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Review Article

Adult anaphylaxis: A state-of-the-art review

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ABSTRACT

Anaphylaxis is the most severe among acute allergic diseases and potentially life threatening. Despite its increasing frequency and related burden, it remains often underdiagnosed and improperly managed. Its multisystemic involvement, protean clinical manifestations and its rapid onset are contributory factors. In recent years new acquisitions have shed light into its pathogenesis pathways (and related biomarkers), triggers, factors increasing its severity, along with peculiar clinical manifestations. These breakthrough discoveries have contributed to phenotyping and endotyping this disease, possibly paving the way to a personalized approach which is not available at present. Moreover, to disseminate awareness and standardize diagnostic criteria and management practices, several guidelines and consensus reports, albeit mainly intended for specialist care, have been issued. We here discuss the latest issues in the field of anaphylaxis from the perspective of the emergency and/or internal medicine physician, so to improve its early recognition and treatment in the acute setting and favor allergology referral to implement therapeutical and preventive strategies, such as allergen identification in unclear cases and desensitizing therapies when available (e.g., for *Hymenoptera* venom allergy).

1. Introduction

Anaphylaxis is an acute, usually rapidly developing, systemic (involving multiple organs) allergic reaction and, among the various clinical forms of allergy, it is the most severe and potentially life-threatening [1]. In the last decades, an epidemiologic increase of anaphylaxis, mainly in terms of hospitalization, has been observed [2]. This is particularly the case of food allergy [3] [4]. The overall incidence of anaphylaxis varies between 50 and 112 episodes per 100.000 person-years while its prevalence is 0.3–5.1% according to various epidemiological and classification factors [5]. Recurrence rate is also a matter of concern, being present in 26.5–54.0% of the cases [6]. Though overall mortality appears to be stable, drug-related fatal anaphylaxis has increased. Drugs, along with *Hymenoptera* venom, represent the most frequent triggers in people over 60 years . Moreover, new relevant knowledge acquisitions on its aetiopathogenesis have accumulated in recent years.

Notwithstanding, its recognition, reporting, and treatment remain suboptimal [7]. In fact, in a nationwide study analyzing emergency department data on food-related adverse events in a US registry, it was attested that roughly 60% of likely anaphylactic events were actually diagnosed as anaphylaxis, and only 19% of patients were treated with adrenaline [8]. According to a UK real life study, in only 33% of cases of anaphylaxis a tryptase determination was obtained in the acute setting in emergency departments [9]. Finally, according to a large US study, only 16.2% of patients an adrenaline autoinjector is prescribed following an emergency department visit for anaphylaxis [10].

Gathered, these data point at the need for a better awareness and management strategies of anaphylaxis, especially in the emergency and in the general/internal medicine setting. A gap in disease knowledge could be a contributing factor according to the World Allergy Organization (WAO), which has recently issued a guidance position paper on anaphylaxis, primarily intended for allergy and immunology specialists, to allow better diagnosis and prevention [1]. Starting from these premises, we herein review in a narrative fashion the most recent concepts on immune-mediated anaphylaxis to offer a state-of-the-art view in terms of pathophysiological mechanisms, defining/diagnostic criteria, with a focus on effector cells and their molecular mediators, triggers, factors modulating its onset/severity, diagnostic biomarkers, and treatment modalities in the acute and preventive settings.

2. New aspects in pathological mechanisms and cellular and molecular mediators (endotype) of immune-mediated anaphylaxis

Historically, immunoglobulin (Ig)-E-mediated anaphylaxis has been

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considered the classical and most important form of anaphylaxis (Fig. 1). It is characterized by the acute degranulation of mast cells and basophils after the crosslinking of the high affinity IgE receptor (FcεRI) with the release of pre-formed mediators, such as tryptase, histamine and platelet activating factor (PAF), of rapidly synthetized mediators, such as leukotrienes, prostaglandins and, lastly, by the synthesis and release of cytokines and interleukins. These products determine the constellation of the anaphylactic signs and symptoms [11].

Despite being the principal mediator of anaphylaxis, histamine is not an ideal biomarker to study or diagnose anaphylaxis, due to its very short half-life (<15 min) and reduced *ex vivo* stability. Of note, histamine metabolites, particularly methylhistamine, determined through a 24 h-urine collection starting from anaphylaxis onset, could be of value, but the reference values are not yet standardised and this test is not broadly available in routine practice.

Tryptase, which reflects mast cell and basophil degranulation, is the gold standard laboratory test for the diagnosis of IgE-mediated anaphylaxis. A significant increase of its value in the acute phase (ideally within 1–2 h, but up to 4 h) as compared with a baseline measurement (≥24 h after the event) is diagnostic [12] [13]. More in depth, tryptase levels ≥ 1.2 × baseline value + 2 ng/mL are significantly increased. This formula also applies to patients with very low baseline tryptase levels.

However, there are cases of IgE-mediated anaphylaxis where no significant tryptase increase is present, depending on the trigger/administration route. More precisely, tryptase levels are usually normal when mucosal mast cells degranulate, as in the case of food allergens, whereas higher levels are usually observed when connective mast cells, residing in the skin and perivascular tissue, degranulate, as stimulated by intravenous drugs and *Hymenoptera* venom stings [11] [14].

Other markers of mast cell degranulation are chymase, carboxypeptidase, PGD2 and its 9-a-11-b metabolite prostaglandin F2, and leukotrienes E4. However, almost all of these biomarkers are not commercially available, usually being adopted only in a research setting, due to low standardization and, for most of them, some intrinsic features, such as high analytical variability and requirement of 24 h urine sample which should ideally start at the onset of symptoms. Despite these limitations, some of these markers display interesting features. For instance, chymase and carbopeptydase can be elevated when tryptase is not, due to their longer half-life (around 24 h and 8 h, respectively) and the absence of correlation with tryptase levels [14]. It can be envisaged that their dosage could potentially reduce the number of cases of "idiopathic anaphylaxis" [12]. Moreover, carbopeptydase can also be determined in saliva samples [12].

More recently, evidence derived from experimental models of anaphylaxis, with some confirmation in human patients, has shown that additional pathogenetic pathways, other than IgE, play a role in immune-mediated anaphylaxis.

Accordingly, these pathways can be classified through the pathogenic mechanisms or endotype into type 1 IgG-mediated reactions, cytokine storm-like reactions, mixed reactions (comprising both type 1 and cytokine storm-like mechanisms), reactions related to the activation of the complement system), (Fig. 1). These forms display also peculiar features related to involved triggers, mediators and clinical presentation and treatment options (Table 1). It is also thought than more than one pathogenic pathway can be simultaneously implicated in the same patient. Moreover the same trigger can activate different pathways [15].

Along with IgE, other antibodies, such IgG, may mediate anaphylaxis, at least in murine models, if a large quantity of antigens is present. This is the case of the so called type-1 IgG-mediated anaphylaxis, where IgG-containing immunocomplexes bind to neutrophils and macrophages, but also mast cells and platelets, through Fcγ receptors, and induce the release of mediators, including lipid-derived ones, such as PAF [16]. Chimeric IgG monoclonal antibodies, such as rituximab, and neuromuscular-blocking agents (NMBA), such as atracurium and rocuronium, protamine-containing drugs, such as insulins, have been shown to induce anaphylaxis, even in the absence of IgE, possibly through this mechanism [17]. Symptoms may be indistinguishable from those of IgE-mediated anaphylaxis. Neutrophil elastase and myeloperoxidase may be promising biomarkers in this form [18, 19].

The cytokine storm-like reaction is determined by the release of pro-inflammatory mediators, such as tumor necrosis factor (TNF) α, interferon (IFN) γ, interleukin (IL) 1β and IL6, from other cellular types than mast cells, such as monocytes, macrophages, mast cells, and other

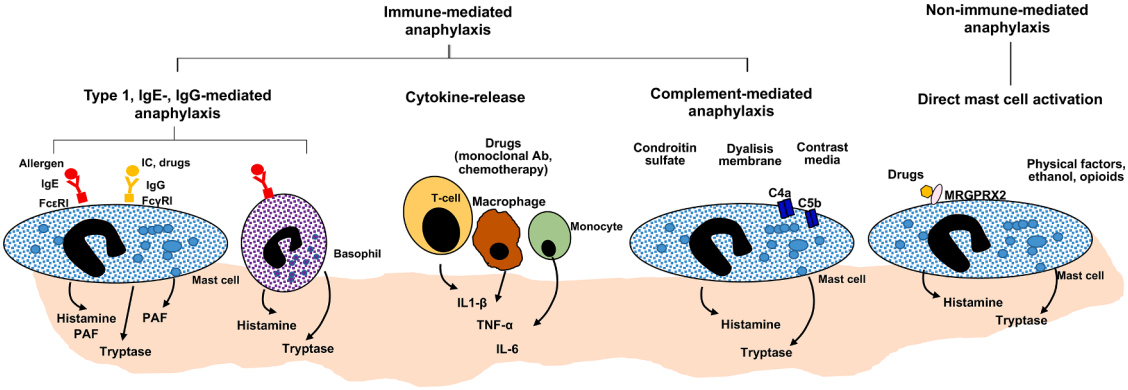

Fig. 1. The pathophysiological classification of anaphylaxis (upper part) and its pathways are illustrated along with triggers, cell targets and receptors, when present, (middle part) and biological effect mediators (lower part). The immune system plays a role in type 1 IgE- and IgG-mediated anaphylaxis (left), cytokine- release (middle), mixed-reactions (not shown for clarity), where the previously described mechanisms are both at play, and complement-mediated anaphylaxis (middle). The last mechanism depicted (right) is the direct activation of mast cells, which can be either mediated by the interaction of drugs (e.g., vancomycin and quinolones) with Mas-Related G protein-coupled receptor X2 (MRGPRX2) or due to direct, e.g., without engagement of receptors, membrane perturbation of mast cells by physical factors (hot and cold temperatures, osmolality variation, ethanol, etc.). Type 1 IgE-mediated anaphylaxis, the prototypical form of anaphylaxis, is triggered by the crosslinking of IgεRI by allergens on mast cells and basophils, leading to the production of vast array of mediators (histamine, tryptase and others, see text). Immunocomplexes, chimeric IgG monoclonal antibodies, protamine-containing drugs bound by IgG crosslink FcγRs on mast cells but also neutrophils, macrophages andplatelets, not shown, and determine the production of mediators, such as PAF. In cytokine-release reactions, mainly induced by chemotherapy agents and monoclonal antibodies, the release of inflammatory mediators, such as interleukin (IL) 1β, IL6 and tumor necrosis factor (TNF) α, by T cells, macrophages and monocytes, is responsible for the clinical picture. Oversulfated chondroitin sulfate, dialysis membrane, contrast media, dextran, some excipient (PEG, polysorbates) activate the complement system and determine mast cell degranulation. For clarity, immunoglobulin (Ig)- mediated activation of mast cells and basophils is shown after the engagement of only one Ig receptor, in complement-mediated anaphylaxis only one mast cell, without a basophil, is shown.
Abbreviations. IC, immunocomplex; IL; PAF, platelet activating factor; PEG, polyethylene glycol, TNF, tumor necrosis factor α.

Table 1
Pathophysiological mechanisms of anaphylaxis and their relevant features and clinical variables.

Pathway	Elicitor or allergen	Target cell	Receptors	Main clinical manifestations	Biomarkers	Treatment	Desensitization
Type 1, IgE & IgG	Aeroallergens, foods, drugs, latex, *Hymenoptera* venom and others	Mast cell, basophil	FcεRI, Fcγ	Flushing, urticaria, pruritus, nausea, vomiting, abdominal pain, bronchospasm, laryngeal edema, hypotension, cardiovascular collapse	Histamine, tryptase, chymase, carboxipeptidase, heparin, PAF	Adrenaline	Yes
Cytokine release	Drugs (e.g., chemotherapy, monoclonal antibodies)	T cell, macrophage, monocyte	No receptor or receptors specific for monoclonal antibodies	Fever, chills, rigors, nausea, pain, headache, hypotension, desaturation	TNFα, IL6, IL1β	Adrenaline	In selected cases
Mixed reactions	Drugs (e.g., chemotherapy, monoclonal antibodies)	T cell, macrophage, monocyte, mast cell, basophil	FcεRI, Fcγ	Flushing, urticaria, pruritus, nausea, vomiting, abdominal pain, bronchospasm, laryngeal edema, hypotension, cardiovascular collapse, fever, chills, rigors, nausea, pain, headache, hypotension, desaturation	Histamine, tryptase, chymase, carboxipeptidase, heparin, PAF, TNFα, IL6, IL1β	Adrenaline	In selected cases
Complement activation	Highly charged glycosaminoglycans, contrast media, dialyses membranes and others	Mast cell, basophil	C5a, C4a	Hypotension, desaturation	Histamine, tryptase	Adrenaline	No
Direct mast cell activation	Drugs (e.g., vancomycin, fluoroquinolones)	Mast cell	Mrxgprx2	Flushing	Histamine, tryptase	Histamine, tryptase	Not known

Abbreviations: FcεRI, high affinity receptor for the Fc region of IgE; Fcγ, Fc portion of IgG; Mrxgprx2, mas-related G protein coupled receptor member X2; PAF, platelet activating factor; TNF, tumor necrosis factor.

immune cells. These mediators induce vascular leakage, by increasing capillary permeability, and activation of the extrinsic coagulation pathway. Laboratory assays are available for most of these markers, but their accuracy has not been thoroughly ascertained. Preferentially involved triggers are monoclonal antibodies and chemotherapeutic agents, such as oxaliplatin. In this type of anaphylaxis, specific inflammatory symptoms such as chills, fever, and generalized malaise are usually observed. Another frequent and typical symptom is pain [11]. Interestingly, the use of anti-inflammatory COX-1 inhibitors, fluid and corticosteroids reduces the intensity of these manifestations, in minor reactions [11].

In mixed reactions, symptoms and mediators are a combination of those taking part in type 1 and cytokine storm-like reactions, respectively.

Lastly, complement-mediated reactions are characterized by the release of the anaphylatoxins, C3a, C4a and C5a, and their subsequent binding on their receptors on the surface of mast cells and basophils. Usual triggers are radio contrast media, dialyses membranes, and dextran containing products. A novel antigen acting through this mechanism is polyethylene glycol with its cross-reactive compounds, such as polysorbates, which are excipients found in some anti-Sars-Cov2- vaccines. Typical manifestations include hypoxia and hypotension due to vasodilation [20, 21, 22].

In other forms of anaphylaxis, the immune system is not directly involved, such as in those related to physical triggers, such as cold, heat and sunlight. Recently, another mechanism of nonimmune-mediated anaphylaxis has been described and is related to the stimulation of Mas-Related G-protein-Coupled Receptor-X2 (MRGPRX2). It is triggered by the rapid intravenous administrations of drugs, such as fluoroquinolones and radio contrast media, and usually characterized by skin manifestations.

3. New aspects in the definition and clinical diagnostic criteria for anaphylaxis

Several definitions of anaphylaxis and diagnostic criteria have been formulated over the last two decades (Table 2), the most important being those issued by the US National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network in 2005 and by the WAO in 2011 and 2020 [1] [23, 24, 25, 26, 27, 28, 29, 30]. The common aspects that are highlighted in these definitions are (*i*) that anaphylaxis usually has a rapid onset; (*ii*) it can be life-threatening and; (*iii*) that generally carries systemic manifestations, meaning that usually more than one system, among the cardiovascular, respiratory and gastrointestinal ones, is affected, in addition to skin involvement, with urticaria and/or angioedema, this latter being a major classifying criterion. More in depth, skin/mucosal involvement is observed in most cases, so that its presence has been traditionally considered a *sine qua non* diagnostic criterium. This latter requisite holds true particularly in those cases where an unknown allergen might be involved. However, despite underpinning a systemic process, isolated widespread skin manifestations, according to the WAO 2020 guidelines, should not be classified as anaphylaxis, and thus treated as such, in the absence of life-threatening manifestations [1]. Moreover, most definitions consider the possibility of diagnosing anaphylaxis in case of the involvement of a single organ/system, even without skin involvement, when manifestations are severe and require prompt treatment, such cardiovascular involvement with hypotension, and respiratory involvement with laryngeal edema, after exposure of a known or highly probable allergen. Recently, also bronchospasm has been included [1].

Moreover, anaphylaxis defining features that pertain to the gastrointestinal system have been clarified and now defined as severe, including crampy abdominal pain, and recurrent vomiting particularly when occurring after exposure to non-food allergens [1].

However, if helping to recognize most forms of anaphylaxis, the available diagnostic criteria have at the same time several limitations, being anaphylaxis a clinical proteiform syndrome [31]. For example, anaphylaxis may have in some instances a delayed onset, albeit rapidly progressing, such as in the case of galactose-α−1,3-galactose (α-gal) syndrome, which occurs from 3 to 5 h after eating α-gal containing products or in other cases of food allergy in which factors altering gastrointestinal absorption may be involved. Moreover, there are

Table 2
Latest definitions of anaphylaxis.

Author (year)	Organization	Definition or classification criteria	Ref.
Brown et al. (2006)	ASCIA	A serious, rapid onset allergy that may cause death; (*i*) any acute onset illness with typical skin features plus involvement of respiratory and/or cardiovascular and/or persistent gastrointestinal symptoms or (*ii*) any acute onset of hypotension or upper way obstruction, even if typical skin features are not present	[26]
Sampson et al. (2006)	NIAID/FAAN	A serious allergic reaction that involves more than one organ system It can begin very rapidly, and symptoms may be severe or life-threatening	[23]
Lieberman et al. (2010)	AAAAI/ ACAAI	An acute life-threatening systemic reaction with varied mechanisms, clinical presentation, and severity	[28]
Simons et al. (2011)	WAO	A serious life-threatening generalized or systemic hypersensitivity reaction […] a serious allergic reaction that is rapid in onset and might cause death	[29]
Muraro et al. (2014)	EAACI	A severe life-threatening generalized or systemic hypersensitivity reaction An acute, potential fatal, multi-organ system, allergic reaction	[24]
No authors listed (2019)	WHO, ICD-11	A severe, life-threatening systemic reaction characterized by being rapid in onset with potential life-threatening airway, breathing, or circulatory problems and is usually, although not always associated with skin/mucosal changes	[30]
Cardona et al. (2020)	WAO	Anaphylaxis represents the most severe spectrum of allergic reactions; it is highly likely in case of (*i*) "typical skin symptoms and significant symptoms from at least 1 other organ system or (*ii*) exposure to a known or probable allergen for that patient, with respiratory and/or cardiovascular compromise	[1]

All definitions have been extrapolated from the published papers. Abbreviations. AAAAI, American Academy of Allergy, Asthma and Immunology; ACAAI, American College of Allergy Asthma and Immunology; ASCIA, Australasian Society of Clinical Immunology and Allergy; EAACI, European Academy of Allergy and Clinical Immunology; FAAN, Food Allergy Anaphylaxis Network; ICD, International Statistical Classification of Diseases; NIAID, National Institute of Allergy and Infectious Disease; WAO, World Allergy Organization.

settings in which skin involvement cannot be detected, as in the operative setting where skin changes cannot be readily observed, due to the presence of surgical drapes covering the patient, and forms where it is almost absent (10–20% of cases), such as in cases of fatal anaphylaxis and in severe *Hymenoptera* venom anaphylaxis in patients with mastocytosis.

4. New severity grading scores

Over the years several classifications have been introduced to define the severity of anaphylactic reactions [13] [32, 33, 34, 35, 36], Table 3 summarizes some of the most frequently adopted severity scores.

An ideal scoring system should be simple, feasible to use in daily practice, applicable across the whole spectrum of anaphylaxis regardless of the trigger (e.g., insect venom, immunotherapy related-adverse effects, food- and drug allergy), and it should be validated and accepted by relevant societies/institutions. Moreover, it should also provide additional detail for healthcare practitioners and for research purposes [36] [37]. Unfortunately, the available scoring systems fail to have all these requisites.

Recently, the WAO has issued a revised grading score for allergic reactions considering 5 grades of increasing severity, which has been previously devised for desensitizing immunotherapy anaphylactic reactions. Grade 1 and 2 reactions, which differ for the involvement of one or two target organs of anaphylaxis, among the skin, upper respiratory system and the conjunctivae, respectively, do not represent proper anaphylactic reactions and should not be treated as such.

Grade 3 anaphylaxis, is defined by the presence of mild lower airway symptoms due to bronchospasm, i.e., which respond to treatment, while the presence of severe lower respiratory symptoms, i.e., that do not respond to treatment or worsen despite treatment along with severe upper respiratory symptoms (laryngeal edema) define grade 4 anaphylaxis. In grade 5 anaphylaxis reactions severe manifestations pertaining the respiratory system (respiratory failure) and/or cardiovascular (collapse/hypotension) and/or loss of consciousness, not related to vasovagal phenomena, are present. Together with the qualifying manifestations,in each anaphylactic grade symptoms of less severe grades can be present.

5. Atypical clinical manifestations of anaphylaxis

Anaphylaxis symptoms are particularly protean so that the diagnostic process can be challenging, since several differential diagnoses should be considered, which are summarized in Table 4. Anaphylaxis may also display atypical manifestations. Here we describe two forms of anaphylaxis which apparently seem to contradict the paradigm of anaphylaxis as being a rapid onset reaction occurring reproducibly after a trigger, since they occur with a delayed onset and only in the presence of a co-factor, such as exercise, respectively. A thorough history taking is therefore key to suspect these entities.

5.1. *The α-gal syndrome*

The α-gal syndrome is an emerging form of IgE-mediated allergy with peculiar features. The allergen is a glycolipid, not a protein as usual allergens, and is present in red mammalian meat, such as pig, veal, venison and lamb, with higher concentrations in kidney and liver, and a in a wide range of mammalian derived edible products, bovine/porcine-derived or gelatin-containing drugs and additives, the most common being cetuximab, plasma expanders, vaccines, pancreatic enzymes, heparins and capsule, magnesium stearate [38] [39]. In case of ingestion of mammalian red meat, clinical manifestations of allergy present with a delayed onset, usually 2–6 h, due the time needed for the systemic availability of the antigen after digestion, absorption and metabolism of lipid particles containing the antigen [40]. However, after eating food with lower percentage of lipids as compared to meat, such as milk, the onset of the clinical manifestations may be more rapid and after the parenteral administration of drug containing this allergen, particularly monoclonal antibodies such as cetuximab and plasma expanders, the onset of the reaction is immediate, as for typical IgE-mediated allergies.

Its pathogenesis is still elusive. Sensitization occurs after tick bites, of various species across the world, so that this form of allergy is frequent in rural areas and in summer months, during which the likelihood of being bitten by ticks is higher, and in susceptible patients, especially those with non-B blood groups, who are involved in outside activities [41] [42].

A high degree of suspicion and a detailed history taking is therefore mandatory and should be particularly focused on identifying all food and drugs ingested up to 5 h before the reaction, on social activities and environmental exposures to detect a history of previous tick bites, and on blood group identification since this information significantly modifies the *a priori* probability of making a diagnosis. Mammalian meat products and derived drugs should be avoided. Plasma expanders must be avoided in the treatment of shock in this form of anaphylaxis since they could have a detrimental effect. Patients should be advised to avoid future tick bites, since an amelioration of this allergy is observed over time.

Table 3
Grading of anaphylaxis.

Classification (year)	Grading			
Mueller HL et al.,1966	I	II	III	IV
	Generalized urticaria, itching, malaise, and anxiety	Any of the previous plus two or more of the following: angioedema, chest constriction, nausea, vomiting, diarrhea, abdominal pain, dizziness	Any of the previous plus two or more of the following: dyspnea, wheezing, stridor, dysarthria, hoarseness, weakness, confusion, feeling of impending disaster	Any of the previous plus 2 or more of the following: drop in blood pressure, collapse, loss of consciousness, incontinence (urine or stool), cyanosis
Ring J et al.,1977	I	II	II	IV
	Generalized skin symptoms (e.g., flush, generalized urticaria, angioedema)	Mild to moderate pulmonary, cardiovascular, and/or gastrointestinal symptoms	Laringeal edema, shock, bronchospasm	Respiratory or cardiac arrest
Brown S et al., 2005	1 Mild	1 Moderate	1 Severe	
	Skin and subcutaneous tissue involvement	Respiratory, cardiovascular or gastrointestinal involvement defined by dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain	Hypoxia, hypotension or neurologic compromise defined by cyanosis or SpO2 < 92% at any stage, hypotension (SBP < 90mmHgin adults), confusion, collapse, loss of consciousness, or incontinence	
Cardona V et al.,2020		III	IV	V
		Lower airway with mild bronchospasms that responds to treatment and/or gastrointestinal and/or uterine cramps[±]	Lower airway with severe bronchospasm not responding or worsening despite treatment and/or upper airway with laryngeal edema[±]	Lower and upper airway with respiratory arrest, cardiovascular with hypotension/collapse and/or loss of consciousness[±]

[±] Any symptoms of previous stages may be present, always including those reported in grade 1, which are described in the text.

Table 4
Differential diagnosis of anaphylaxis.

Organ involvement	Clinical entities
Skin	Acute generalized urticaria[#], flush syndromes (e.g., carcinoid, medullary thyroid carcinoma, pery-menopause), red man syndrome (vancomycin), non-allergic/hereditary angioedema, mastocytosis/mast cell activation syndrome
Gastrointestinal	Toxic syndromes (e.g., sgombroid syndrome, glutamate toxicity), infection, mastocytosis/mast cell activation syndrome, vasointestinal polypeptide tumors, somatoform conditions
Respiratory (upper and lower airways)	Acute asthma[#], foreign body aspiration vocal cord dysfunction, anxiety/panic attack, somatoform conditions, hyperventilation, sulfites effect, mastocytosis
Cardiovascular	Myocardial infarction[#], pulmonary embolism, syncope, shock (hypovolemic, cardiogenic, distributive[#]), pheochromocytoma, Takotsubo syndrome[#], mastocytosis/mast cell activation syndrome, cardiac arrhythmias, hypoglycemia, thyrotoxic crisis
Neurological	Seizure, cerebrovascular event, medullary paralysis with neurogenic shock, neuropsychiatric diseases (such as anxiety and panic disorders, psychoses, somatoform disorders), hypoglycemia, thyrotoxic crisis

[#] These clinical manifestations can also occur during anaphylaxis.

5.2. *Food-dependent exercise-induced anaphylaxis (FDEIA)*

The peculiarity of this form of food allergy is that it usually occurs only if a cofactor is present, most frequently exercise, but also non-steroidal anti-inflammatory drugs, alcohol, fever and possibly other unknown factors, whereas the ingestion of the causal food at rest does not trigger any clinical manifestation. So, despite eating a certain food is a necessary condition, it is not enough to evoke symptoms in most cases. Moreover, clinical manifestations are highly variable, including anaphylaxis with cardiovascular and/or respiratory involvement, but also gastrointestinal and skin manifestations, which can be the sole manifestation, depending on the number and intensity of co-factors.

Wheat is most frequently implied food and in this case this form of allergy is called wheat-dependent exercise-induced anaphylaxis or WDEIA; the most important allergen is omega- 5 gliadin, *Tri a 19*, but also low molecular weight glutenin and the wheat lipid transfer protein (LTP), *Tri a 14*, play a role, the latter being of particular importance in the Mediterranean area [43]. Cases of FDEIA are reported, occurring after other food types, including shrimps, nuts, cereals other than wheat, and meat [44].

The pathogenesis of this food allergy is still elusive. As opposed to other forms of food allergy, such as “classical” IgE-mediated allergy to wheat, the presence of comorbid atopic disorders seems not be a relevant factor, at least in Central and Northern Europe, and has no gender prevalence [45] [46]. Exercise is thought to increase allergen absorption by modifying gastric and intestinal permeability, or through an increased plasma osmolarity, favoring mast cell activation [44].

The clinical features of WDEIA, particularly the tolerance at rest, of a certain food, could greatly hamper its recognition. The diagnosis can be particularly challenging and is usually based on the combination of an evocative history, with the results of allergy skin- and blood tests, including wheat-specific serum IgE antibodies, particularly omega-5 gliadin, and in some cases, on exercise provocation test [47]. The latter comprises the administration of a certain amount of wheat or gluten followed by exercise, and/or in combination with NSAID or alcohol, to mimic the *in vivo* conditions.

In the acute setting, the first-line therapy, as in other cases of anaphylaxis, is adrenaline. If, after allergology referral, a diagnosis of WDEIA is confirmed, a gluten-free diet, due to the presence of gliadin in many related monocots cereals, is usually recommended for severe cases. In less severe cases, strict limitation of wheat ingestion before exercise (up to 3 h) and after (up to 2 h) and avoidance of other cofactors may be sufficient [48]. Its natural history is still elusive, as compared to other forms of IgE mediated wheat allergy, which can resolve over time [49] [50].

6. Clinical management

6.1. Recognition of risk factors and co-factors

Not only allergen-related factors, such as its type, quantity, and physical and chemical stability, are of importance in triggering anaphylaxis, but also factors related to the patient (intrinsic or endogenous) and external/environmental (extrinsic or exogenous) factors play a significant role. Risk factors are usually nonmodifiable and defined as variables increasing the risk of anaphylaxis, i.e., its occurrence, and/or its severity [51] [1]. However, they remain poorly defined, and their role varies across different populations, being influenced by genetics, habits and environmental exposures, and other unknown factors [1].

Among endogenous risk factors, age, sex, atopy, and concomitant disorders such as poorly controlled asthma and mast cell disorders, are the most commonly recognized endogenous risk factors [1] [51, 52]. Increasing age is the dominant risk factor in a European Registry study and it seems to associate to augmented mast cell degranulation, at least in an animal model [51] [53]. Female sex has been traditionally considered a risk factor for allergies, such as asthma and food allergy, due to the experimental evidence of increased mast cell activation and allergic sensitization due to biological sex-specific hormones. However, more recently, male sex has been found to be predominant in anaphylaxis in both children and adults, after exposure to various triggers [54] [55, 56, 57]. Male sex and older age, together with insect sting as a cause of anaphylaxis, are associated with an increased requirement for adrenaline administrations [58]. Mastocytosis and mast cell disorders confer a highly increased risk due to increased mast cell numbers and activation [59]. Higher levels of basal tryptase seem to correlate to more severe cases of anaphylaxis, especially *Hymenopthera* venom-triggered [1] [57].

Among exogenous risk factor medications such as angiotensin converting enzyme (ACE)-inhibitors beta blockers exert a relevant role [60] [61, 52],. The former class of drugs increases the risk of anaphylaxis, while the latter reduces the pharmacological effect of adrenaline.

Co-factors or augmentation factors are usually extrinsic and are defined as factors increasing the severity of anaphylaxis, although in some instances they can even elicit it, as in the case of physical exercise in FDEIA. Physical exercise, acetylsalicylic acid and other NSAIDs, and ethanol are traditionally considered the most important co-factors. Among them, also acute infection, emotional stress, disruption of routine (e.g., travel or sleep deprivation) and postmenstrual status have a role [1]. Co-factors are thought to increase gastrointestinal permeability to allergens and mast cell activation, among other hypotheses [47]. The avoidance of co-factors, although not always feasible, is the principal therapeutic option in WDEIA [47] [48], and, despite a still ambiguous definition and incomplete knowledge of risk and co-factor, their manipulation, when possible, through preventative strategies aimed at decreasing the frequency and intensity of anaphylaxis, is envisaged to greatly contribute to better patient care in the future.

6.2. Therapeutics and prevention

The milestone of acute treatment of anaphylaxis, whether in the hospital or community setting, is the timely and intramuscular (mid-thigh) administration of adrenaline, named epinephrine in the US, (0.01 mg/kg, up to a maximum total dose of 0.05 mg/kg of body weight in adults, which is equivalent to 0.5 ml of a 1 mg/ml or 1:1000 solution), since this is the only life-saving treatment and is effective for all symptoms. Adrenaline can be repeated every 5–15 min if needed [1] [62, 63]. Adrenaline exerts multilevel effects and, most importantly, both on the cardiovascular (mainly vasoconstrictive effect) and respiratory (reversal of edema and bronchospasm) system, but also on the key cellular actors of anaphylaxis, *i.e.*, mast cells and basophils, through the stabilization of their membrane. It is also thought to prevent biphasic anaphylaxis, which is defined by the recurrence of anaphylaxis after trigger removal, within 1 to 71 h since its first resolution.

Additional interventions, usually performed by health care professionals, are the administration of intravenous fluids (5–10 ml/kg in the first 5 to 10 min) through a large caliber intravenous access (ideally 14 o 16 gage), of high flow oxygen (through a 100% non-rebreather mask) in case of respiratory distress, placing the patient in a recumbent position (left side in pregnant patients).

According to a recent systematic review, there is no definitive evidence supporting the use of systemic antihistamines and glucocorticoids, [63]. Accordingly, antihistamines have been shown to improve only skin symptoms. Interestingly, their use and that of glucocorticoids proved useful in special settings, such as before allergen-specific immunotherapy, to prevent hypersensitivity reactions.

In case of respiratory symptoms, inhaled beta2-agonist and nebulized adrenaline, for lower and upper respiratory tract involvement, respectively, can be administered [63] [62].

Another key aspect is the length of the observation time after an anaphylaxis episode, which varies significantly according to different guidelines, although there is a general consensus on its prolongation up to the full resolution of the clinical manifestations and a minimum duration of 6–8 h, and up to 12–24 h in severe cases (with respiratory involvement or hypotension, respectively) [62] [27]. In case of an increased risk of biphasic anaphylaxis (administration of more than 1 adrenaline injection, particularly severe manifestations, unknown elicitor, continuous allergen absorption) and poor outcome (co-morbidities, lack of access to emergency medical services and adrenaline or poor self-treatment skills), the observation time should be extended and/or hospital admission should be considered [62].

Lastly, it is of great importance to give the patient a written individualized anaphylaxis action plan and one or two, if feasible, adrenaline auto- injector or pre-filled syringes/vials that patients should always carry. Referral to an allergist for diagnosis confirmation, trigger identification, if present or if not clear from the clinical history, allergen avoidance strategies and exclusion of mastocyte clonal/activation disorders is also important. The latter applies particularly to recurrent episodes and/or severe cases of anaphylaxis characterized by cardiovascular involvement and absence of skin involvement in male patients [64]. The most important issues or questions to be addressed by the internal medicine or emergency medicine physician regarding diagnosis and management of patients with suspected anaphylaxis are listed in Table 5.

7. Conclusion

Due to its sudden and often unpredictable onset, anaphylaxis is admittedly a difficult to study phenomenon. Despite new acquisitions on its pathogenesis, allergens and triggers, provoking- and severity-modulating factors in individual cases, that could favor a precision medicine-based approach, several unmet needs remain. New strategies are awaited to implement the applicability of available guidelines, large Registers and Biobanks of samples should be established to find and validate novel and more feasible biomarkers. Lastly, novel and more practical routes of administration of adrenaline (sublingual, inhalatory) and/or pathogenically oriented therapies are needed.

Statement of author contributions

All authors significantly participated in the drafting of the manuscript or critical revision of the manuscript for important intellectual content and provided approval of the final submitted version. Individual contributions are as follows: CMR wrote the manuscript, MVL reviewed the manuscript. ADS reviewed the paper and made final critical revision for important intellectual contents.

Table 5
Relevant questions or issues that should be addressed when assessing a patient with suspected anaphylaxis.

Area of interest Diagnosis	Relevant questions	Comments or examples
	Are the clinical manifestations immediate (<1 hour) or delayed (up to 5 yours)?	Different allergens should generally be suspected depending on the timing of symptoms onset; for example, food allergy due to αgal usually has a delayed onset
	Does the patient have known allergic diseases?	In the past medical history, look for atopic dermatitis, food allergy, allergic rhinitis, asthma, eosinophilic esophagitis
	Has the patient undergone multiple surgical interventions? Has the patient spina bifida and requires urinary catheterization? Is the patient a health care provider?	Latex allergy should be considered due to high exposure to this allergen (due to latex containing devices, use of latex-containing personal protective equipment)
	Are there risk factors for anaphylaxis?	Older age, male sex, baseline tryptase elevation, others
	Is the patient a male suffering from severe anaphylaxis without urticaria/ angioedema? Are there skin lesions, like urticaria pigmentosa?	Systemic mastocytosis should be suspected in the differential diagnosis
	Has the patient been previously stung by a tick?	α-gal allergy should be considered
Acute management		
	Has the trigger of anaphylaxis been removed?	Discontinue intravenous infusions, remove latex-containing devices, remove the sting (bee), others
	Is the patient taking ACE-inhibitors or beta-blockers?	An increased severity of the reaction or a reduced response to adrenaline could be expected; discontinue ACE-inhibitors and beta-blockers when feasible
	Is the patient pregnant?	Left recumbent position is recommended in case of anaphylaxis
	Is the patient suffering from asthma?	Aerosolized adrenaline could be considered in addition to standard treatment
	Has the patient experienced biphasic anaphylaxis or needed >1 dose of adrenaline during previous episodes?	If yes, observation time should be prolonged
	Has the patient the αgal syndrome?	Plasma expanders should be avoided, since it may contain this allergen
Prevention		
	Does the patient live in a remote area, far from medical services?	If yes, the indication of an adrenaline autoinjector should be considered even for mild reactions; for severe reactions two adrenaline autoinjectors should be given
	Is the patient at risk for future episodes of anaphylaxis?	Hobbies and outdoor activities, especially for *hymenoptera* venom allergy, should be avoided
	Are there risky behaviors?	Teenagers usually have low adherence with adrenaline autoinjector carriage
	Is the patient suffering from asthma and food allergy?	Uncontrolled asthma is a risk factor for more severe reactions to foods
	Is there a specific therapy availably for the patient?	Immunotherapy for *hymenoptera* venom allergy or desensitizing therapy for drug allergy
	Are there cofactors?	Exercise, alcohol, and NSAIDs in WDEIA, among others, should be avoided

Abbreviations: ACE, angiotensin converting enzyme; NSAID, non-steroidal anti-inflammatory drugs; WDEIA, wheat-dependent exercise-induced anaphylaxis.

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