REVIEW

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Darío Antolín-Amérigo, Carmen Vidal-Albareda, David González de Olano, Belén de la Hoz-Caballer

Current update on anaphylaxis: anaphylaxis management in recent guidelines

Allergy Service, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain

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Corresponding author
Darío Antolín-Amérigo
Allergy Service
Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS)
Carretera de Colmenar, Km 9,100
28034 Madrid, Spain
ORCID: 0000-0001-5699-4022
E-mail: dario.antolin2@gmail.com

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Summary

Anaphylaxis is a potentially fatal hypersensitivity reaction but frequently underrecognized. Although its incidence rates vary according to geographical location, it seems clear that there has been a general increase in recent years, either because of greater recognition of this entity or because it is progressing proportionally to the presence of allergic diseases in the world. The development of anaphylaxis management guidelines adapted to local or regional needs seems of utmost importance. Furthermore, it is necessary to assess their implementation and their positive effect regarding diagnosing and treating anaphylaxis. In this review we explore the currently existing definitions of anaphylaxis and its epidemiology, the potential triggers of anaphylaxis and guideline recommendations in terms of diagnosis and management, proposing a novel anaphylaxis calculator and reviewing the current scoring methods for anaphylactic episodes.

Impact statement

Currently existing definitions, scoring methods, potential triggers of anaphylaxis and its epidemiology, and guideline recommendations are reviewed, proposing a novel anaphylaxis calculator.

Introduction

The awareness of anaphylaxis as a life-threatening medical condition and its incidence have been increasing among different specialties, and so is the growth of evidence in the field. The reported increases probably reflect a true increase in the prevalence of allergic disease, but they are also confounded by the cumulative incidence of anaphylaxis, better awareness and recognition of anaphylaxis, and due to changes in anaphylaxis coding.

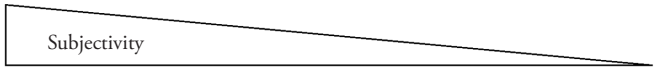
Anaphylaxis is recognized as a severe, life-threatening systemic hypersensitivity reaction, characterized by rapid onset and the potential to endanger life through respiratory or circulatory compromise.

In our article we aimed to cover not only what it is included in the scientific Societies guidelines, but also other means of scoring the severity of the anaphylactic episodes which is in our view not sufficiently gathered in the literature.

Definitions

Anaphylaxis is an underrecognized acute syndrome comprising a life-threatening generalized or systemic hypersensitivity reaction characterized by a severe acute onset of symptoms, involv-

Figure 1 *- Severity scoring.*



Small expert groups	Expert consensus (*e.g.* Delphi)	Data-informed	Data-driven
Most existing scoring systems were developed by a limited number of experts, and fit into this category	Dribin *et al.*	This approach uses data to inform otherwise subjective decisions by experts as to what symptoms constitute what level of severity	This approach uses raw symptom data and mathematical modelling to derive a score independent of expert input (*e.g.* nFASS score)

**Modified from Shaker et al. (72); subjectivity of studies regarding scoring anaphylaxis.*

ing different organ systems, generally involving airway, breathing or circulatory problems and is usually, although not always, associated with skin and mucosal changes, requiring immediate medical intervention (**figure 1**) (1-4).

The mechanism of anaphylaxis may be either: 1) immunologic, involving Immunoglubulin E (IgE), IgG or immune complexes; or 2) non-immunological (5).

The presenting symptoms can be very varied. However, in over 90% of cases, there are associated skin and mucosal changes. Furthermore, it usually (> 50% of cases) involves the airway (pharyngeal or laryngeal oedema) and/or breathing (bronchospasm with tachypnoea) and/or circulation (hypotension and/or tachycardia).

Epidemiology

None of the actual Academy guidelines, namely, EAACI, WAO, AAAAI, NICE, or the Australian Society of Allergology and Clinical Immunology, has a major focus in this area, but all include important information about epidemiology, supported by relevant references. Therefore, focusing on anaphylaxis remains as an unmet need, in terms of trustable data. The potential challenges could be the diverse and sometimes overlapping nomenclature and criteria for diagnosis of anaphylaxis. Hitherto, prevalence estimates of anaphylaxis vary widely, and many studies, particularly in developed countries, suggest that the prevalence is increasing.

There are differences in prevalence and causes throughout the world probably due to distinct environmental factors which might act differently to affect risk of different types of allergies according to genetic predisposition in diverse areas of the globe and that would account for the rise in the prevalence more rapidly than expected (**table I**) (1-13).

Data from the European anaphylaxis registry revealed that over one-quarter of cases (25%) occurred in patients under 18 years of age (14).

Although the fatality rate attributable to anaphylaxis remains low (15), the frequency of hospitalization for food and drug-induced anaphylaxis has been increasing in recent years (7, 16, 17).

The main causes of fatal anaphylaxis are drugs (29%-58.5%), insect stings (3.3%-54%) and food (2%-6.7%) (**table II**) (9, 18-25).

An important aspect are biphasic anaphylactic reactions which account for up to 20% but other studies report a prevalence from 1% to 7% among patients with anaphylaxis (26, 27). Existing anaphylaxis guidelines therefore recommend continuous follow-up for several hours after resolution of the initial reaction after administering intramuscular injection of adrenaline as first-line anaphylaxis treatment and glucocorticoids, histamine-1 receptor blockers, and beta-2-adrenergic receptor stimulants as second-line treatments (27). In a meta-analysis of retrospective-observational studies performed in Japan of the 31,570 eligible patients, 28,145 (89.2%) were treated with glucocorticoids on the day of admission. The overall percentage of biphasic reactions within 7 days of admission was 11.2%, and the authors stated that there were no significant differences in rates of biphasic reactions (10.7% in the glucocorticoids group *vs* 10.5% in the control group; odds ratio 1.03; 95% confidence interval 0.85-1.24; p = 0.77) between patients with anaphylaxis

Table I *- Worldwide incidence, prevalence and mortality of anaphylaxis.*

	European (globally)	**U.K.**	**U.S.A.**	**WAO**	**Children**	**AAAAI/ ACAAI**	**Spain**
Incidence	1.5-7.9/100,000 person-years	1-7 cases/100,000 person-years		50-112/100,000 persons-years	1-761/100,000 person-years	42/100,000 persons-years	
Prevalence	0.3%		1.6%	0.3-5.1%		1.6-5.1%	
Mortality		0.47-0.69 per 10^6 persons-years	63-99 deaths/ year (> 75% in hospitalized patients)	Drugs: 0.005-0.51 per 10^6 persons-years Food: 0.09-0.13			0.002-2.51 deaths/10^6 persons-years

Table II *- Principal triggers of anaphylaxis*.*

Trigger	Frequency in Spain	Frequency in Europe	Frequency in USA	Frequency Worldwide
Drugs/medication	46.7-62% NSAIDs, beta-lactams, iodinated contrast media	Beta-lactams and NSAIDNSAID	29%-58.5% Antibiotics, NSAIDs, immunomodulators, and biological agents	Geographical variations
Foods	22.6-24.1% Adults: fruits, nuts, shellfish and fish Children: egg, milk, nuts, fish and shellfish	Central: peanut, tree nuts, seeds like sesame, wheat, and shellfish Southern: LTP Children: peanut, hazelnut, milk, and egg Adults: wheat, celery, and shellfish; fruits such as peaches are also typical causes of food-induced anaphylaxis in adults in some European countries such as Spain and Italy	2%-6.7% Peanut and tree nuts are dominating elicitors of food-induced anaphylaxis in adults in North America and Australia	Vary locally. Food-induced anaphylaxis in children toto hen's egg (in infants and pre-school children), cow's milk, wheat, and peanut. Adults: nuts (U.S.A.), shellfish (Asia), buckwheat (Korea)
Insect stings	8.6-13.9%	Wasp: Central Europe	3.3%-54%	Bee: South Korea Wasp: Central Europe Snake Antivenom: Australia
Physical factors	3.4-4%			
Others (including latex)	7.26%			
Idiopathic	3.4-5%			6.5-35%

There are regional differences in terms of culprit agents related to anaphylaxis; modified from Tanno *et al.* (3) and Gold *et al.* (49).

treated with and without glucocorticoids on the day of admission and the authors concluded that they would not support the use of glucocorticoids to prevent biphasic reactions in hospitalized patients with severe anaphylaxis requiring adrenaline.

Therefore, the prevalence of the various causes of anaphylaxis is age-dependent and varies between different geographical areas (**tables I** and **II**). In general, food, drugs, and Hymenoptera venom are the most frequent elicitor groups worldwide (10, 24-41).

Drug-induced anaphylaxis is typically caused by antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) with age and geographical variations (42-44). In terms of quality standards, NICE guidelines are a unique document as it proposes some criteria which are expected to contribute to improvements in the following outcomes (45):

- Incidence of anaphylactic episodes.
- Admission rate due to anaphylactic episodes.
- Mortality from anaphylactic episodes.

NICE quality standards are centered on aspects of health and social care that are commissioned locally and comprise a brief set of prioritized statements designed to drive measurable improvements in the 3 dimensions of quality – safety, experience and effectiveness of care, in terms of anaphylaxis (2, 45-49).

Key triggers include food, drugs, and stinging insects; in up to 20%, the elicitor is not identified. Their relative importance varies with age and geography studied. For ED (Emergency Department) presentations, drugs and foods are the most common elicitors of anaphylaxis, with age-related differences (6, 50).

Foods are the most frequent cause of anaphylaxis in children, with pollen allergy and asthma being important risk factors (4, 6).

Drug- and Hymenoptera venom-triggered anaphylaxis are more common in adults than in children (6) in general, and specifically to plant foods and NSAID. Drugs are the most frequent cause of anaphylaxis in hospitalized patients.

Compared to males, adult females have a higher frequency of anaphylaxis.

Cumulative incidence of anaphylaxis ranges from 26.5% to 54%, with a follow-up time of 1.5 years to 25 years (9). In general terms, long-term management, and several structured

actions could achieve the desired prevention of recurrence [(extracted from references 8 and 34):

- Avoidance and/or allergen immunotherapy and/or desensitization.
- Medical identification alert: *e.g.*, bracelet or wallet card.
- Register in electronic or paper medical record the suspected trigger(s).
- Anaphylaxis education and training.
- Public health measures, *e.g.*, improved food labelling.

Methods

As this is a narrative review, evidence has been retrieved from different sources. A literature search was performed using keywords agreed on by the authors. The search was performed using electronic databases (MEDLINE and PubMed), electronic libraries (Clinical Key, Science Direct, OVID), resources of clinical guidelines (UpToDate, Allergy Societies Society Guidelines, and Dynamed: https://www.dynamed.com/condition/anaphylaxis), and a database of systematic reviews (Cochrane Library). Publications were selected from between January 2015 and December 2022. The selection took into account the keywords: "anaphylaxis" and "guideline". Due to the revolution in terms of vaccines and adverse effects, we have also used the Brighton Collaboration Guideline for scoring anaphylaxis, which is currently used worldwide for drug/vaccination regulatory issues (available at: https://brightoncollaboration.us/anaphylaxis-case-definition-companion-guide/).

In addition, the filters used in PubMed were as follows: guideline, consensus development conference and consensus development conference (NIH), practice guidelines, review, systematic review, and meta-analysis. Guidelines, consensus reports, systematic reviews, and meta-analysis were included; nonsystematic reviews, comments, and other types of articles were excluded. We also included studies examining incidence, prevalence, natural history, clinical manifestations, pathogenesis, diagnosis, and treatment. All articles were reviewed by the authors. Following this review process, 89 publications were finally selected.

Diagnosis management − scoring systems: beyond the guidelines?

Anaphylaxis, as mentioned above, is known as a life-threatening generalized or systemic hypersensitivity reaction involving different organ systems (1, 3, 34, 51).

There is a list of criteria that detail the symptoms or combination of symptoms which meet the clinical characteristics of anaphylaxis. Traditionally, anaphylaxis was labeled when any of the 3 proposed criteria were met (**table IIIA**) (52), although recently the World Allergy Organization (WAO) has proposed a new set of criteria (34, 52–55).

There are 2 recently proposed criteria for diagnosing anaphylaxis:

1. EAACI guidelines 2021 (**table IIIA**).
2. WAO guidelines 2020 (**table IIIB**).

The first one, probably is more specific, including the concept of likely and/or known allergen in its criteria and the WAO guidelines specify the possibility of the absence of typical skin involvement in the symptoms - WAO guidelines 2020 (**table IIIB**).

Classification of severity of anaphylactic episodes

Classification of severity implies a challenge, given that there are not homogeneous definitions of subtypes of anaphylaxis (4). In fact, there are different classifications that attempt to classify anaphylaxis according to its severity (34, 52, 55-59). They are divided into grades, ranging from I to V, based on the degree of vital compromise. Not all of them cover the full range of symptoms that patients may present, and some of them were created specifically for a particular trigger, such as Hymenoptera venom (56) or food (58). This has led to the recent proposal of a classification that attempts to unify the previous ones (59-61) or to the creation of a new way of classifying anaphylaxis proposed by the WAO (34) but none of them have been widely used up to now. Given the trend on immunization, the Brighton Collaboration (BC) was established in 2000 with the aim of developing globally accepted standardized case definitions for adverse events following immunization (AEFI) as well as guidelines for the collection, analysis and presentation of surveillance data (61). It has served to improve the classification of the severity of an anaphylactic episode following immunization. The Brighton Collaboration Cased Definitions (BCCD), which are evidence based, were developed by a group of experts to describe, in simple terms, all signs and symptoms used to constitute the BCCD on anaphylaxis (62). The descriptive terms used in the case definitions could be used as a guide to develop educational and recording material (63). The checklist could be used when sudden or unexpected symptoms or signs occur post-vaccination, and where anaphylaxis is a possibility. In contrast, checklist 2 collects additional details such as demographic information as well as vaccine data. Such checklists are more comprehensive and are better suited to clinical trials or to the analysis of AEFI data at a regional or national level. For example, more extensive checklists could be used as part of an investigation of individual cases. If correctly completed, such checklists will aid in the assignment of a BCCD for anaphylaxis (63, 64).

Once the symptoms and signs that may indicate anaphylaxis have been reported on an AEFI report form and/or through the use of a checklist, a case definition for anaphylaxis can be assigned. It is intended that the task of assigning a case definition is performed at a regional or national level because of the complexity of the case definition. In addition, online tools are being developed by the BC to facilitate this process and these

Table III - (A) *Clinical criteria for diagnosing anaphylaxis (EAACI guidelines 2021) (4);* ***(B)*** *WAO anaphylaxis guidelines 2020 (36).*

A	B
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (*e.g.*, generalized hives, pruritus or flushing, swollen lips-tongue- uvula and at least one of the following: **a**. respiratory compromise (*e.g.*, dyspnea, wheeze-bronchospasm, stridor, reduced PEF and hypoxemia); **b**. reduced BP or associated symptoms of end-organ dysfunction (*e.g.*, hypotonia [collapse], syncope, incontinence).	1. Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (*e.g.*, generalized hives, pruritus or flushing, swollen lips–tongue-uvula) and at least one of the following: **a**. respiratory compromise (*e.g.*, dyspnea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia); **b**. reduced BP or associated symptoms of end-organ dysfunction (*e.g.,* hypotonia (collapse), syncope, incontinence); **c**. severe gastrointestinal symptoms (*e.g.*, severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens.
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): **a**. involvement of the skin–mucosal tissue (*e.g.,* generalized hives, itch-flush, swollen lips-tongue-uvula; **b**. respiratory compromise (*e.g.,* dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia); **c**. reduced BP or associated symptoms (*e.g.,* hypotonia [collapse], syncope, incontinence); **d**. persistent gastrointestinal symptoms (*e.g.,* crampy abdominal pain, vomiting).	2. Acute onset of hypotension or bronchospasm or laryngeal involvement after exposure to a known or highly probable allergen for that patient (minutes to several hours), even in the absence of typical skin involvement.
3. Reduced BP after exposure to known allergens for that patient (minutes to several hours): **a**. infants and children: low systolic BP (age specific) or > 30% decrease in systolic BP*; **b**. adult: systolic BP of < 90 mmHg or > 30% decrease from that person's baseline PEF, peak expiratory flow; BP, blood pressure. *Low systolic blood pressure for children is defined as < 70 mmHg: - from 1 month to 1 year, less than (70 mmHg + [2 × age]) - from 1 to 10 years and < 90 mmHg from 11 to 17 years.	

(A) Anaphylaxis is highly likely when any one of the three criteria is fulfilled; **(B)** Anaphylaxis is highly likely when any one of the two criteria is fulfilled.

will be freely accessed at the Brighton Collaboration website: http://www.brightoncollaboration.org/internet/en/index.html.
A potential limitation to collecting exhaustive adverse event reports is that health care providers are unlikely to spontaneously report enough symptoms and signs to allow application of BCCD. A checklist, based on the terms used in the case definition, could be developed and incorporated in an AEFI reporting form to remind vaccine providers to note whether specific features of anaphylaxis were present. Another limitation of the anaphylaxis case definition is the hypothetical inconsistencies in the reporter's use of the terms used to describe possible anaphylaxis. This would be addressed by the development of a glossary to describe those terms used in the anaphylaxis case definition. With these barriers in mind, Stafford *et al*. have created a clinical checklist for the application of the BCCD and a glossary of terms to harmonize the use of reporting terms (65).
As Stafford *et al*. stated recently, having a standardized, internationally agreed on quantitative measure of severity might be useful in facilitating risk communication, both with patients and with industry/regulators. Consistency and translatability in recording results are essential and currently constitute unmet needs in the field of anaphylaxis. However, any severity score must be fit for purpose, be informed by patient and clinician experience, and ideally be data driven to minimize the impact of subjectivity and provide objective validation (**figure 1** modified from Dribin *et al.*) (66).
In the meantime, the severity score proposed by Dribin *et al*. highlights the inconsistencies and limitations of the NIAID criteria for anaphylaxis (66).
Developing our acquaintance of the relationship between the definition of anaphylaxis (and indications for epinephrine treatment) and severity grading of symptoms is essential for further progress in this area. We need to achieve a global consensus on updated anaphylaxis criteria to improve anaphylaxis recognition and thus patient care − it is what patients deserve.

Calculator of anaphylaxis

For the diagnosis of anaphylaxis in an acute context, the 2020 EAACI Task Force on anaphylaxis, has suggested using clinical criteria, including rapid onset of multiple symptoms, measuring serum tryptase half to two hours after the start of the reaction, and baseline tryptase at least 24 hours after complete resolution of symptoms, to support diagnosing anaphylaxis retrospectively. A number of studies have assessed the diagnostic accuracy of

serum tryptase measurements for anaphylaxis, but the evidence is of very low certainty, derived from consecutive case series or case control studies (55, 67, 68).

In terms of practical management, taking the blood sample should not delay treating a patient with adrenaline where necessary. A sample taken later than 2 hours after the reaction may still demonstrate a raised tryptase level.

An event-related transient elevation of the serum tryptase level by at least 20% over the individual baseline plus 2 ng/mL absolute (20%+2) within a 2-4 h window after reaction supports a diagnosis of anaphylaxis (*tryptase peak rising level ≥ (20% × baseline tryptase) + 2 µg/L*) (69, 70).

It is interesting to note that a recent study quantified the actual benefit of measuring tryptase in Emergency Department patients with anaphylaxis, which found that around 2% of the patient cohort who did not meet diagnostic criteria for anaphylaxis would have elevated levels of serum-tryptase, higher than the normal ranges of the local laboratory (> 12 µg/L) (57).

A raised serum tryptase level can be associated with a mast cell disorder or hereditary alpha tryptasemia (71-73), so it is important to compare with a baseline level at least 24 hours after complete resolution of a reaction. Moreover, serum tryptase is not always elevated in anaphylaxis, especially in children and with food triggers in all ages (74).

Apart from tryptase, a number of other MC-derived compounds may serve as suitable parameters to document severe reactions following systemic MC activation. These substances include, among others, histamine and its metabolites, PGD2 and its metabolites, and heparin (75-77).

However, except for heparin, these mediators are less specific for MC compared to tryptase. Methods to determine these mediators are also much less available through widely distributed commercial assays and, moreover, none of these laboratory exams are validated for the diagnosis of anaphylaxis, so far (69).

Management

The evidence base for the acute management of anaphylaxis is weak and is established mainly by means of systematic reviews, due to the absence of randomized controlled trials. However, there seems to be a global consensus that intramuscular (IM) adrenaline is the treatment of choice as the first step in the management of acute anaphylaxis (19, 34, 78).

All in all, there is room for improvement in its management which shall be systematic (79).

Some of the unmet needs with regard to anaphylaxis are acute management and with regards prophylactic measures (3).

There are several factors influencing the successful treatment of an anaphylactic reaction such as specific training in anaphylaxis management along with rapid identification and treatment, which are critical (52, 79).

The basic principles for the treatment of anaphylaxis are common for all age groups, but it may be influenced by the context/setting, personnel, equipment and by the available medication (79, 80).

The necessary materials and medications to treat an anaphylactic episode are (5, 6):

1. Stethoscope, pulse-oxymeter and tensiometer (including equipment for blood pressure and cardiac continuous monitoring), watch or clock.
2. Tourniquets, syringes (with needles:1 mL, 10 mL, 20 mL) and needles IV (gauge 19, 21, 23 and 25) and IM, and catheter (gauges 14, 16, 18, 20 and 22).
3. Aqueous Adrenaline (1 mg/ml or 1/1,000) 0.01 mg/kg to a maximum of 0.5 mg (adult) and 0.3 mg (child).
4. Equipment to deliver oxygen (oxygen tank, valve with flow-meter, and extension tubing).
5. Equipment to deliver IV fluids.
6. Intubation material: ambu bag/valve/mask, self-inflating with reservoir (volume 700-1,000 mL (adult), 100-700 (child) and disposable face masks; oropharyngeal airways: 6 cm, 7 cm, 8 cm, 9 cm, 10 cm; pocket masks and nasal cannula, laryngeal mask airways.
7. Antihistamines IV (chlorpheniramine 10 mg (adult), 2.5-5 mg (child) or diphenhydramine 25-50 mg (adult) (1 mg/kg, maximum 50 mg (child)).
8. Corticosteroids IV (hydrocortisone 200 mg (adult), maximum 100 mg child or methylprednisolone 50-100 mg (adult) 1 mg/kg, maximum 50 mg (child).
9. Vasopressors IV (dopamine, noradrenaline…).
10. Glucagon.
11. Defibrillator.
12. Inhaled Beta-Adrenergics: salbutamol solution 2.5 mg/3 mL or 5 mg/3mL (adult) (2.5 mg/3 mL, child) given by nebulizer and face mask.
13. Other supplies: extension tubing, T connectors, 3-way stopcocks, armboards, written emergency protocol for anaphylaxis treatment, flow chart for recording times and events, gloves.

The emergency treatment of a patient who is suffering an anaphylactic reaction may differ if it occurs outside of a healthcare institution or inside a hospital/ambulatory center. Both the available resources and the accessibility to a hospital/ambulatory center may influence the first approach.

Management outside of a healthcare institution

The first step, regardless of the context and the severity of the anaphylactic reaction, would be the use of adrenaline autoinjector and subsequently an immediate phone calling for emergency support (**table IV**). Any healthcare professional shall be capable of initiating the treatment of a patient who is suffering from an anaphylactic reaction and calling for emergency support.

Table IV - *Indications for prescribing adrenaline autoinjectors, regardless of the context and the severity of the anaphylactic reaction.*

A	B	
Previous (severe or near fatal)* anaphylaxis triggered by foods, medication, aeroallergens, exercise- induced, latex or idiopathic	Arguments for 2 autoinjectors	Arguments for 1 autoinjector
Coexistent unstable or moderate-severe/severe asthma and food allergy*	European Medicines Agency recommends 2 autoinjectors	Only needing to carry one device may improve adherence
Venom allergy in untreated patients and risk of re-exposure	About 10% patients required a 2nd dose of adrenaline due to insufficient response to the 1st dose	Most autoinjectors are not used and have to be replaced after 12-18 months
Underlying systemic mastocytosis in adults with any previous systemic reaction. Children with very severe skin involvement (>50% body surface) and increased basal serum tryptase levels (>20 ng/ml) and with blistering in the first three years of life*	Rarely, injection in the wrong place	Most patients respond to 1 dose and 2nd doses are usually administered by emergency services
Previous mild-moderate reactions to food	Likelihood of delayed medical assistance (remote location or travel)	
Remote from medical help or repeated travel abroad with mild moderate reactions to food, medication, insect, latex or idiopathic*		
Cardiovascular disease		
Oral immunotherapy for food allergy		
Previous requirement of more than 1 adrenaline dose before arriving a healthcare institution*		
If available adrenaline dose is too low for body weight*		

(A) *At least 1 adrenaline autoinjector. Notwithstanding, consider prescribing 2 adrenaline autoinjectors; Modified from (4); **(B)** reasons for prescribing one or two adrenaline autoinjectors (modified from references 4, 6, 79, 87).

Rescue volunteers, paramedics, lifeguards, and nurses shall be trained, updated, and sufficiently skilled to cope with an anaphylactic reaction (81, 82).

Equipment and available medication (in a healthcare institution)

Every healthcare institution shall have a crash cart containing all the necessary equipment and medication to make a complete cardiorespiratory resuscitation and to treat a potential anaphylactic reaction (see paragraph Management). Every health care professional shall be familiar with the equipment and every medication shall be reviewed periodically. Whenever a patient begins to suffer an anaphylactic reaction, it has to be monitored as soon as possible (79).

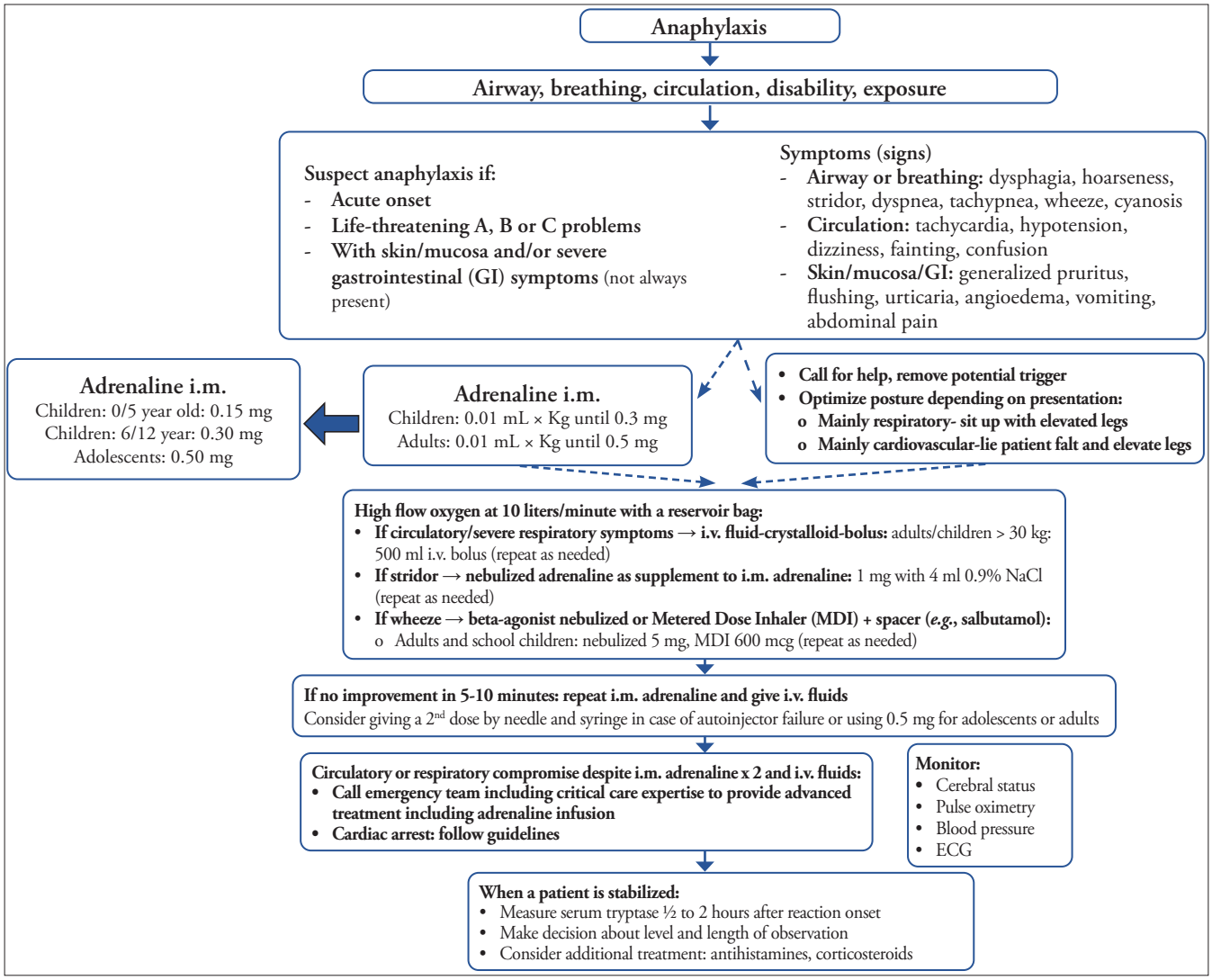
Minimal approach requirements for a potential anaphylactic episode

1. Stratifying patient's severity (**figure 2**).
2. Early emergency support request.
3. Initial treatment based on ABCDE approach.
4. Adrenaline (when indicated).
5. Preferential study and follow-up by an allergist: essential.

Patient position (extensible for inside and outside a healthcare institution)

Whenever a patient is being treated or has suffered from an anaphylactic episode, it should be placed in a comfortable position, laid down and with raised legs to gain venous return. This position shall be avoided when vomiting or any kind of respiratory failure. Postural changes shall be made with caution as they may cause the worsening of a hemodynamic compromise. Unconscious patients shall be placed in a lateral position. Pregnant women shall be placed in the left lateral position to avoid cava vein compression (83). Airways permeability shall be warranted at all times (79). In case of respiratory failure, semi-recumbent position can be considered. Anyhow, the UK Resuscitation Council 2021 Guidelines comprise further details on patient positioning in anaphylaxis (71).

Figure 2 *- Treatment scheme of an anaphylactic episode.*



*Modified from references 4, 79, 84. *Adrenaline preferably shall be adjusted by weight.*

In patients with a history of prior anaphylaxis, acute management consists of two steps:

1. Self-management of the patient using an emergency protocol, in which it is important to emphasize the key role of intramuscular adrenaline, encouraging the possibility of self-administration of adrenaline using auto-injector devices, no matter the severity of the anaphylactic reaction (**table IV**).
2. Additional interventions given by healthcare professionals once medical help has arrived, which must include further adrenaline if symptoms of anaphylaxis ongoing.

It is of note that the most effective and evidence-based treatment for anaphylaxis is adrenaline, based on observational studies, extrapolation from retrospective case reports, and scarce clinical trials (3, 32).

Airway protection

As patients with anaphylaxis can rapidly develop critical airway compromise, it is crucial to protect the airway while other treatments are administered (27).

Intubation should be considered early, as patients can decompensate rapidly, which can make endotracheal intubation more difficult or impossible and necessitate the placement of a surgical airway. If the patient shows intense laryngeal edema, non-invasive positive pressure ventilation or supraglottic airways

should be used with caution, as they may not be effective. Endotracheal intubation with direct or video laryngoscopy should be attempted first by an experienced clinician if the oral edema is judged to be navigable.
Supplemental oxygen should be administered to maintain oxygen saturation > 90% (27).

Medication
Delayed epinephrine administration is associated with biphasic reactions (78). It is a matter of debate whether glucocorticoids would prevent biphasic reactions in patients with anaphylaxis as they inhibit inflammatory responses by suppressing the function of mast cells (78). Recent retrospective cohort studies have failed to show any preventive effects of glucocorticoids on biphasic reactions.
Moreover, antihistamines have no role in the primary management of life-threatening signs and symptoms of anaphylaxis, including upper airway edema and shock. The rationale for their use arises from the effectiveness in other allergic diseases, but there are no specific data that suggest benefit in anaphylaxis (80).

Healthcare institution discharge after anaphylaxis
If the diagnosis of anaphylaxis (or suspicion) has been reached, patients shall remain for 6-8 hours after complete resolution of symptoms and up to 12-24 hours whenever a patient shows refractory symptoms, or in the event of very severe reactions or having a history of biphasic reactions. Other patients, who would also need to stay longer, would be the following: 1) patients with difficult access to a healthcare institution, 2) severe idiopathic anaphylaxis with slow progression; 3) severe asthma or severe respiratory symptoms; 4) reactions in which the allergen could be present if the patient is discharged; 5) severe condition of the patient (cardiocirculatory compromise) (79).
It is mandatory to have a complete medical record indicating all received medications and the evolution of the patient.
Recommendations after healthcare institution discharge because of anaphylaxis:
- Emergency department visit: if symptoms reappear.
- Antihistamines, corticosteroids, and prescription of adrenaline autoinjector(s) (independently of the severity of the anaphylactic reaction) (**table IV**).
- Avoidance of potential culprit agents (foods, medications, insects, *etc*.).
- Continued follow-up plan for general practitioners.
- Personalized plans, including referral to psychological support and patients' organizations (4).
- Allergen immunotherapy and desensitization: allergen immunotherapy (AIT) is potentially a curative therapy. AIT may increase the amount of food that the patient can tolerate, preventing allergic symptoms and reducing the risk of potentially life-threatening allergic reactions (77).

Venom immunotherapy (VIT) is the model of immunotherapy with regards the studies, its efficacy and the knowledge of the physiologic modifications of induction of immune tolerance produced (78). Moreover, it has been shown to improve the quality of life of venom-allergic patients when compared with patients who do not receive immunotherapy but carry adrenaline (79).
Food Allergy-OIT is recommended for persistent Cow's Milk, Hen Egg, or peanut allergy for children from around 4 to 5 years of age on the basis of its ability to increase the threshold for clinical reactions while on OIT (Grade A). At present, there are insufficient data to be able to recommend AIT for other foods and for adults outside clinical trials (77).

Personalized plans
Every patient should receive a written record with instructions such as: avoidance measures and when and how to use the adrenaline autoinjector (**table IV**). All patients shall be referred to an Allergy Department to investigate the potential culprit agent and to minimize present and future risks. New guidelines point out the importance of prescribing personalized plans to achieve the best approach in terms of continued follow-up of patients who have suffered an anaphylactic reaction (4, 6, 52, 79, 85-87).

Education and training for health care professionals (HCP) and patients at risk of anaphylaxis
The EAACI Task Force on anaphylaxis, along with other guidelines, recommends providing structured, comprehensive training to improve the knowledge and use of adrenaline autoinjectors in people at risk of anaphylaxis. This is in addition to basic instructions about autoinjector use (4).
Although it is unclear what types of training and support are most effective, education is essential if patients at risk of anaphylaxis are to successfully recognize and manage future episodes. Diverse approaches are available, including the use of adrenaline, autoinjector training devices, and online approaches. Training HCP using anaphylaxis simulators will improve its management (4).

Other potential educational interventions
Some studies have also found that supporting patients to practice using an adrenaline autoinjector or needle and syringe containing 0.9% saline can reduce anxiety or improve quality of life.
In the case of anaphylaxis during an in-hospital-based food/drug challenge, patients and caregivers may be encouraged to administer their own adrenaline autoinjector to improve their confidence in this procedure. It is also important for allergists to follow a patient's anaphylaxis management plan during a provocation challenge (*e.g.*, giving in adrenaline at the first sign of anaphylaxis) to reinforce this self-management approach (88).

Approaches to prevent anaphylaxis in schools

School policies should reflect anaphylaxis guidelines, but more research is needed to understand how guidelines and legislation in schools are best implemented. Anaphylaxis due to food allergy, occurs in schools more than in any other community location (6).

Therefore, it may be helpful to target secondary schools and community settings with educational support to help raise general awareness, empower adolescents to confident self-manage food allergy, and enable schools to develop protocols to minimize any adverse events if they occur.

Other approaches investigated to improve the management of anaphylaxis included nurses checking whether students were carrying autoinjectors and availability of a 24-hour helpline (89).

Knowledge gaps

In our opinion, there are three main areas of work that we consider should be a priority to improve the management of anaphylaxis as described in the guidelines, which are those related to the diagnosis of the disease, its classification and its management (66, 88-91).

The difficulty in diagnosing anaphylaxis is that there is no pathognomonic set of signs or symptoms, especially when no cutaneous manifestations are present and there is not an immediate history of drug administration or allergen exposure. What is typical is the rapid progression in severity or intensity of symptoms. For this reason, it would be advisable to unify the diagnostic criteria and disseminate them, especially among specialties that handle clinical emergencies.

Although the most important aspect is to recognize the entity and initiate appropriate treatment (88, 89), it is also necessary to use the same tools to classify the severity of a reaction. It would be advisable to find a consensus and try to find a single and suitable classification of anaphylaxis.

It would also be important to improve knowledge and tools for the treatment of anaphylaxis (87). Turner *et al*. undertook a thorough literature search about the pharmacokinetics (PK) of adrenaline autoinjectors (66, 92, 93).

In community settings, adrenaline can be provided for emergency use as an adrenaline autoinjector (AAI) device (**table IV**), although these are not available in many countries (88, 89). Besides, there is a barrier in the use of AAI and is the price. Allergy societies and Patients' Organizations in Spain are joining forces to achieve a symbolic price, which is for many patients high, given the expiration date of the AAI, so as to assure that every patient at risk would carry AAI.

Given the currently available data, it takes at least 5-10 min to achieve early peak plasma concentration for most devices and the authors state that the specific autoinjector device seems to be the most important determinant of pharmacokinetics, with different devices giving rise to different plasma adrenaline profiles. Needle length does not seem to be the most important factor; rather, the force and speed of injection (which varies from one device to another) is likely to be of greater importance. In general, peak plasma adrenaline concentration is lower and time-to-peak concentration is longer with increased skin-to-muscle depth. However, it is difficult to draw conclusions with the current available data, due to a lack of head-to-head comparisons, small numbers of study participants, and the failure to acknowledge the biphasic nature of intramuscular adrenaline absorption for analysis purposes.

Several studies tried to assess the impact of body mass index, using the parameter of skin-to- muscle depth (STMD), assessed by ultrasound. Notwithstanding, the numbers in each subgroup would not allow to detect any small differences between groups. Other studies found significant differences in terms of lower SMTD and faster and greater increase in plasma adrenaline in the normal weight men and *vice versa* (66, 78, 88, 89).

Although PK data are available, the most helpful study comparing three different devices is unpublished. According to all international guidelines, the recommended dose of IM adrenaline in adults is 0.5 mg; thus, a dose of 0.3 mg given by AAI may be inadequate and should be repeated after 5-10 min in the absence of resolution of symptoms (66).

Conclusions

Anaphylaxis is a potentially fatal hypersensitivity reaction. Although its incidence rates vary according to geographical location, it seems clear that there has been a general increase in recent years, either because of greater recognition of this entity or because it is progressing proportionally to the presence of allergic diseases in the world. On many occasions, episodes of anaphylaxis are treated by physicians working in Emergency departments and are not directly evaluated by an allergist. It is necessary to establish common and consensual guidelines to help professionals and patients to know how to recognize anaphylaxis, as well as to be able to classify it, treat it correctly and make future recommendations after the acute episode.

Studies comprising the epidemiology of anaphylaxis, as well as the importance of biphasic reactions seem crucial to exactly define priorities in terms of research and resources.

Preventive measures, including personalized action plans may circumvent the burden of anaphylaxis for patients, relatives, and caregivers.

The development of anaphylaxis management guidelines adapted to local or regional needs seems of utmost importance, but it is necessary to assess their implementation and their positive effect regarding diagnosing and treating anaphylaxis.

There is a clear need for establishing multinational, large databases/registries to collect high-quality epidemiologic risk factor

data and diagnosis or treatment outcomes for improving the management of patients with anaphylaxis.

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Contributions

DA-A: conceptualization, formal analysis, methodology, project administration, writing - original draft, writing - review & editing. CV-A, DGdO, BDlH-C: conceptualization, writing - original draft, writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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