Turkish Journal of Pediatric Disease
Türkiye Çocuk Hastalıkları Dergisi

Anaphylaxis: Current Approach

Anafilaksi: Güncel Yaklaşım

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ABSTRACT

Anaphylaxis is the most important acute systemic allergic reaction. The incidence of anaphylaxis has been increasing in recent years. Therefore, all healthcare providers should know the diagnosis and management of anaphylaxis. In this article, the current approach to anaphylaxis is presented, considering the criteria accepted by the World Allergy Organization (WAO) and the European Academy of Allergy and Clinical Immunology (EACCI). Intramuscular epinephrine is the first-line treatment for anaphylaxis. However, it is still not used at the desired level. Children at risk of anaphylaxis should be trained to use adrenaline autoinjectors. After anaphylaxis develops, children should be referred to an allergist to investigate the underlying causes.

Key Words: Anaphylaxis, Children, Current approach

ÖZ

Anafilaksi en önemli akut sistemik alerjik reaksiyondur. Anafilaksi insidansı son yıllarda giderek artmaktadır. Bu nedenle, tüm sağlık çalışanları anafilaksinin tanı ve yönetimini bilmelidir. Bu makalede, Dünya Alerji Örgütü (WAO) ve Avrupa Alerji ve Klinik İmmünoloji Akademisi (EACCI) tarafından kabul edilen kriterler göz önünde bulundurularak anafilaksiye güncel yaklaşım sunulmuştur. İntramüsküler epinefrin anafilaksi için ilk basamak tedavidir. Ancak hala istenilen düzeyde kullanılmamaktadır. Anafilaksi riski taşıyan çocuklar adrenalin otoenjektörlerini kullanmak üzere eğitilmelidir. Anafilaksi geliştikten sonra, altta yatan nedenlerin araştırılması için çocuklar bir alerji uzmanına yönlendirilmelidir.

Anahtar Kelimeler: Anafilaksi, Çocuk, Güncel yaklaşım

INTRODUCTION

Anaphylaxis is a rapid onset serious life threatening systemic hypersensitivity reaction. Although potentially life-threatening, this risk can be reduced with accurate and prompt diagnosis and treatment. In this article, the current approach to anaphylaxis is presented, considering the criteria accepted by the World Allergy Organization (WAO) and European Academy of Allergy and Clinical Immunology (EAACI) (1, 2).

Epidemiology

Although the incidence of anaphylaxis varies according to age and diagnostic criteria, the lifetime prevalence of anaphylaxis is estimated to be 0.05-2 % (3). In recent studies, the incidence of anaphylaxis in children varies between 1-761/100.000 (4). Although the incidence has increased 5-7 fold in the last decade, mortality rates are stable or show a decreasing trend due to the adoption of guidelines in diagnosis and treatment and increased awareness (5, 6). It should be kept in mind that

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Conflict of Interest /Çıkar Çatışması: *On behalf of all authors, the corresponding author states that there is no conflict of interest.*

Contribution of the Authors / Yazarın Katkısı: YILMAZ D: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***ŞENGÜL EMEKSİZ Z:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***DİBEK MISIRLIOĞLU E:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Reviewing the article before submission scientifically besides spelling and grammar.

How to cite / Atıf Yazım Şekli : Yılmaz D, Şengül Emeksiz Z and Dibek Mısırlıoğlu E. Anaphylaxis: Current Approach. Turkish J Pediatr Dis 2024;18:146-151.

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Received / Geliş tarihi : 23.12.2023
Accepted / Kabul tarihi : 06.02.2024
Online published : 06.03.2024
Elektronik yayın tarihi
DOI: 10.12956/tchd.1408171

26.5-54 % of anaphylaxis patients develop anaphylaxis again in 1.5-25 years of follow-up (5).

Risk factors

Several risk factors for anaphylaxis have been identified. Infants are among the risk groups due to difficulties in diagnosis due to their inability to describe their symptoms, and adolescents are among the risk groups due to their tendency to exhibit risk-taking behavior (7).

Asthma and other respiratory diseases, cardiovascular diseases, mastocytosis and clonal mast cell disorders, psychiatric diseases such as depression may increase the mortality risk of anaphylaxis. Physical exercise, infections, fever, premenstrual period, insomnia, alcohol consumption, and drug use can potentially increase the risk of anaphylaxis by lowering the allergen exposure threshold required to trigger anaphylaxis (8-11). The use of beta-blockers and angiotensin-converting enzyme (ACE) inhibitors has been shown to cause severe anaphylaxis by inhibiting the adrenaline response to treatment (12, 13).

Pathophysiology

Despite common clinical symptoms, the mechanisms underlying anaphylaxis may vary (14). The classic and most common IgE-mediated anaphylaxis is initiated by an antigen that interacts with allergen-specific IgE binding to high-affinity IgE receptors (FcεRI) on mast cells and basophils. After this binding, clinical findings occur due to mediators and cytokines secreted by activated cells (15).

Non-IgE mediated anaphylaxis is divided into immunologic and non-immunologic. Non-IgE mediated immunologic anaphylaxis may be mediated by the complement system (anaphylatoxins, C3a and C5a), contact and coagulation system activation or IgG Non-immunologic anaphylaxis (opiates, vancomycin, radiocontrast agents, etc.) develops with direct stimulation of mast cells and basophils (16).

Triggers

Food is the most common cause of anaphylaxis in children, followed by drugs and venom (7,17,18). The frequency of triggering anaphylaxis with certain foods may vary according to dietary habits, food preparation, and type of exposure. Theoretically, anaphylaxis can develop with any type of food in sensitized children. Peanuts, tree nuts, seafood, and cow's milk have been implicated as the most frequent culprits of fatal anaphylaxis (10). In studies conducted in Turkey, cow's milk was found to be the most responsible food (7,19). Cow's milk and hen's egg are the most common foods causing anaphylaxis in infants, cow's milk and tree nuts in preschoolers, and tree nuts and legumes in school children (19).

Drug-induced anaphylaxis is most common with antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) (20). Chemotherapy drugs, biological agents such as cetuximab, rituximab, infliximab, and omalizu

mab, and enzyme replacement therapies are among the causes of drug-induced anaphylaxis (21-24). In addition, disinfectants such as chlorhexidine, and preservatives in drugs and vaccines such as polyethyleneglycol may also trigger anaphylaxis (25,26). In addition to the drugs mentioned above, anaphylaxis has been shown to develop with latex, radiocontrast agents and perioperative rocuronium, thiopental, propofol, opiates, protamine and plasma expanders (27). Anaphylaxis can also occur during skin prick tests and intradermal tests, food and drug challenge tests, as well as during immunotherapy and desensitization (28). "Idiopathic anaphylaxis" is defined as cases in which the cause of anaphylaxis has not been established despite detailed investigations and the presence of conditions such as systemic mastocytosis that may be associated with anaphylaxis has not been demonstrated (29).

Diagnosis

Anaphylaxis is diagnosed clinically by recognizing symptoms and signs that occur suddenly (within minutes to a few hours)

Table I: Signs and symptoms of anaphylaxis *

Systems	Signs and symptoms	Incidence rates %
Skin and mucous membranes	Redness, itching, urticaria, angioedema, morbiliform rash, conjunctival erythema, tearing, itching and swelling of the lips, tongue, palate and uvula	80-90
Respiration	Nose: itching, congestion, discharge, sneezing Larynx: itching, feeling of narrowness, dysphonia, coarsening of the voice, dry-hard cough, stridor Lung: shortness of breath, feeling of tightness in the chest, deep cough, wheezing, bronchospasm (reduced PEF), Cyanosis	70
Gastrointestinal	Nausea, cramping abdominal pain, vomiting, diarrhea, dysphagia	30-45
Cardiovascular	Chest pain, palpitation, tachycardia, bradycardia, dysrhythmia, feeling faint, mental change, hypotension, loss of sphincter control, shock, arrest	10-45
Neurologic	Feeling of death, restlessness, throbbing headache, dizziness, confusion; sudden behavioral changes in infants and young children (irritability, interruption of play, clinging to parents, etc.)	10-15
Others	Metallic taste in the mouth, uterine contractions (postpubertal)	

*****Table taken from 30 with permission. **PEF:** Peak expiratory flow*

Table II: Criteria for anaphylaxis according to EACCI*

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:
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 least one of the following a.Respiratory compromise (eg; dyspnoea, wheeze-bronchospasm, stridor, reduced PEF and hypoxemia) b.Reduced BP or assosicated symptoms of end-organ dysfunction (eg hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a.Involvement of the skin-mucosal tissue (eg; generalized hives, itch-flush, swollen lips-tongue-uvula) b.Respiratory compromise (eg; dyspnoea, wheeze-broncohospasm, stridor, reduced PEF, hypoxemia) c.Reduced BP or associated symptoms (eg; hypotonia [collapse], syncope, incontinence) d.Persistent gastrointestinal symptoms (eg; crampy abdominal pain, vomiting)
3.Reduced BP after exposure to known allergen for that patient (minutes to several hours): a.Infants and children: low systolic BP (age spesific) or >30% decrease in systolic BP† b.Adults: systolic BP of <90 mmHg or >30% decrease from that person's baseline

Table taken from 32 with permission. †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, **EAACI: Eaccı the European Academy of Allergy and Clinical Immunology **PEF:** Peak expiratory flow, **BP:** Blood pressure*

Table III: Criteria for anaphylaxis according to WAO*

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

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 flushing, swollen lips-tongue-uvula) and at Least one of the following
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   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. Acute onsef of hypotension[a] or bronchospasm[b] or laryngeal involvement[c] after exposure to a known or highly probable allergen[d] for that patient (minutes to several hours), even in the absence of typical skin involvement.

Table taken from 33 with permission. **WAO: World Allergy Organisation. **PEF:** Peak expiratory flow, **BP:** blood pressure. [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 + [2x age in years]) ii. Adults and children over 10 years: systolic BP less than <90 mmHg. [b]Excluding lower respiratory symptoms triggered by common inhalant allergens or food allergens perceived to cause "inhalational" reactions in the absence of ingestion. [c]Laryngeal symptoms include: stridor, vocal changes, odynophagia. [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).*

after exposure to a known or possible trigger. Common findings during anaphylaxis are shown in Table I (30).

Skin manifestations are present in 80-90 % of anaphylaxis cases. However, in 10-20 % of patients, the diagnosis of anaphylaxis may be missed due to its absence (31). Anaphylaxis has a very broad spectrum. Different clinical pictures can be observed from mild clinical findings to severe form with shock. It was observed that not all cases could be diagnosed with the current diagnostic criteria because not all cases had multi-system involvement, there were patients without cutaneous findings or shock findings, and there were patients presenting with isolated respiratory system findings. For this reason, revision of the criteria was brought to the agenda and the criteria were revised by WAO in 2020 and by EAACI in 2021 (1, 2). The diagnostic criteria for anaphylaxis revised by EAACI are shown in Table II and the diagnostic criteria revised by WAO are shown in Table III (1, 2).

Laboratory

The diagnosis of anaphylaxis is based on clinical findings. Laboratory tests have a limited role in the diagnosis of anaphylaxis. Measurement of serum tryptase level may help the diagnosis in suspected cases. Serum tryptase increases within 15 minutes to 3 hours after the onset of anaphylaxis symptoms. Tryptase levels remain at peak level for 1-2 hours (34). Elevated tryptase levels support the diagnosis of anaphylaxis, whereas normal levels do not exclude anaphylaxis (35). Tryptase levels are found to be elevated more frequently in cases of severe anaphylaxis in which the allergen enters the body by injection, drug and venom anaphylaxis and hypotension and shock develop, compared to anaphylaxis induced by food and in which arterial blood pressure remains normal (36).

Even if the serum basal tryptase level measured during anaphylaxis results within normal limits, it is recommended to measure the serum basal tryptase level again 24 hours after the symptoms of anaphylaxis have completely resolved (37). A peak mast cell tryptase (MCT) >1.2 x basal tryptase + 2 ng/L has been proposed to diagnose acute mast cell activation (38). However, if both acute and baseline tryptase levels are greater than 11.4 ng/mL, the diagnosis of mastocytosis or clonal mast cell disorder should be excluded (39).

Differential Diagnosis

Clinical conditions that may be confused with anaphylaxis are shown in Table IV (1, 31).

Treatment

Anaphylaxis is an emergency that needs to be rapidly diagnosed and treated. Initially, the substance that triggers anaphylaxis, such as medication or therapeutic agent, if any, should be removed from the environment. Airway, respiration, circulation, mental status and skin should be assessed. Intramuscular adrenaline should be administered to the vastus lateralis part of the patient's quadriceps muscle and the patient should be placed in position according to the patient's findings. If there is respiratory distress, the patient should be seated. If loss of consciousness has developed, a rescue position should be given (40).

Although intramuscular adrenaline is the first drug to be administered in the treatment of anaphylaxis, its use is still not at the desired level (41-43). Adrenaline should be administered intramuscularly at a dose of 0.01 mg/kg with a maximum dose of 0.3 mg in children and 0.5 mg in adolescents. The time of adrenaline administration should be recorded and if symptoms persist despite treatment, adrenaline should be repeated every 5-15 minutes. There is a possibility of fatal arrhythmia if adrenaline is administered intravenously. Therefore, the intramuscular route should be preferred as the safest route (44). However, if there is no response to adrenaline given intramuscularly 2 times and there are signs of severe hypotension and cardiovascular shock, adrenaline can be given by infusion. In children, it is started at a dose of 0.1-1 ug/kg/min and the dose is adjusted according to blood pressure (1, 45). If stridor is present, adrenaline can be additionally nebulized (1).

Patients who develop respiratory distress or need repeated adrenaline should be given oxygen at a rate of 6-8 L/min with a non-rebreather facemask immediately until transport to hospital. An intravenous line should be opened using broad cannulas. If hypotension and collapse develop, 10 mL/kg saline should be given (1).

If bronchoconstriction occurs, a short-acting beta agonist (salbutamol/albuterol) should be given by inhalation. The patient's blood pressure, heart rate and circulation, respiration and mental status should be checked at frequent and regular intervals (1).

Antihistamines and corticosteroids are the second used drugs in the treatment of anaphylaxis. H1 antihistamines have a limited role in the treatment of anaphylaxis. They can be used to treat skin manifestations (46). Steroids are widely used, especially to prevent biphasic anaphylaxis. However, there is growing evidence that they are not useful in the acute management of anaphylaxis, may be harmful and their routine use is controversial (22, 47). Glucagon can be used when the desired response to adrenaline is not obtained, especially in patients using beta blockers (48).

Table IV: Clinical conditions that may be confused with anaphylaxis*

Common diagnostic dilemmas
Acute asthma
Syncope
Anxiety/panic attack
Acute generalized urticaria[a]
Foreign body aspiration
Cardiovascular events (myocardial infarction,[a] pulmonary embolus)
Neurologic events (seizure, cerebrovascular event)
Postprandial syndroms
Scombroidosis[b]
Pollen-food allergy syndrome[c]
Monosodium glutamate
Sulfites
Food poisoning
Excess endogenous histamine
Mastocytosis/ clonal mast cell disorders[d]
Basophilic leukemia
Flush syndromes
Peri-menopause
Carcinoid syndrome
Autonomic epilepsy
Medullary carcinoma of the thyroid
Nonorganic Disease
Vokal cord dysfunction
Hyperventilation
Psychosomatic episode
Shock
Hypovolemik
Cardiogenic
Distributive[e]
Septic
Other
Nonallergic angioedema
Hereditary angioedema types 1,2 and 3
ACE inhibitor- associated angioedema
Systemic capillary leak syndrome
Red man syndrome (vancomycin)
Pheochromocytoma (Paradoxical response)

**Table taken from 31 with permission. [a]Acute asthma symptoms, acute generalized urticaria, or myocardial infarction symptoms can also occur during an anaphylactic episode. [b]Histamine poisoning from fish, eg, tuna that has been stored at an elevated temperature; usually, more than one person eating the fish is affected. [c]Pollen-food allergy syndrome is elicited by fruits and vegetables containing various plant proteins that cross-react with airborne allergens. Typical symptoms include oral allergy symptoms (itching, tingling and angioedema of the lips, tongue, palate, thorat, and ears) after eating raw, but not cooked, fruits and vegetables, [d]In mastocytosis and clonal mast cell disorders, there is an increased risk of anaphylaxis; also, anaphylaxis may be the first manifestion of the disease. [e]Distributive shock may be due to anaphylaxis or to spinal cord injury.*

It is recommended to follow up with the patients for at least 6-8 hours after anaphylaxis and 12-24 hours for those presenting with circulatory disturbance (40). The majority of biphasic anaphylaxis reactions occur within the first 6-12 hours after anaphylaxis is treated (49). Therefore, the observation period

Table V: Adrenaline autoinjector doses according to weight

Weight	Adrenaline dose
Children <25-30 kg	0.15 mg
Adults/children ≥ 25-30 kg	0.3 mg

should be prolonged, especially in severe reactions and in patients receiving multiple doses of adrenaline (22).

Prevention

Although it is difficult to prevent anaphylaxis, it is possible to reduce its frequency and severity with preventive measures. Anaphylaxis education should be individualized according to the patient's history, age, triggers, comorbidities, and medications. A written personalized anaphylaxis emergency action plan should be prepared. Patients at risk of anaphylaxis should be prescribed two adrenaline autoinjectors. Adrenaline autoinjector doses according to weight are shown in Table V (2). They should be trained on why, when and how to use it and this training should be repeated at intervals (40). It may be protective for patients to wear markers such as name cards, bracelets and badges indicating their allergy status, the treatment to be administered and contact information (40).

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