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POSITION PAPER

World Allergy Organization Anaphylaxis Guidance 2020

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ABSTRACT

Anaphylaxis is the most severe clinical presentation of acute systemic allergic reactions. The occurrence of anaphylaxis has increased in recent years, and subsequently, there is a need to continue disseminating knowledge on the diagnosis and management, so every healthcare professional is prepared to deal with such emergencies. The rationale of this updated position document is the need to keep guidance aligned with the current state of the art of knowledge in anaphylaxis management. The World Allergy Organization (WAO) anaphylaxis guidelines were published in 2011, and the current guidance adopts their major indications, incorporating some novel changes. Intramuscular epinephrine (adrenaline) continues to be the first-line treatment for anaphylaxis. Nevertheless, its use remains suboptimal. After an anaphylaxis occurrence, patients should be referred to a specialist to assess the potential cause and to be educated on prevention of recurrences and self-management. The limited availability of epinephrine auto-injectors remains a major problem in many countries, as well as their affordability for some patients.

Keywords: Anaphylaxis, Acute systemic allergic reaction, Adrenaline, Cofactors, Epinephrine, Guidance, Guidelines, Antihistamines, Glucocorticoids, Food allergy, Venom allergy, Drug allergy

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FORMAL REVIEW

This guidance document was reviewed and endorsed by the following national, associate, regional, and affiliate member societies of the World Allergy Organization during a formal review process conducted in February and March 2020.

Algerian Academy of Allergology

American College of Allergy Asthma and Immunology

Argentine Association of Allergy and Clinical Immunology

Australasian Society of Clinical Immunology and Allergy

Austrian Society of Allergology and Immunology

Belarus Association of Allergology & Clinical Immunology

Brazilian Society of Allergy and Immunopathology

British Society for Allergology and Clinical Immunology

Canadian Society of Allergy and Clinical Immunology

Chilean Society of Allergy and Immunology

Commonwealth of Independent States (CIS) Society of Allergology and Immunology

Croatian Society of Allergology and Clinical Immunology

Czech Society of Allergology and Clinical Immunology

Danish Society of Allergology

Dominican Society of Allergy, Asthma, and Immunology

Ecuadoran Society of Allergy Asthma and Immunology

Egyptian Society of Allergy and Clinical Immunology

Egyptian Society of Pediatric Allergy and Immunology

Global Allergy and Asthma European Network

Hellenic Society of Allergology and Clinical Immunology

Honduran Society of Allergy and Clinical Immunology

Hong Kong Institute of Allergy

Indian College of Allergy and Applied Immunology

Italian Association of Territorial and Hospital Allergists

Japanese Society of Allergology

Allergy Society of Kenya

Kazakhstan Association of Allergology and Clinical Immunology

Korean Academy of Allergy Asthma and Clinical Immunology

Kuwait Society of Allergy and Clinical Immunology

Latin American Society of Allergy Asthma and Immunology

Lebanese Society of Allergy and Immunology

Malaysian Society of Allergy and Immunology

Mexican College of Allergy and Clinical Immunology

Mexican College of Pediatricians Specialized in Allergy and Clinical Immunology

Mongolian Society of Allergology

Pakistan Allergy Asthma and Immunology Society

Pan-Arab Society of Allergy Asthma and Immunology

Paraguayan Society of Immunology and Allergy

Philippine Society of Allergy, Asthma and Immunology

Polish Society of Allergology

Allergy and Clinical Immunology Society (Singapore

Romanian Society of Allergology and Clinical Immunology

Salvadoran Association of Allergy Asthma and Clinical Immunolog

Slovenian Association for Allergology and Clinical Immunology

Allergy Society of South Africa

Southern European Allergy Societies

Spanish Society of Allergology and Clinical Immunology

Taiwan Academy of Pediatric Allergy Asthma Immunology

Allergy, Asthma and Immunology Society of Thailand

Turkish National Society of Allergy and Clinical Immunology

Uruguayan Society of Allergology

INTRODUCTION

Anaphylaxis is the most severe clinical presentation of acute systemic allergic reactions. The rationale of this updated position document is the need to keep guidance aligned with the current state of the art of knowledge in anaphylaxis management. Special focus has been placed on regions in which national guidelines are lacking. All aspects have been assessed based on scientific evidence supporting statements. This guidance adopts the major indications from the previous anaphylaxis guidelines of the World Allergy Organization (WAO)[1] and incorporates some slight changes in specific aspects such as the diagnostic criteria.

The objectives of this guidance are to increase global awareness of current concepts in the assessment and management of anaphylaxis in healthcare settings globally, to prevent anaphylaxis recurrences in the community, to reduce avoidable deaths, and to improve allocation of resources for anaphylaxis.

The World Allergy Organization Anaphylaxis Guidance has been developed primarily for use by allergy/immunology specialists in countries without anaphylaxis guidelines and as an additional resource in areas where such guidelines are available. In addition, this will be a resource for other healthcare professionals who may encounter anaphylaxis patients in their settings. This includes primary care physicians, other medical specialties, and allied health staff caring for patients of any age, and in particular those who work in the emergency and peri-operative settings.

The current update was developed based on the previous guidelines,[1] based on the best evidence available, such as that from systematic reviews performed to inform other guidelines,[2] in the absence of randomized controlled trials[3] with which to answer most clinical questions relevant to anaphylaxis. A first draft of the Guidance was compiled, and further discussed and refined through electronic correspondence and face-to-face meetings. The updated draft was circulated to the WAO Board of Directors for review and comment. The Guidance was circulated to the WAO member societies for review, comments, and voting. Comments from responding organizations were evaluated and incorporated appropriately.

EPIDEMIOLOGY

Recent publications show a global incidence of anaphylaxis between 50 and 112 episodes per 100 000 person-years while the estimated lifetime prevalence is 0.3–5.1%, variations depending on the definitions used, study methodology, and geographical areas.[4,5] According to a recent systematic review, in children, the incidence of anaphylaxis ranged from 1 to 761 per 100 000 person-years.[6] Worrying data indicate that recurrence of reactions occurs in 26.5–54.0% of anaphylaxis patients during a follow-up time of 1.5 years–25 years.[7] Despite an increasing time trend for hospitalizations due to anaphylaxis, mortality remains low, estimated at 0.05–0.51 per million people/year for drugs, at 0.03–0.32 for food and at 0.09–0.13 for venom induced anaphylaxis, with no evidence in most regions of a change in incidence of fatal anaphylaxis.[8,9]

DEFINITION AND CLINICAL DIAGNOSTIC CRITERIA FOR ANAPHYLAXIS

Anaphylaxis represents the most severe end of the spectrum of allergic reactions. A number of different definitions for anaphylaxis are currently used in the literature (Table 1).[1,10–16]

Some definitions imply the need of multiple organ involvement, however severe symptoms can present in only one organ system;[17–19] thus such a definition is misleading and can lead to inappropriate treatment. Many of these define

WAO 2011 (1)	EAACI 2013 (2)	AAAAI/ACAAI 2010 (11)	ASCIA 2016 (16)	NIAID 2006 (13)	WHO ICD-11 2019 (14)
A serious life-threatening generalized or systemic hypersensitivity reaction.	A severe life-threatening generalized or systemic hypersensitivity reaction.	An acute life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity that results from the sudden release of mediators from mast cells and basophils.	Any acute onset illness with typical skin features (urticarial rash or erythema/flushing, and/or angioedema), PLUS involvement of respiratory and/or cardiovascular and/or persistent severe gastrointestinal symptoms; or Any acute onset of hypotension or bronchospasm or upper airway obstruction where anaphylaxis is considered possible, even if typical skin features are not present.	Anaphylaxis is a serious allergic reaction that involves more than one organ system (for example, skin, respiratory tract, and/or gastrointestinal tract). It can begin very rapidly, and symptoms may be severe or life-threatening.	Anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes.
A serious allergic reaction that is rapid in onset and might cause death	An acute, potentially fatal, multi-organ system, allergic reaction.				

Table 1. Current definitions of anaphylaxis in the literature. *AAAAI/ACAAI: American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma, and Immunology; ASCIA: Australasian Society of Clinical Immunology and Allergy; EAACI: European Academy of Allergy Asthma and Clinical Immunology; NIAID: National Institute of Allergy and Infectious Diseases; WAO: World Allergy Organization; WHO ICD-11: World Health Organization International Classification of Diseases 11th Edition*

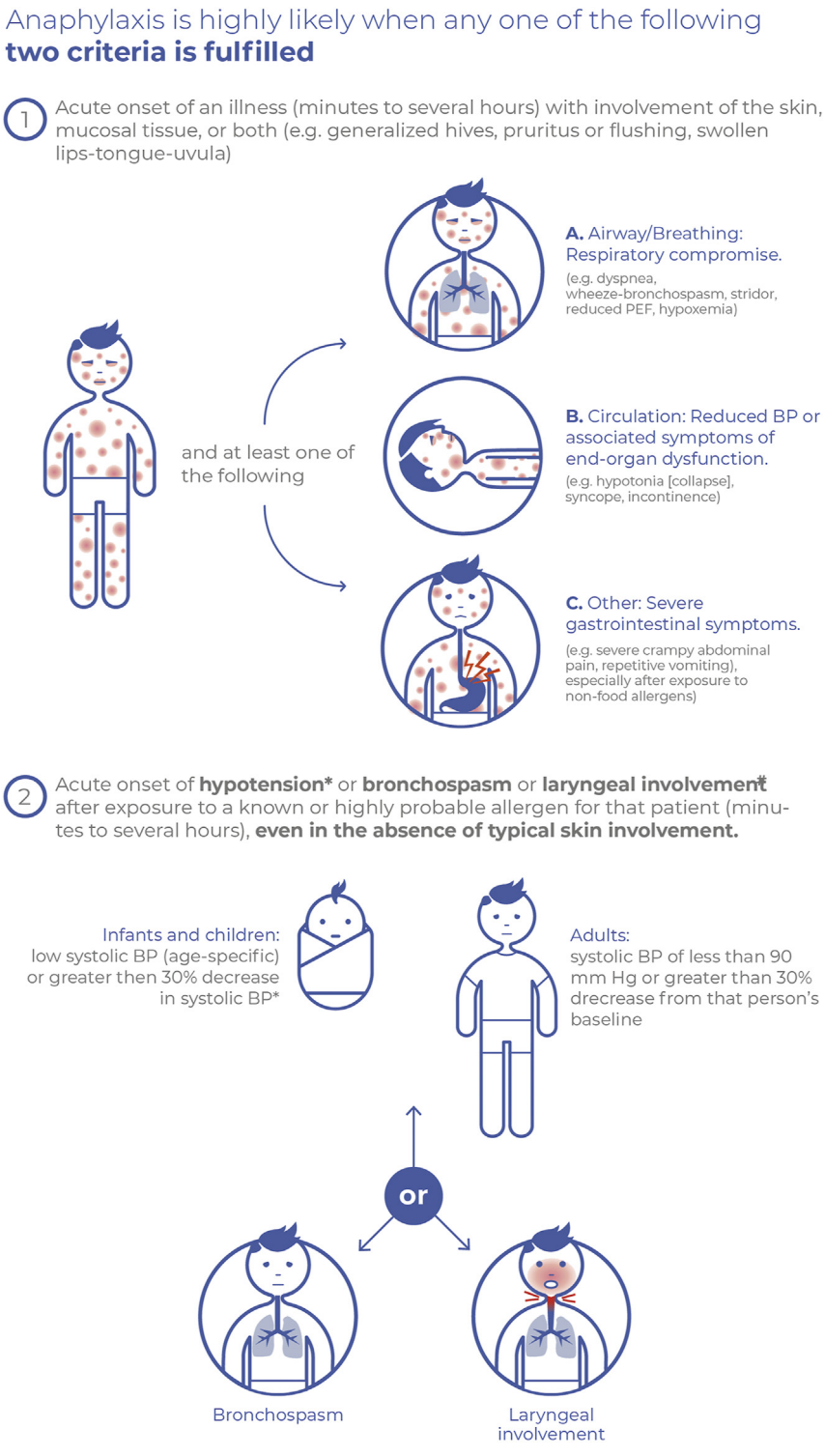
Anaphylaxis is highly likely when any one of the following 2 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING:
a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
c. Severe gastrointestinal symptoms (eg, severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens
2. Acute onset of hypotension[a] or bronchospasm[b] or laryngeal involvement[c] after exposure to a known or highly probable allergen[d] for that patient (minutes to several hours), even in the absence of typical skin involvement.

Table 2. Amended criteria for the diagnosis of anaphylaxis. *PEF, Peak expiratory flow; BP, blood pressure. a. Hypotension defined as a decrease in systolic BP greater than 30% from that person's baseline, OR i. Infants and children under 10 years: systolic BP less than (70 mmHg + [2 x age in years]) ii. Adults and children over 10 years: systolic BP less than <90 mmHg. b. Excluding lower respiratory symptoms triggered by common inhalant allergens or food allergens perceived to cause "inhalational" reactions in the absence of ingestion. c. Laryngeal symptoms include: stridor, vocal changes, odynophagia. d. An allergen is a substance (usually a protein) capable of triggering an immune response that can result in an allergic reaction. Most allergens act through an IgE-mediated pathway, but some non-allergen triggers can act independent of IgE (for example, via direct activation of mast cells). Adapted from ([26])*

anaphylaxis as a serious life-threatening reaction; however, the literature indicates that fatal and near-fatal events are rare even when reactions are not appropriately treated.[20–25] Therefore, the majority of anaphylaxis reactions cannot be described as life-threatening in themselves; although given our inability to predict reaction progression,[24] we emphasize that all anaphylaxis reactions must be appropriately treated with intramuscular adrenaline (epinephrine, indistinctively used in the document) to help reduce risk of death.[25]

In 2005, the second US National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) symposium proposed clinical criteria for diagnosing anaphylaxis,[13] which were subsequently adopted by WAO.[1] These criteria are not a definition, but rather an aid to diagnosis. At the time, it was acknowledged that the criteria were designed to correctly identify at least 95% of episodes of anaphylaxis (ie, with a sensitivity of >95%); however, the authors identified the "need to establish their utility and determine whether there is need for further refinement in prospective multicenter clinical surveys".[13] The WAO Anaphylaxis Committee recently considered a number of issues regarding these criteria:[26]

- Some reactions present initially with isolated respiratory or cardiovascular symptoms;[17] such presentations are not uncommon in fatal anaphylaxis triggered by exposure to food and other allergens,[18,19] and are increasingly seen with oral immunotherapy/desensitization protocols. However, while such presentations would not constitute anaphylaxis under the current NIAID/FAAN criteria, such reactions must be considered as anaphylaxis and managed accordingly.
- Some definitions equate anaphylaxis as a systemic reaction – yet it is not uncommon for allergic reactions to involve only the skin, remote to the site of allergen exposure: this is clearly a systemic manifestation, but should not be classified as anaphylaxis in the absence of potentially life-threatening compromise affecting the respiratory and/or cardiovascular systems.[27]
- Some triggers of anaphylaxis cause rapidly progressing symptoms, but are of delayed onset after allergen exposure eg, galactose-alpha-1,3-galactose (alpha-gal allergy).[28]
- The lack of definition of "persistent" when applied to gastrointestinal symptoms in the current NIAID/FAAN framework is ambiguous. There has long been regional differences of opinion with respect to the inclusion of



PEF, Peak expiratory flow; BP blood presure.

*Hypotension defined as a decrease in systolic BP greater than 3% from that person's baseline, OR
i. Infants and children under 10 years: systolic BP less than (70mmHg + [2 x age in years])
ii. Adults: systolic BP les than < 90 mmHg

Laryngeal symptoms include: stridor, vocal changes, odynophagia.

Fig. 1 Diagnostic criteria for the diagnosis of anaphylaxis

Common diagnostic dilemmas	Flush syndromes
Acute asthma[a]	Peri-menopause
Syncope (faint)	Carcinoid syndrome
Anxiety/panic attack	Autonomic epilepsy
Acute generalized urticaria[a]	Medullary carcinoma of the thyroid
Aspiration of a foreign body	**Nonorganic Disease**
Cardiovascular (myocardial infarction,[a] pulmonary embolus)	Vocal cord dysfunction
Neurologic events (seizure, cerebrovascular event)	Hyperventilation
Postprandial syndromes	Psychosomatic episode
Scombroidosis[b]	**Shock**
Pollen-food allergy syndrome[c]	Hypovolemic
Monosodium glutamate	Cardiogenic
Sulfites	Distributive[d]
Food poisoning	Septic
Excess endogenous histamine	**Other**
Mastocytosis/clonal mast cell disorders[e]	Nonallergic angioedema
Basophilic leukemia	Hereditary angioedema types I, II, & III
	ACE inhibitor-associated angioedema
	Systemic capillary leak syndrome
	Red man syndrome (vancomycin)
	Pheochromocytoma (paradoxical response)

Table 3. Differential diagnosis of anaphylaxis. *a. Acute asthma symptoms, acute generalized urticaria, or myocardial infarction symptoms can also occur during an anaphylactic episode. b. Histamine poisoning from fish, eg, tuna that has been stored at an elevated temperature; usually, more than one person eating the fish is affected. c. Pollen-food allergy syndrome is elicited by fruits and vegetables containing various plant proteins that cross-react with airborne allergens. Typical symptoms include oral allergy symptoms (itching, tingling and angioedema of the lips, tongue, palate, throat, and ears) after eating raw, but not cooked, fruits and vegetables. d. Distributive shock may be due to anaphylaxis or to spinal cord injury. e. In mastocytosis and clonal mast cell disorders, there is an increased risk of anaphylaxis; also, anaphylaxis may be the first manifestation of the disease.* [1]

gastrointestinal symptoms as a defining feature of *food*-induced anaphylaxis.[29,30]

- Anaphylaxis may occur in the absence of skin involvement or cardiovascular shock; such a presentation is common in fatal anaphylaxis.[18] Skin signs are absent in 10–20% of anaphylaxis reactions, and this may result in delays in the recognition of anaphylaxis.[1] Therefore, the WAO Anaphylaxis Committee has proposed the following definition for anaphylaxis.[26]

"Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise in airway, breathing and/or the circulation, and may occur without typical skin features or circulatory shock being present."

Furthermore, the WAO Anaphylaxis Committee has proposed to amend the current NIAID/FAAN

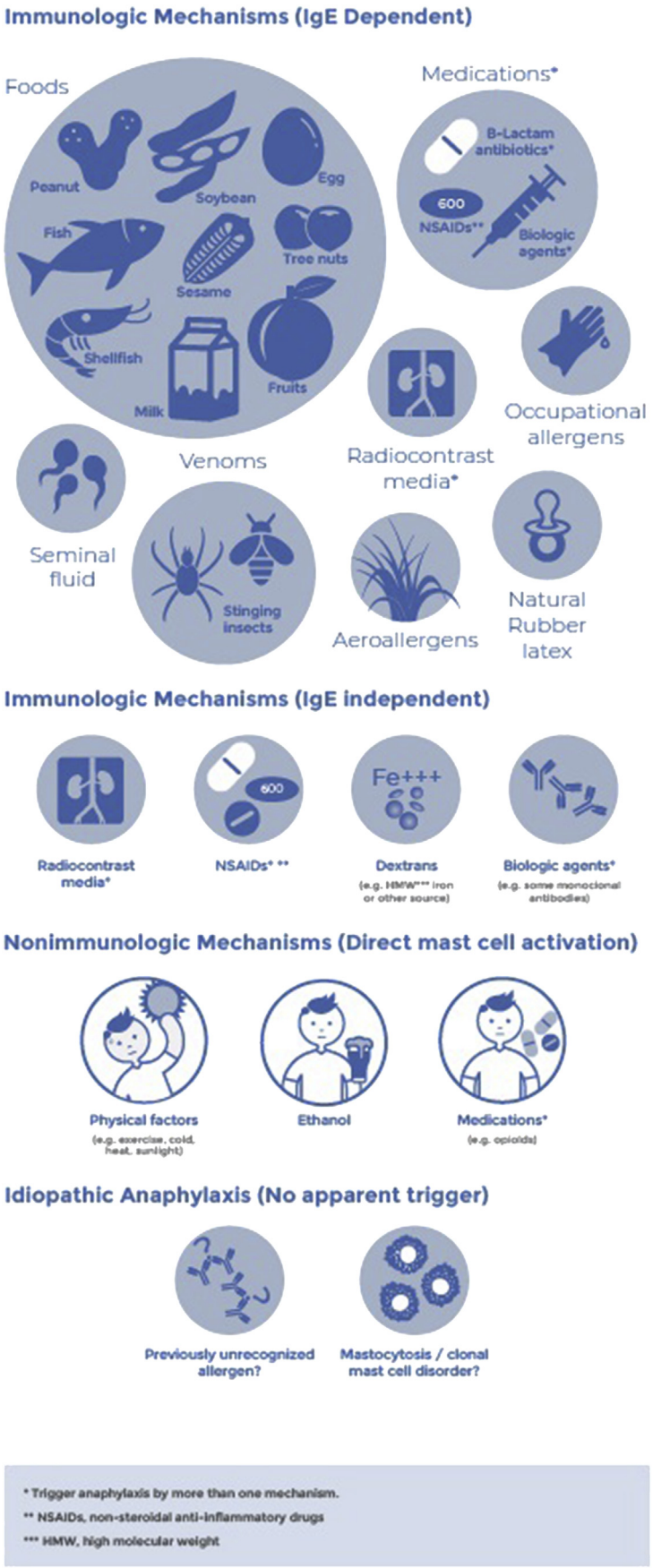


Fig. 2 Types of anaphylaxis

FOOD	INSECT VENOM	DRUGS
celery	bee and wasp venom	analgesics
cow's milk	fire ants	antibiotics
hen's egg	horse fly	biologics
peach		chemotherapeutics
peanut		contrast media
seeds eg, sesame		proton pump inhibitors
shellfish		
tree nuts		
wheat and buckwheat		

Table 4. Examples of anaphylaxis elicitors worldwide (frequency depends on age, geographical region and lifestyle) *Adapted from ([21,53,55-57])*

criteria, as shown in Table 2. The aim is to simplify the existing criteria, by combining the first 2 NIAID/FAAN criteria and modifying the third (Fig. 1)

1. Typical skin symptoms AND significant symptoms from at least 1 other organ system; OR

2. Exposure to a known or probable allergen for that patient, with respiratory and/or cardiovascular compromise.

Given the uncertainty over the definition of "*persistent*" gastrointestinal symptoms discussed above, this wording has been modified to "severe gastrointestinal symptoms (severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens". This acknowledges that gastrointestinal symptoms, particularly after exposure to non-food allergens, are indicative of anaphylaxis, without requiring such symptoms to become persistent in order to be treated appropriately. The choice of "severe" rather than "persistent" is also consistent with the grading system for allergic reactions used within the US-based Consortium of Food Allergy Research (CoFAR).[31] These symptoms should appear more or less simultaneously

The second criterion reflects the reality that the occurrence of objective respiratory signs in isolation following exposure to a known allergen is indicative of anaphylaxis

Importantly, these criteria do not preclude the treatment of early, but potentially evolving systemic reactions in the context of allergen immunotherapy (particularly via the sub-cutaneous route) as anaphylaxis

Differential diagnosis of anaphylaxis includes acute asthma, localized angioedema, syncope, and anxiety/panic attacks, among others (see Table 3)

Pathogenesis of anaphylaxis

Despite expressing common clinical features, the underlying mechanisms of anaphylaxis may vary.[32] Nevertheless, some of the activated pathways may be common to different types of anaphylaxis reactions or be present simultaneously (Fig. 2).

IgE-mediated anaphylaxis is considered the classic and most frequent mechanism. In this type, anaphylaxis is triggered by the interaction of an allergen (usually a protein) interacting with the allergen-specific IgE/high-affinity receptor (FcεRI) complex expressed on effector cells, predominantly mast cells and basophils.[33] This initiates intracellular signaling resulting in the release of preformed and *de novo* synthesis of mediators.[34]

Non-IgE-mediated anaphylaxis may be immunologic or non-immunologic. The most relevant non-IgE-mediated immunologic mechanisms may involve the activation of pathways such as the

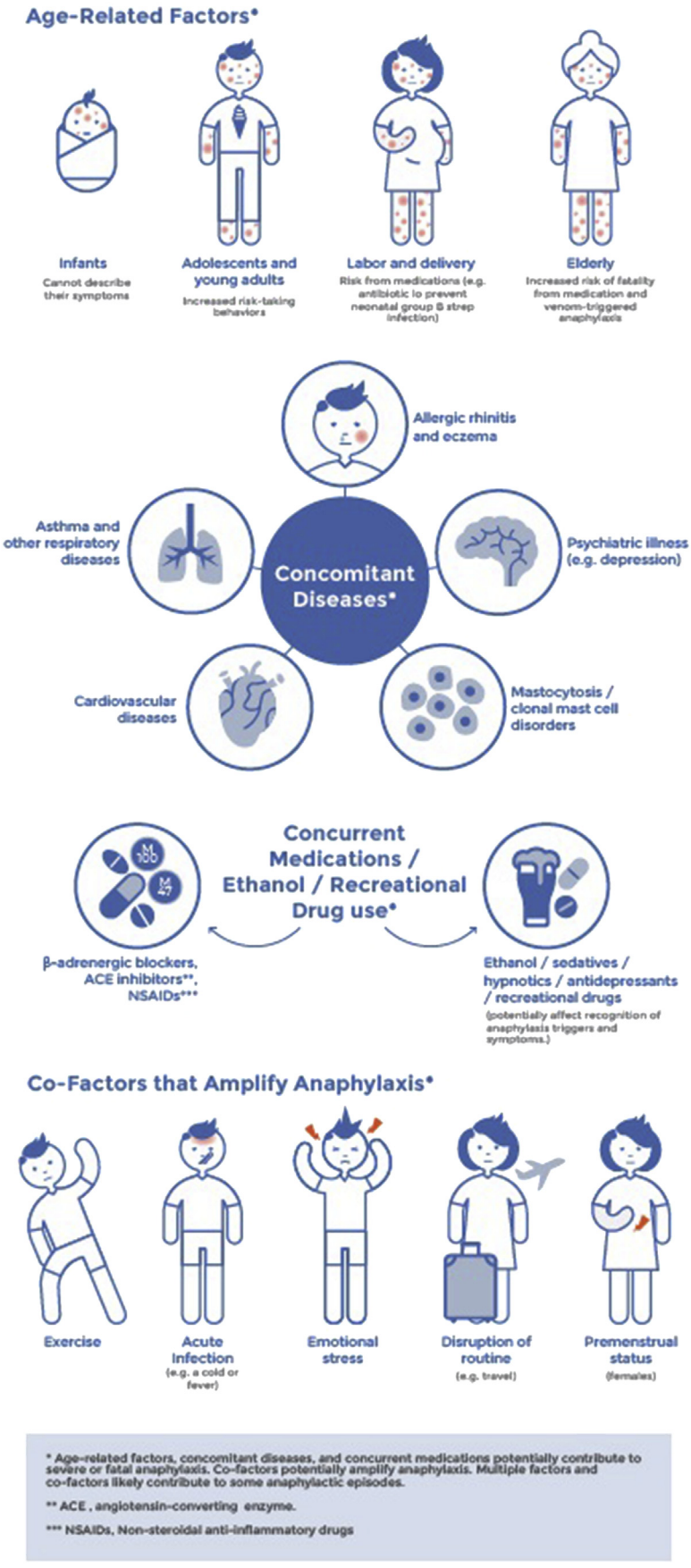


Fig. 3 Factors and cofactors influencing anaphylaxis

Endogenous	Exogenous
sex, age	medication
cardiovascular disease	physical activity
mastocytosis	psychological burden
atopic disease	certain elicitors
elevated tryptase	sleep deprivation
ongoing infection	

Table 5. Factors, which can increase severity of anaphylaxis

complement system (anaphylatoxins, C3a, and C5a),[35] the contact and coagulation system activation,[36-38] or immunoglobulin G (IgG)-mediated anaphylaxis.[39-41] Non-immunologic mechanisms have been described for some drugs (opioids).[42] Ethanol and physical factors, such as exercise, may be involved in triggering anaphylaxis through mechanisms which are not fully elucidated. Mast cells may be activated through receptors such as Mas-related G-protein coupled receptor member X2 (MRGPRX2) by certain drugs such as neuromuscular blocking agents and fluoroquinolones.[43,44]

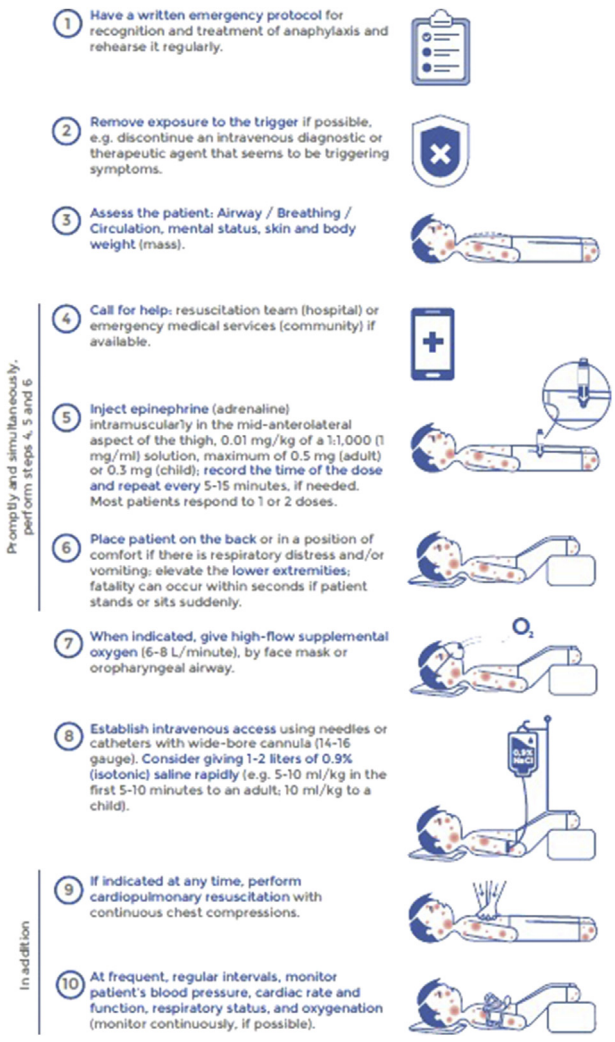


Fig. 4 Management of anaphylaxis

Anaphylaxis is classified as idiopathic when no trigger can be identified and currently represents between 6.5 and 35.0% of cases, depending on the studies.[45] In such cases, mast cell disorders should be ruled out. Excluding urticaria pigmentosa does not exclude mastocytosis, neither does a normal baseline tryptase. Detecting KIT mutation in peripheral blood or in bone marrow may be necessary.[46,47] Also, the role of allergens previously unrecognized (such as alpha-Gal)[48] or less straightforward to identify (omega-5-gliadin, oleosins)[49] has to be considered.

ELICITORS AND COFACTORS OF ANAPHYLAXIS

The elicitor profile of anaphylaxis is age-dependent and varies between different geographic areas. Therefore, allergy testing should be based on patient history and local data regarding the common causes of anaphylaxis in the region. The most frequent elicitor groups worldwide are food, insect venom, and drugs (Table 4) (Fig. 2).[21,50-56]

The most frequent elicitors of food-induced anaphylaxis in children are hen's egg (in infants and pre-school children), cow's milk, wheat, and peanut.[58] In adults, food-induced anaphylaxis varies depending on the region and local food exposure. Peanut and tree nuts are dominating elicitors of food-induced anaphylaxis in adults in North America and Australia; whereas, shellfish is a

0.01 mg/kg of body weight, to a maximum total dose of 0.5 mg - This is equivalent to 0.5 mL of 1 mg/mL (1:1000)[a] epinephrine (adrenaline)	
Infants under 10 kg	0.01 mg/kg = 0.01 mL/kg of 1 mg/mL (1:1000)
Children aged 1–5 years	0.15 mg = 0.15 mL of 1 mg/mL (1:1000)
Children aged 6–12 years	0.3 mg = 1 mg/mL (1:1000)
Teenagers and adults	0.5 mg = 1 mg/mL (1:1000)

Table 6. Recommended doses for intramuscular epinephrine (adrenaline). *a. 1 mg/mL (1:1000) is recommended for intramuscular injections as this allows a more appropriate volume to be injected*

frequent elicitor of food-induced anaphylaxis in Asia. In central Europe the most frequent elicitors of food-induced anaphylaxis are peanut, tree nuts, seeds like sesame, wheat, and shellfish.[21,50–56] Frequent food allergens in southern Europe are lipid transfer protein containing plant-foods, frequently associated with cofactors,[59,60] while sesame seed is a frequent elicitor in the Middle East.[61] Buckwheat is a very common cause of anaphylaxis in Korea.[62] Mite ingestion (oral mite anaphylaxis) is considered an infrequent allergen which deserves further studies.[63]

Venom-induced anaphylaxis also displays regional patterns. A recent report suggested bee venom as the most frequent elicitor in South Korea;[50] whereas, in central Europe (Austria, Germany, and Switzerland) wasp is the predominating insect inducing anaphylaxis.[21] In other regions, different stinging or biting insects have been reported to induce anaphylaxis, eg, red ants in America and Asia and parts of Australia;[64]; antivenom used for snake bites in Australia are not uncommon causes of anaphylaxis.[65]

Drug-induced anaphylaxis is most frequently triggered by antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs), again with age and geographical variations worldwide. Drugs in general have been mentioned as being a main cause of anaphylaxis deaths in adults.[7,66] Among drug-induced anaphylaxis, new elicitors have been identified; these include biologics containing alpha-gal (cetuximab), small molecules, or novel chemotherapeutics like olaparib.[67] Disinfectants like chlorhexidine,[68] or drug ingredients like polyethyleneglycol,[69] or recently methylcellulose[70] have been identified as novel substances inducing anaphylaxis.

Key points

- Anaphylaxis management and education should be personalized according to the patient's history.
- Anaphylaxis management can be divided into two steps:[108]
  - The first step is based on the primary role of intramuscular epinephrine (adrenaline), and provision of injectable epinephrine for self-injection, as part of a patient's self-management using an emergency protocol.
  - The second step includes additional interventions that start upon transfer to the care of healthcare professionals.

Elicitor groups other than the above mentioned are natural rubber latex, seminal fluid, radiocontrast media, medical dyes, and a variety of substances which are administered to patients in the perioperative setting (eg, suxamethonium, rocuronium, thiopental, propofol, opioids, protamine, chlorhexidine, plasma expanders).[71]

Taken together, a large variety of molecules can induce anaphylaxis. These are most frequently proteins, which induce anaphylaxis in an IgE-dependent manner or molecules, which directly activate mast cells via the G-protein receptor MRGPRX2 or complement.[72–74]

(Not anaphylaxis)		ANAPHYLAXIS		
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Symptom(s)/sign(s) from 1 organ system present	Symptom(s)/ sign(s) from ≥2 organ	Lower airway	Lower airway	Lower or upper airway
Cutaneous		Mild bronchospasm, eg, cough, wheezing, shortness of breath which responds to treatment	Severe bronchospasm eg, not responding or worsening in spite of treatment	Respiratory failure and/or
Urticaria and/or erythema-warmth and/ or pruritus, other than localized at the injection site		And/or	And/or	Cardiovascular
And/or		Gastrointestinal	Upper airway	Collapse/ hypotension
Tingling, or itching of the lips[a] or Angioedema (not laryngeal)*		Abdominal cramps* and/or vomiting/ diarrhea	Laryngeal edema with stridor	And/or
Or Upper respiratory		Other	Any symptom(s)/ sign(s) from grades 1 or 3 would be included	Loss of consciousness (vasovagal excluded)
Nasal symptoms (eg, sneezing, rhinorrhea, nasal pruritus, and/or nasal congestion)		Uterine cramps		Any symptom(s)/ sign(s) from grades 1, 3, or 4 would be included
And/or		Any symptom(s)/ sign(s) from grade 1 would be included		
Throat-clearing (itchy throat)[a]				
And/or				
Cough not related to bronchospasm				
Or Conjunctival				
Erythema, pruritus, or tearing				

(continued)

(Not anaphylaxis)		ANAPHYLAXIS		
Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Or Other				
Nausea				
Metallic taste				

Table 7. (Continued) WAO systemic allergic reaction grading system. *a. Application-site reactions would be considered local reactions. Oral mucosa symptoms, such as pruritus, after sublingual immunotherapy (SLIT) administration, or warmth and/or pruritus at a subcutaneous immunotherapy injection site would be considered a local reaction. Gastrointestinal tract reactions after SLIT or oral immunotherapy (OIT) would also be considered local reactions, unless they occur with other systemic manifestations. SLIT or OIT reactions associated with gastrointestinal tract and other systemic manifestations would be classified as SARs. SLIT local reactions would be classified according to the WAO grading system for SLIT local reactions. Adapted from Cox LS et al and Passlacqua G et al* [110,112]

The outcome and severity of an anaphylaxis reaction does not only depend on the elicitor itself and its dose, but also the presence of cofactors, which can impact the onset and severity of a given reaction. Such cofactors include a variety of endogenous and exogenous circumstances (Fig. 3).[25,75,76]

Importantly, mast cell disorders should also be ruled out even when a trigger is found, especially in the case of anaphylaxis after hymenoptera stings.[77]

Endogenous circumstances include underlying systemic mastocytosis, unstable bronchial asthma, or the hormonal status of a given individual (eg, pre-menstrual).[24,78] Exogenous factors, which may increase the risk of an anaphylaxis reaction, include physical exercise, infections, psychological burden, sleep deprivation, alcohol intake, and medications.[75,79–81] Among concomitant medication, beta-blockers and angiotensin converting enzyme (ACE) inhibitors have recently been identified to influence the outcome of a severe allergic reaction, although their effect is not fully established.[82,83] The role of cofactors is elicitor and age-dependent and their relative relevance varies (Table 5).[79] However, in a given patient these factors should always be considered in the history and if possible eliminated to reduce the risk for a severe reaction in the future.

ACUTE TREATMENT OF ANAPHYLAXIS

Early suspicion of anaphylaxis, either by patients or health-professionals, based on the development of symptoms suggestive of allergy usually affecting several organ systems more or less simultaneously, should prompt immediate management. Anaphylaxis is a medical emergency that requires rapid identification and treatment. In patients with a history of prior anaphylaxis,[1,2] acute management consists of two steps:

1. Self-management by the patient using an emergency protocol, in which it is important to emphasize the key role of intramuscular epinephrine (adrenaline)
2. Additional interventions given by healthcare professionals once medical help has arrived, which must include further epinephrine (adrenaline) if symptoms of anaphylaxis are ongoing

Fig. 5 Long-term management of anaphylaxis

- Identification of trigger(s)
  - Detailed history taking
  - Confirmatory *in vivo* and *in vitro* tests
  - Consultation with an allergist-immunologist or specialized health care professional
- Written action plan; have patient or care-giver "teach back" when to administer epinephrine (adrenaline) and emergency medications
- Availability of epinephrine (eg, as an auto-injector) for prompt administration as early as possible (ideally at discharge after anaphylaxis reaction)
- Management of risk factors for fatality: eg, poorly controlled asthma and cardiovascular diseases, risk taking behavior, nihilism over dangers of anaphylaxis
- Recommendation to always carry a mobile-phone, especially in cases such as of exercise-induced anaphylaxis
- Prevention of recurrence
  - Avoidance and/or allergen immunotherapy and/or desensitization
  - Medical identification alert: eg, bracelet or wallet card
  - Register in electronic or paper medical record the suspected trigger(s)
  - Anaphylaxis education and training
  - Public health measures eg, improved food labelling
- Follow up/reassess for veracity of original cause of anaphylaxis

Table 8. Key considerations for the longer-term management of anaphylaxis

Therefore, when a patient has anaphylaxis it is important to follow the steps outlined (Fig. 4): remove exposure to the trigger if possible (eg, discontinue administration of drugs/therapeutic agents), assess airways, breathing, circulation, mental status, and skin, and simultaneously call emergency services, injecting epinephrine (adrenaline) intramuscularly into the *vastus lateralis* of the quadriceps (antero-lateral thigh), and positioning the patient according to his/her presenting features. Most patients should be placed in a supine position during anaphylaxis unless there is respiratory distress in which case a sitting position may optimize respiratory effort; if pregnant, position the patient in a semi-recumbent position on the left side; if unconscious, place in the recovery position.[84] The benefit of elevation of the lower extremities (Trendelenburg position) is controversial.[85]

Despite intramuscular epinephrine (adrenaline) being the first-line drug recommended to treat anaphylaxis, its use remains suboptimal.[22,47] The dose recommended for use by healthcare professionals is 0.01 mg/kg of body weight, to a maximum total dose of 0.5 mg, given by the intramuscular route[1,2,29,86] and may be simplified as shown in Table 6. Dosing should be repeated every 5–15 min if symptoms are refractory to treatment. Epinephrine administered by the intramuscular route is generally well-tolerated.[87] This is in contrast to the intravenous route, where potentially fatal arrhythmias can occur as a result of bolus administration of epinephrine (adrenaline)[87,88] For this reason, the intravenous route is not recommended for the initial treatment of anaphylaxis, and if used, it should be administered in monitored patients by personnel with experience in diluting and administering the correct doses, and preferably given as an intravenous infusion via an infusion pump. A number of protocols exist for low-dose epinephrine infusions via a peripherally-sited cannula to treat reactions refractory to intramuscular epinephrine. One in particular, developed by Brown et al,[89,90] is widely used in Australia, New Zealand,[91] and Spain[92] as part of these countries' national anaphylaxis guidelines, and has an excellent safety and efficacy profile. In case of upper airway obstruction consider adding nebulized adrenaline.[91]

The management of anaphylaxis continues upon transfer to a healthcare setting (including in the ambulance) with: high flow oxygen (preferably 100% using a non-rebreather facemask) to all patients with respiratory distress and those receiving further doses of epinephrine; establish intravenous access using needles or catheters with a wide-bore cannula (14 or 16 gauge for adults); intravenous fluids to patients with cardiovascular instability (20 mL/kg bolus using crystalloids). Where indicated, perform cardiopulmonary resuscitation with continuous cardiac compressions.

In patients with anaphylaxis and symptoms of bronchoconstriction, inhaled short-acting beta-2 agonists can be given (eg, salbutamol/albuterol). Note, however, that bronchodilators given by inhalation or nebulization are not an alternative to the repeated administration of intramuscular epinephrine (adrenaline) in the presence of ongoing symptoms. In case of upper airway obstruction, consider nebulized epinephrine.[91] At frequent and regular intervals, evaluate the patient's blood pressure, heart rate and perfusion, and respiratory and mental status. If pertinent, consider invasive monitoring.

Second-line medications include beta2-adrenergic agonists, glucocorticoids, and antihistamines.[93] Local guidelines may indicate different drugs according to availability. The use of H1-antihistamines has a limited role in treatment of anaphylaxis,[94] but can be helpful in relieving cutaneous symptoms. Second generation antihistamines may overcome unwanted side effects such as sedation which may be counterproductive in anaphylaxis, but first generation H1-antihistamines are currently the only available for parenteral use (eg, chlorphenir-amine diphenhydramine, clemastine). Rapid intravenous administration of first-line antihistamines such as chlorphenamine can also cause hypotension.[95] Of note, antihistamines are now a third line treatment in some guidelines,[84] due to concern that their administration can delay more urgent measures such as repeated administration of intramuscular epinephrine.

Glucocorticosteroids are commonly used in anaphylaxis, with the objective of preventing protracted symptoms, in particular in patients with asthmatic symptoms, and also to prevent biphasic reactions (eg, intravenous hydrocortisone, or methylprednisolone). However, there is increasing evidence that glucocorticosteroids may be of no benefit in the acute management of anaphylaxis, and may even be harmful; their routine use is becoming controversial.[86,96–100]

Parenteral administration of glucagon may be used in patients with anaphylaxis with no optimal response to epinephrine (adrenaline), in particular, in patients taking beta-blockers, despite very limited evidence.[11,101]

Around half of biphasic reactions occur within the first 6–12 h following reaction.[102] Patients with anaphylaxis need to be observed: this is important especially in severe reactions and those requiring multiple doses of epinephrine.[86]

Fig. 4 outlines the steps considered essential for appropriate treatment of anaphylaxis, which is needed to be urgently applied in patients who present with this condition.[84,103]

Anaphylaxis education and management should be personalized according to the patient's clinical history and presentation, considering their age, concomitant diseases, concurrent medications, and triggers.[78,104]

For early self-management, it is important to educate the patient regarding the risk of anaphylaxis and self-treatment of any recurrence. Patients must be prescribed one or more epinephrine (adrenaline) auto-injectors (EAI),[2] although we recognize that auto-injectors are not available in many regions (see below). It is therefore necessary to explain to these patients why, when, and how to inject EAI or alternatives (such as marketed pre-filled epinephrine syringes or vials) where EAI are not available.[105] In addition, it is recommended that they always carry a personalized written anaphylaxis emergency action plan that illustrates how to recognize anaphylaxis symptoms (eg, tingling in the extremities, sense of heat, sense of dizziness/fainting, swollen lips-tongue-uvula, shortness of breath, wheeze, stridor, collapse) and instruct them to inject epinephrine rapidly, via the intramuscular route, in the mid-anterolateral thigh, holding the EAI in place for about 3–10 s and then to call for medical assistance.[106,107]

ANAPHYLAXIS SEVERITY GRADING

It can be difficult to grade the severity of anaphylaxis reactions. There is no overall consensus on which is the most appropriate system among the several that have been published; this is partly due to some being designed to grade reactions due to a specific trigger eg, anesthetic or venom-related anaphylaxis may rate vomiting as a more concerning symptom, in contrast to those used for food-related anaphylaxis. Further differences can be found according to the systems involved or the intensity of symptoms. A recent article has compared the performance of 23

different systems, highlighting the differences among these (although their validation is still lacking).[109] One of these, is the modification of the WAO grading system originally designed to classify systemic reactions due to allergen immunotherapy, but which has been adapted for use with systemic reactions of any cause (Table 7).[110] In this classification, only some grade 3 or grades 4–5 would be consistent with the definition of anaphylaxis, while grades 1–2 constitute non-anaphylaxis. Some additional symptoms, such as drooling or neurological symptoms, may be applicable in the pediatric setting.[111] The potential for the severity of reactions to change must be recognized.

DIAGNOSTIC TESTS IN ACUTE ANAPHYLAXIS

During acute anaphylaxis, serum tryptase levels are increased from 15 min to 3 h or even longer, after the onset; levels peak between 1 and 2 h after the onset with 36–40% remaining <11.4 μg/L.[113] Commercial assays measure mature β-tryptase released upon mast cell activation and α- and β-protryptase which is secreted constitutively (this reflects mast cell burden rather than anaphylaxis). Although elevated levels support a diagnosis of anaphylaxis, normal levels do not exclude anaphylaxis having occurred (eg, children with food induced anaphylaxis).[114] It is recommended to evaluate baseline serum tryptase at least 24 h after resolution of anaphylaxis symptoms, even when tryptase concentration during episode remains within normal range. In 2010 a consensus equation (peak MCT should be > 1.2x baseline tryptase + 2 ng/L) was proposed to diagnose acute mast cell activation.[115] Nevertheless, the consensus equation and the other methods of comparing baseline and peak serum tryptase are unable to detect all anaphylactic reactions.[116,117]

LONG-TERM MANAGEMENT OF ANAPHYLAXIS

Tailored individual anaphylaxis management plans should be a part of the longer-term care of patients who have experienced anaphylaxis, even once.[118] Where resources are limited, post-discharge management is severely compromised by lack of availability and affordability of EAI or consultation with allergy/immunology specialists.[119]

Implementing guideline recommendations in routine clinical practice is challenging.[120] The WAO Guidelines for the Assessment and Management of Anaphylaxis in health care and community settings is a widely disseminated and used resource (Fig. 5). They include information about prevention of recurrences, a global agenda for anaphylaxis research, and detailed colored illustrations linked to key concepts within the text.[1] The recommendations in the original WAO 2011 Anaphylaxis Guidelines remain clinically relevant and have been updated in 2012, 2013, and 2015[93,103,121] and were strengthened by the International Consensus (ICON) on Anaphylaxis in 2014.[119]

Key considerations in the longer-term management of anaphylaxis are presented in Table 8. At the time of discharge from a health care setting, patients, at risk of another episode of anaphylaxis, should be prescribed and taught about self-administration of epinephrine (adrenaline), and have a written personalized anaphylaxis emergency action plan and medical identification method.[2] One of the major concerns is the underuse of epinephrine self-infectors by patients who experience anaphylaxis recurrences, despite having the medication.[122]

Where EAIs are not available or affordable, physicians may recommend alternative formulations, such as a prefilled epinephrine syringe (or if this is not available, 1-mL syringe/needle and epinephrine ampoule with adequate training and written instructions for drawing up the correct dose).[1,105] It remains a concern that while most guidelines recommend a 500 μg (0.5 mg) dose in older children and adults >50 kg (2,86), 500 μg EAI devices are, in general, not available in most countries. Ultrasound studies (but not clinical trials) suggest that the needles in 300 μg (0.3 mg) EAI may be too short to deliver an intramuscular dose in many patients weighing more than 30 kg, while conversely, there is a risk of intraosseous injection when using "junior" EAI in young children weighing less than 15 kg.[123] A newly available 0.1 mg EAI has a lower dose and shorter needle which may be better suited to

children weighing 7.5–15 kg.[124] An EAI exists that provides audio and visual cues for patients.[125] Rapidly disintegrating epinephrine (adrenaline) sublingual tablets (RDSTs) are in development as an alternative to injection, but are yet to be approved for use.[126]

Guidelines recommend that patients with anaphylaxis be referred to an allergy/immunology specialist for confirmation of the suspected trigger, advice on prevention and, where indicated, consideration for allergen immunotherapy (eg, insect venom). Idiopathic anaphylaxis is a consideration if a carefully-performed history, examination for lesions of cutaneous mastocytosis (urticaria pigmentosa), skin tests, and measurement of allergen-specific IgE levels have not revealed the trigger.[127] An elevated baseline tryptase concentration may uncover systemic mastocytosis in some instances, but mast cell disease may be present even when these levels are not elevated.[103,128]

Vigilant avoidance prevents anaphylaxis recurrence from culprit allergens. However, it can be frustrating and associated with impaired quality of life, including bullying of food-allergic children, fear of anaphylaxis during airline travel, and anxiety over restrictions on exercise.[129,130] In medication-triggered anaphylaxis, avoidance of relevant medications, and use of safe substitutes are mandatory. If indicated, skin testing for penicillin allergy, or other drugs, and graded challenge to rule out immediate hypersensitivity or desensitization in the absence of alternative therapies, can be attempted.[1,103,121]

Guidelines from WAO, the American Academy of Allergy Asthma and Immunology (AAAAI)/ American College of Asthma Allergy and Immunology (ACAAI), and European Academy of Allergy and Clinical Immunology (EAACI) all address the recommendation of follow-up with a physician and if possible with an allergy/immunology specialist.[1,11,84] The WAO Guideline recommends annual follow-up for review of prevention of recurrence, EAI use, and optimizing control of relevant comorbidities such as asthma.[1,11,84] The WAO and EAACI Guidelines note the importance of follow-up with a dietician and a psychologist, if relevant.[84] Recently, the AAAAI/ACAAI have published an update of their Practice Parameter, specifically assessing some prevention strategies.[86]

GLOBAL AVAILABILITY OF EPINEPHRINE (ADRENALINE) AUTOINJECTORS (EAI)

Epinephrine (adrenaline) is recommended as an essential medication for the treatment of anaphylaxis by the World Health Organization (WHO).[131] Despite its pivotal role, the auto-injectable form is not readily available in the majority of countries.[132] It is limited to only 32% of all 195-world countries, mostly high-income countries.[133]

In some countries in which EAIs are not available through official distribution networks, they are available through distribution by special license arrangements, through distribution on a "named-patient" basis, or through the so-called "suitcase trade".[133] This latter, unofficial source is unreliable and undesirable.[133] Some patients and families can afford to order EAIs online or travel to purchase them while others cannot.[134,135] EAI costs have increased over time, which creates obvious problems for patients and families, particularly those on low incomes.[136] This is a major problem, and WAO strongly advocates for reasonable availability.

Five regional and international allergy academies: AAAAI, EAACI, WAO, Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI), and the Latin American Society of Allergy, Asthma, and Immunology (SLAAI) support initiatives to narrow these gaps.[133] A five-step action plan of advocacy was proposed:

(I) To gather accurate morbidity and mortality statistics on anaphylaxis.

(II) To confirm partnership: collaboration with national bodies and stakeholders in order to reach health and/or social security administrations.

(III) To strengthen awareness of anaphylaxis.

(IV) To include EAI into the WHO Model List of Essential Medicines[137]

(V) To provide worldwide data regarding the use of EAIs.

Unmet needs

Anaphylaxis has a significant impact on clinical practice and healthcare expenditures. We present here the key unmet needs based on previous data, updated with a preliminary analysis of data from a WAO Survey on Diagnosis and Management of Anaphylaxis, in which we collected information from representatives of 42 countries.

- A key issue is that anaphylaxis often remains poorly recognized, perhaps, in part, due to variability in diagnostic criteria. As a consequence, this can lead to delays in appropriate treatment, increasing the risk of severe outcomes. A further issue is the impact on the collection of reliable epidemiological data, since medical records form the basis of national and international registries.
- Severity scoring systems for anaphylaxis have been used to try and identify those at greatest risk of severe reactions and support their management. However, despite the efforts of allergy organizations to develop a standardized, internationally-accepted scoring system, there is still no consensus. Current controversies and disagreements between guidelines need to be addressed through further research.
- Although many countries have national guidelines, most follow international guidelines or positions papers. Recent efforts to achieve harmonization are underway.[72]
- Limited comparable epidemiological studies or research to increase understanding and to develop diagnostic and predictive tests remain key unmet needs. Data can differ widely depending on the number of variables.[4,5] The most widely discussed issues in the epidemiology of anaphylaxis over the last 10 years are: (I) regional variations in concepts and definitions, (II) whether prevalence or incidence is the best measure of the frequency of anaphylaxis in the general population, (III) whether the frequency of anaphylaxis is higher than previously thought, and (IV) whether current epidemiological trends in incidence are real or reflect different methodologies and definitions used.
- Epidemiology related to etiology and risk factors/co-factors for anaphylaxis are poorly characterized and may be influenced by regional/national differences in allergen exposure and genetics. In general, the most frequent triggers of anaphylaxis are drugs, food, and insect venom. The frequency varies with the age groups, but other specific triggers are described including antiseptic skin preparations, Anisakis, allergen immunotherapy, latex, and skin testing.[138–140]
- Large prospective population-based studies can support the understanding of the natural history of anaphylaxis. The implementation of the International Classification of Diseases (ICD)-11 may be a key instrument to achieve this aim.[141,142]
- Standardized diagnostic procedures should be tailored to specific triggers, combination of manifestations, and specific age groups. Although standardized diagnostic procedures have been published, validation of these for all allergens is lacking, and multicenter multinational studies are needed for this purpose.
- Serum (or plasma) tryptase measurements are recommended in the diagnostic evaluation of anaphylaxis, especially to confirm unclear reactions and to study a potential underlying mast cell disorder. However, the availability of tryptase is limited to less than 3% of all countries participating in the survey.
- The diagnosis of allergen sensitization is made using skin tests (foods, aeroallergens, venom, drugs), serum allergen-specific IgE (foods, aeroallergens, venom, and some drugs), and provocation tests (foods, drugs). Other complementary tests such as basophil activation test (BAT) and cellular allergen stimulation test (CAST) are not available in many countries.
- Further elucidation of underlying mechanisms of anaphylaxis is required in order to better characterize anaphylaxis phenotypes and endotypes, and decrease the number of cases labeled as idiopathic anaphylaxis.
- While appropriate medications are available to treat anaphylaxis in all countries, epinephrine autoinjectors are not. In the mentioned survey, 60% of the participant countries declared having EAIs; however, EAIs are available in only 32% of world countries, absent mainly in low and middle-income countries.[133] In some countries,

EAI are only available by importation and with high costs.

- Though there is no absolute contraindication to intramuscular epinephrine for the treatment of anaphylaxis, antihistamines and corticosteroids remain the most frequently drugs used to treat anaphylaxis.
- There is still a lack of consensus regarding how long a patient with anaphylaxis should be observed in a healthcare setting.
- Most cases of anaphylaxis are first seen by emergency doctors or general practitioners, but only 50% are referred to a specialist for further investigation and/or treatment. Provision of advice relating to trigger avoidance and emergency protocols, at the time of discharge from the emergency room, are practically nonexistent, according to the international survey. This highlights the need of optimizing care pathways for patients at risk of anaphylaxis, including patient/caregiver education and training. More education must be provided through medical schools and residency and postgraduate training programs that include recognition of anaphylaxis and its management, as well as increased funding for the postgraduate education of specialists.
- National policies regarding the availability of EAIs in public settings (at schools, public transports, parks, etc) are limited to a few countries (16%).
- As we have limited knowledge about the natural history of anaphylaxis, it is not clear whether lifelong avoidance from the allergens is mandatory. Anaphylaxis research is poorly supported by private and national programs.
- In general, implementation of strategies and healthcare policies follow country-based priorities, but there is a clear need for establishing multinational, large databases/registries. These would enable observations to be collected and compared, which would in turn facilitate epidemiologic, risk factor, and research analyses in order to support consistent high quality management of patients with anaphylaxis.

Abbreviations

ACE: Angiotensin converting enzyme; BAT: basophil activation test; CAST: cellular allergen stimulation test; EAI: epinephrine auto-injectors; IgE: immunoglobulin E; IgG: immunoglobulin G; FcεRI: IgE high-affinity receptor; MRGPRX2: Mas-related G-protein coupled receptor member X2; NSAIDs: nonsteroidal anti-inflammatory drugs

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All authors approved and agreed to publish the manuscript.

Author contributions

VC coordinated the development of the guidance. All the authors, members of the Anaphylaxis Committee of the World Allergy Organization, contributed to writing and approved the manuscript.

Ethics statement

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