹Department of Dermatology of the University Medical Center Freiburg; ¹⁰Center for Rhinology and Allergology Wiesbaden, ENT Dept. University of Mannheim; ¹¹St.-Marien-Hospital Bonn; ¹²Department of Dermatology, University Aachen; ¹³DRK Kliniken Berlin Westend, Berlin; ¹⁴Department of Dermatology and Allergology, Hospital of the Ludwig Maximilians University, Munich; ¹⁵Department of Pediatrics, University Hospital Cologne; ¹⁶German Allergy and Asthma Association, Mönchengladbach; ¹⁷Institute of Pharmacology, Hannover Medical School; ¹⁸Institute for Surgical Research, Philipps University of Marburg; ¹⁹Department of Pediatrics, Medical University of Graz, Austria; ²⁰Department of Dermatology, Venereology and Allergology, Allergie-Centrum-Charité, Charité University Medical Centre, Berlin

Level of
development
S2

AWMF-guideline-
register-number
061-025

Finalised
Dezember 1, 2013

Valid until
April 2019

Check
April 1, 2018

ICD-10-numbers
T 78, T 80, J 45, L 23

German Version
www.springer-
medizin.de/
allergo-journal

Cite this as: Ring J, Beyer K, Biedermann T, Bircher A, Duda D, Fischer J et al. Guideline for acute therapy and management of anaphylaxis. S2 guideline of DGAKI, AeDA, GPA, DAAU, BVKJ, ÖGAI, SGAI, DGAI, DGP, DGPM, AGATE and DAAB. *Allergo J Int* 2014; 23: 96–112

DOI 10.1007/ 10.1007/s40629-014-0009-1

Background

Anaphylaxis is an acute systemic reaction with symptoms of an immediate-type allergic reaction which can involve the whole organism and is potentially life-threatening [1–3].

The definition of anaphylaxis is not globally uniform. At present different classification systems are used. In German-speaking countries, the classification used here has generally been applied until now.

Abbreviations

ACE	Angiotensin-converting enzyme
FiO ₂	Fraction of inspired oxygen
HES	Hydroxyethyl starch
NaCl	Sodium chloride
NSAID	Nonsteroidal anti inflammatory drugs

Anaphylactic reactions are the most severe and potentially life-threatening dramatic conditions seen in allergy. Acute treatment is based on international guidelines and recommendations in textbooks. In 1994, a position paper of the German Society for Allergology and Clinical Immunology (DGAKI), was published in the *Allergo Journal* as the result of an interdisciplinary consensus conference [4]. This was subsequently updated and published as a guideline in 2007 [5].

On resolution of the board of directors of the DGAKI of 2009, the anaphylaxis working group was asked to update the guideline. The members of this working group have met several times, together with experts from other associations such as allergology, anaesthesiology and intensive care medicine, dermatology, pediatrics, internal medicine, otolaryngology, emergency medicine, pharmacology, pneumology and theoretical surgery.

In addition to DGAKI members, members of the Association of German Allergologists (AeDA), the Society of Pediatric Allergy and Environmental Medicine (GPA), the German Professional Association of Pediatricians (BVKJ), the German Academy of Allergology and Environmental Medicine (DAAU), the Austrian Society for Allergology and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Anaesthesiology and Intensive Care Medicine (DGAI), the German Society of Pharmacology (DGP), the German Society for Psychosomatic Medicine (DGPM), the German Working Group of Anaphylaxis Training and Education (AGATE) as well as the patient organisation German Allergy and Asthma Association (DAAB) were included. There were consensus conferences in Wiesbaden in September 2009, in Grainau in March 2011, in Munich in January 2012, October 2012 and December 2012 and finalizing via electronic mail rounds. The recommendations worked out at the conferences are based on literature searches with assessment of clinical studies, case series, singular case reports, experimental investigations, on participants' experience as well as on theoretical reflections. Case series were of greatest importance, whereas theoretical reflections influenced the assessment only when sin-

gular cases, nor case series or experimental investigations could not be used for the evaluation. As a whole, the number of meaningful studies of anaphylaxis treatment is so low that its management remains empirical in many fields and is often derived from pathophysiological reflections.

Anaphylactic reactions may come to a spontaneous standstill at any symptomatic stage, but they may also progress in spite of adequate therapy. This unpredictability makes it difficult to evaluate the effectiveness of therapeutic measures. Observations of a single case do not allow assessments as to whether specific measures were effective. It is, however, evident that patients received inadequate follow-up care after anaphylaxis due to an insect sting [6, 7]. The fact that basic patient care is suboptimal underlines the need for more research as well as the importance of the present guideline.

This guideline is for all doctors and other persons working in the medical field who are concerned with acute treatment, diagnostics and counselling of patients with anaphylaxis.

Epidemiology of anaphylaxis

Since anaphylaxis was first described [8], there have been few exact epidemiological studies on the frequency (prevalence and incidence) of anaphylactic reactions. Because of the non-uniform definition (see below), a considerable number of undetected cases must be assumed.

A limitation of the data on the epidemiology of anaphylaxis is due to the non-uniform ICD-10 coding terms of anaphylaxis. There are numerous ICD-10 coding terms that may include anaphylaxis. In addition, the definition of anaphylaxis is globally non-uniform [9]. It has to be clarified in particular whether recurrent cutaneous reactions due to type I allergy should already be considered as anaphylaxis, whether participation of at least two organ systems should be present per definition or whether only the involvement of the organs of the respiratory and cardiovascular systems represent a severe reaction that should be regarded as anaphylaxis. At present there is neither national nor international consensus regarding this. Published data regarding epidemiology must therefore be evaluated in consideration of these aspects [10].

Retrospective studies suggest that up to 1 % of patients present to the emergency department of a maximum care hospital because of an anaphylactic reaction [11]. One to three anaphylaxis-induced fatalities per year per 1 million inhabitants are estimated [12].

There are up-to-date studies from the USA, Great Britain and Australia on the epidemiology of anaphylaxis. They show incidence rates of anaphylaxis of between 7 to 50 per 100,000 / year [13–15]. These

numbers imply an increase in anaphylaxis over the last few decades, the cause being unclear. Numbers from the anaphylaxis register of the German-speaking countries and also data from other countries in the world show that foods are the most frequent triggers of anaphylaxis in childhood [10]. Insect venoms as well as drugs are the most frequent triggers in adults in Germany (**Tab. 1**), whereby internationally the order varies. In childhood, boys suffer anaphylaxis more frequently than girls with distribution adaptation between the genders occurring after puberty [16].

Pathophysiology

The symptoms of anaphylactic reactions are caused by release of different mediators (e.g. histamine, prostaglandins, leukotrienes, tryptase, platelet-activating factor, cytokines, chemokines) from mast cells and basophil granulocytes [17–19], the individual significance of each of these is not assessed clearly in detail. However, there is a consensus that histamine plays a central role in anaphylactic reactions.

The pathomechanism of anaphylaxis usually represents an immunological reaction, most often an immunoglobulin E mediated allergy. However, specific antibodies of other classes can trigger similar complement-dependent symptoms through the formation of circulating immune complexes (immune complex anaphylaxis) [20].

There are also a high number of anaphylactic reactions where no immunological sensitization is detectable; these reactions are called „pseudo-allergic reactions” [20] or recently „non-allergic anaphylaxis” [1]. The mechanisms of this non-allergic anaphylaxis comprise G protein-induced, direct release of vasoactive mediators, direct activation of the complement system, interactions with the kallikrein-kinin system, interactions with arachidonic acid metabolism as well as psychoneurogenic reflex mechanisms. Knowledge on the pathophysiology of these reactions is much more limited than on allergic anaphylaxis.

In patients with increased basal serum tryptase and/or mastocytosis, anaphylaxis may be particularly severe [21–23].

Preceding intake of β -adrenoceptor antagonists and ACE inhibitors can lead to a deterioration of the anaphylactic symptoms [24]. For β -adrenoceptor antagonists, blocking of the cardiostimulatory effect of adrenaline as well as its mast cell-stabilizing effect play a role, and, in the case of ACE inhibitors, reduced bradykinin clearance with resulting marked vasodilatation. Also the intake of nonsteroidal anti-inflammatory drugs (NSAIDs) can result in severe anaphylactic reactions due to increased leukotriene formation and facilitated absorption of ingested allergens.

Table 1

Common elicitors of severe anaphylactic reactions in children and adults [10]

Elicitor	Children	Adults
Food	58 %	16 %
Insect venoms	24 %	55 %
Drugs	8 %	21 %

Clinical Symptoms

Anaphylactic reactions essentially manifest on the skin, in the respiratory tract, gastrointestinal tract, and cardiovascular system. The working group has discussed whether the guideline should be based on a severity classification, as the treatment of anaphylaxis is symptom-related. The majority voted for a severity classification. There are different severity classifications in the literature [7, 9, 25, 26]. Each severity classification has advantages and disadvantages. The majority of the group opted to modify the severity classification which is most frequently used in Germany at present [26]. Anaphylaxis is classified by degrees of severity from I–IV, depending on the intensity of the clinical symptoms (**Tab. 2**).

The symptoms of anaphylactic reactions usually begin acutely and may progress very quickly. Thus, symptoms can deteriorate within minutes resulting in death. The reaction may, however, also come to a spontaneous standstill at any stage and regress spontaneously. In a reaction of grade I severity, the further development and dynamics of the reaction are primarily not foreseeable. The symptoms may occur either simultaneously or sequentially. There may be primarily circulatory reactions without preceding cutaneous or respiratory signs. Occasionally there are protracted or biphasic courses with recurrent symptoms 6–24 hours after successful initial therapy [27]. Apart from acute onset of symptoms and biphasic courses, delayed anaphylactic reactions may occur where symptoms only begin some hours after exposure. The most striking example of this particular dynamic has been documented for the allergen galactose- α -1,3-galactose in mammalian meat allergy and is probably based on delayed release or systemic availability of allergens or their binding sites [28].

At the beginning of an anaphylaxis, minor prodromal symptoms or signs can appear, like itching or burning of the palms and soles or in the genital area, a metallic taste, fearfulness, headache or disorientation. Young children cannot specifically express these feelings and they may present with symptoms such as restlessness or withdrawal behaviour even before the occurrence of objective signs.

In anaphylaxis most often the skin and mucous membranes are affected with pruritus, erythema (flush) as well as urticaria and angioedema (Quincke's edema). These may occur in areas of the skin having had no direct contact with the trigger (systemic spread).

In the upper respiratory tract, patients often describe burning, tingling or itching of the tongue or palate as early symptoms. In the oropharynx, swelling of uvula and tongue can be observed. Clinical signs are a muffled voice, dysphagia with salivation or inspiratory stridor. The possible consequences of laryngeal edema are airway obstruction with life-threatening hypoxia within a short time period.

In the lungs, in particular patients with asthma can develop bronchoconstriction and dyspnoea. Clinical signs are wheezing, prolonged expiration and increased respiratory rate. Bronchial obstruction is the leading symptom in life-threatening reactions especially in children and adolescents. The degree of asthma correlates directly with the severity of the anaphylactic reaction. Also to a variable extent vasoconstriction can occur, at times resulting in an extreme increase in pulmonary vascular resistance, respiratory arrest and the need for resuscitation. Pulmonary edema can also occur as a consequence of this permeability disturbance [29–32].

Gastrointestinal symptoms include crampy abdominal pain, nausea, vomiting and diarrhea. There may also be increased intestinal motility with meteorism, the urge to defecate and even involuntary defecation. Further abdominal symptoms consist of the urge to urinate, micturition as well as uterine cramps. In children, mild oral symptoms or perioral reddening with vomiting may be the only symptoms of food-induced anaphylaxis.

Because of vasodilatation and increased vascular permeability, fluid loss into the extravascular space occurs leading to hemoconcentration and hypovolemia, followed by arterial hypotension and tachycardia. Direct cardiac symptoms include arrhythmia, bradycardia or myocardial infarction.

Central nervous system symptoms are restlessness, withdrawal behaviour, headache, seizures, impaired and loss of consciousness. In children, a change in behaviour is often observed, expressed by anxiety or sometimes aggression. Older children, adolescents and adults can experience “a sense of impending doom”.

In particular the causes of fatal anaphylaxis are airway obstruction and/or cardiovascular failure, either due to direct cardiac involvement or as a consequence of the microcirculatory dysfunction with shock; rare causes are disseminated intravascular coagulation or adrenaline overdose [32].

Table 2

Severity grading of anaphylactic reactions (modified according to [26])

Grade	Skin	Abdomen	Airways	Cardiovascular system
I	Itch Flush Urticaria Angioedema	–	–	–
II	Itch Flush Urticaria Angioedema	Nausea Cramps	Rhinorrhea Hoarseness Dyspnea	Tachycardia (> 20/min) Hypertension (> 20 mm Hg syst.) Arrhythmia
III	Itch Flush Urticaria Angioedema	Vomiting Defecation	Laryngeal edema Bronchospasm Cyanosis	Schock
IV	Itch Flush Urticaria Angioedema	Vomiting Defecation	Respiratory arrest	Cardiac arrest

Classification according to the most severe symptom, no symptom is mandatory.

Allergens and triggers

The most frequent triggers of severe anaphylactic reactions are drugs, insect venoms and foods. The ranking of the triggers depends on age and circumstances. In children, foods are very frequent triggers, whereas for adults insect stings or drugs (including preparations for allergen-specific immunotherapy and chemotherapeutic agents) are more often mentioned (Tab. 1).

The contact with the anaphylaxis trigger most frequently occurs via the oral or parenteral/hematogenous route. In strongly sensitized persons, anaphylaxis can also be triggered by air-borne allergens or by application to the skin surface [33].

Anaphylactic symptoms can also occur depending on the combination of various factors, e.g. allergen exposure together with physical exertion (“exercise-induced anaphylaxis”) [34], alcohol, mental stress or emotional stress, acute infections or simultaneous exposure to other allergens as well as concurrent intake of anaphylaxis-enhancing drugs. This phenomenon is called “augmentation” or “summation” anaphylaxis. A more common form is food-dependent exercise-induced anaphylaxis (FDEIA), which is most frequently triggered by wheat flour [35].

Risk factors for severe anaphylaxis

There are several risk factors for severe (grade III and grade IV) anaphylaxis. Risk factors which exist independent of the trigger are high age [16], severe cardiovascular diseases, pre-existing and in particular poorly controlled bronchial asthma, intake of drugs promoting mast cell activation or leukotriene formation (e.g. NSAID) and mastocytosis. For insect venom allergy, the intake of β -adrenoreceptor antagonists and ACE inhibitors, physical and psy-

Relevant differential diagnoses of anaphylaxis	
Cardiovascular diseases	— Vasovagal syncope — Cardiogenic shock — Cardiac arrhythmia — Hypertensive crisis — Pulmonary embolism — Myocardial infarction
Endocrinological diseases	— Carcinoid syndrome — Pheochromocytoma — Thyrotoxic crisis — Hypoglycemia
Neuropsychiatric diseases	— Hyperventilation syndrome — Anxiety/panic attacks — Dissociative disturbances and conversion disorders (e.g. globus hystericus) — Psychoses — Factitious disorders (Münchhausen syndrome) — Somatoform disturbances (e.g. psychogenic dyspnea, „vocal cord dysfunction“) — Epilepsy — Coma (e.g. metabolic, traumatic)
Respiratory diseases	— Status asthmaticus (acute severe asthma without involvement of other organs) — Acute obstructive laryngo-tracheitis — Tracheal/bronchial obstruction (e.g. foreign objects)
Skin diseases	— Urticaria and hereditary/ acquired angioedema Note: in physical urticaria extensive exposure to the respective elicitor can induce anaphylaxis
Pharmacologic/toxic substances	— Ethanol — Histaminosis (e.g. scombroid poisoning) — Opioids (morphine) — Hoigné-Syndrome

Table 3

chological stress as well as an increased basal serum tryptase are also mentioned [24].

In consideration of the trigger-related subgroups of anaphylaxis, there are data for food anaphylaxis showing that here again allergic bronchial asthma is an important risk factor [36]. The specific trigger may in itself act as a risk factor; it is known, for example, that peanut as a potent allergen is a risk factor for severe reactions [37].

Diagnosis and important differential diagnoses

The clinical symptoms of anaphylaxis are not always characteristic so that diagnosis may be difficult. In these situations it is especially important to distinguish other conditions from symptoms of an anaphylactic reaction, e.g. other triggers of isolated urticaria, airway obstruction, vomiting, nausea, diarrhea, restlessness, unconsciousness, cardiac arrhythmia or cardiac arrest. Important differential diagnoses are listed in **Tab. 3**. After adequate acute treatment, it is helpful to measure mediators in the

blood, above all serum tryptase, ideally about one to three hours after the onset of anaphylaxis and – if possible – a comparison to basal serum tryptase should be made. Serum tryptase can also be measured at a later time, even post mortem [38, 39].

In a consensus conference, the following symptoms were regarded as being of specific importance for the diagnosis of anaphylaxis [9]:

- Sudden occurrence of symptoms on the skin (e.g. acute urticaria, angioedema, flush, swelling of mucous membranes) in addition to rapid onset respiratory symptoms (e.g. dyspnoea, wheeze, cough, stridor) or a sudden blood pressure drop or clinical manifestations thereof (e.g. collapse, tachycardia, incontinence) or
- Sudden occurrence of symptoms in two or more of the following organs or organ systems: skin (e.g. acute urticaria, angioedema, flush, swelling of mucous membranes), gastrointestinal tract (e.g. abdominal cramps, vomiting), respiratory tract (e.g. dyspnoea, wheezing, cough, stridor) or circulatory system (e.g. hypotension, collapse, incontinence) after contact with a probable allergen or anaphylaxis trigger or
- Hypotension following contact with an allergen known to the patient or another anaphylaxis trigger.

Pharmacology of the most important drugs in anaphylaxis treatment

In specific pharmacotherapy, the following substances have proven to be effective:

Vasoactive substances

Adrenaline: The most important drug in the acute therapy of anaphylaxis is adrenaline (epinephrine). Through the activation of α - and β -adrenergic receptors, adrenaline functionally antagonises all of the important pathomechanisms of anaphylaxis by vasoconstriction, reduction of vascular permeability, bronchodilatation, edema reduction and positive inotropy in the heart. Administered intravenously, it shows the fastest onset of action of all anaphylaxis drugs.

In a patient not in need of resuscitation, immediate intramuscular application of a dose of 0.3 to 0.5 mg adrenaline (body weight range 30 to 50 kg) to the outer upper thigh is the drug therapy of first-choice. Compared with intravenous application, the risk of severe cardiac side effects is considerably lower. In case of no response, the injection can be repeated every 5–10 minutes, depending on side effects.

Subcutaneous injection of adrenaline is no longer recommended because of insufficient absorption resulting in delayed onset of action.

If the patient is unstable or during resuscitation, i.e. in case of respiratory and/or circulatory arrest,

adrenaline should be applied intravenously [40]. For this, a dilution of 1 mg adrenaline in 10 ml NaCl 0.9%, i.e. a solution of 0.1 mg/ml is administered, depending on effects and side effects, under continuous control of circulatory parameters. A continuous infusion of approx. 0.05–1 µg/kg/minute is equally effective. Control of pulse and blood pressure is mandatory. In patients receiving treatment with β-adrenoreceptor antagonists and not responding to the repeated injection of adrenaline or other vasoactive substances (see below), administration of glucagon is recommended [41]. Glucagon, however, only has an effect on cardiac symptoms.

Additional inhalation of adrenaline after intramuscular application is effective in the case of laryngeal edema and also in bronchospasm. For this purpose, administration of adrenaline (e.g. 2 ml of 1 mg/ml) given with oxygen through a nebuliser and respiratory mask is recommended. Application of inhaled adrenaline cannot replace parenteral administration.

In the case of mainly bronchial obstruction, additional administration of an inhalative β-adrenoreceptor agonist, e.g. salbutamol or terbutaline, at a dose of 2–4 puffs, is effective. A spacer device should be used in order to improve the efficacy of inhalation when using an aerosol spray.

In the past, in case of hypotension during pregnancy, administration of ephedrine instead of adrenaline was sometimes recommended. There is, however, even less information on ephedrine than on adrenaline. Therefore we also recommend – in agreement with other authors – the application of adrenaline for anaphylaxis during pregnancy [42].

Even when adrenaline is adequately applied, treatment failure or side effects can be observed. The increase in cardiac output leads to elevated oxygen consumption and can be arrhythmogenic, so that, in patients with coronary heart disease, the intravenous application of adrenaline may cause angina pectoris or a myocardial infarction. In case of severe life-threatening anaphylaxis there is no absolute contraindication for adrenaline. The indication should, however, be carefully considered in patients with pre-existing heart disease.

Other vasoactive substances

Dopamine, noradrenaline and vasopressin are applied in life threatening situations by emergency doctors and under intensive care conditions with continuous monitoring of vital signs.

Dopamine: A favourable action profile for the treatment of cardiovascular reactions is offered by dopamine which affects α and β adrenoreceptors and has a short half-life. Dopamine leads in low doses, via vascular D1 dopaminergic receptors, to vasodilatation in the renal, mesenteric and coronary vascular

bed [43, 44]. At higher concentrations, the blood pressure reducing effect by stimulation of the α and β1 receptors prevails. Bronchodilatation also occurs through activation of the β2 adrenoreceptor. It is, however, less marked than with adrenaline because dopamine is only a partial β2 adrenoreceptor agonist. If adrenaline and volume substitution are insufficient to control symptoms, dopamine can be administered as a continuous intravenous infusion instead of adrenaline. The usual dose is 2–15 µg/kg/minute. Application of dopamine is bound to pulse and blood pressure monitoring. Dopamine is used above all in patients that are receiving treatment with β adrenoreceptor antagonists.

Noradrenaline: Noradrenaline is a potent α und β1 adrenoreceptor agonist and stimulates the β2-adrenoreceptor to a lesser extent than adrenaline so that, at a therapeutic dose, the bronchodilatory effect is lower. Therefore an increase in peripheral resistance and systolic blood pressure prevails. There is little effect on the lung. Noradrenaline is used especially when the effect of volume substitution and adrenaline/dopamine is insufficient [45, 46]. Due to its marked vasoconstrictive effect, it should be administered only as a continuous intravenous infusion under strict blood pressure and pulse monitoring. The usual dose is 0.02–0.15 µg/kg/minute.

Vasopressin: In anaesthesiological literature, the application of vasopression for the treatment of severe hypotension is described [47].

Oxygen

In case of manifest cardiovascular or pulmonary reactions, immediate supply of oxygen via an oxygen mask with reservoir bag, is recommended. Administration of high flow 100 % oxygen is recommended. A laryngeal mask or a laryngeal tube can be helpful. Only in rare cases will endotracheal intubation by an experienced physician (usually emergency physician, anaesthesiologist) become necessary.

Volume substitution

An important pathophysiological aspect of anaphylaxis is the resulting hypovolemia which is treated with adequate volume substitution [48–51]. For severe anaphylactic reactions, the supply of large amounts of fluid within a short time is necessary. This can only be achieved through large-bore venous access. If intravenous access is not possible, a special intra-osseous needle can be inserted preferably into the tibia. In case of anaphylactic shock, a supply of 0.5–1 liters, and possibly up to 2–3 liters of fluid – depending on the response – in a very short time is required for adults, for children initially 20 ml/kg body weight.

Primarily, normal saline (NaCl 0.9 %) or balanced electrolyte solutions should be used. When large quantities of electrolyte solutions are given, they remain in the intravascular space for a short time only. Therefore, failing stabilization after the application of larger volumes of electrolytes (> 1 l) the additional application of colloid volume substitutes can be considered.

Gelatine and dextran solutions are – in spite of their positive qualities – to be viewed cautiously because of their histamine-liberating potential and the possibility of themselves triggering anaphylaxis (e.g. dextran without pretreatment with low-molecular hapten dextran).

Hydroxyethyl starch (HES) preparations, such as mean-molecular weight HES (HES 6 % 200/0.5) are the most commonly used volume substitutes in anaphylactic shock. Deposits in the reticular endothelial system have been observed after infusion of more than 1.5 l HES 200/0.5 in adults [48]. For emergency or intensive care use in unstable circulatory situations hypertonic, hyperoncotic solutions or mean-molecular weight HES 130/0.4 in 6 % solution are also available. For short-term infusions the risk of a possible renal insufficiency is low [52]. In recent literature the use of colloidal volume substitutes, compared with crystalline solutions in the acute treatment of shock conditions is being discussed more and more critically [53].

Antihistamines H₁ receptor antagonists

The central role of histamine as a mediator of allergic reactions and the efficacy of H₁ antagonists in acute urticaria or rhinoconjunctivitis are evident. Their effects on circulatory parameters and bronchoconstriction, however, are poorly documented [54]. Compared to adrenaline, antihistamines show a slower onset of action; however, they show a favorable benefit/side effect profile in a broad range of indications. An effect upon the allergic reaction can be assumed and therefore, antihistamines should be given early in all anaphylactic reactions in order to block the effects of histamine.

The only H₁ antihistamines registered for intravenous application in the acute treatment of anaphylaxis are the first-generation substances dimetindene (0.1 mg/kg bw) and clemastine (0.05 mg/kg bw) with their well-known sedating side effects. Officially the maximum licensed dose of oral antihistamines is recommended. The expert group, however, had a consensus that in single selected cases higher doses (up to a maximum of the four-fold dose of the respective substance) can be given, as has been recommended for the treatment of chronic urticaria [55]. In higher doses antihistamines, however, can exert anticholinergic effects leading to tachycardia, dry mouth, gastrointestinal

atony, urinary retention, an increase in ocular pressure up to acute glaucoma attack as well as irritability and paradoxical excitability [56]. These symptoms should be kept in mind.

H₁ antihistamines of the second generation are not currently licensed for the treatment of anaphylaxis and are not available for intravenous injection. In spite of this for emergency oral treatment, the newer more selective H₁ antagonists are often recommended; in placebo-controlled skin test studies they have shown a rapid onset of action [54]. Further studies with newer H₁ antihistamines for the treatment of anaphylaxis should be performed. In particular intravenous preparations of modern non-sedating H₁ antagonists would be helpful.

There is little evidence supporting the efficacy of H₂ receptor antagonists in the treatment of acute anaphylactic reactions. One study reported a reduction of cutaneous symptoms after additional application of ranitidine compared with H₁ antagonists alone in the treatment of anaphylactic reactions [57]. The prevention of hypersensitivity reactions by addition of H₂ receptor antagonists is better documented; however, this effect was not analyzed independently from other given medication [58, 59]. There are single case reports for ranitidine in the treatment of anaphylactic reactions [60]. We recommend the additional application of H₂ receptor antagonists in severe and treatment-resistant anaphylaxis, since although there is only limited evidence regarding efficacy, there are no major side effects to be expected [61].

Glucocorticosteroids

Due to their slow onset of action, glucocorticosteroids play a minor role in the acute phase of anaphylaxis treatment [62]. There are no systematic clinical trials regarding this indication. However, glucocorticosteroids are effective in the treatment of asthma and against protracted or biphasic anaphylactic reactions. An unspecific membrane stabilizing effect within the first 10–30 minutes of application of high dose glucocorticosteroids (500–1,000 mg) independent of the potency of the glucocorticosteroids has been postulated in review articles [2,4,62]. When there is no intravenous catheter, glucocorticosteroids may be applied rectally, especially in small children (e.g. prednisolone suppositories) or orally.

Treatment

The emergency, symptom-orientated treatment of anaphylaxis has to be carried out rapidly. A diagram illustrating the treatment steps for physicians and the emergency team has been published and is updated in the development of this guideline (Fig. 1) [63].

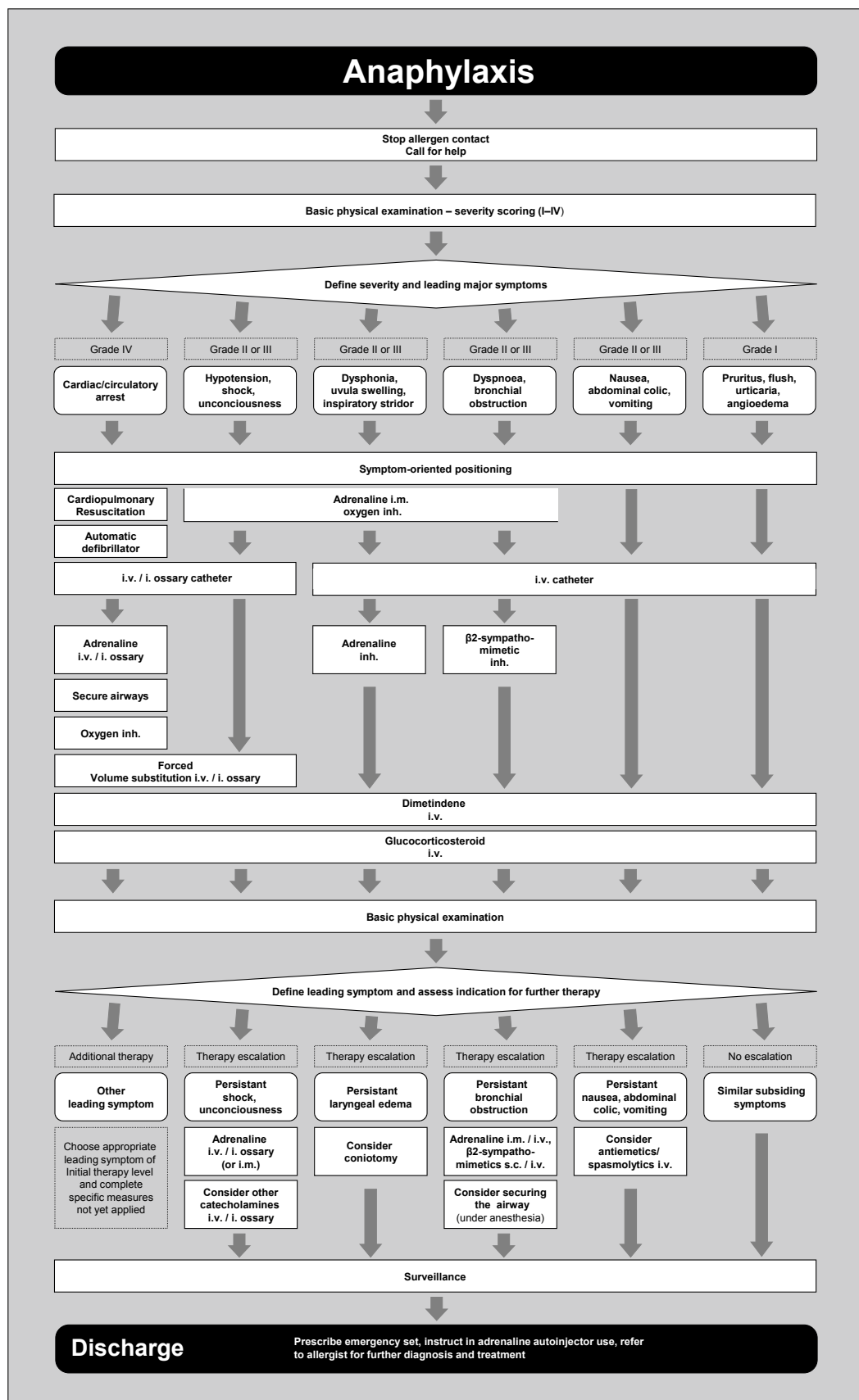


Fig. 1: Regimen of acute anaphylaxis treatment

Emergency equipment for treatment of anaphylactic reactions

Table 4

Stethoscope, blood pressure monitor
Tourniquet, syringes, in-dwelling catheter, infusion set
Oxygen with mask/nasal cannula
Guedel-tube, bag valve mask, suction unit, intubation set
Adrenaline for injection
H ₁ antihistamines for intravenous injection
Infusion solutions (0.9 % NaCl solution, balanced electrolytes/ colloids)
Glucocorticosteroids for intravenous injection
Bronchodilator (rapidly acting β_2 adrenoreceptor agonist for inhalation or intravenous injection)
Automatic external defibrillator (optional)
Pulse oximeter (optional)

At first further allergen exposure should be stopped if possible. In some situations (e.g. intravenous infusion) this can be done easily without losing time. The application of a tourniquet and/or the subcutaneous injection of epinephrine surrounding a local allergen depot (e.g. a wasp sting or injection site of specific immunotherapy) is no longer recommended due to the limited therapeutic benefit and risk of losing time for more important measures. Further assistance should be called in order to guarantee adequate medical care. Each physician should have emergency equipment for the treatment of anaphylactic reactions (Tab. 4) in his practice. A teamapproach with the opportunity to delegate procedures is advisable.

First, a quick history and basic physical examination have to be done (Fig. 1). This includes:

- Check of vital signs (spontaneous movements and breathing)
- Evaluation of pulse and blood pressure (strength, frequency, regularity)
- Evaluation of breathing (dyspnea on speaking, inspiratory or expiratory stridor, wheezing, optional: auscultation, measurement of the peak flow using a mechanical peak flow meter, pulse oximetry),
- Inspection of visible skin and mucous membranes,
- Questioning for further complaints, e.g. nausea, impulse to vomit, headache, sternal pressure, disturbance of vision, pruritus),
- Questioning for known allergies.

Regarding vital parameters, possible alarm values are listed in Tab. 5. These examinations should be repeated regularly in the course of acute management.

Smaller children can initially be examined in the arms of the parents. It is important to calm the child and the parents in order to allow adequate examination

and treatment. When the child is fidgety, inspection of the mouth or auscultation may be difficult or even impossible. Irritation by the use of a spatula may increase airway obstruction and should be avoided. Clinical signs of airway obstruction like prolonged expiration, in- or expiratory stridor, wheezing, salivation, retraction of the thoracic wall and constriction nasal alae should be looked for.

Evaluation of severity

Based on the examination the degree of severity of the anaphylaxis should be evaluated and the most threatening symptom of anaphylaxis identified (Fig. 1). The most life-threatening symptom of anaphylaxis should be treated with priority. This may lead to 6 possible scenarios:

- Anaphylaxis with cardiac or circulatory arrest (anaphylaxis grade IV)
- Anaphylaxis with predominant cardiac and circulatory reaction (anaphylaxis grade II/III)
- Anaphylaxis with predominant obstruction of upper airways (anaphylaxis grade II/III)
- Anaphylaxis with predominant obstruction of lower airways (anaphylaxis grade II/III)
- Anaphylaxis with predominant gastrointestinal involvement (anaphylaxis grade II)
- Anaphylaxis with systemic generalized skin manifestations and subjective symptoms (anaphylaxis grade I).

Positioning

Immediately after examination, the patient should be positioned according to symptoms. Horizontal positioning and avoidance of further physical exercise (walking or trying to sit up) are the basic strategies. Depending on the situation the positioning can be varied. Getting up and physical exercise should be avoided because of possible further aggravation of anaphylaxis (as with co-factors). When consciousness is impaired especially in a preclinical situation, the recovery position is preferred. For improvement of the hemodynamic situation the patient may be placed in the Trendelenburg position (elevated legs). In situations with predominant respiratory symptoms a (half) sitting position is preferable. In the treatment of children actions should not be forced in order to avoid increasing distress.

Anaphylaxis with cardiac or circulatory arrest

Cardiopulmonary resuscitation with cardiac massage and aided ventilation in a ratio of 30 :2 must be started (Fig. 1). An automatic defibrillator should be connected. And in case of ventricular fibrillation early defibrillation has to be initiated. For further pharmacotherapy an intravenous or intraosseous catheter is mandatory. Intravenously applied adrenaline is the substance of choice. 1 ml adrenaline

(1 mg/ml) is diluted in a ratio of 1 : 10 to a volume of 10 ml (0,1 mg/ml) and given as a 1 mg bolus (= 10 ml) in 2–5 minute intervals until circulation is stabilized. For sufficient oxygenation the airway must be secured. This can be done via endotracheal intubation. Alternatively a laryngeal mask or a laryngeal tube or a combined tube can be used depending on the experience of the physician.

The flow of the inspiratory oxygen (FiO_2) should be above 0,8. For this, the application of high-flow oxygen with a reservoir bag is necessary. Based on the pathophysiology of anaphylaxis, forced volume substitution and high dose anti-allergic treatment (antihistamines, glucocorticosteroids) are mandatory for the correction of hypovolemia and successful resuscitation. Immediate transfer to an intensive care unit is advisable (**Tab. 6**).

Anaphylaxis with predominant cardiovascular reaction

The immediate action is intramuscular injection of epinephrine, especially when there is no intravenous catheter (**Fig. 1, Tab. 6**). Epinephrine autoinjectors for self-treatment of patients can be helpful in such situations due to their rapid application. The standardized adrenaline autoinjector doses of between 0,3 mg and 0,15 mg are feasible. When the response is insufficient a further intramuscular injection of epinephrine can be repeated after approx. 5 minutes.

The application of oxygen with the aim to increase the inspired oxygen content (FiO_2) above 0,5 is recommended. This can be achieved using an oxygen mask with a reservoir bag; a nasal cannula has only a limited effect on FiO_2 .

In all forms of altered consciousness, the patient may vomit and this should be accounted for when positioning. The mouth can be opened with the Es-march hand maneuver and the oral cavity inspected for vomitus that should be removed. A suction unit is helpful.

For further treatment an intravenous catheter is mandatory (**Tab. 6**). Failing this, an intraosseous catheter is indicated. The major therapeutic goal is the correction of a relative hypovolemia. Forced volume substitution of an electrolyte solution (5–10 ml/kg bw within 5 minutes) is mandatory. The application of such volumes requires a large bore intravenous cannula (> 8 Gauge) or several venous catheters. The application of colloidal volume substitutes in the phase of forced volume substitution is a common emergency medical measure.

Antiallergic substances (antihistamines [beware of anticholinergic side effects] and glucocorticosteroids) should be used in high doses (**Tab. 6**). In persisting or imminent shock the fractionated intravenous/interosseous or intramuscular application of

Possible alarm thresholds for vital parameters*				
Alarm thresholds depending on age	upto 1 year	1–5 years	6–14 years	> 14 years
Pulse rate (/min)	> 160	> 130	> 120	> 110
Blood pressure (systolic, mmHg)	< 50	< 60	< 60	< 70
Respiratory rate (/min)	> 40	> 35	> 30	> 25
Oxygen saturation (%)	< 92	< 92	< 92	< 92

** These values show a high individual variability and should only be regarded as approximate information. There are no studies from larger cohorts.*

adrenaline is indicated. Continuous monitoring of blood pressure and pulse are necessary. Other sympathomimetic substances like dopamine or nor-adrenalin may be given as a continuous infusion via a pump system under monitoring of experienced physicians.

Anaphylaxis with predominant obstruction of the upper airways

Typical signs are due to swellings in the region of the upper airway. This can present with a clinically visible swelling of the tongue or uvula, dysphonia or inspiratory stridor. These situations can be life-threatening due to obstruction of the larynx. Immediate measures in this case are the intramuscular injection of adrenaline and application of oxygen (**Fig. 1**). The administration of inhaled adrenaline is indicated (**Tab. 6, Tab. 7**). In the case of insufficient response to these therapeutic measures, cricotomy may be required.

Anaphylaxis with predominant bronchial obstruction

Bronchial symptoms belong to the most common symptoms of severe anaphylaxis. In all potentially life-threatening situations the immediate intramuscular application of adrenaline is indicated. Also topical bronchodilatory treatment is of central importance (**Fig. 1**). Several short acting β_2 sympathomimetics (e.g. salbutamol, terbutaline) are available for the treatment of bronchial obstruction (**Tab. 6, Tab. 7**).

It must be considered that some anaphylaxis patients are not experienced in inhalation therapy and may need the help of a spacer device in the case of aerosol sprays or continuous aerosol application (aerosol masks with a pressure/oxygen attachment or electric nebulizers). In the meantime practical battery-based spray nebulizers are available which can be used in paramedical and preclinical situations. Should more intensive therapy be required the intravenous application of adrenaline or injectable β_2 sympathomimetics (terbutaline s.c. or reproterol i.v.) are possible (**Tab. 6**). In the case of sta-

Table 6

Pharmacotherapy for children, adolescents and adults in intensive care					
Substance	Route of application	< 15 kg bw	15–30 kg bw	30–60 kg bw	> 60 kg bw
Adrenaline	Intravenous, bolus ¹	0.1 ml/kg bw (from 1 mg/10 ml) ¹	0.1 ml/kg bw (from 1 mg/10 ml) ¹	0.05–0.1 ml/kg bw (from 1 mg/10 ml) ¹	0.05–0.1 ml/kg bw (from 1 mg/10 ml) ¹
Adrenaline	Continuous infusion	0.05–1.0 µg/kg/min	0.05–1.0 µg/kg/min	0.05–1.0 µg/kg/min	0.05–1.0 µg/kg/min
Adrenaline	Inhaled via nebulizer	2 ml ²	2 ml ²	2 ml ²	2 ml ²
Dimetindene	Intravenous	1 ml ³	2–3 ml ³	4 ml ³	8 ml ³ oder 1 ml/10 kg bw
Prednisolone	Intravenous	50 mg	100 mg	250 mg	250–1000 mg
Salbutamol Terbutalin	Inhaled	2 puffs DA per spacer	2 puffs DA per spacer	2–4 puffs DA per spacer	2–4 puffs DA per spacer
Reproterol ⁴	Continuous infusion	0,1 µg/kg/min	0,1 µg/kg/min	0,1 µg/kg/min	0,1 µg/kg/min
Volume	Bolus (0,9% NaCl)	20 ml/kg bw	20 ml/kg bw	10–20 ml/kg bw	10–20 ml/kg bw
Volume	Infusion (electrolyte solution)	1 to 2 ml/kg/min	1 to 2 ml/kg/min	1 to 2 ml/kg/min	1 to 2 ml/kg/min
Oxygen	Inhaled	2 to 10 l/min	5 to 12 l/min	5 to 12 l/min	5 to 12 l/min

¹For the application of a bolus a 1 mg/ml adrenaline solution is diluted (1 ml plus 9 ml 0.9% NaCl) to a final concentration of 0.1 mg/ml);
²For inhalation the original concentration is used (1 mg/ml);
³of the (original) concentration of 1 mg/ml (1 ml = 1 mg);
⁴Reproterol can also be given as bolus
bw, body weight

Table 7

Pharmacotherapy for children, adolescents and adults under out-patient conditions					
Substance	Route of application	< 15 kg bw	15–30 kg bw	> 30–60 kg bw	> 60 kg bw
Adrenaline	Intramuscular	0.01 ml/kg bw (1 mg/1 ml)	0.01 ml/kg bw (1 mg/1 ml)	0.01 ml/kg bw (1 mg/1 ml)	0.01 ml/kg bw (1 mg/1 ml)
Adrenaline	Autoinjector i.m.	see i.m.	150 µg	300 µg	300–600 µg
Adrenaline	Inhaled via nebulizer	2 ml ²	2 ml ²	2 ml ²	2 ml ²
Adrenaline	Intravenous bolus ¹	0.1 ml/kg bw (of 1 mg/10 ml) ¹	0.1 ml/kg bw (of 1 mg/10 ml) ¹	0,05–0,1 ml/kg bw (of 1 mg/10 ml) ¹	0,05–0,1 ml/kg bw (of 1 mg/10 ml) ¹
Dimetindene	Intravenous	1 ml ³	1 ml/10 kg bw ³ (max. 4 ml)	1 ampule = 4 ml ³	1–2 ampule = 4–8 ml ³ (1 ml/10 kg bw)
Prednisolone	Intravenous	50 mg	100 mg	250 mg	500–1000 mg
Salbutamol Terbutalin	Inhaled	2 hubs DA per spacer	2 hubs DA per spacer	2–4 hubs DA per spacer	2–4 hubs DA per spacer
Volume	Bolus (NaCl 0.9%)	20 ml/kg bw	20 ml/kg bw	10–20 ml/kg bw	10–20 ml/kg bw
Volume	Infusion (Ringer solution)	1 to 2 ml/kg/min	1 to 2 ml/kg/min	1 to 2 ml/kg/min	1 to 2 ml/kg/min
Oxygen	Inhaled	2 to 10 l/min	5 to 12 l/min	5 to 12 l/min	5 to 12 l/min

¹For the application of a bolus a 1 mg/ml adrenaline solution is diluted (1 ml plus 9 ml 0.9% NaCl) to a final concentration of 0.1 mg/ml);
²For inhalation application the original concentration is used (1 mg/ml)
³of a (original) concentration of 1 mg/ml (1 ml = 1 mg)
bw, body weight

tus asthmaticus, when muscular exhaustion occurs, artificial ventilation may be necessary [64].

Anaphylaxis with predominant abdominal symptoms

Abdominal symptoms are treated in the same way as anaphylaxis with predominant skin symptoms (Fig. 1). Only in the case of insufficient response to systemically applied antiallergic substances do gastrointestinal symptoms require specific treatment. Nausea, vomiting, as well as abdominal colic represent the relevant symptoms. Antiemetics like metoclopramide, antihistamines and dimenhydrinate or

the application of a serotonin (5 HTR3) antagonist (e.g. ondansetron) can be considered. For abdominal cramps the intravenous application of butylscopolamine may have alleviating effects.

Anaphylaxis with predominant skin manifestations

The application of an intravenous catheter is the first measure of choice. It is recommended to keep the catheter open by infusion of electrolyte solutions. Anti-allergic substances like dimetindene and glucocorticosteroids should be given in the usual dose (Fig. 1, Tab. 7).

Table 8

Ingredients of an "emergency set for self-help" for patients

Substance	Route of application and dosage
Adrenaline	Autoinjector for intramuscular application, adapted to body weight: > 15 kg 150 µg adrenaline > 30 kg 300 µg adrenaline
H ₁ antihistamine	According to age and preference of patients as liquid or fast-melt tablet. The licensed daily dose of the respective antihistamine is recommended as single dose. Dimetindene drops can be taken orally in a dosage adapted for bodyweight and corresponding to the intravenous dose.
Glucocorticosteroid	According to age and preference of the patient oral or rectal (tablets or liquid) with 50–100 mg Prednisolone equivalent.
Optional	In patients with bronchial asthma: β ₂ adrenoceptor agonists When airway obstruction can be expected an adrenaline preparation for inhalation with spray head (to be ordered especially from the pharmacist)

Note: "The emergency set for self-help" should contain written instructions for the application of its constituents (e.g. anaphylaxis-passport and/or anaphylaxis-emergency plan)

Management of therapy control

The observation of the anaphylaxis patient until he/she is in definite long-lasting remission is crucial (Fig. 1). The possibility of a biphasic course of anaphylaxis has to be kept in mind. Therefore in all severe anaphylactic reactions (grade II grade II and higher) in-patient hospital observation is indicated. In anaphylaxis with life-threatening systemic reactions monitoring in an intensive care unit is recommended. On discharge the indication for the prescription of an emergency set for self-treatment (adrenaline auto-injector, antihistamines, glucocorticosteroids and possibly a topical bronchodilatory aerosol spray) should be considered. The practical use of the emergency equipment for self-treatment – especially the application of the epinephrine auto-injector – should be trained via educational programs (Tab. 8; see below). The referral to an allergist for further diagnostic work-up and possible long-term therapy is necessary. In order to gather information on triggers, associated circumstances and co-factors of anaphylaxis, an anaphylaxis registry has been installed in Germany where physicians can report severe anaphylactic reactions online (www.anaphylaxie.net).

Special considerations in childhood

With regard to dosing of certain drugs in the treatment of anaphylaxis the particular dosages for children have to be considered.

Patient management and self-medication

Target group

Each patient who has suffered from an anaphylaxis must be informed about the most important behavioral steps that may help in the prevention and treatment of anaphylaxis. This is particularly important for patients with an increased risk of anaphylaxis like adults with mastocytosis or a prognostically significant symptom constellation. This

is equally important when the patient successfully undergoes allergen-specific immunotherapy (ASIT), e.g. against insect venoms.

Self-medication ("emergency set for self-help")

Basically all patients who have survived an anaphylaxis and cannot avoid with certainty the elicitor as well as all adult patients with mastocytosis should be prescribed an "emergency set for self-help" [65, 66]. In Germany, Austria and Switzerland commonly the following drugs are included in the emergency set: an adrenaline autoinjector, H₁ antihistamine, glucocorticosteroid and for patients with asthma, an inhaled bronchodilator (Tab. 8). Each patient with an "emergency set for self-help" must be reminded to always carry the set with him/her. He/she must be informed about the correct storage and shelf life of the substances as well as possible sedative side effects caused by older antihistamines (influence on driving performance). Patients as well as persons in their social network – in the case of children parents and caretakers – must be instructed in the use of the medication. For this standardized anaphylaxis emergency plans are available.

Several adrenaline autoinjectors preparations, that apply various single doses (150 µg for patients of 15–30 kg bw, 300 µg for patients over 30 kg bw), are available for intramuscular injection. There is information, that in otherwise healthy children with a body weight between 10 and 15 kg, the dose of 150 µg is not hazardous. Parents must be informed about off-label use in this indication. The available adrenaline autoinjectors differ in their practical administration: Patients receiving a second or subsequent autoinjector, should be prescribed a preparation requiring the same administration technique. In order to train patients and their social environment in the application of the autoinjector, it is helpful to give them a dummy (without needle) and to motivate them to practice frequently.

Table 9

Indications for the prescription of an adrenaline autoinjector

- Patients with a systemic allergic reaction and bronchial asthma (even without a history of anaphylaxis)
- Progressive severity of symptoms of a systemic allergic reaction
- History of previous anaphylactic reactions to elicitors which cannot be avoided with certainty
- Systemic allergy to potent allergens e.g. peanuts, tree nuts, sesame
- High degree of sensitization, e.g. patients who react to even minute amounts of allergen
- Adults with mastocytosis (even without a history of anaphylaxis)

Table 10

Recommendations for long term management for prevention of anaphylaxis and self-medication

A) Prevention

1. Issuing of an anaphylaxis passport und anaphylaxis emergency plan
2. Emergency set, anaphylaxis-passport and mobile phone should always be at hand
3. Knowledge of the symptoms of anaphylaxis and being able to distinguish them from other symptoms (e.g. fear)
4. If possible autonomous training with the adrenalin-autoinjector (dummy without needle and drug) to be repeated every 3–6 months (cave: do not mix up with the "real" autoinjector!)
5. Shelf life of substances has to be checked regularly. For the Adrenalin-autoinjector the reminder service of the producing company can be used.
6. Inform the social network: organize support, delegate tasks for emergency situation (emergency call, application of drugs, receiving the emergency physician etc.)
7. Possibly further counseling, information material and exchange with other patients via patient organizations (e.g. Deutscher Allergie- und Asthmabund daab, mastocytosis self help group, anaphylaxis education in small groups according to anaphylaxis group education and training AGATE in Germany)

B) Emergency self-treatment

8. Application of the emergency set (see Anaphylaxis-passport / Anaphylaxis emergency plan)
9. Positioning
 - a) with predominant heart and cardiovascular symptoms: lying down, legs up (shock positioning)
 - b) with predominant respiratory symptomatology; sitting ("coachman position")
 - c) when there is unconsciousness: recovery position
10. Emergency telephone number: EU 112 (CH 144), the word "anaphylaxis/anaphylactic shock" should be mentioned first, the conversation should be guided by the rescue central office
11. Ask for help and support from the social surrounding

In the selection of an H_1 antihistamine, the ease with which it can be swallowed and individual preferences should be considered regarding the application form (drops for small children, tablets or fast-melt tablets for older children or adults). If difficulty in swallowing prevails (laryngeal angioedema), liquid applications are to be preferred. The same criteria are valid for glucocorticosteroids, whereby rectal application should also be considered.

In asthma patients, additional inhaled β receptor agonists should be prescribed and when there is a history of laryngeal edema adrenaline for inhalation.

Patients supplied with an emergency set for self-help must be shown how to administer the medication and also receive written information regarding this. Not all patients having suffered an immediate-type allergic reaction need an emergency set or autoinjector. There is no need, when the elicitor is known and easily avoided like in drug-induced anaphylaxis. Also after allergen-specific immunotherapy with insect venom, patients without additional risk factors, have no increased risk for anaphylaxis compared to the normal population. It is therefore

not compulsory for these patients to continuously carry self-medication with them. Indications for the prescription of an adrenaline autoinjector are listed in **Tab. 9**. Occasionally (e.g. very severe anaphylaxis, high body weight, mastocytosis, long distance to medical care) the prescription of a second autoinjector is advisable.

In addition to the emergency set for self-help an "anaphylaxis passport" should be issued which, apart from the elicitors, also contains the dosage of drugs and application of the drugs dependent upon the reaction.

Practical emergency management

Most anaphylactic emergencies occur at home. Therefore information on emergency self-management has to include all measures that have to be performed by the patient him-/herself or by his/her immediate surroundings. The patient should be trained in

- the recognition of an anaphylactic reaction
- symptom-orientated self-medication
- correct positioning

—making an emergency call (telephone no. 112 in D and A, 144 in CH). The word “anaphylaxis/anaphylactic shock” should be mentioned first, the conversation should then be guided by the rescue centre.

Potential suspected elicitors (foods, insects, drugs) should be preserved if possible.

Self-medication should be taken depending on symptoms and certainty of allergen contact. It is essential that patients receive information on when to take which medications as here often an uncertainty prevails in patients and their relatives. When there has been a definite contact with an elicitor of anaphylaxis (e.g. insect sting without preceding allergen-specific immunotherapy or consumption of allergy-inducing foods or intake of allergy-eliciting drugs), the anaphylaxis emergency plan (Fig. 2) must be followed. The immediate application of oral drugs is recommended even if the patient is asymptomatic. The emergency plan and anaphylaxis passport are important aids (Fig. 2).

Long-term therapy and prevention management

After an attack of anaphylaxis, allergy diagnostics should be performed. The identification of the elicitor, the targeted issuing of an anaphylaxis passport and individual counseling regarding risks and dangers are the necessary basis for all preventive measures (Tab. 10). Diagnostics comprise all methods allowing the doubtless identification of an elicitor. Relevant risk factors for anaphylaxis (e.g. asthma, mastocytosis or medication with certain drugs) should be identified and their significance explained to the patient. If possible, allergen-specific immunotherapy should be started [24]. In the case of recurrent anaphylactic reactions regular monitoring and long-term pharmacotherapy (e.g. anti-IgE, omalizumab) should be considered [67].

Elicitor-specific prevention

Patients with food allergy as elicitor of anaphylaxis should get complete information and nutritional counseling regarding the identification and possible avoidance from the eliciting food by an experienced nutritionist (www.ak-dida.de, www.daab.de). This should comprise information regarding alternative food choices and advice on preventing potential nutritional deficiencies when consequent avoidance of the culprit food is necessary. In particular patients should be informed about recent food declaration regulations and their implications, in order to allow for the low risk purchase of foods e.g. at the supermarket and when eating out. In patients with insect venom allergy precautionary strategies for the avoidance of repeated stings have to be dis-

Anaphylaxis Action Plan

Name: _____

Photo: _____

Date of birth: _____

Confirmed allergens, that cause anaphylaxis: _____

Asthma?
☐ Yes (higher risk for a severe reaction)
☐ No

Family emergency contact: name / phone _____

Where is emergency medication stored? _____

Plan prepared by (physician): _____

Date / Signature _____

How to administer the adrenaline autoinjector

Sticker with instructions how to use prescribed adrenaline autoinjector

Mild to moderate allergic reaction

Signs and symptoms

- Tingling mouth and throat
- Itching on palms, soles or genital area
- Redness of the skin
- Wheals, hives
- Swelling of lips and face
- Nausea, vomiting
- Feeling of impending doom

First Aid Action

1. Stay with the patient/ child. **Call for help: 112** (ambulance and inform emergency contact)
2. Give **antihistamine and corticosteroid**

Name and dose of antihistamine _____

Name and dose of corticosteroid _____

3. Locate **adrenaline autoinjector** and **watch patient** for further signs and symptoms of anaphylaxis

Severe reaction

Signs and symptoms

- Sudden hoarseness
- Shortness of breath
- Combination of two or more symptoms from different body areas (skin, gastrointestinal tract, respiratory system, cardiovascular system) e.g. abdominal pain and skin-reaction
- Any (even mild) reaction, after definite allergen contact (e.g. eating allergenic food or being stung by bee or wasp)
- Wheezing
- Loss of consciousness

First Aid Action

1. **Administer adrenaline autoinjector** into outer mid-thigh

Name of adrenaline autoinjector _____

2. **Position of patient:**
 - with respiratory symptoms: sit or position of comfort
 - with cardiovascular symptoms while conscious: lay flat
 - unconscious: recovery position
3. **If short of breath** (airway symptoms) administer asthma reliever (blue inhaler) in addition

Name of asthma reliever _____

4. **Call for help: 112** (ambulance and ask for emergency physician)
5. Inform **emergency contact** (see left)
6. Give **antihistamine and corticosteroid** in addition (see above)

Published by: **daab** Endorsed by: **AEDA** **DGÖKI**

© German Allergy and Asthma Association · Fließstr. 114 · 41061 Mönchengladbach · www.daab.de · 02161 - 814940

Fig. 2: Anaphylaxis emergency plan (available at info@daab.de)

cussed; in patients with drug allergy the risk of cross-reactions to related substances and the problem of synonyms should be mentioned.

Counseling, educational programs and helpful tools

In order to communicate all the necessary theoretical and practical information, educational programs as they have been developed by the “Arbeitsgemeinschaft Anaphylaxie Training und Edukation (AGATE)” (Working Group Anaphylaxis Education and Training), have proven helpful [68, 69]. Various target groups (adult patients, parents of children at risk of anaphylaxis, children, adolescents, child care workers and teachers) are trained in interdisciplinarily guided group sessions on how to behave in case of anaphylaxis. Equally, seminars for education of “anaphylaxis trainers” (train-the-trainer seminars) are offered (www.anaphylaxieschulung.de).

Following allergy diagnostics it is helpful to inform patients and their relatives of patient organizations (www.daab.de, www.mastozytose.de) which are experienced in the further counseling of patients with regard to coping with the disease in everyday life. They also provide information material and helpful tools such as restaurants cards, preprints of relevant travel documents, liability exclusion and cards with emergency telephone numbers.

Prof. Dr. med. Dr. phil. Johannes Ring

Dept. Dermatology and Allergology Biederstein
Christine Kuehne-Center Allergy Research and Education (CK-CARE)
Technical University Munich
Biedersteinerstr. 29
80802 Munich
Germany
Email: johannes.ring@lrz.tum.de

Cite this as: Ring J, Beyer K, Biedermann T, Bircher A, Duda D, Fischer J et al. Guideline for acute therapy and management of anaphylaxis – S2 Guideline of DGAKI, AeDA, GPA, DAAU, BVKJ, ÖGAI, SGAI, DGAI, DGP, DGPM, AGATE and DAAB. *Allergy J Int* 2014; 23: 96–112
DOI 10.1007/s40629-014-0009-1

Conflict of Interest

The authors declare that there is no conflict of interest. More detailed information can be seen on the AWMF website (www.awmf.org).

References

1. Johansson SG, Biebert T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004; 113: 832–6

2. Ring J, Grosber M, Mührenschrager M, Brockow K. Anaphylaxis: acute treatment and management. *Chem Immunol Allergy* 2010; 95: 201–10
3. Simons FE, Arduoso LR, Bilo MB, El-Gamal YM, Ledford DK, Ring J et al. World Allergy Organization anaphylaxis guidelines: summary. *J Allergy Clin Immunol* 2011; 127: 587–93.e1–22
4. Tryba M, Ahnefeld F, Barth J, Dick W, Doenicke A, Fuchs T et al. Akuttherapie anaphylaktoider Reaktionen. Ergebnisse einer interdisziplinären Konsensuskonferenz. *Allergo J* 1994; 3: 211–22
5. Ring J, Brockow K, Duda D, Eschenhagen T, Fuchs Th, Huttegger I et al. Emergency treatment of anaphylactic reactions. *Allergo J* 2007; 16: 420–34
6. Bresser H, Sander CH, Rakoski J. Emergencies by insect stings in Munich in 1992. *Allergo J* 1995; 4: 373–6
7. Mehl A, Wahn U, Niggemann B. Anaphylactic reactions in children – a questionnaire-based survey in Germany. *Allergy* 2005; 60: 1440–5
8. Portier P, Richet C. De l'action anaphylactique de certains venins. *C R Soc Biol* 1902; 54: 170
9. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A 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: 391–7
10. Worm M. Epidemiology of anaphylaxis. *Chem Immunol Allergy* 2010; 95: 12–21
11. Moneret-Vautrin DA, Morisset M, Flabbee J, Beaudouin E, Kanny G. Epidemiology of life-threatening and lethal anaphylaxis: a review. *Allergy* 2005; 60: 443–51
12. Helbling A, Hurni T, Mueller UR, Pichler WJ. Incidence of anaphylaxis with circulatory symptoms: a study over a 3-year period comprising 940,000 inhabitants of the Swiss Canton Bern. *Clin Exp Allergy* 2004; 34: 285–90
13. Decker WW, Campbell RL, Manivannan V, Luke A, St Sauver JL, Weaver A et al. The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. *J Allergy Clin Immunol* 2008; 122: 1161–5
14. Sheikh A, Hippisley-Cox J, Newton J, Fenty J. Trends in national incidence, lifetime prevalence and adrenaline prescribing for anaphylaxis in England. *J R Soc Med* 2008; 101: 139–43
15. Poulos LM, Waters AM, Correll PK, Loblay RH, Marks GB. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993–1994 to 2004–2005. *J Allergy Clin Immunol* 2007; 120: 878–84
16. Worm M, Edenharter G, Rueff F, Scherer K, Pföhler C, Mahler V et al. Symptom profile and risk factors of anaphylaxis in Central Europe. *Allergy* 2012; 67: 691–8
17. Smith PL, Kagey-Sobotka A, Bleecker ER, Traystman R, Kaplan AP, Gralnick H et al. Physiologic manifestations of human anaphylaxis. *J Clin Invest* 1980; 66: 1072–80
18. Vadas P, Perelman B, Liss G. Platelet-activating factor, histamine, and tryptase levels in human anaphylaxis. *J Allergy Clin Immunol* 2013; 131: 144–9
19. Lee JK, Vadas P. Anaphylaxis: mechanisms and management. *Clin Exp Allergy* 2011; 41: 923–38
20. Ring J. *Angewandte Allergologie*. München: Urban & Vogel 2004
21. Rueff F, Przybilla B, Bilo MB, Müller U, Scheipl F, Aberer W et al. Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum tryptase—a study of the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity. *J Allergy Clin Immunol* 2009; 124: 1047–54
22. Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy* 2008; 63: 226–32

23. Guenova E, Volz T, Eichner M, Hoetzenecker W, Caroli U, Griesinger G et al. Basal serum tryptase as risk assessment for severe Hymenoptera sting reactions in elderly. *Allergy* 2010; 65: 919–23
24. Przybilla B, Ruëff F, Walker B, Råwer HC, Aberer W, Bauer CP et al. Diagnosis and therapy of bee and wasp venom allergy. *Allergo J* 2011; 20: 318–39
25. Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. *Allergy* 2007; 62: 857–71
26. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977; 1: 466–9
27. Stark BJ, Sullivan TJ. Biphasic and protracted anaphylaxis. *J Allergy Clin Immunol* 1986; 78: 76–83
28. Commings SP, Platts-Mills TA. Anaphylaxis syndromes related to a new mammalian cross-reactive carbohydrate determinant. *J Allergy Clin Immunol* 2009; 124: 652–7
29. Barnard JH. Studies of 400 Hymenoptera sting deaths in the United States. *J Allergy Clin Immunol* 1973; 52: 259–64
30. Delage C, Irey NS. Anaphylactic deaths: a clinicopathologic study of 43 cases. *J Forensic Sci* 1972; 17: 525–40
31. Fisher MM. Clinical observations on the pathophysiology and treatment of anaphylactic cardiovascular collapse. *Anaesth Intensive Care* 1986; 14: 17–21
32. Pumphrey RS, Roberts IS. Postmortem findings after fatal anaphylactic reactions. *J Clin Pathol* 2000; 53: 273–6
33. Krogh G von, Maibach HI. The contact urticaria syndrome – an updated review. *J Am Acad Dermatol* 1981; 5: 328–42
34. Kemp SF, Lockey RF. Anaphylaxis: a review of causes and mechanisms. *J Allergy Clin Immunol* 2002; 110: 341–8
35. Morita E, Kunie K, Matsuo H. Food-dependent exercise-induced anaphylaxis. *J Dermatol Sci* 2007; 47: 109–17
36. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000; 30: 1144–50
37. Mullins RJ, Dear KB, Tang ML. Characteristics of childhood peanut allergy in the Australian Capital Territory, 1995 to 2007. *J Allergy Clin Immunol* 2009; 123: 689–93
38. Schwartz LB. Clinical utility of tryptase levels in systemic mastocytosis and associated hematologic disorders. *Leuk Res* 2001; 25: 553–62
39. Brockow K, Vieluf D, Püschel K, Grosch J, Ring J. Increased postmortem serum mast cell tryptase in a fatal anaphylactoid reaction to nonionic radiographic contrast medium. *J Allergy Clin Immunol* 1999; 104: 237–8
40. Nolan JP, Soar J, Zideman DA, Biarent D, Bossaert LL, Deakin C et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 1. Executive summary. *Resuscitation* 2010; 81: 1219–76
41. Thomas M, Crawford I. Best evidence topic report. Glucagon infusion in refractory anaphylactic shock in patients on beta-blockers. *Emerg Med J* 2005; 22: 272–3
42. Simons FE, Schatz M. Anaphylaxis during pregnancy. *J Allergy Clin Immunol* 2012; 130: 597–606
43. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet* 2000; 356: 2139–43
44. Friedrich JO, Adhikari N, Herridge MS, Beyene J. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med* 2005; 142: 510–24
45. Gronemeyer. Noradrenalin statt Adrenalin beim anaphylaktischen Schock. *Dtsch Med Wochenschr* 1980; 102: 101
46. Hoffmann BB. Catecholamines, sympathomimetic drugs and adrenergic receptor antagonists. In: Hardman JG, Limbird LE, Goodman A, eds. *Goodman & Gilman's. The pharmaceutical basis of therapeutics*. New York: Mc Graw Hill, 2002
47. Schummer C, Wirsing M, Schummer W. The pivotal role of vasopressin in refractory anaphylactic shock. *Anesth Analg* 2008; 107: 620–4
48. Meßmer K. Plasma substitutes and indications for their use. In: Tinker J, Rapin M, eds. *Care of the critically ill patient*. Berlin – Heidelberg – New York: Springer, 1983. S. 569–575
49. Stölting RK. Systemic circulation. Pharmacology & physiology in anesthetic practice. Philadelphia: J.B. Lippincott Company, 2006. S. 661–78
50. Walther A, Böttiger BW. Anaphylaktoide Reaktionen in der Prähospitalphase. *Internist* 2004; 45: 296–304
51. Vincent JL, De Backer D. Circulatory shock. *N Engl J Med* 2013; 369: 1726–34
52. Martin C, Jacob M, Vicaut E, Guidet B, Van Aken H, Kurz A. Effect of waxy maize-derived hydroxyethyl starch 130/0.4 on renal function in surgical patients. *Anesthesiology* 2013; 118: 387–94
53. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; 367: 1901–11
54. Sheikh A, Ten Broek V, Brown SG, Simons FE. H1-antihistamines for the treatment of anaphylaxis: Cochrane systematic review. *Allergy* 2007; 62: 830–7
55. Zuberbier T, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Giménez-Arnau AM et al. EAACI/GA(2) LEN/EDF/WAO guideline: management of urticaria. *Allergy* 2009; 64: 1427–43
56. Pragst F, Herre S, Bakdash A. Poisonings with diphenhydramine – a survey of 68 clinical and 55 death cases. *Forensic Sci Int* 2006; 161: 189–97
57. Lin RY, Curry A, Pesola GR, Knight RJ, Lee HS, Bakalchuk L et al. Improved outcomes in patients with acute allergic syndromes who are treated with combined H1 and H2 antagonists. *Ann Emerg Med* 2000; 36: 462–8
58. Ring J, Rothenberger KH, Clauss W. Prevention of anaphylactoid reactions after radiographic contrast media infusion by combined histamine H1- and H2-receptor antagonists: results of a prospective controlled trial. *Int Arch Allergy Appl Immunol* 1985; 78: 9–14
59. Brockow K, Kiehn M, Riethmüller C, Vieluf D, Berger J, Ring J. Efficacy of antihistamine pretreatment in the prevention of adverse reactions to Hymenoptera immunotherapy: a prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 1997; 100: 458–63
60. Aouam K, Bouida W, Ben Fredj N, Chaabane A, Boubaker H, Boukef R et al. Severe ranitidine-induced anaphylaxis: a case report and literature review. *J Clin Pharm Ther* 2012; 37: 494–6
61. Winbery SL, Lieberman PL. Histamine and antihistamines in anaphylaxis. *Clin Allergy Immunol* 2002; 17: 287–317
62. Choo KJ, Simons E, Sheikh A. Glucocorticoids for the treatment of anaphylaxis: Cochrane systematic review. *Allergy* 2010; 65: 1205–11
63. Fischer J, Biedermann T. Anaphylaxis due to allergological testing or therapy – a compact compendium for emergency management. *Allergo J* 2009; 18: 124–31
64. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale Versorgungsleitlinie Asthma – Langfassung, 2. Aufl. Version 5. 2009, zuletzt geändert: August 2013 [cited: 26.02.2014]; <http://www.versorgungsleitlinien.de/themen/asthma>
65. Hartmann K, Biedermann T, Brockow K, Grabbe J, Horny H-P, Lippert U et al. Mastocytosis. Guideline of the German Society for Allergology and Clinical Immunology (DGAKI) and the German Society for Dermatology (DDG). *Allergo J* 2009; 18: 196–207
66. Simons FE, Arduzzo LR, Dimov V, Ebisawa M, El-Gamal YM, Lockey RF et al. World Allergy Organization Anaphylaxis Guidelines: 2013 update of the evidence base. *Int Arch Allergy Immunol* 2013; 162: 193–204

67. Lieberman JA, Chehade M. Use of omalizumab in the treatment of food allergy and anaphylaxis. *Curr Allergy Asthma Rep* 2013; 13: 78–84
68. Ring J, Beyer K, Dorsch A, Biedermann T, Fischer J, Friedrichs F et al. Anaphylaxis school – a new educational program for tertiary prevention in patients with anaphylaxis. *Allergo J* 2012; 21: 96–102
69. Fischer J, Kupfer J, Grosber M, Friedl T, Schallmeyer S, Rueff F, et al. Practical skills in the self therapy of anaphylaxis – development and evaluation of a test on decision making and prtctical performance. *Allergo J* 2013; 22: 18–24

Correspondence to the “Guideline for acute therapy and management of anaphylaxis”

It was with great interest that we followed the updated version of the “Guideline for acute therapy and management of anaphylaxis” published in the May issue of the *Allergo Journal* [1]. As the manufacturers of a variety of adrenaline preparations used for, amongst others, the treatment of anaphylaxis, we would like to draw attention to a number of recommendations in the guideline that, in our opinion, require critical scrutiny:

In Tables 6 and 7 (pharmacotherapy for children, adolescents and adults), the use of an „original concentration (1 mg/ml)“ is recommended for the administration of inhaled adrenaline. Similarly, the „administration of adrenaline“ (e.g., 2 ml at 1 mg/ml) via a nebulizer is recommended in the guideline text. However, there is no mention in the guideline that the available adrenaline solutions at a concentration of 1 mg/ml (adrenaline 1:1.000 InfectoPharm; Suprarenin®) are not approved for inhaled use and, moreover, contain sulphites. Yet in Germany, the product InfectoKrupp Inhal® in a 4-mg/ml concentration represents an adrenaline product that does have drug approval.

Why the guideline gives preference here to the off-label use of parenteral adrenaline over the administration of a preparation approved for inhaled use is not specified in more detail. However, we consider it misleading to recommend the off-label use of emergency medication in an official guideline without stating the rationale for this, while at the same time failing to mention that an alternative medication with drug approval is available. In the case of liability, any physician following this recommendation will find himself legally in a difficult position.

In Table 8, moreover, you recommend including a preparation with a spray head for pharmaceutical vials in the „emergency set for self-help“ for those patients in whom airway obstruction is to be expected. The only adrenaline preparation (InfectoKrupp Inhal®) approved for inhaled use in Germany is a solution for use in a nebulizer. Here again, the use of a spray head on a pharmaceutical vial is an off-label recommendation. In the past, a suitable spray head was used for reasons of practicability, since small, convenient electric nebulizer systems enabling mobile use were not available. However, a number of compact, battery-powered and even reimbursable nebulizers have been available for several years now, permitting the preparation to also be inhaled in a mobile setting (e.g., InfectoPharm pocket nebulizer, Omron-U22®). One study showed that rele-

vant epinephrine plasma concentrations were achieved in healthy adults by inhaling InfectoKrupp Inhal using a mobile nebulizer [2]. No comparable study data are available for spray systems.

We are aware that anaphylaxis represents a medical emergency requiring rapid action and speed and practicability in terms of using a drug may sometimes be more important than drug approval. Nevertheless, we would like to expressly point out here that, under the current legal framework, explicit reference should be made to off-label use and, where available, an approved alternative named in the guideline. A reference to off-label use is after all made in the guideline in relation to the use of autoinjectors in children weighing between 10 and 15 kg.

Naturally, we would be happy to engage in a more in-depth discussion of the above. Above this, we would kindly request that these points be rectified in the next guideline update.

Dr. Markus Rudolph

Dr. Marcel Fischer

Infectopharm

Von-Humboldt-Straße 1

64646 Heppenheim, Germany

E-Mail: kontakt@infectopharm.com

Cite this as

Rudolph M, Fischer M. Correspondence to the “Guideline for acute therapy and management of anaphylaxis”.

Allergo J Int 2015;24:44

DOI: 10.1007/s40629-015-0036-6

References

1. Ring J, Beyer K, Biedermann T, Bircher A, Duda D, Fischer J et al. Guideline for acute therapy and management of anaphylaxis. S2 Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Association of German Allergologists (AeDA), the Society of Pediatric Allergy and Environmental Medicine (GPA), the German Academy of Allergology and Environmental Medicine (DAAU), the German Professional Association of Pediatricians (BVKJ), the Austrian Society for Allergology and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Anaesthesiology and Intensive Care Medicine (DGAI), the German Society of Pharmacology (DGP), the German Society for Psychosomatic Medicine (DGPM), the German Working Group of Anaphylaxis Training and Education (AGATE) and the patient organization German Allergy and Asthma Association (DAAB). *Allergo J Int* 2014; 23: 96–112
2. Breuer C, Wachall B, Gerbeth K, Abdel-Tawab M, Fuhr U. Pharmacokinetics and pharmacodynamics of moist inhalation epinephrine using a mobile inhaler. *Eur J Clin Pharmacol* 2013;69:1303–10

Reply to the correspondence to the “Guideline for acute therapy and management of anaphylaxis”

The authors of the guidelines [1] thank Drs. Rudolph and Fischer (InfectoPharm) for their comments [2] and would like to respond as follows:

1. It is correct that the administration of 2 ml of a 1-mg/ml adrenaline solution in inhaled form, as stated in Tables 6 and 7, does not conform to the drug approval for ampoules available on the market. The authors regret that they did not make explicit reference to this „off-label“ status. Possible side effects due to sulphite content should be of minor importance in an emergency setting. However, the alternative mentioned, i.e., inhaling with InfectoKrupp Inhal®, is similarly not approved for use in anaphylaxis.
2. While it is also correct that an adrenaline solution is available for use in a nebulizer, this preparation is not – as mentioned above – approved for the treatment of anaphylaxis. The above-mentioned study by Breuer et al. [3] was commissioned by the manufacturer as a preclinical pilot study in eight healthy adults that used a nebulizer system of this kind. Said study had serum concentration as its sole endpoint and did not investigate the clinical effect of adrenaline. Thus, it is not possible to draw any valid conclusions on the efficacy of this method in the treatment of anaphylaxis. Furthermore, the preparation appears to be difficult to handle in an emergency setting to the extent that, following intense discussion, the guideline group decided against recommending it for this indication.

In summary, it is correct that the off-label use of medicinal products should be explicitly mentioned in guidelines. This omission is hereby rectified. We express our thanks to Drs. Rudolph and Fischer for drawing our attention to this point. The recommen-

dation regarding the described treatment procedure remains otherwise unchanged.

Prof. Dr. Dr. Johannes Ring
(Guideline coordinator)
Klinikum rechts der Isar
Technische Universität Munich
Biedersteiner Straße 29
80802 Munich, Germany
E-Mail: johannes.ring@tum.de

Cite this as

Ring J. Reply to the correspondence to the “Guideline for acute therapy and management of anaphylaxis”. *Allergo J Int* 2015;24:45
DOI: 10.1007/s40629-015-0040-x

References

1. Ring J, Beyer K, Biedermann T, Bircher A, Duda D, Fischer J et al. Guideline for acute therapy and management of anaphylaxis. S2 Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Association of German Allergologists (AeDA), the Society of Pediatric Allergy and Environmental Medicine (GPA), the German Academy of Allergology and Environmental Medicine (DAAU), the German Professional Association of Pediatricians (BVKJ), the Austrian Society for Allergology and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Anaesthesiology and Intensive Care Medicine (DGAI), the German Society of Pharmacology (DGP), the German Society for Psychosomatic Medicine (DGPM), the German Working Group of Anaphylaxis Training and Education (AGATE) and the patient organization German Allergy and Asthma Association (DAAB). *Allergo J Int* 2014; 23: 96–112
2. Rudolph M, Fischer M. Correspondence to “Guideline for acute therapy and management of anaphylaxis”. *Allergo J Int* 2015;24:44
3. Breuer C, Wachall B, Gerbeth K, Abdel-Tawab M, Fuhr U. Pharmacokinetics and pharmacodynamics of moist inhalation epinephrine using a mobile inhaler. *Eur J Clin Pharmacol* 2013;69:1303–10

German version
www.springer-medizin.de/allergo-Journal