ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Anaphylaxis: updating Practice Parameter 2023 recommendations

Anafilaxia: atualizando as recomendações do Practice Parameter 2023

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ABSTRACT

Anaphylaxis is a potentially life-threatening medical emergency that requires prompt and effective intervention. Understanding and updating clinical practices is crucial to ensure optimal patient care. This update is based on evidence and expert clinical experience and discusses aspects focusing on 7 different areas with new evidence and different from those of previous practice guidelines. The text summarizes aspects related to the diagnosis of anaphylaxis, mastocytosis, with emphasis on the indication rate of bone marrow biopsy and hereditary alpha tryptasemia, investigation of perioperative anaphylaxis, and influence of beta blockers and angiotensin-converting enzyme inhibitors, in addition to the important prescriptions for epinephrine auto-injectors, highlighting practical aspects in the management of self-medication.

Keywords: Anaphylaxis, epinephrine, diagnosis, mastocytosis.

RESUMO

A anafilaxia é uma emergência médica potencialmente fatal que requer intervenção rápida e eficaz. Compreender e atualizar as práticas clínicas é crucial para garantir os melhores cuidados aos pacientes. Esta atualização baseada em evidências e experiência clínica de especialistas mostra uma discussão de aspectos focados em sete diferentes áreas com novas evidências e diferentes das diretrizes práticas anteriores. O texto resume desde aspectos do diagnóstico da anafilaxia, mastocitose, com destaque para o escore de indicação de biópsia de medula óssea e alfa triptasemia hereditária, investigação da anafilaxia perioperatória, influência dos betabloqueadores e inibidores da enzima de conversão da angiotensina, além das importantes indicações da prescrição dos autoinjetores de adrenalina, destacando-se aspectos práticos no manejo da autoprescrição.

Descritores: Anafilaxia, epinefrina, diagnóstico, mastocitose.

Introduction

The ICD-11 defines anaphylaxis as a serious, life-threatening systemic hypersensitivity reaction, characterized by the rapid onset of changes in the airways, breathing, or circulation, usually associated with changes in the skin and mucous membranes.[1] The diagnosis is clinical, without definitive markers or quintessential symptoms.[2] In 2019, the World Allergy Organization (WAO) proposed modifications to

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simplify the diagnosis and to include severe reactions that were not classified as anaphylaxis by the previous criteria (Table 1).[3]

Rapidly progressing reactions may occur even if the onset of symptoms is delayed after allergen exposure, such as reactions caused by alpha-gal and immunotherapy.[3]

Mastocytosis and mast cell activation syndrome (MCAS)

Mast cell diseases are commonly associated with anaphylaxis. The risk of anaphylaxis in patients with systemic mastocytosis is estimated to be 40%-50% in adults and 10% in children. Currently, there is greater knowledge of the different phenotypes of the disease, more accurate diagnostic methods, and effective treatments for both the prevention and management of anaphylactic conditions. Risk factors for mastocytosis-related anaphylaxis include male sex, serum IgE > 15 kU/L, atopy, and baseline serum tryptase < 42 ng/mL.[4]

Serum tryptase levels should be measured whenever possible during anaphylaxis investigation. However, in cases of suspected systemic mastocytosis, even with normal tryptase levels, a bone marrow biopsy is required for diagnosis. Additionally, it is crucial to exclude differential diagnoses when tryptase levels are elevated, such as neoplasms, helminth infection, renal failure, hypereosinophilic syndrome, hereditary alpha tryptasemia, and mast cell activation syndrome (MCAS), in addition to systemic mastocytosis itself. Baseline serum tryptase is particularly relevant in cases of anaphylaxis triggered by hymenoptera stings (especially with hypotension independent of urticaria), idiopathic anaphylaxis, and suspected mastocytosis. In these cases, a bone marrow biopsy is recommended, especially when the Spanish Network on Mastocytosis (REMA) prediction score, which establishes clonal mast cell disorders, is ≥2 (Table 2).[5]

The laboratory-defined normal value for serum tryptase is 11.4 ng/mL. An elevation of serum total tryptase level, within 2 hours of the anaphylactic episode, of at least 20% plus 2 ng/mL above the patient's baseline level may provide evidence of MCAS. Furthermore, an elevated baseline level (above 8 ng/mL) may be indicative of hereditary alpha tryptasemia.[6]

In mastocytosis, according to the World Health Organization (WHO) criteria, anaphylaxis can occur spontaneously and, in some cases, be triggered by aerobic exercise. Other potential triggers include food allergies, drug allergies, and pollen-food allergy syndrome.[3] While cutaneous mastocytosis

Table 1
Criteria for the diagnosis of anaphylaxis

Anaphylaxis is highly likely when any one of the following 2 criteria are fulfilled:

1. Acute onset (minutes to several hours) with involvement of the skin, mucosal tissue, or both (hives, pruritus, swollen lips-tongue-uvula) and at least one of the following:

a. Respiratory compromise: dyspnea, bronchospasm, stridor, reduced peak expiratory flow, hypoxemia;
b. Reduced blood pressure or associated symptoms of end-organ dysfunction: hypotonia, syncope, incontinence;
c. Severe gastrointestinal symptoms: severe crampy abdominal pain, repetitive vomiting.

2. Acute onset of hypotension or bronchospasm or laryngeal involvement after exposure to a known or highly probable allergen even in the absence of typical skin involvement, defined as one of the following:

a. Decrease in systemic blood pressure;
b. Bronchospasm;
c. Laryngeal involvement.

Source: Cardona V, et al.[3].

Table 2
Spanish Network on Mastocytosis (REMA) Score

Sex	Female	-1
	Male	+1
Clinical symptoms	Absence of urticaria and angioedema	+1
	Presence of urticaria and angioedema	-2
	Presyncope or syncope	+3
Baseline tryptase	< 15 ng/mL	-1
	> 15 ng/mL	+2

Source: Alvarez-Twose I, et al.[5].

and benign mastocytomas can occur in children, they are not usually associated with systemic mastocytosis. Patients with mastocytosis and anaphylaxis after hymenoptera stings should receive lifelong subcutaneous immunotherapy with allergen extracts, starting during pregnancy if necessary. In these cases, the risk of systemic reactions increases with immunotherapy, and caution is required in its administration. The addition of omalizumab may be considered to prevent potential anaphylaxis, especially in rapid desensitization protocols.[7]

MCASs share the characteristic of degranulation of anaphylaxis mast cell mediators. They can be classified into 3 groups: primary/clonal (systemic monoclonal mastocytosis); secondary (IgE-mediated); and idiopathic nonclonal (idiopathic anaphylaxis). Therefore, any patient who does not meet the criteria for anaphylaxis should be evaluated for the following criteria (include all 3)[8]:

(1) Symptoms in at least 2 different organ systems (cardiovascular, respiratory, naso-ocular, gastrointestinal, and cutaneous);

(2) Biochemical documentation of the release of anaphylaxis mediators (tryptase, prostaglandin D2, prostaglandin F2-alpha, leukotriene E4, and catecholamines);

(3) Positive response to antimediators, membrane stabilizers, and producers of vasoactive substances (H1 and H2 antihistamines, anti-leukotriene, ketotifen, cromoglycate, omalizumab, and corticosteroids).

Patients with chronic, nonspecific multiorgan symptoms and patients with food and environmental intolerances who do not meet the criteria mentioned above should not be diagnosed with MCAS.

The diagnostic algorithm shows the updated criteria for the investigation of anaphylaxis (Figure 1).

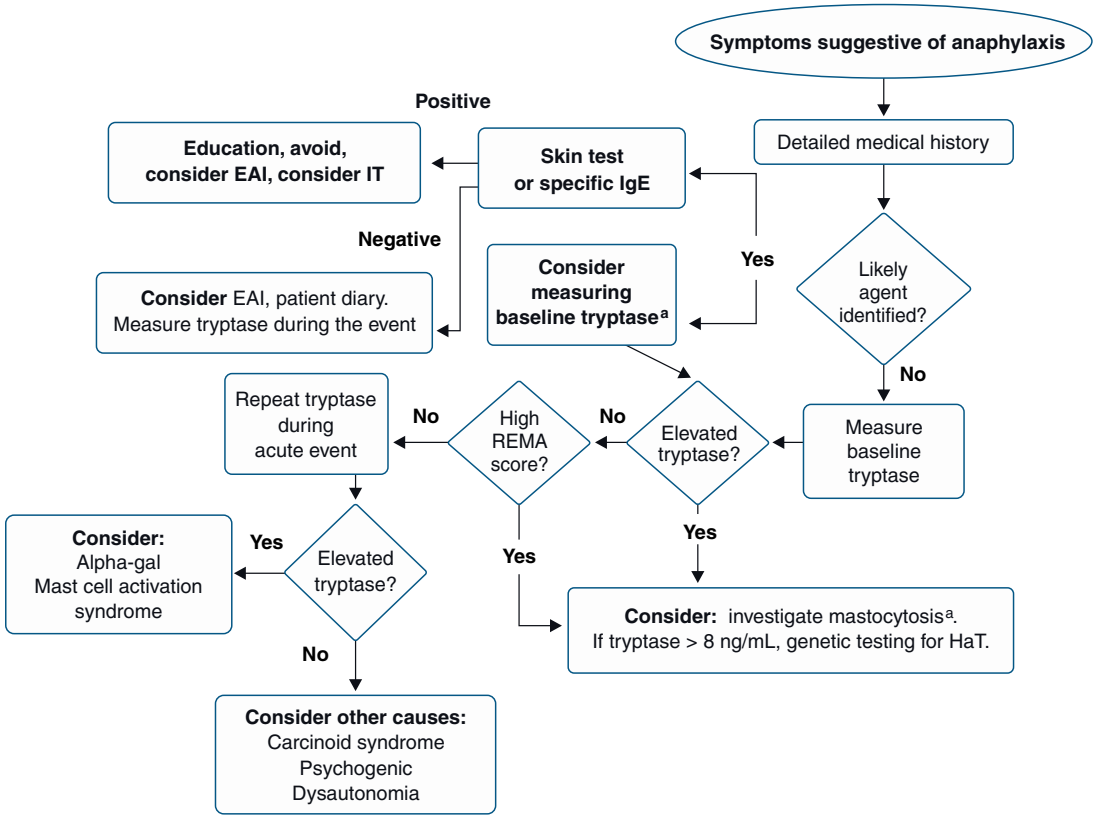
Anaphylaxis in infants and children

The same anaphylaxis criteria have been applied to both children and adults, despite limited evidence supporting this practice for children, due to a lack of consensus for this age group. In infants and young children, age does not correlate with reaction severity, and anaphylaxis is unlikely as an initial reaction to a food or drug on first exposure. Clinically, infants and young children more often have skin and subjective symptoms, such as pulling and scratching, and less frequently experience respiratory symptoms compared with older children.[9] Behavioral changes such as withdrawal, inconsolable crying, irritability, or clinging may be observed in infants. While self-

injectable epinephrine in 0.1 mg or 0.15 mg doses may be prescribed for infants/children weighing less than 15 kg, caution is advised as longer needles increase the risk of the needle hitting bone. Further research is needed to determine the true risk of intraosseous injection and its impact on epinephrine effectiveness.[10]

Beta-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEIs) in anaphylaxis

Regarding the use of beta-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEIs) in anaphylaxis, it is important to consider their previous contraindication in patients at risk of anaphylaxis, since most previous studies focused on non-selective BBs and did not account for cardiac comorbidities that could independently explain the increased risk of severe anaphylaxis. In addition, discontinuation or change of treatment may pose greater risks than the potential for more severe anaphylaxis. In specific cases, such as a history of anaphylaxis to hymenoptera venom before immunotherapy, venom immunotherapy, and during the maintenance phase of immunotherapy, the continued use of BBs and ACEIs may be justified as long as the need outweighs the risk of more severe anaphylaxis. However, the use of BBs and ACEIs should be discouraged in situations with a significant risk of recurrent or unpredictable anaphylaxis, such as severe food allergies, mastocytosis, MCAS, and exercise-induced anaphylaxis. For planned procedures, such as contrast-enhanced imaging, challenge/desensitization, and infusion, clinicians



AAI = epinephrine auto-injector, HaT = hereditary alpha tryptasemia, IT = immunotherapy.
[a] Example: severe reaction to hymenoptera venom, recurrent idiopathic anaphylaxis.

Figure 1
Algorithm for the investigation of anaphylaxis[4]

should engage patients in a shared decision-making process regarding the continuation or discontinuation of BBs and ACEIs. This process should carefully weigh the relative risk of anaphylaxis, the potential for a more severe reaction if the medication is continued, and the risk of discontinuing the medication.[11]

Perioperative anaphylaxis

Perioperative anaphylaxis (POA) occurs at a rate of 15.3 per 100,000 cases.[1] While there has been a trend toward a decrease in latex-induced anaphylaxis, an increase has been observed in cases due to antimicrobials, particularly cefazolin. Anaphylaxis can be triggered by either immunologic or non-immunologic activation of mast cells. There is sufficient evidence to demonstrate that resuscitation itself cannot account for serum tryptase level elevation. Therefore, increased tryptase levels are directly linked to cases of severe anaphylaxis. Plasma histamine measurement is not recommended due to its rapid degradation and decline in blood levels following anaphylaxis. Interpretation of tryptase levels obtained near death or postmortem may be unreliable due to nonspecific increases during ischemia. While tryptase is estimated to be stable for up to 1 year in a frozen blood sample, the timing of collection is crucial, with an initial peak around 30 minutes followed by a decrease in approximately 120 minutes. If the serum tryptase level is elevated after POA, a repeat measurement should be performed once the patient has recovered to establish a baseline tryptase level.[12]

Immediate hypersensitivity skin testing (percutaneous and intradermal) and/or in vitro specific IgE testing should be performed to all potential pharmacologic and non-pharmacologic culprits used perioperatively. If testing is not feasible, the patient should be referred to another center, or the most effective agents structurally different from the most likely culprit should be used.[1]

Neuromuscular blocking agents (NMBAs) are frequently implicated as causes of POA. Therefore, testing should always include the potential culprit NMBA and any alternative NMBA agents to rule out cross-reactivity among chemically related agents, an area that remains poorly documented. Immediate hypersensitivity skin testing to opioids or vancomycin may be unreliable due to high rates of false-positive results, since they are direct mast cell activators. Furthermore, avoidance of drugs with a positive skin test result is the best option when equally effective, structurally unrelated alternatives are available. Administration of agents with negative test results can proceed safely, suggesting that testing may be helpful in drug selection for subsequent anesthesia. In the case of negative skin test results (eg, latex, lidocaine, chlorhexidine, povidone-iodine), provocative challenges should be performed due to the uncertainty surrounding the sensitivity of these tests. For some agents, such as NMBAs, midazolam, and propofol, it would be appropriate for an anesthesiologist to administer them in a graded dose (ie, "test dose") of 10% immediately before the planned procedure, followed by full dosing after a period of observation as indicated. Delaying immediate hypersensitivity skin testing for 4 to 6 weeks after anaphylaxis is recommended. If testing or referral to another center are not possible, or the procedure is urgent, the most likely culprits should be avoided, and the most effective structurally different agents should be used.[13]

Regarding penicillin, immediate hypersensitivity skin testing has been validated. If the test result is positive only to the beta-lactam and a challenge for other alternatives is not feasible, all perioperative drugs except for the beta-lactam should be used. In cases of suspected latex allergy where the investigation is still pending, a latex-free environment should be provided.

There is currently no consensus on the use of pretreatment before returning to the operating room in patients with a negative allergy investigation. This decision should be made on a case-by-case basis.

Repeat anesthesia can proceed within the context of shared decision-making, based on the patient's history and the results of the diagnostic evaluation. Studies indicate that the recurrence of POA is 1.7% when the aforementioned measures are adopted.[14]

Anaphylaxis in community settings

The literature indicates a higher frequency of anaphylaxis events in younger populations, particularly at home. However, an increase in these events has been observed in schools and restaurants, with 1 in 10 childhood allergic reactions and anaphylaxis cases occurring in childcare centers or schools. Although deaths from anaphylaxis are rare, they can occur in any setting. There is no recommendation to prohibit specific foods in childcare centers or schools. However, implementing allergen-restricted zones (eg, a milk-free table) may be appropriate when there are

children who lack the capacity to self-manage. Other strategies include handwashing before and after eating, avoiding sharing food and drinks with others, and checking ingredient lists for suspected allergens. Adult supervision during meals and snacks, cleaning surfaces where food is prepared or eaten, and taking allergen-avoidance measures when planning classroom activities (eg, parties, crafts, science projects) or field trips are also essential.[15]

Clinicians should advise patients that, despite labeling regulations (disclosure of major allergens on the labels of prepackaged foods), restaurants are not required to declare the ingredients. Ideally, restaurant staff should be educated on this, especially for online and takeout orders from Asian restaurants. In this case, restaurants should list allergens (particularly peanuts, tree nuts, and milk) or ingredients on their menus, especially for foods such as sesame, recently added by the Food and Drug Administration (FDA). Most countries do not allow restaurants to purchase self-injectable epinephrine without a prescription.

One study showed that epinephrine was administered in 10% to 15% of inflight allergic reactions, but less than 50% of these cases were reported to airlines. Inflight anaphylaxis is estimated to occur once for every 37,750 flights. While many airlines provide information to passengers with allergies, few offer allergen-free meals or allow priority boarding. In addition, pilots can refuse boarding to passengers who pose a potential risk of flight diversion or danger to themselves.

In parks and other outdoor spaces, anaphylaxis is primarily triggered by insect stings. Food-dependent exercise-induced anaphylaxis is also more common during outdoor dining, while drug reactions are more common at home.[16]

Advising individuals at risk of anaphylaxis to wear or carry medical identification (eg, jewelry or wallet card) is considered optional. If it is worn or carried, the wording on medical alert items should be verified for accuracy by a health care professional. The effectiveness of medical alert jewelry or wallet cards in reducing the risk of anaphylaxis or enabling more rapid treatment remains unknown.[1]

When to prescribe epinephrine auto-injectors (EAIs)?

While there is no validated guideline that determines when to prescribe epinephrine auto-injectors (EAIs), expert guidance indicates their prescription in several scenarios (Table 3).[17-19]

The omalizumab package insert indicates the use of self-injectable epinephrine, but this practice is not recommended by the FDA based on updated studies. EAI prescription for patients on sublingual immunotherapy is currently indicated only in the United States. Therefore, the indication for EAIs should be evaluated on a case-by-case basis considering the individual risk of the patient, especially if there is a previous history of anaphylaxis, asthma, or other potential risk factors.[20,21]

Table 3
Indications for the prescription of epinephrine auto-injectors

History of systemic allergic reaction or anaphylaxis to their food allergen
Idiopathic anaphylaxis
Frequent allergen exposure through occupation or other activities (for venom, latex, drug allergy)
Prior systemic allergic reaction to specific allergen immunotherapy or specific venom immunotherapy
Bee venom allergy with elevated baseline serum tryptase and/or older age and/or cardiovascular disease
Venom-induced anaphylaxis not treated or with incomplete specific venom immunotherapy
Exercise-induced anaphylaxis (all phenotypes)
Cold-induced urticaria

For lower-risk patients, a shared decision-making process is recommended. This approach should consider the patient's risk factors, values, and preferences. While some risk factors can significantly increase the relative risk of anaphylaxis, the absolute risk remains small. A patient's risk of anaphylaxis depends in part on their specific diagnosis, history of previous reactions, ease of avoidance of causative agents or circumstances, presence of cofactors, and completion of specific immunotherapy.[1]

It is recommended that factors such as dosage, needle length, cost, access, and patient treatment preferences be considered when prescribing an EAI.[22] For example, subcutaneous injection may be preferable to intramuscular injection in patients with obesity due to the needle length, which may be insufficient to reach the muscle. In addition, the fixed dose of EAIs may be insufficient or excessive for children. Despite this, EAIs remain the safest and most effective option for the vast majority of patients with anaphylaxis, and all patients at risk of future anaphylactic episodes should be encouraged to carry their own EAI. Table 4 provides an overview of the characteristics of the main EAIs currently available.

Prescribing 2 EAI devices is justified, even with the increased cost, because less than 10% of anaphylactic reactions require 2 or more doses of epinephrine during a single episode.[23] Additionally, delayed access to medical care is possible, particularly in remote areas or during travel. Prescribing a single device would be more feasible if generic or stock auto-injectors were available in public places such as schools, similar to cardiac defibrillators. However, this practice is not yet common in our context.[1]

It is important to highlight that, despite increased awareness of anaphylaxis, the prescription and use of epinephrine by health professionals remain low. Patients and family members, even when properly trained and guided, often feel insecure and afraid about using the auto-injector. We therefore stress the importance of continuous and accessible training for patients and family members, with a focus on early symptom recognition and prompt treatment.[24,25]

Regarding dose recommendations, the FDA approves 0.3 mg for patients weighing 30 kg or more, 0.15 mg for patients weighing between 15 and 30 kg, and 0.1 mg (Auvi-Q) for those weighing between 7.5 and 15 kg.[26] However, several medical organizations, including the American Academy of Allergy, Asthma, and Immunology (AAAAI), the American Academy of Pediatrics, the Canadian Society of Allergy and Clinical Immunology, and the European Academy of Allergy and Clinical Immunology, support the option of using 0.1 mg (if available in the country) for patients weighing 7.5-13 kg; 0.15 mg for patients weighing 13-25 kg; and 0.3 mg for patients over 25 kg. For patients weighing 45 kg or more, a 0.5 mg dose is recommended, but few manufacturers market auto-injectors with 0.5 mg of epinephrine (Table 5).[27]

Additionally, when a 0.3 mg dose of epinephrine is administered and repeated doses are needed, the higher 0.5 mg dose should be used. Training on how and when to use epinephrine is also essential and should be part of patient counseling. Early administration of epinephrine in anaphylaxis reduces the risk of biphasic reaction and hospitalization.[26]

Our review highlights an important update regarding the activation of emergency medical services (EMS) in cases of anaphylaxis.[28,29] While EMS activation was previously recommended in all situations, recent evidence suggests that it may not be necessary after using an auto-injector if the patient experiences a prompt, complete, and durable response to treatment and is carrying a second EAI. However, EMS activation remains crucial in cases of severe anaphylaxis or when symptoms fail to resolve promptly, fail to resolve almost completely, or return or worsen. The decision to activate EMS should be made through shared-decision making, considering the personal and social limitations of each patient.[30,31] Table 6 shows the recommendations regarding EMS activation and the administration of a second epinephrine dose.

Patients and caregivers should always remember to replace EAIs after the devices have been used or expired. If they forget to replace an expired EAI or cannot do so for other reasons, it is preferable to use the expired device rather than no device at all to treat anaphylaxis. Recent studies have shown that expired EAIs retain epinephrine concentrations (80%-90%) well beyond their expiration date.32,33 Pediatric doses may degrade more rapidly after expiration than adult doses.[26,33]

Table 4
General characteristics of the main epinephrine auto-injectors currently available

Brand	Manufacturer	How to store	Concentration	Needle lenght	Excipient
Anapen® 	Owen Mumford Limited	Store below 25 °C	150 µg 300 µg 500 µg	10 mm ± 1.5 mm	Sodium metabisulfite (E223), sodium chloride, hydrochloric acid, and water for injections
Auvi Q® 	Kaleo, Inc.	Store between 20 °C and 25 °C. Do not freeze. DO NOT expose to extreme heat or cold	100 µg 150 µg 300 µg	8.9 mm 14 mm 17.3 mm	Sodium chloride, sodium bisulfite, hydrochloric acid, and water for injections
Emerade® 	Bausch & Lomb U.K. Limited	Store below 25 °C. Do not freeze	150 µg 300 µg 500 µg	16 mm 23 mm 23 mm	Sodium chloride, sodium metabisulfite (E223), disodium edetate hydrochloric acid, and water for injections
EpiPen® 	ALK-Abelló	Store below 25 °C. Do not freeze	150 µg 300 µg	13 mm 15 mm	Sodium chloride, sodium metabisulfite (E223), disodium edetate, hydrochloric acid, and water for injections
Jext® 	ALK-Abelló	Store below 25 °C. Do not freeze	150 µg 300 µg	13 mm 15 mm	Sodium chloride, sodium metabisulfite (E223), hydrochloric acid, and water for injections
Penepin® 	MEFAR ILAÇ SANAYI A.S	Store at temperature below 25 °C and protected from light	150 µg 300 µg	Information not available	Sodium metabisulfite (E223), sodium chloride

Table 5
Epinephrine dosage recommendations according to weight

EAI 0.15 mg:	recommended for children weighing between 7.5 and 25-30 kg. This device provides a dosage suitable for younger children, ensuring treatment effectiveness while minimizing the risk of overdose.
EAI 0.3 mg:	recommended for children weighing 25-30 kg and also for adolescents and adults. This dosage is adequate for most cases of anaphylaxis in individuals with higher body weight, providing an effective response.
EAI 0.5 mg:	recommended for adolescents and adults weighing ≥ 45 kg. This dosage is used in situations when higher doses are necessary due to body weight (obese) or the severity of the anaphylactic reaction.

EAI = epinephrine auto-injector.

Table 6
Recommendations for activation of emergency medical services and administration of a second dose of epinephrine

Home observation following first dose of epinephrine	Signs and symptoms resolve within minutes of epinephrine administration, without recurrence, or the patient is asymptomatic. Patients with hives or rash (including erythema), even those with newly emerging but isolated hives or erythema without other symptoms occurring after epinephrine administration.
Consider EMS activation and second dose of epinephrine, and home observation may be maintained	Symptoms improve or resolve within minutes of epinephrine administration. For example, persistence of a mild sensation of globus, nausea, coughing, or epigastric pain may be observed at home provided symptoms are improving and do not persist for longer than 10-20 minutes.
Activate EMS immediately, consider second dose of epinephrine, do not observe at home	Symptoms that fail to resolve or worsen, particularly respiratory distress, stridor, altered consciousness, cardiovascular instability, incontinence, episodes of vomiting (> 2), cyanosis, persistent hoarseness, dysphagia, wheezing, or lightheadedness.

EMS = emergency medical services.

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