



Therapeutic approach of anaphylaxis

Luciana Kase Tanno^{a,b,c}, Alberto Alvarez-Perea^{d,e}, and Guillaume Pouessel^{f,g}

Purpose of review

Anaphylaxis is a recognized cause of death in all ages, which requires prompt recognition and treatment. We here propose to review the current and new pharmacological treatment of anaphylaxis in the view of the new knowledge in the field that can support the quality practice and empower allergists and health professionals with new tools that can be used to treat symptoms and prevent anaphylaxis.

Recent findings

The recent description of phenotypes provides new insight and understanding into the mechanisms and causes of anaphylaxis through a better understanding of endotypes and application of precision medicine. Several biologic therapies and new devices are emerging as potential preventive treatment for anaphylaxis.

Summary

Adrenaline (epinephrine) is still the first-line treatment for any type of anaphylaxis and is recognized as the only medication documented to prevent hospitalizations, hypoxic sequelae and fatalities. β_2 -adrenergic agonists and glucagon remains as the second-line treatment of anaphylaxis, meanwhile glucocorticoids and antihistamines should be used only as third-line treatment. Their administration should never delay adrenaline injection in anaphylaxis. More intuitive adrenaline autoinjectors design and features are required as well as a worldwide availability of adrenaline autoinjectors. Biological drugs, such as omalizumab, have been used as therapeutic adjuvants as a preventive treatment of anaphylaxis, but cost-effectiveness should be considered individually. Understanding the specifications of underlying mechanisms can potentially support improvements in the patients' allergological work-up and open the opportunity of developments of potential new drugs, such as biological agents. Expanding knowledge with regard to the presentation, causes, and triggers for anaphylaxis among healthcare providers will improve its diagnosis and management, increase patient safety, and decrease morbidity and mortality.

Keywords

adrenaline, adrenaline autoinjectors, anaphylaxis, evidence-based, management, pharmacology, prevention, treatment

INTRODUCTION

Anaphylaxis: a relevant health issue that requires immediate recognition and treatment

From clinical anaphylaxis to endotypes

Anaphylaxis is currently clinically defined as a severe, life-threatening systemic hypersensitivity reaction characterized by rapid onset and the potential to endanger life through airway, breathing, or circulatory problems [1–6], which requires prompt identification and treatment. Although the allergy academies have been working in the awareness of anaphylaxis, there is still not a consensus in the definition of anaphylaxis, which is fundamental to avoid the consequences of a delayed action against anaphylaxis. Anaphylaxis is a syndrome with a

constellation of features and signs, which can manifest at any age, with multiple triggers and any health professional may face it. The treatment of anaphylaxis comprises medications at the

^aDepartment of Pulmonology, Division of Allergy, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Montpellier, ^bSorbonne Université, INSERM UMR-S 1136, IPLESP, Equipe EPAR, Paris, ^cWHO WHO Collaborating Centre on Scientific Classification Support, Montpellier, France, ^dAllergy Service, Hospital General Universitario Gregorio Marañón, ^eGregorio Marañón Health Research Institute, Madrid, Spain, ^fDepartment of Pediatrics, Children's Hospital, Roubaix and ^gPediatric Pulmonology and Allergy Department, CHU Lille, Lille, France

Correspondence to Luciana Kase Tanno, MD, PhD, Department of Pulmonology, Division of Allergy, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, 371, av. du Doyen Gaston Giraud 34295, Montpellier Cedex 5, France. Tel: +33 467336107; fax: +33 467633645; e-mail: luciana.tanno@gmail.com

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KEY POINTS

- Developments in the field of anaphylaxis have been consistently following pharmacological developments offering possibilities of better management and prevention.
- Adrenaline is still the treatment of choice in all cases of anaphylaxis and its administration should not be delayed.
- A worldwide availability of AAls should be a key measure to ensure the safety of patients at-risk.
- More intuitive AAI devices design and features are needed to improve their safety and effectiveness.
- Biologicals, as the single medications or as combined therapy to food or venom immunotherapy, are effective as preventive treatments to reduce the most severe anaphylactic reactions.
- Expanding knowledge with regard to the presentation, causes, and triggers for anaphylaxis among healthcare providers will improve its diagnosis and management, increase patients' safety, and decrease morbidity and mortality.

acute phase (mainly adrenaline) and prevention measures.

The clinical definition, classification, nomenclature, and treatment of anaphylaxis have been points of controversy varying among different medical subspecialties and in different countries, as it became clear that an important goal for the field would be to achieve a true international consensus. For this reason, multinational and multidisciplinary collaboration, led by allergy academies resulted in the International Consensus on Anaphylaxis [6]. Recent publications suggest changes in the definition considering a more mechanistic description based on precision medicine into phenotypes with underlying endotypes. Currently, anaphylaxis phenotypes are defined by clinical presentation into type-I-like reactions, cytokines storm-like reactions, and mixed reactions. The endotypes underlying these phenotypes include IgE and non-IgE-mediated mechanisms, cytokines release, mixed reactions, and direct activation of immune cells [7].

Anaphylaxis: the 'killing lady'

The worldwide burden of anaphylaxis is difficult to quantify. Although considered a high priority public health issue in some countries, it is still considered to be secondary conditions in many other countries. The reported rate of occurrence appears to vary widely from one country to another. The lifetime prevalence has been estimated at 0.05% to

2% based on international studies [8]. Anaphylaxis is a recognized cause of death in all ages, anaphylaxis-related mortality rate is less than 1 per million per year in most high-income countries [9–13,14¹¹, 15,16¹²,17,18¹³]. There are limited epidemiological data from middle and low-income countries.

As anaphylaxis is characterized by rapidly developing life-threatening airway and/or breathing and/or circulatory problems, which can potentially evolve to fatality, the need of rapid management of this condition is well known. Over the last decade, the allergy community has been moving efforts to better manage, diagnose, and prevent anaphylaxis, but there are still recognized challenges because of many factors such as the difficulties on recognition of symptoms, limited availability of first-line medications in different countries and, correct and prompt use of the treatment. Despite the evolution of Medicine, anaphylaxis continues to be under-recognized, its diagnosis is often missed and, therefore, the treatment is delayed or absent, increasing the risk of death.

We here propose to review the current and new pharmacological treatment of anaphylaxis in the view of the new knowledge in the field that can support the quality practice and empower allergists and health professionals with new tools that can be used to treat symptoms and prevent anaphylaxis.

TEXT REVIEW

Pharmacological treatment of anaphylaxis

Acute management of anaphylaxis: epinephrine, epinephrine, epinephrine...

To decrease the risk of death and optimize the treatment of anaphylaxis, all the guidelines [1–5] convey to the need of a standardized protocol in which the removal of the trigger, the prompt initial pharmacological treatment (epinephrine mainly), the appropriate positioning of the patient, and call for help should be started simultaneously.

Adrenaline (epinephrine) is the first-line treatment for any type of anaphylaxis and is recognized as the only medication documented to prevent hospitalizations, hypoxic sequelae and fatalities. Its autoinjectable form is critically important for its treatment in case of a new reaction, and should be widely available in the community for first-aid treatment [6]. Adrenaline (epinephrine) is a life-saving nonselective adrenergic agonist. Its α 1-adrenergic vasoconstrictor activity prevents and relieves laryngeal edema, hypotension, and shock. Its β 1-adrenergic activity produces inotropic and chronotropic effects [14¹⁴,15], increasing the force and rate of cardiac contractions. Its β 2-activity

includes bronchodilation and decreases release of mediators of inflammation. Its effects are time-dependent, mandating a recommendation for prompt administration. Despite its pivotal role, the autoinjectable form is not readily available in the majority of countries [19²²,20,21²²,22,23²²] in which best management of patients with anaphylaxis is therefore impossible.

The recommended adrenaline (epinephrine) administration route is intramuscular route in the vastus lateralis muscle (outer thigh) because of its vasodilator effect in skeletal muscle, which facilitates rapid absorption and pharmacologic effects. Recommended dose is 0.01 mg/kg, with maximum dose per injection of 0.5 mg for teenagers and adults. Injections can be repeated at least once or twice at 5–15 min intervals, in first dose nonresponder cases, in which the reaction is progressing rapidly or in biphasic anaphylaxis [1–6,24²²].

Pharmacological adverse effects of adrenaline (epinephrine) in therapeutic doses are minor, well known, and predictable such as tachycardia, headache, pallor, and tremor. Severe adverse effects (ventricular arrhythmias, pulmonary edema, malignant hypertension, and intracranial hemorrhage) are rare and usually because of over dosage or in bolus intravenous administration. There is any formal contraindication of adrenaline (epinephrine) use in anaphylaxis [25²²]. However, risk–benefit should be assessed in the case of patients with underlying cardiovascular disease [26]. Nonetheless, the heart is actually a potential target organ in anaphylaxis and acute coronary syndrome can occur during anaphylaxis in the absence of epinephrine [27].

Evidence-based data of second-line pharmacological treatment of anaphylaxis

Several drugs may be used as additional treatment of anaphylaxis, after the administration of epinephrine (Table 1). None of them should be used and

Table 1. Dosage and routes of drugs recommended to the management of anaphylaxis

Recommendations of drugs used in anaphylaxis	Treatment	Route	Doses
FIRST-LINE TREATMENT	Adrenaline (epinephrine)	Intramuscular	Child (7.5–25kg): 0.15mg Child (> 30kg): 0.30mg Adolescents and Adult: 0.01mg/kg, up to 0.5 mg (repeated at least once or twice at 5 to 15 min intervals if needed)
		Inhaled	2–5 ml, 1mg/ml
SECOND-LINE TREATMENT	Salbutamol	Inhaled	200–600 µg/10 min
	Glucagon	Nebulized i.v.	2.5–5 mg in 3 ml saline /15–30 min Child: 20–30 µg/kg, up to 1 mg Adult: 1–5 mg
THIRD-LINE TREATMENT	H1-antihistamines		
	Diphenhydramine	i.v.	Child: 1mg/kg, up to 50mg Adult: 25–50mg
	Dexchlorpheniramine	i.v.	Child: 0.15–0.3 mg/kg, up to 5 mg Adult: 5 mg
	Ranitidine	i.v.	Child: 12.5–50mg Adult: 50 mg
	Glucocorticoids		
	Methylprednisolone	i.v.	1–2 mg/kg/day
	Hydrocortisone	i.v.	5 mg/kg/day, up to 200 mg
	Prednisone	Oral	0.5 mg/kg/day
	Prednisolone	Oral or i.v.	
	Vasopressors		
	Methylene blue	i.v.	1–2 mg/kg (single bolus over 20 min)
	Dopamine	i.v.	1–5 µg/kg/min
	Norepinephrine	i.v.	0.05–1 µg/kg/min
	Sugammadex	i.v.	12–16 mg/kg

i.v. = intravenous.

first-line or sole treatment, because they do not have its global effect reversing anaphylaxis symptoms. Need of any additional drug will depend on patient's response to epinephrine [1–6].

β₂-adrenergic agonists

Bronchodilators (e.g., salbutamol) may be useful for treatment of bronchospasm refractory to epinephrine, or even by acting in addition to the effect of epinephrine [28]. They can be administered by nebulizer or spacer, as needed. However, the administration of inhalers should never delay the administration of epinephrine, because they do not act on mucosal edema in the upper airway or α₁-adrenergic-mediated vascular effects [6].

There is no evidence for the role of these drugs in anaphylaxis, so the recommendation for the use of bronchodilators is extrapolated from the use in asthma exacerbation [29].

Glucagon

Patients taking β-blocker therapy may present with less than desired response to epinephrine during anaphylaxis. Instead, epinephrine would cause predominately α-adrenergic effects [30[■]]. Glucagon is a peptide hormone physiologically produced by α cells of the pancreas, with inotropic and chronotropic activity. Its administration may reverse refractory hypotension and bronchospasm associated with anaphylaxis bypassing β-adrenergic receptors, as glucagon directly activates adenylyl cyclase [31[■]]. Thus, although epinephrine remains first-line therapy for patients taking β-blockers, glucagon is recommended in patients that appear refractory to epinephrine, and so it is supported in international guidelines [1–6]. Rapid administration of glucagon can induce emesis, resulting in an increased risk of aspiration. Therefore, protection of the airway is important in patients with altered level of consciousness. Evidence supporting the role of glucagon in anaphylaxis is weak, based on case reports [32,33[■]]. In fact, a retrospective study did not observe the traditional statement that patients taking β-blockers need additional doses of epinephrine [34[■]].

Third-line pharmacological treatment of anaphylaxis

H1-antihistamines

There are no studies that support the use of H1-antihistamines for the treatment of anaphylaxis [35]. They may be useful for relieving itching, flushing, and urticaria. However, their use in anaphylaxis, including doses, is extrapolated from studies of urticaria. H1-antihistamines do not act on upper or lower

airway obstruction or hypotension. Benefits often attributed to these drugs have been explained by endogenous release of epinephrine [36].

Furthermore, onset of action of antihistamines is slower (30–40 min) than that of epinephrine taking too long to provide immediate response. Yet, several studies have reported that antihistamines remain the most frequently used drugs for the treatment of anaphylaxis in the ED [37,38[■]].

Availability of H1-antihistamines in parenteral form for use in anaphylaxis is limited to first-generation compounds [39]. Although they are considered secure, they may cause mild side-effects (e.g., somnolence and confusion). Less frequently, they may induce severe adverse effects (e.g., seizures, hypotension, and cardiac toxic events) [40]. Second-generation H1-antihistamines are more secure; however, they are not available for parenteral use [41].

H2-antihistamines

There is evidence that the effect of H2-antihistamines (e.g., ranitidine), when administered concurrently with H1-antihistamines, could provide additional relief of urticaria [42]. Yet, not randomized controlled trials have supported these findings, neither for urticaria or anaphylaxis. In any case, H2-antihistamines, would not have any effect on airway obstruction or shock [43,44].

Glucocorticoids

Corticosteroids are very frequently administered to patients suffering anaphylaxis [37,38[■]]. Guidelines traditionally have recommended them to prevent biphasic or protracted anaphylaxis [24[■]]. However, recent studies focusing on the effect of glucocorticoids in biphasic reactions have not confirmed these claims [45,46[■],47[■]]. Furthermore, systematic reviews have failed to find any evidence on the effectiveness of these drugs for the treatment of anaphylaxis [48,49[■]].

Their use in for the treatment of asthma indicates that the onset of glucocorticoids' pharmacological action may take several hours after administration. Therefore, corticosteroids have little or no effect on initial symptoms or signs [50].

Methylene blue

Methylene blue has been reported as a safe and successful treatment for refractory hypotension in patients with anaphylactic shock [31[■]]. Its action has been suggested to be mediated by inhibition of the nitric oxide and guanylate cyclase pathways, both related to vasoplegia syndrome occurring in some cases of refractory anaphylaxis [51[■]]. Methylene blue may result in false readings of pulse oximetry, because of blue dyeing of the blood.

Other vasopressors

Recommendations to use other vasopressors (e.g., vasopressin, norepinephrine, and dopamine) in hypotension refractory to epinephrine and fluids are suggested in most international guidelines. In spite of this, there are no high-quality studies available [31[¶]]. Critical care specialists should be consulted before administration of these drugs [52].

Sugammadex

Neuromuscular blocking agents, such as rocuronium, are one of the most common triggers of perioperative anaphylaxis [53[¶]]. Sugammadex is a γ -cyclodextrin that encapsulates and subsequently inactivates with great affinity rocuronium and other steroidal neuromuscular blocking agents. It has been proposed as a useful treatment for anaphylaxis caused by these agents, as stated by several case reports [54,55[¶]], including inhibition of intradermal tests [56[¶]]. However, evidence is weak and remains controversial. A recent study, including 13 cases of perioperative anaphylaxis treated with sugammadex, concluded that it does not modify the clinical reaction [57].

NEW TREATMENTS AND BIOLOGICALS

The recent description of phenotypes provides new insight and understanding into the mechanisms and causes of anaphylaxis through a better understanding of endotypes and application of precision medicine. Several biologic therapies are emerging as potential preventive or adjuvant treatment for anaphylaxis.

Omalizumab is 95% humanized monoclonal antibody that recognizes and binds to the Fc portion of the IgE molecule, to block IgE binding in mast cells and basophils. It prevents IgE expression on allergic effector cells and subsequent allergen-induced cross-linking of IgE [58]. Nowadays this treatment is formally indicated for moderate-to-severe persistent allergic asthma with proven sensitization to perennial aeroallergen in patient's refractory to usual treatment and for chronic idiopathic urticaria in patients who remain symptomatic despite H1-antihistamine treatment. Therapeutic strategies based on omalizumab administration in other disorders are currently only based on small clinical trials, observations, case series, and expert opinions [59^{¶¶}].

Biological agents can be used as adjuvants in the desensitization procedures, such as in cases of desensitization to drugs, such as antibiotics and chemotherapy agents. Recent data have provided evidence of successful desensitizations to an increased number of mAbs, including rituximab, ofatumumab,

obinutuzumab, trastuzumab, cetuximab, tocilizumab, infliximab, etanercept, adalimumab, golimumab, certolizumab, brentuximab, bevacizumab, and omalizumab [60[¶]]. Desensitization to antibiotics has been successfully done in targeted populations, such as patients with cystic fibrosis, with a similar protocol as for chemotherapy drugs. Desensitization to aspirin for aspirin-exacerbated respiratory disease has provided increased sense of smell, prevented the regrowth of polyps, and helped stabilize asthma symptoms.

Omalizumab is a potential adjuvant in food oral immunotherapy. A recent phase 2 randomized, double-blind, placebo-controlled trial of 37 peanut-allergic children undergoing oral immunotherapy showed that omalizumab administration (12 weeks) allowed for tolerance of 2000 mg of peanut upon discontinuation of immunotherapy more often than placebo (74% versus 13%, $P < 0.01$) [61[¶]]. Participants assigned to omalizumab were also less likely to experience adverse reactions to peanut immunotherapy. Omalizumab, administered solely or in combination for 28 months, has also been shown to improve safety but not efficacy, in 57 study participants (7–32 years) with a cow's milk allergy undergoing oral immunotherapy [62].

Omalizumab has been shown to be a successful treatment for idiopathic anaphylaxis, effectively reducing the number of episodes and improving the quality of life [63–66]. Idiopathic anaphylaxis patients who were not controlled despite continuous use of oral corticosteroids and/or antihistamines were treated with omalizumab (300–375 mg every 2–4 weeks) for 10–14 months [63,64,65]. In these four patients, no anaphylaxis episode was recorded after onset of omalizumab injection. Omalizumab may be a preventive therapeutic option in cases of idiopathic anaphylaxis depending on the severity and frequency of episodes, but the cost–benefit ratio should be taken individually.

Mastocytosis and mast cell activation disorders can be identified as a cause of idiopathic anaphylaxis [67]. Omalizumab has been shown also to reduce anaphylaxis episodes and skin symptoms and increase quality of life in 13 adult patients with systemic mastocytosis who received this treatment with a median duration of 17 months (range: 1–73 months) [68^{¶¶}].

Hymenoptera venom immunotherapy is indicated in patients with mastocytosis who developed sting anaphylaxis. However in these patients, the venom immunotherapy is likely to provide incomplete protection and adverse reactions. Pretreatment with omalizumab has demonstrated to be effective as an adjunctive treatment in patients with mastocytosis, used for both symptom improvement and to

dampen adverse effects caused by venom immunotherapy [69–76].

PERSPECTIVES

Autoinjectable adrenaline for all and new ways of use

A worldwide availability of adrenaline autoinjectors (AAIs) should be a key measure to ensure the safety of patients at risk [19²²], and the Montpellier World Health Organization Collaborating Center is much involved in this process. AAI is still not available in more than 60% world countries, mostly in low and middle-income countries [21²²]. In high-income countries, the priorities are different, an example is the need of harmonizing standard dosage and having a wider availability of stocked AAIs in public places, as well as in schools, needs to be further evaluated as preventive measure in near-fatal and fatal events in the community settings [77²²].

In parallel with the availability of AAIs, more intuitive AAI devices design and features are needed to improve their safety and effectiveness. Recently the needle length of AAIs has become a topic of controversy [78²²,79,80²²]. A device with a shorter autoretractable needle may prevent unintended injuries or bone injection in the youngest children. In 2017, in the United States, the Food and Drug Administration has approved the use of Auvi-Q 0.1 mg autoinjector in infants and small children weighing 7.5–15 kg (16.5–33 lbs). This device has a shorter needle and a lower adrenaline dose (0.10 mg) than the currently approved 0.15, 0.3, or 0.50 mg AAIs available in other countries. AAIs using electronic voice instruction system that guides the user through the delivery process as Auvi-Q are of interest to help people who have never used an AAI before.

Needle phobia highly contributes to AAI under-use, leading to near-fatal and fatal cases, particularly in children. Devices using needle-free injection technology (Bioject from Inovio Pharmaceuticals, Zeneo from Crossject) have been shown to deliver intramuscular liquid preparations with consistency and may be of a great interest, particularly in those patients who fear adrenaline injection [81,82²²].

The bioavailability of a taste-masked rapidly disintegrating sublingual tablet of adrenaline (30 mg) has been evaluated in comparison with an AAI 0.15 mg in a rabbit model [83²²]. The authors concluded that sublingual adrenaline has the potential to be used as an easy-to-carry palatable, noninvasive treatment for children. A wide variety of features that may help to improve future AAIs can be listed: smaller devices, innovative designs, new

delivery options (sublingual and needle-free injection), two autoinjectable doses in one device, better temperature stability and longer shelf life for adrenaline, intuitive options (indicators to know if the dose is successfully delivered) [80²²].

Taking the example of food-induced anaphylaxis: new therapeutic and prevention

Beside anti-IgE therapies, immunotherapy using modified food proteins combined with a variety of adjunctive therapies targeting specific immunologic pathways is emerging and may prevent food-induced anaphylaxis. A number of biologic therapies are being explored to target other key molecules and may be potential future therapies in food allergic patients to prevent anaphylaxis (anti-IL-33, anti-IL-5, anti-IL-5R, anti-IL4RA...) [84²²].

One novel approach for the treatment of food allergy, particularly peanut allergy, is based on the potential use of immunotherapy in which the allergenic proteins have been chemically modified, theoretically with the potential to induce desensitization or tolerance without the same risk of Ig-E reactions [84²²].

Therapies have been developed to enhance the efficacy and/or improve the safety of food allergen immunotherapy through either shifting the immune response from a Th2 polarized response to a Th1 and regulatory T-cell dominated response. Upstream therapies that shifts toward a Th1/Treg response include toll-like receptor (TLR4) agonists (e.g., Montpellier and GLA), TLR9 agonists 5CpG nucleotides), nanoparticles encapsulating peanut allergen (e.g., CpG or rapamycin), Chinese herbal medicine (FAHF-2), probiotics and IFN γ [85²²].

Food allergy herbal formula-2 (FAFH-2) is a formulation of nine traditional Chinese herbs that appeared to be efficacious in reducing allergic reactions [86²²]. In a murine model, Srivastava *et al.* [86²²] reported that a combined B-FAFH-2/peanut–tree nut oral immunotherapy was safer and produced longer posttreatment protection and more tolerance-prone immunological and epigenetic modifications than oral immunotherapy. A phase 1 trial enrolling 14 patients who received 3.3 g (six tablets) of FAHF-2 three times a day for 6 months found FAHF-2 to be well tolerated with positive in-vitro immunomodulatory effects [87]. However no efficacy has been observed in a double-blind, placebo-controlled phase 2 trial for 6 months enrolling 68 study participants aged 12–45 years with allergies to peanut, tree nut, sesame, fish, and/or shellfish [88].

There is evidence implicating the role of the microbiome in allergic disease and probiotics have been used in a few oral immunotherapy trials. In one study, 62 children (1–10 years) with peanut

allergy received either peanut oral immunotherapy combined with the probiotic *Lactobacillus rhamnosus* or placebo without probiotics, once daily for 18 months. Two to 5 weeks after, possible sustained unresponsiveness was achieved in 82.1% of the active group and 3.6% of the placebo group ($P < 0.001$) [89].

DNA vaccines (product referred as ASP0892) may be another therapeutic approach for the treatment of peanut allergy as a preventive treatment of anaphylaxis. A phase 1 trial is underway to evaluate the safety, tolerability, and immune responses of this product (ASP0892, one dose every 2 weeks, four times) in peanut-allergic adults.

Anti-IgE-based therapies appear to be furthest along with probiotics, Chinese herbal medicines, and TLR64 agonists currently in early phase clinical trials. Nanoparticles may represent an innovative delivery vehicle for immunotherapy that could improve efficacy and decrease allergic side-effects.

CONCLUSION

Glucocorticoids and antihistamines should be used only as third-line treatment in anaphylaxis treatment. Their administration should never delay adrenaline injection in anaphylaxis. More intuitive AAI design and features are required as well as a worldwide availability of AAI. Omalizumab, as the single medication or as adjunctive therapy to food or venom immunotherapy, has been demonstrated to be effective on reducing the most severe reactions in patients who experienced episodes of anaphylaxis. The widespread of new treatments and combined therapies into routine clinical practice will revolutionize daily care in allergic patients. Real-world questions about safety and effectiveness of such novel approaches remain unclear. The cost of such medications and knowledge gaps about long-term benefit–risk, adherence and comparative effectiveness require an expertise in allergology centers, through international scientific collaborations and studies involving large, real-world populations. Further studies are required to determine the appropriate use of specific therapeutic and preventive approaches in different anaphylaxis phenotypes and endotypes.

Understanding the specifications of underlying mechanisms can potentially support improvements in the patients' allergological work-up and open the opportunity of developments of potential new drugs, such as biological agents. Expanding knowledge with regard to the presentation, causes, and triggers for anaphylaxis among healthcare providers will improve its diagnosis and management,

increase patients' safety, and decrease morbidity and mortality.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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