

NARRATIVE REVIEW

Current Developments in Anaphylaxis: Challenges and Contradictions

 Çağla Karavaizoğlu¹,  Öner Özdemir²

¹Division of Pediatric Allergy and Immunology, Department of Pediatrics, Çam and Sakura City Hospital, İstanbul, Türkiye

²Division of Pediatric Allergy and Immunology, Department of Pediatrics, Sakarya University, Training and Research Hospital Faculty of Medicine, Sakarya, Türkiye

Abstract

Anaphylaxis is a sudden onset, rapidly progressive, life-threatening systemic hypersensitivity reaction. Immunological and non-immunological mechanisms cause anaphylaxis. Factors that play a role in the etiology of anaphylaxis differ according to age groups. In general, the diagnosis of anaphylaxis is made by a careful history and physical examination. Epinephrine is the life-saving first-choice treatment in anaphylaxis. All patients and their families should be educated about anaphylaxis and how to use adrenaline autoinjectors.

Keywords: Adrenaline; Allergen, Anaphylaxis; Autoinjector, Child, Diagnosis; Hypersensitivity

Anaphylaxis is a rapidly progressing, potentially fatal systemic hypersensitivity reaction.^[1] Diagnosis is generally based on clinical history and physical examination findings. Early recognition and immediate intervention are of vital importance. According to recent literature, anaphylaxis in children occurs at rates varying from 1 to 761 per 100,000.^[2] In Türkiye, data from İstanbul based on ICD-10 coding indicate an annual incidence of 1.95 per 100,000 individuals.^[3] Several factors influence the incidence of anaphylaxis, including age, sex, presence of atopy, geographic region, ethnicity, socioeconomic status, comorbid conditions, the route of allergen exposure, and concurrent medical therapies. The signs and symptoms of anaphylaxis typically emerge within minutes following contact with the triggering allergen.^[4] Although common triggers include foods, medications,

and insect stings, the prevalence of specific triggers may vary across different populations. In the pediatric population, the increasing prevalence of food allergies has been accompanied by a rise in both the frequency and awareness of anaphylaxis. Preventive measures aimed at reducing the risk of recurrence in individuals with a previous history of anaphylaxis are as critical as the treatment itself.^[5–9] The mortality rate associated with anaphylaxis is approximately 0.35%, with the leading causes being medications (29–58.5%), insect stings (3.3–54%), and food-related reactions (2–6.7%).^[10]

This review aims to discuss the diagnosis, differential diagnosis, and treatment of anaphylaxis and evaluate recent developments in the approach to this condition.

Here, in the light of current literature data, developments in the diagnosis and treatment of anaphylaxis will be

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Correspondence: Çağla Karavaizoğlu, M.D. Çam ve Sakura Şehir Hastanesi, Pediatri Anabilim Dalı, Çocuk Alerji ve İmmünolojisi Kliniği, İstanbul, Türkiye
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discussed with a PubMed search of the last 10 years. A literature search in PubMed for the previous 10 years used the keywords anaphylaxis, criteria, treatment, diagnosis, and management.

Signs and symptoms of anaphylaxis. Promptly recognizing anaphylaxis is essential for effective and appropriate treatment and initiating further investigations. A detailed history is the most critical step in guiding subsequent clinical decisions. Therefore, in patients suspected of anaphylaxis, a thorough history should be obtained from individuals present at the time of the event regarding the onset, progression, and nature of symptoms.

A hypersensitivity reaction to a specific allergen typically triggers anaphylaxis. The clinical course, including potential triggers, symptom pattern, onset time, duration, and the patient's response to treatment, plays a vital role in the follow-up process. The history should include information on foods or medications consumed in the past few hours, relation to physical activity, exposure to heat or cold, viral infections, emotional stress, and any insect or bee stings. Since food-related and idiopathic anaphylaxis are more common in atopic individuals, a personal or family history of atopy should always be explored.

The route of allergen exposure significantly affects the timing of symptom onset. For instance, parenterally administered allergens may cause immediate symptoms, while orally ingested allergens may lead to reactions within two hours. In exercise-induced anaphylaxis, symptoms may appear up to four hours after food intake. In alpha-Gal allergy, symptoms can occur for up to six hours following red meat consumption.^[11] In patients suspected of having alpha-Gal syndrome, red meat consumption and a history of tick bites should be specifically questioned. Additionally, the potential association between anaphylactic episodes and the menstrual cycle (catamenial anaphylaxis), particularly in adolescents, should be carefully investigated.^[12]

Following the patient history, clinical signs should be thoroughly assessed. In over 90% of cases, anaphylaxis presents with cutaneous and mucosal involvement. Common symptoms include urticaria, flushing, angioedema, and pruritus. However, it is essential to remember that anaphylaxis can occur without skin manifestations. Respiratory symptoms are the second most frequent presentation, observed in more than 50% of cases, and include dry cough, stridor, wheezing, and dyspnea, these being the most common causes of death in pediatric patients. Less commonly, gastrointestinal

symptoms (nausea, vomiting, abdominal pain, cramping, diarrhea) and cardiovascular manifestations (tachycardia, arrhythmias, weak pulse, vascular collapse, hypotension) may also occur. Central nervous system findings such as headache, seizures, altered consciousness, dizziness, syncope, sudden behavioral changes, irritability, and crying episodes may also be seen, though rarely.^[1,13]

Assessing the severity of anaphylaxis is crucial for clinical management. The systems involved and the intensity of symptoms may vary, even between episodes in the same patient. Several risk factors have been identified, including characteristics of the allergen (e.g., dose and route of exposure) and individual patient factors (e.g., immune response, concurrent medications, comorbidities).^[14,15] Various classification systems have been proposed, ranging from mild reactions with limited skin involvement to life-threatening events involving hypoxia, hypotension, neurological impairment, or cardiovascular collapse.^[16] Risk factors for severe anaphylaxis include older age, pre-existing lung disease, and drug-induced etiology. Although these classifications may not be perfect for practical use, they serve as a helpful guide in patient monitoring. One important consideration is that patients may progress from a mild reaction to a severe, life-threatening episode within minutes, emphasizing the need for timely and appropriate intervention.^[17]

Diagnosis Criteria, Contradictions, Difficulties

In 2006, the National Institute of Allergy and Infectious Diseases (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) developed clinical criteria to facilitate the diagnosis of anaphylaxis. It was reported that if any of these criteria are met, the likelihood of anaphylaxis is very high, allowing for the identification of approximately 95% of cases.^[18] Definitions published between 2004 and 2016 emphasized the term "multi-organ" involvement. However, it was noted that although some systems may be less frequently affected, their involvement, such as the cardiovascular or respiratory systems, may carry greater clinical importance and play a critical role in the course of the disease.^[19] Accordingly, the World Allergy Organization (WAO) revised the criteria in 2020, simplifying them into two main diagnostic points.^[13] Nonetheless, in 2021, the EAACI Task Force updated the anaphylaxis definition to be more similar to the earlier version, providing a more specific framework. A comparative summary of both groups' criteria is shown in Table 1.

Table 1A. WAO 2020 anaphylaxis diagnostic criteria	Table 1B. EAACI 2021 Anaphylaxis diagnostic criteria
1. Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or urticaria, swollen lips-tongue-uvula)	1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (eg generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING	AND AT LEAST ONE OF THE FOLLOWING
a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)	a. Respiratory compromise (eg dyspnoea, wheeze-bronchospasm, stridor, reduced PEF and hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)	b. Reduced BP or associated symptoms of end-organ dysfunction (eg hypotonia [collapse], syncope, incontinence)
c. Severe gastrointestinal symptoms (eg, severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens	2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
2. Acute onset of hypotension or bronchospasm or laryngeal involvement after exposure to a known or highly probable allergen for that patient (minutes to several hours), even in the absence of typical skin involvement.	a. Involvement of the skin-mucosal tissue (eg generalized hives, itch-flush, swollen lips-tongue-uvula)
a. Hypotension defined as a decrease in systolic BP greater than 30% from that person's baseline, OR i. Infants and children under 10 years: systolic BP less than (70 mmHg + [2 x age in years]) ii. Adults and children over 10 years: systolic BP less than <90 mmHg.	b. Respiratory compromise (eg dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b. Excluding lower respiratory symptoms triggered by common inhaled allergens or food allergens perceived to cause "inhalational" reactions in the absence of ingestion.	c. Reduced BP or associated symptoms (eg hypotonia [collapse], syncope, incontinence)
c. Laryngeal symptoms include: stridor, vocal changes, odynophagia.	d. Persistent gastrointestinal symptoms (eg crampy abdominal pain, vomiting)
d. An allergen is a substance (usually a protein) capable of triggering an immune response that can result in an allergic reaction. Most allergens act through an IgE-mediated pathway, but some non-allergen triggers can act independent of IgE (for example, via direct activation of mast cells).	3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
	a. Infants and children: low systolic BP (age specific) or >30% decrease in systolic BP*
	b. Adults: systolic BP of <90 mmHg or >30% decrease from that person's baseline
	PEF, peak expiratory flow; BP, blood pressure.
	*Low systolic blood pressure for children is defined as <70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 x age]), from 1 to 10 years and <90 mmHg from 11 to 17 years

Anaphylaxis diagnostic criteria World Allergy Organization (WAO) 2020;^[13] European Academy of Allergy & Clinical Immunology (EAACI);^[4] PEF: Peak expiratory flow; BP: Blood pressure; IgE: Immunoglobulin E.

Dribin et al.^[20] defined anaphylaxis as a condition encompassing IgE-mediated and non-immunologic mechanisms. Their definition notably emphasizes that anaphylaxis can occur without classical cutaneous manifestations such as urticaria and angioedema, particularly in infants. Furthermore, they prioritize rapid onset and multisystem involvement as key clinical criteria for diagnosis. Importantly, "anaphylactoid" has been abandoned to encompass all systemic hypersensitivity reactions under "anaphylaxis."

As with the previous definitions, the presence of multiple rapidly onset symptoms, measurement of serum tryptase 30 minutes to 2 hours after symptom onset, and evaluation of baseline tryptase levels at least 24 hours after complete

resolution of symptoms are recommended to support the diagnosis retrospectively.^[4] Unlike the older definitions, "systemic hypersensitivity" has replaced the term "allergic," which is considered less accurate. Furthermore, while the older criteria accepted hypotension following known allergen exposure as sufficient for diagnosis even in the absence of typical skin findings, the 2020 WAO criteria expanded this to include isolated bronchospasm or laryngeal involvement (e.g., stridor, voice changes, or odynophagia) following known or likely allergen exposure. Although the onset of symptoms is typically described as occurring within "minutes to a few hours," WAO guidelines note that specific reactions, such as those due to alpha-Gal or immunotherapy, may be delayed by

Table 2. Severity grading of anaphylaxis (adapted from Brown)^[16]

Mild	Signs and symptoms isolated to the skin, such as generalized erythema, urticaria, periorbital edema, or angioedema
Moderate	Signs and symptoms suggesting respiratory, cardiovascular, or gastrointestinal involvement, such as dyspnea, stridor, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain
Severe	Signs and symptoms reflective of hypoxia, hypotension, and/or neurologic compromise, such as cyanosis or oxygen saturation $\leq 92\%$, hypotension (systolic blood pressure <90 mm Hg in adults), confusion, collapse, altered level of consciousness, or incontinence.

up to 10 hours.^[21] Also, while previous criteria required gastrointestinal symptoms to be persistent, the 2020 WAO criteria accept “severe” gastrointestinal symptoms. Due to inconsistencies in gastrointestinal involvement in food-induced anaphylaxis, the requirements also specify that these findings are particularly applicable to exposures to non-food allergens.^[1]

Challenges Related to Diagnostics

In some instances, laboratory markers can help confirm or differentiate the diagnosis, especially when skin symptoms are absent. In such situations, serum tryptase, plasma histamine levels, and urinary histamine metabolites can aid in diagnosis. The marker choice depends on the sample collection timing after the reaction. Plasma histamine levels should be measured within 1 hour, and serum tryptase within 3 hours post-reaction. Urinary histamine metabolites (such as N-methyl histamine, N-methyl imidazole) should be measured in urine samples collected within the first 24 hours. Although platelet-activating factor (PAF) correlates well with clinical severity, its rapid degradation within 15–20 minutes limits its utility in diagnosis. Other potential markers include bradykinin, carboxypeptidase, leukotrienes, mediators released by mast cells (e.g., heparin, prostaglandin D2), and the basophil activation test. However, due to their short half-lives and technical challenges, these methods are not feasible for routine clinical practice.^[1]

Therefore, measuring serum tryptase remains the most appropriate approach in standard practice. A tryptase level above the laboratory’s upper limit of normal (commonly >11.4 ng/mL; however, some sources use >8 ng/mL) or a level exceeding the patient’s baseline by $20\% + 2$ ng/mL supports the diagnosis. Nevertheless, normal levels may still occur in some cases.^[22] For patients with no apparent trigger, particularly those with a history of recurrent, severe, or idiopathic anaphylaxis (IA), evaluating acute-phase tryptase or, if unavailable, baseline serum tryptase is informative.

Despite all these criteria, clinical manifestations in infants can be easily overlooked if not assessed carefully. In early infancy, anaphylaxis may manifest without classic cutaneous findings and instead present with less typical

features such as transient hypotonia, perioral pallor, limited eye contact, cessation of play, excessive irritability, and clinging to the mother, posing significant diagnostic challenges. Abdominal pain, cramping, and nausea may present as excessive crying.^[20]

If the patient’s history suggests an IgE-mediated trigger, specific tests (e.g., skin testing or serum-specific IgE) should be performed to confirm the etiology. However, because skin tests conducted during the refractory period following anaphylaxis may yield false negatives, these tests should be deferred for at least 4–6 weeks. In addition, if a long period has passed since the anaphylactic event, sensitization to the triggering allergen may wane. Therefore, it is recommended to perform diagnostic skin tests within 6 months after the reaction.

Clinical Features Biphasic anaphylaxis is defined as the recurrence of clinical symptoms within hours after their spontaneous resolution or resolution with treatment, following at least one hour of symptom-free observation, without re-exposure to the allergen. Meta-analyses report the incidence of biphasic anaphylaxis to be approximately 6.5%, though this rate can range between 0.4% and 20%.^[23] Although the exact mechanism is not fully understood, delayed medical intervention or insufficient dosing of epinephrine is thought to be a contributing factor. Recent evidence suggests that the development of biphasic anaphylaxis may be influenced not only by delayed administration of epinephrine and severe initial presentation but also by inadequate intravascular fluid resuscitation and specific triggers such as medications, latex, or unidentified allergens.^[24] It has been observed more frequently with increasing severity of anaphylaxis (Table 2). Additional potential risk factors for biphasic anaphylaxis include hypotension, age group 6–9 years, drug-induced anaphylaxis, unknown trigger, wheezing, the need for inhaled beta-2 agonists at presentation, and diarrhea.^[23]

Persistent anaphylaxis refers to cases in which the clinical picture of anaphylaxis continues for at least 4 hours. Unlike biphasic anaphylaxis, there is no symptom-free interval, and the persistent reaction occurs independently of the initial management.

Refractory anaphylaxis is defined as anaphylaxis that continues despite administering three or more appropriate doses of epinephrine and adequate medical treatment to control symptoms (e.g., intravenous fluid resuscitation for hypotension).^[25] Its incidence is reported to be less than 0.5%. The etiology is most commonly associated with medication during the perioperative period.^[26] The mortality rate in refractory anaphylaxis is 26.2%. Therefore, rapid recognition and effective management of anaphylaxis are of critical importance.^[27]

Differential Diagnosis Since anaphylaxis often involves multiple organ systems and presents with a wide range of symptoms and severity, it has an extensive differential diagnosis (Table 3). A detailed medical history is crucial, including potential triggers, cofactors, duration, nature of symptoms, and response to treatment. Confirming the diagnosis is of vital importance. Additionally, suppose physical examination reveals findings related to mast cell activation (e.g., urticaria, wheezing on lung auscultation, or hypotension). In that case, serum tryptase levels should also be assessed to help exclude other diagnoses.^[22]

If anaphylaxis is strongly suspected but no trigger can be identified, idiopathic anaphylaxis (IA) should be considered. This diagnosis can only be made after a thorough history and diagnostic workup, including allergy skin tests, serum-specific IgE measurements, and, in selected cases, oral food challenges ruling out all known causes of anaphylaxis.^[1] In patients with recurrent IA, alpha-gal allergy and mast cell activation syndromes should also be considered.^[28] One such condition is hereditary alpha tryptasemia (HaT), characterized by an inherited increase in the copy number of the tryptase alpha/beta-1 gene (TPSAB1), which results in elevated baseline serum tryptase levels (>8 ng/mL). This should be considered in recurrent or severe cases of anaphylaxis.^[29,30] In patients with recurrent mast cell-mediated symptoms or IA, systemic mastocytosis or clonal mast cell disorders (CMD) should also be suspected. These are more commonly seen in adults. Childhood mastocytosis, in contrast, is typically cutaneous with rare systemic symptoms but should still be considered in the differential diagnosis.^[31]

Acute generalized urticaria and angioedema may sometimes be mistaken for anaphylaxis; however, isolated skin findings without involvement of other systems and normal serum tryptase levels are distinguishing features.^[32] Hereditary angioedema (HAE) is an autosomal dominant disorder characterized by recurrent isolated angioedema episodes. When involving the larynx, respiratory symptoms may occur, and erythema marginatum, present in about

Table 3. Differential diagnosis of anaphylaxis

Skin and mucous membrane findings
Urticaria and angioedema
Oral allergy (pollen-food) syndrome
Mastocytosis, hereditary alpha-tryptasemia (HaT), clonal mast cell disease (CMD)
Hereditary angioedema
Respiratory system findings
Upper airway obstruction (foreign body aspiration)
Severe acute asthma attack
Cardiovascular diseases
Vasovagal syncope
Myocardial infarction
Cardiac arrhythmia
Hypertensive crisis
Pharmacological or toxic reactions
Fish (mackerel) poisoning (histamine)
Chinese restaurant syndrome (monosodium glutamate (MSG), sulfides)
Drugs (opiates, calcium channel blockers, vancomycin...)
Systemic capillary escape syndrome
Food protein-induced enterocolitis syndrome (FPIES)
Munchausen syndrome
Anxiety, panic attack syndrome, hyperventilation syndrome
Vocal cord dysfunction

half of cases, can mimic anaphylaxis. However, the absence of urticaria and lack of response to anaphylaxis treatment are key differentiators.^[33]

Oral allergy syndrome is another condition, particularly in adolescents and adults with allergic rhinitis. It is an IgE-mediated food hypersensitivity reaction involving cross-reactivity between pollens and certain raw fruits or vegetables, leading to localized mast cell degranulation in the oral mucosa. Symptoms such as itching, swelling, or tingling of the lips, tongue, mouth, throat, or ears occur shortly after ingestion. The absence of systemic involvement is a distinguishing feature from anaphylaxis.^[34]

Severe asthma attacks can emerge with respiratory distress and may be confused with anaphylaxis, but the absence of skin and other systemic findings helps differentiate it. Foreign body aspiration, more common in younger children, presents with sudden respiratory symptoms, clinical findings unresponsive to inhalers, and differences in lung aeration on chest X-ray, which should raise suspicion. Vocal cord dysfunction, a non-organic condition characterized by paradoxical vocal cord closure, especially

during inspiration, is observed with symptoms such as cough, dyspnea, stridor, and wheezing, and is unresponsive to inhaled bronchodilators. Congenital anomalies like laryngeal web, vascular rings, or tracheomalacia should also be considered. These presents from birth are persistent and lack skin findings or systemic symptoms, aiding differentiation.^[35]

In children, vasovagal syncope (VVS) is a common differential diagnosis. It results from reflex activation of the autonomic nervous system, leading to bradycardia, vasodilation, hypotension, and altered consciousness. Some cases may present prodromal symptoms (palpitations, weakness, sweating, flushing, abdominal pain, or visual disturbances). Triggers include prolonged standing, sudden postural changes, painful procedures, fear, fasting, coughing, and certain medications. Since VVS is self-limiting, it is generally not dangerous. The absence of urticaria, angioedema, and bronchospasm helps differentiate it from anaphylaxis. Also, while anaphylaxis often involves reflex tachycardia due to hypotension, bradycardia in VVS is a key clue.^[36]

Among non-IgE-mediated food allergies, Food Protein-Induced Enterocolitis Syndrome (FPIES) is commonly seen in infants. It is characterized by profuse vomiting 1–3 hours after ingesting the trigger food, followed by pallor, lethargy, and hypotension, with diarrhea appearing 5–8 hours later. It is distinguishable from anaphylaxis by the absence of skin and respiratory symptoms and its delayed onset.^[37]

Other conditions to consider in the differential diagnosis include Red Man Syndrome associated with vancomycin use, Munchausen by proxy, flushing syndromes in older children, and panic attacks, which are more commonly seen in adolescents. Additionally, though rare in children, Scombroid poisoning is a histamine-related reaction following ingestion of foods such as fish, sulfite-containing products, or monosodium glutamate. It can present with acute, non-specific symptoms such as urticaria, nausea, vomiting, sweating, and headache that may mimic anaphylaxis. A detailed dietary history is helpful for diagnosis.^[20]

Finally, rare in children, Systemic Capillary Leak Syndrome (SCLS) is characterized by sudden-onset severe hypotension due to acute plasma and protein leakage into the interstitial space. It emerges through edema, transient fever, fatigue, and cold-like symptoms. The absence of skin manifestations and the development of hypoalbuminemia help distinguish it from anaphylaxis.^[38] Differentiating all these conditions from anaphylaxis is critical for appropriate management.

Treatment for Anaphylaxis is a life-threatening condition if not managed promptly, and therefore, all necessary preparations and equipment must be readily available in advance. It should be remembered that respiratory or cardiac arrest and death can occur within minutes. In patients experiencing anaphylaxis, exposure to the suspected allergen should be immediately discontinued, such as stopping an infusion if a drug is suspected, and emergency assistance must be summoned. Airway patency, breathing, and circulation should be stabilized promptly, and intramuscular epinephrine should be administered swiftly in the appropriate dose. Oxygen supplementation and intravenous fluid resuscitation must be provided. The patient should be placed in a supine position with elevated legs and must not be made to stand. If vomiting is present, the patient should be placed in the left lateral position to prevent aspiration.^[20] Epinephrine should be administered intramuscularly at a dose of 0.01 mg/kg (from a 1 mg/mL [1:1000] solution), with a maximum of 0.3 mg in children and 0.5 mg in adults, into the anterolateral thigh. If there is no clinical response, the intramuscular dose may be repeated after at least 5 minutes. If repeated intramuscular doses are ineffective, intravenous epinephrine infusion should be initiated, and the patient should be closely monitored, with vital signs continuously observed. All of these interventions must be performed swiftly and simultaneously.^[17]

Patients presenting with hypotension and circulatory collapse should be given rapid intravenous fluids, which should be continued until peripheral perfusion is restored. If hypotension and circulatory compromise persist despite epinephrine and fluid therapy, additional intravenous vasopressors should be considered.^[1,13] Parenteral glucagon may benefit patients unresponsive to epinephrine, particularly those on beta-blocker therapy.^[13,39] In patients with wheezing, nebulized short-acting beta-2 agonists may be administered. In cases unresponsive to such treatments, the patient should be evaluated for potential endotracheal intubation or tracheostomy and monitored in an intensive care setting.^[20] Antihistamines may be used to relieve associated urticaria and pruritus. Combined use of H1 and H2 antihistamines is often recommended, though they are not first-line treatments for anaphylaxis.^[13,39] Although corticosteroids may control delayed inflammatory responses and are considered beneficial in prolonged symptoms or biphasic reactions, their routine use is not recommended. They may be administered as adjunctive therapy in patients with severe asthma or those who do not respond adequately to initial treatment.^[1,17]

In children and adolescents, the maximum recommended dose of epinephrine is 0.3 mg, while in adults it is 0.5 mg. According to the American Academy of Pediatrics (AAP), a 0.1 mg dose (if available) is recommended for children weighing 7.5 and 13 kg, 0.15 mg for those between 13 and 25 kg, and 0.3 mg for children over 25 kg. However, a 0.1 mg epinephrine auto-injector (EAI) is not universally available, and both the AAP and the Joint Task Force on Practice Parameters (JTFPP) support the use of the 0.15 mg EAI in infants weighing less than 15 kg. Although administration of a 0.15 mg dose in infants under 7.5 kg may exceed the 0.01 mg/kg threshold, no data indicate that this dose is either unsafe or ineffective in this population.^[13,17]

Intramuscular (IM) administration is currently recommended due to its more rapid onset of action, higher and earlier peak plasma concentrations, and potentially fewer adverse effects. Nonetheless, practical challenges such as administration in very young infants, individuals with muscle atrophy, obese patients, and those wearing thick clothing have led to the continued use of the SC route in specific settings.^[17]

There is currently a lack of data on whether the needle lengths of available EAI are optimal for intramuscular delivery. Recent studies have emphasized the importance of needle length, particularly in infants and toddlers. Ultrasound-based assessments of skin-to-bone distance have shown that longer needles may increase the risk of contact with bone, potentially reducing the efficacy of epinephrine administration and growing pain, stress, or complications such as the need for surgical removal of a lodged needle. Needle length may be critical in small infants with low body weight, women, and adults with a high body mass index (BMI >25). Due to manufacturing variability, some differences in EAI needle lengths exist.^[40,41]

The AAAAI update introduced the approval of Neffy™, a needle-free intranasal epinephrine formulation, marking a significant advancement in emergency anaphylaxis care. Clinical studies have shown that Neffy™ achieves plasma epinephrine levels and cardiovascular responses comparable to traditional intramuscular auto-injectors. Its ease of use provides a meaningful advantage by improving treatment accessibility, particularly for patients hesitant to use injectable devices.^[9] Additionally, alongside intranasal epinephrine, sublingual applications have also been introduced. However, further research and long-term studies are needed to establish their clinical efficacy and safety before they can be considered reliable alternatives to current standard practices.^[17]

Long-term Management of Anaphylaxis

The duration of observation after initial treatment is crucial. Factors such as the severity of the initial presentation, need for epinephrine, presence of respiratory symptoms, and the time elapsed between symptom onset and treatment should guide monitoring decisions. A 6–8 hour observation period may be sufficient in patients with a stable clinical course. According to EAACI, patients with respiratory compromise should be observed for 6–8 hours, whereas those with hypotension should be monitored for at least 12–24 hours.^[4] Studies have indicated that approximately 18% of children who experience anaphylaxis may have a recurrence within one year.^[42]

Preventing recurrence begins with identifying and avoiding the trigger allergen. Before discharge, patients should be thoroughly educated on how to avoid the causative allergen. The next step involves ensuring preparedness in case of future episodes. Patients should be informed about foods with potential cross-reactivity due to shared allergenic components. For example, children with cow's milk allergy are likely to react to milk from other animals; those allergic to eggs may also respond to eggs from different animal sources; individuals with nut or fish allergies often exhibit sensitivity to other types within the same group. Packaged food labels must always be carefully checked, as allergens may exist under different names or derived proteins.^[1]

Patients must be aware that anaphylaxis can occur anywhere and should carry identification or medical alert tags describing their condition. Epinephrine auto-injectors should be prescribed for patients who have had or are at high risk of anaphylaxis, and detailed instructions on when and how to use them must be provided.^[17] A written emergency action plan should be developed for these individuals, including a clear list of symptoms and signs of anaphylaxis. Patients should be encouraged to use their auto-injector without hesitation at the onset of symptoms, contact their physician, or seek emergency care promptly.^[39]

Conclusion

Anaphylaxis is an acute, potentially fatal systemic hypersensitivity reaction. It can manifest through various mechanisms and present with differing clinical severity. Although patient history is central to diagnosis, timely identification using current diagnostic criteria and rapid intervention are critical. Securing the airway, followed by immediate intramuscular epinephrine administration, remains the first and most reliable step in management. After acute care and proper observation, long-term management should

focus on providing a written emergency action plan, training on auto-injector use, educating patients and caregivers on allergen avoidance, and tailoring care to individual needs.

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